ORIGINAL ARTICLE

Effect of Invasive Treatment on Prognosis in Non-ST-Segment Elevation Acute Coronary Syndrome With or Without Systolic Dysfunction

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Introduction and objectives. Few data are available on the use of invasive treatment in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) and systolic dysfunction. The aim of this study was to determine the effect of invasive treatment on the prognosis of patients with NSTEACS, with or without systolic dysfunction.

Methods. The study included 972 consecutive patients admitted for NSTEACS (i.e. ST-segment depression or an elevated troponin-I level). Systolic dysfunction was defined as an ejection fraction <50% on transthoracic echocardiography. The primary long-term endpoint was death or myocardial infarction. The effect of invasive treatment on prognosis was evaluated by Cox regression analysis.

Results. Overall, 23.4% of patients had systolic dysfunction, and 303 (31.2%) reached the primary endpoint, which was more frequent in those with systolic dysfunction (49.8% vs. 25.5%; *P*<.001). Usage of coronary angiography and revascularization procedures were similar in patients with systolic dysfunction and those with an ejection fraction ≥50% (59% vs. 63.4%; *P*=.239; and 38.3% vs. 38.8%; *P*=.9; respectively). Detailed adjusted multivariate analysis, including the use of a propensity score, demonstrated that coronary angiography had a differential effect on prognosis depending on the presence or absence of systolic dysfunction (interaction, *P*=.01). Catheterization was clearly beneficial in patients with systolic dysfunction (hazard ratio [HR]=0.47; 95% confidence interval [CI], 0.3-0.75; *P*=.001) but not in those with an ejection fraction ≥50% (HR=0.9; 95% CI, 0.63-1.29; *P*=.567).

Conclusions. The presence of systolic dysfunction identifies those patients with NSTEACS who will benefit most from invasive treatment.

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Impacto pronóstico de una estrategia invasiva en el síndrome coronario agudo sin elevación del segmento ST según la presencia o no de disfunción sistólica

Introducción y objetivos. Escasa evidencia respalda la implantación de una estrategia invasiva (EI) en pacientes con síndrome coronario agudo sin elevación del segmento ST (SCASEST) y disfunción sistólica (DS). El objetivo de este trabajo es evaluar el impacto pronóstico atribuible a una EI en sujetos con SCASEST según tengan DS o no.

Métodos. Se incluyó a 972 pacientes consecutivos ingresados por SCASEST (descenso del segmento ST y/o elevación de troponina I). Se definió la DS como fracción de eyección < 50% mediante ecocardiografía transtorácica. El objetivo principal fue la muerte o infarto a largo plazo. Se analizó el impacto pronóstico atribuible a una EI mediante regresión de Cox.

Resultados. El 23,4% presentó DS. Un total de 303 (31%) pacientes alcanzaron el objetivo primario, hecho que fue más frecuente en los pacientes con DS (el 49,8 frente al 25,5%; p < 0,001). La realización de coronariografías y procedimientos de revascularización fue similar entre pacientes con DS y pacientes con fracción de eyección ≥ 50% (el 59 frente al 63,4%; p = 0,239 y el 38,3 frente al 38,8%; p = 0,9). Tras un minucioso ajuste multivariable que incluyó un índice de propensión, se observó un impacto pronóstico diferencial atribuible a la realización de una coronariografía según hubiera DS o no (interacción, p = 0,01). Así, el beneficio del cateterismo fue evidente en los pacientes con DS (*hazard ratio* [HR] = 0,47; intervalo de confianza [IC] del 95%, 0,3-0,75; p = 0,001), pero no en aquellos con fracción de eyección ≥ 50% (HR = 0,9; IC del 95%, 0,63-1,29; p = 0,567).

Conclusiones. La presencia de DS permite la identificación de los SCASEST que más se benefician de aplicar una EI.

Palabras clave: *Síndrome coronario agudo sin elevación del segmento ST. Disfunción sistólica. Revascularización. Pronóstico.*

ABBREVIATIONS

AMI: acute myocardial infarction
LVEF: left ventricular ejection fraction
NSTEACS: non-ST-segment elevation acute coronary syndrome
RIS: routine invasive strategy
SD: systolic dysfunction

INTRODUCTION

Current guidelines on clinical practice recommend a routine invasive strategy (RIS) in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS).[1,2] The available evidence indicates a consistent reduction in minor adverse events when using an RIS to manage patients with NSTEACS.[3,4] However, there is little information on reductions in death or infarction, and when this is available it is frequently contradictory.[3,4] In contrast, and despite their limitations, observational studies, which commonly include patients with greater baseline risk, have shown that an RIS decreases the risk of major adverse events compared to a selective invasive or conservative revascularization strategy.[5-9]

Left ventricular systolic dysfunction (SD) is a known independent predictor of adverse events in patients with acute coronary syndrome[10-12]; however, the prognostic scores most commonly used in daily clinical practice do not include this among their components.[13-15] Furthermore, the scientific evidence regarding this issue is mainly based on the results of contemporary clinical trials that either did not systematically assess systolic function,[16-18] or, when they did,[19] showed a marginal percentage of patients with SD. Recently, the results from the GRACE registry showed that revascularization was associated with a marked reduction in the risk of mortality after hospital discharge in the subgroup of patients with congestive heart failure (CHF).[20] In the light of this, and due to the fact that conventional clinical examination has limited specificity and sensitivity to identify patients with ventricular dysfunction,[21-22] we suggest that, in patients with NSTEACS, the identification of SD by routine echocardiographic examination would facilitate the early selection of the subgroup of patients with greater and more severe myocardial ischemia, and thus greater expected prognostic benefit from an RIS.

The aim of the present study was to establish whether the prognostic impact (long-term mortality or myocardial infarction) of coronary angiography and subsequent revascularization during hospitalization for NSTEACS differs according to the presence or absence of SD.

METHODS

Study Population

We analyzed a total of 1017 patients consecutively admitted to our hospital between January 2001 and May 2005 with a diagnosis of high-risk NSTEACS, defined by the presence of chest pain during the previous 24 hours and increased troponin I (TnI) levels or electrocardiographic evidence of ST segment depression. The patients who died during index hospitalization (n=45) were excluded from the present analysis, leaving 972 patients in the study group. The type of revascularization strategy followed was decided by the clinical cardiologist; however, as of 2002, due to the publication of new clinical guidelines,[23] an RIS was recommended in these patients. The left ventricular ejection fraction (LVEF) was assessed by transthoracic echocardiography during initial admission. Coronary angiography, when performed, was conducted during index hospitalization at a mean of 96 (48) hours after admission. In 94% of catheterized patients, echocardiography preceded coronary angiography and in only 36 patients was coronary angiography performed after echocardiography.

For the main analysis, systolic function was considered preserved when LVEF was ≥50% and depressed if it was <50%. The LVEF was calculated using Simpson's method in patients with regional wall-motion abnormalities, and by using Teichholz's method in the other patients. All the patients were treated with aspirin and low-molecular-weight heparin. The use of glycoprotein IIb-IIa receptor inhibitors was limited to abciximab in the catheterization laboratory and its indication was decided by the interventional cardiologist. Any other pharmacological treatment was decided by the attending clinical cardiologist.

Definition of Adverse Events and Follow-up

The appearance during follow-up of all-cause mortality or myocardial infarction was the main endpoint in the present study. Acute myocardial infarction (AMI) was defined as follows: *a)* elevated cardiac enzyme markers (TnI or CK-MB) associated with typical chest pain or ST segment deviation; or *b)* increased CK-MB level 3 times its upper limit after percutaneous transluminal coronary angioplasty (PTCA) or more than 5 times after coronary revascularization surgery.[24]

Clinical follow-up was conducted during successive outpatient visits or, in their absence,

TABLE 1. **Baseline Characteristics Stratified According to Coronary Angiography**

	No (n=366)	Yes (n=606)	*P*
Demographic data and medical record			
Age, mean (SD), y	74 (12)	65 (11)	<.001
Male, n (%)	195 (53.3)	430 (71)	<.001
AHT, n (%)	251 (68.6)	366 (60.4)	.010
Dyslipidemia, n (%)	138 (37.7)	297 (49)	.001
Smoker, n (%)	50 (13.7)	171 (28.2)	<.001
Ex-smoker, n (%)	101 (27.6)	177 (29.2)	.590
Diabetes mellitus, n (%)	130 (35.5)	213 (35.1)	.907
Insulin-dependent diabetes mellitus, n (%)	60 (16.4)	69 (11.4)	.026
Family history of IHD, n (%)	20 (5.5)	50 (8.2)	.103
History of AMI, n (%)	101 (27.6)	131 (21.6)	.034
CKF, n (%)	65 (17.8)	47 (7.8)	<.001
Creatinine, mg/dL[a]	1.32 (0.97)	1.12 (0.48)	<.001
COPD, n (%)	43 (11.7)	46 (7.6)	.029
Stroke, n (%)	42 (11.5)	37 (6.1)	.003
TIMI risk score	3 (1.1)	2.8 (1.2)	.067
Peripheral artery disease, n (%)	30 (8.2)	37 (6.1)	.212
Previous aspirin use, n (%)	185 (50.5)	246 (40.6)	.002
Elevated troponin I levels, n (%)	329 (89.9)	496 (81.9)	<.001
ST depression, n (%)	143 (39.1)	316 (52.1)	<.001
Recurrent angina, n (%)	16 (4.4)	113 (18.6)	<.001
LVEF, %	57 (11)	60 (11)	<.001
LVEF <50%, n (%)	93 (25.4)	134 (22.1)	.239
Killip class >I, n (%)[b]	109 (29.8)	67 (11.1)	<.001
Treatment at discharge			
Beta-blockers, n (%)	297 (81.8)	502 (82.8)	.504
ACEI, n (%)	194 (53)	270 (44.5)	.011
ARA II, n (%)	40 (10.3)	117 (19.3)	.001
Statins, n (%)	160 (43.7)	387 (63.9)	<.001
Clopidogrel, n (%)	18 (4.9)	293 (44.4)	<.001
ASA, n (%)	346 (94.5)	585 (96.5)	.133

ACEI, angiotensin-converting enzyme inhibitors; AHT indicates arterial hypertension; AMI, acute myocardial infarction; ARA II, angiotensin II receptor antagonists; ASA, acetylsalicylic acid: CKF, chronic kidney failure; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction.
Continuous variables are expressed as mean (standard deviation) (SD). Discrete variables are expressed as percentages. Comparisons were made using the Student t-test and the χ^2, respectively.
[a]At admission.
[b]At admission or during hospitalization.

by telephone contact (patients who, for whatever reason, could not attend programmed visits). The protocol followed in the present study was approved by the ethics committee of our hospital.

Statistical Analysis

The risk of death or AMI during follow-up for both categories (LVEF <50% and ≥50%) was stratified according to coronary angiography and revascularization procedures. The differences were estimated using Kaplan-Meier curves and were compared using the log-rank test.

Due to the observational character of the present study, and to the presence of baseline differences on coronary angiography (Table 1), we decided to create a propensity index to minimize this selection bias.[25] Thus, by using a multivariate logistic regression model, we identified the variables associated with coronary angiography, which we consider to be the crucial and defining step for a patient to subsequently be revascularized. The propensity index was constructed by including all variables with a $P \leq .25$ in the univariate analysis, as well as those that the literature has shown to be associated with invasive procedures regardless of the *P* value and the year of admission, since revascularization guidelines have changed over time. The final model used for constructing the propensity index included the following: age, sex, year of admission, smoking history, CHF history, stroke history, peripheral artery disease, chronic obstructive pulmonary disease,

previous use of aspirin, ST segment deviation, serum creatinine level, presence of CHF, stress testing, and recurrent angina during hospitalization. The area under the receiver operating characteristic curve of the propensity index was 0.89, indicating excellent discrimination. Cox proportional hazard analysis was used to determine the risk of a combined episode for long-term mortality and myocardial infarction. The final multivariate model was adjusted by the propensity index (individual probability of being catheterized), dividing into quintiles the TIMI risk score,[16] comorbidity estimated by the Charlson index,[26] Killip class >I at admission or during hospitalization, and elevated serum creatinine levels. The proportional hazards assumption was assessed by analysis of Schoenfeld residuals. The estimated coefficients were expressed as hazard ratio (HR) with their respective 95% confidence intervals (95% CI). The final discriminatory capacity of the prognostic multivariate models was determined using Harrell's C statistic. In all cases, a $P<.05$ was used as the cutoff for statistical significance. The STATA 9.2 software package was used for the statistical analysis.

RESULTS

Baseline Characteristics of the Population

The mean age of our sample was 68.7 (12.4) years, 625 (64.3%) were men, 343 (35.3%) had diabetes mellitus, 825 (84.9%) presented elevated troponin I levels, 459 (47.2%) had ST segment depression, 152 (15.6%) were in Killip class >I, and 227 (23.4%) had an LVEF <50%. The proportion of catheterized and revascularized patients during the index event was 62.4% and 38.7%, respectively. The most frequent revascularization modality used was percutaneous intervention (75%) and a stent was used in 94.7% of these procedures. In general, the catheterized and revascularized patients presented a better baseline risk profile (Tables 1 and 2, respectively).

Baseline Characteristics Stratified According to Systolic Function

In total, 227 (23.4%) and 141 (14.5%) patients had an LVEF <50% and <45%, respectively. The patients with an LVEF <50% were older, presented greater creatinine levels at admission, had higher TIMI risk scores, and presented a greater percentage of diabetes mellitus, chronic kidney failure, stroke, previous aspirin use, and peripheral artery disease. Regarding treatment, the patients with SD were more frequently prescribed beta-blockers, and underwent coronary angiography and PTCA less frequently; in contrast, they underwent coronary revascularization surgery more frequently (Table 3). Finally, no differences were observed in the overall rates of revascularization according to the presence or absence of SD (Table 3).

Coronary Angiography and Long-term Adverse Events

During a median follow-up of 24 months (interquartile range, 6-42), 193 (19.9%) patients died, 176 (18.1%) presented an infarction and 303 (31.2%) reached the combined endpoint of death/AMI.

The proportion of death/AMI during follow-up was lower among the catheterized patients (21% vs 48.1%, $P<.001$) compared to noncatheterized patients. However, these prognostic differences were not homogeneous after stratifying the patients according to the presence or absence of SD. Thus, the cumulative probability of death, myocardial infarction and the combined endpoint of death and AMI, was considerably higher in the subgroup of noncatheterized patients with an LVEF <50% compared to the 3 remaining categories (noncatheterized patients, LVEF ≥50%; catheterized patients, LVEF <50%; and catheterized patients, LVEF ≥50%); these differences were already marked in the first days of follow-up (Figure 1).

The differential prognostic effect attributable to performing coronary angiography according to the presence or absence of SD (P for interaction = .010) was confirmed by the multivariate analysis, after adjusting by the propensity index (individual probability of being catheterized), the TIMI risk score, accompanying comorbidity (Charlson index), elevated serum creatinine level, and Killip class >I at admission. Thus, those with an LVEF <50% showed greater prognostic benefit after catheterization (HR=0.47; 95% CI, 0.30-0.75; $P=.001$) than catheterized patients with an LVEF ≥50% (HR=0.90; 95% CI, 0.63-1.29; $P=.567$).

Coronary Angiography, Revascularization, and Long-term Prognosis

In a subsequent analysis, we investigated whether the prognostic differences observed between the catheterized patients in the 2 LVEF categories was due, at least partly, to the revascularization procedures. To this end, we divided our population into 3 groups: *a)* noncatheterized patients and, obviously, nonrevascularized patients (n=366, reference category); *b)* catheterized and nonrevascularized patients (n=230); and *c)* revascularized patients (n=376). After multivariate adjustment: *a)* the catheterized and nonrevascularized patients did not present better long-term prognosis, regardless of the presence or absence of SD (P for interaction = .201) as

TABLE 2. **Basal Characteristics Stratified According to Revascularization**

	No (n=596)	Yes (n=376)	*P*
Demographic data and medical record			
Age, mean (SD), y	71 (12)	65 (11)	<.001
Male, n (%)	337 (56.5)	288 (76.6)	<.001
AHT, n (%)	392 (65.8)	225 (59.8)	.061
Dyslipidemia, n (%)	246 (41.3)	189 (50.3)	.006
Smoker, n (%)	100 (16.8)	121 (32.2)	<.001
Ex-smoker, n (%)	158 (26.5)	120 (31.9)	.069
Diabetes mellitus, n (%)	209 (35.1)	134 (35.6)	.856
Insulin dependent diabetes mellitus, n (%)	89 (14.9)	40 (10.6)	.055
Family history of IHD, n (%)	33 (5.5)	37 (9.8)	.011
History of AMI, n (%)	158 (26.5)	74 (19.7)	.015
CKF, n (%)	90 (15.1)	22 (5.8)	<.001
Creatinine, mg/dL[a]	1.25 (0.82)	1.1 (0.48)	.001
COPD, n (%)	62 (10.4)	27 (7.2)	.090
Stroke, n (%)	57 (9.6)	22 (5.8)	.039
Peripheral artery disease, n (%)	45 (7.5)	22 (5.8)	.308
TIMI risk score	2.9 (1.2)	2.8 (1.2)	.256
Previous aspirin use, n (%)	282 (47.3)	149 (39.6)	.019
Elevated troponin I levels, n (%)	205 (54.5)	250 (41.9)	<.001
ST depression, n (%)	272 (45.6)	187 (49.7)	.213
Recurrent angina, n (%)	51 (8.6)	78 (20.7)	<.001
LVEF, %	60 (14)	60 (12)	.501
LVEF <50%, n (%)	140 (23.5)	87 (23.1)	.900
Killip class >I, n (%)[b]	36 (9.6)	140 (23.5)	<.001
Multivessel disease, n (%)[c]	75 (30.4)	179 (47.6)	<.001
Treatment at discharge			
Beta-blockers, n (%)	487 (81.7)	312 (83)	.615
ACEI, n (%)	292 (49)	172 (45.7)	.323
ARA II, n (%)	87 (14.6)	70 (18.6)	.097
Statins, n (%)	290 (48.7)	257 (68.3)	<.001
Clopidogrel, n (%)	36 (6.04)	275 (73.1)	<.001
ASA, n (%)	555 (93.1)	376 (100)	<.001

AAHT indicates arterial hypertension; ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARA II, angiotensin II receptor antagonists; ASA, acetylsalicylic acid; CKF, chronic kidney failure; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction.
Continuous variables are expressed as mean (standard deviation) (SD). Discrete variables are expressed as percentages. Comparisons were made using the Student t-test and the χ^2, respectively.
[a]At admission.
[b]At admission or during hospitalization.
[c]Percentage of the 606 (62.3%) catheterized patients.

shown in Table 4 and Figure 2) the magnitude of the prognostic benefit attributable to revascularization was far greater in the patients with an LVEF <50% (*P* for interaction =.012). Thus, the reduction of risk attributable to coronary revascularization was 2 times greater in the patients with an LVEF <50% (HR=0.32; 95% CI, 0.18-0.56; *P*<.001) versus the patients with an LVEF ≥50%, where revascularization was marginally associated with long-term prognosis (HR=0.69; 95% CI, 0.44-1.08; *P*=.108) (Table 4). Harrell's C statistic for the final model was 0.734, indicating good discrimination.

The magnitude and direction of the results was substantially different in the 4 sensitivity analyses: *a)* adjusting the multivariate model for the pharmacological treatment groups at discharge; *b)* excluding those patients with Killip class >I; *c)* including only those with a history of AMI; and *d)* varying the LVEF cutoff point to define SD (LVEF<45%) (Table 4).

DISCUSSION

In the present study, we assessed a large consecutive cohort of patients with high-risk NSTEACS, and found that the greatest benefit attributable to routine coronary angiography was observed in the subgroup of patients with an LVEF <50%. As expected, this

TABLE 3. **Basal Characteristics Stratified According to Ejection Fraction**

	LVEF<50% (n=227)	LVEF ≥50% (n=745)	*P*
Demographic data and medical record			
Age, mean (SD), y	71 (11)	68 (13)	<.001
Male, n (%)	154 (67.8)	471 (63.2)	.203
AHT, n (%)	144 (63.4)	473 (63.5)	.988
Dyslipidemia, n (%)	101 (44.5)	334 (44.8)	.928
Smoker, n (%)	39 (17.2)	182 (24.4)	.023
Ex-smoker, n (%)	70 (30.8)	208 (27.9)	.394
Diabetes mellitus, n (%)	107 (47.1)	236 (37.1)	<.001
Insulin-dependent diabetes mellitus, n (%)	50 (22)	79 (10.6)	<.001
Family history of IHD, n (%)	13 (5.7)	57 (7.6)	.326
History of AMI, n (%)	101 (44.5)	131 (17.6)	<.001
CKF, n (%)	47 (20.7)	65 (8.7)	<.001
Creatinine, mg/dL[a]	1.42 (1.15)	1.12 (0.49)	<.001
COPD, n (%)	19 (8.4)	70 (9.4)	.639
Previous stroke, n (%)	29 (12.8)	50 (6.7)	.003
Peripheral artery disease, n (%)	37 (16.3)	30 (4)	<.001
TIMI risk score	3.3 (1.1)	2.8 (1.2)	<.001
Previous aspirin use, n (%)	144 (63.4)	287 (38.5)	<.001
Elevated troponin I levels, n (%)	211 (92.9)	614 (82.4)	<.001
ST depression, n (%)	106 (46.7)	353 (47.4)	.856
Recurrent angina, n (%)	34 (15)	95 (12.7)	.387
Killip class >I, n (%)[b]	87 (38.3)	89 (11.9)	<.001
Multivessel disease, n (%)[c]	85 (59.9)	169 (35.1)	<.001
LVEF, %	41 (7)	65 (7)	<.001
Pharmacological treatment			
Beta-blockers, n (%)	198 (87.2)	601 (80.7)	.024
ACEI, n (%)	100 (44)	364 (48.9)	.204
ARA II, n (%)	39 (17.2)	118 (15.8)	.631
Statins, n (%)	112 (53.7)	425 (57)	.380
ASA, n (%)	220 (96.9)	711 (95.4)	.331
Clopidogrel, n (%)	63 (27.8)	248 (33.3)	.118
Revascularization procedure			
Coronary angiography, n (%)	134 (59)	273 (63.4)	.239
PTCA, n (%)	52 (22.9)	231 (31)	.019
Surgery, n (%)	35 (15.4)	58 (7.8)	.001
Revascularization, n (%)	87 (38.3)	289 (38.8)	.900

AHT indicates hypertension; ACEI, angiotensin-converting enzyme inhibitors; ARA II, angiotensin II receptor antagonists; ASA, acetylsalicylic acid; CKF, chronic kidney failure; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction.
Continuous variables are expressed as mean (standard deviation) (SD). Discrete variables are expressed as percentages. Comparisons were made using the Student t-test and the χ^2, respectively.
[a]At admission.
[b]At admission or during hospitalization.
[c]Percentage of the 606 (62.3%) catheterized patients.

differential prognostic effect was confirmed in the revascularized patients. This differential prognostic effect was consistent despite adjusting by a propensity index (individual probability of undergoing coronary angiography), TIMI risk score, Charlson comorbidity index, Killip class >I and elevated serum creatinine levels. Furthermore, the same results were found after adjusting the model for the pharmacological treatment groups at discharge, excluding those with Killip class >I, varying the cutoff point defining SD, or even when only the subgroup of patients with a history of AMI was analyzed. In view of these results, we suggest that the routine and early assessment of LVEF in patients with NSTEACS would help to identify a population subgroup who would benefit from an RIS.

Systolic Dysfunction in Patients With Non-St-Segment Elevation Acute Coronary Syndrome. A Gap Between Observational Studies and Randomized Studies?

Unlike randomized studies, where there is scarce evidence in support of an RIS,[3-4] the adoption of an

TABLE 4. **Hazard Ratio of Death or Reinfarction Attributable to Coronary Revascularization in Patients With NSTEACS and According to the Presence or Absence of Systolic Dysfunction**

	HR (95% CI)		*P* for Interaction
	LVEF<50%	LVEF≥50%	
Total sample[a]			
C2 versus C1	0.71 (0.41-1.21)	1.07 (0.7-1.62)	.201
C3 versus C1	0.32 (0.18-0.56)	0.69 (0.44-1.08)	.012
Adjusting the model by pharmacological groups at discharge[b]			
C2 versus C1	0.74 (0.43-1.28)	1.05 (0.69-1.61)	.283
C3 versus C1	0.32 (0.18-0.57)	0.69 (0.43-1.08)	.015
Excluding patients with Killip class >I (n=820)			
C2 versus C1	0.66 (0.32-1.34)	0.96 (0.59-1.57)	.365
C3 versus C1	0.27 (0.14-0.51)	0.69 (0.44-1.08)	.010
Including only patients with a history of AMI (n=232)			
C2 versus C1	0.54 (0.24-1.20)	0.54 (0.22-1.34)	.983
C3 versus C1	0.18 (0.08-0.42)	0.55 (0.25-1.21)	.037
	LVEF<45%	**LVEF≥45%**	
C2 versus C1	0.62 (0.33-1.11)	0.96 (0.65-1.43)	.178
C3 versus C1	0.28 (0.14-0.54)	0.59 (0.39-0.9)	.030

C1 indicates no coronary angiography; C2, coronary angiography-not revascularized; C3, revascularized; NSTEACS, non-ST-segment elevation acute coronary syndrome; HR, hazard ratio; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction.
[a]Multivariate model adjusted by the propensity index (individual probability of being catheterized), for TIMI risk score, accompanying comorbidity (Charlson index), elevated serum creatinine levels and Killip class >I at admission.
[b]Multivariate model adjusted for previous variables and treatment with the following at discharge: clopidogrel, aspirin, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and statins.

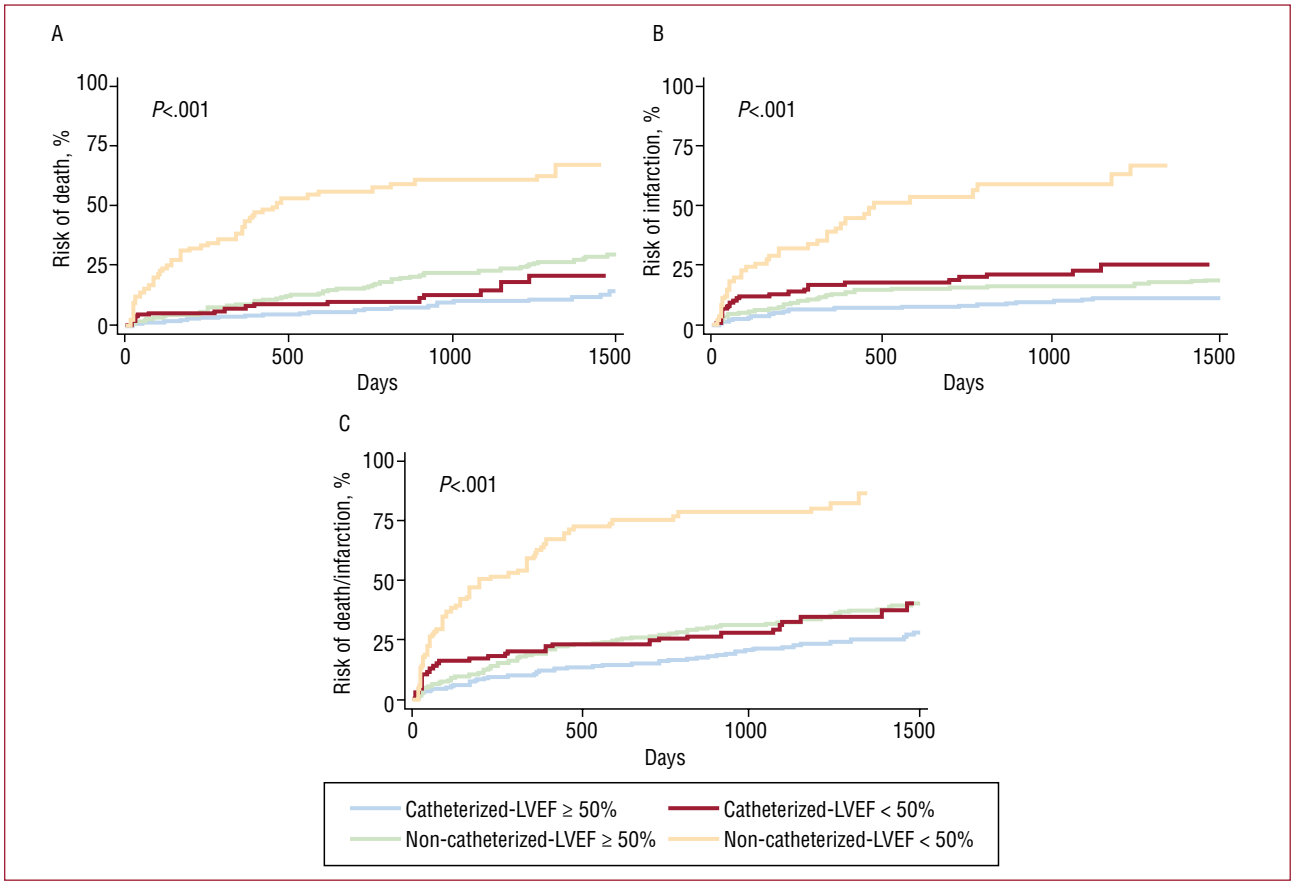

Figure 1. Cumulative risk of death (A), AMI (B), and the combined endpoint of death/AMI (C) stratified according to coronary angiography and the presence of systolic dysfunction in patients with NSTEACS.

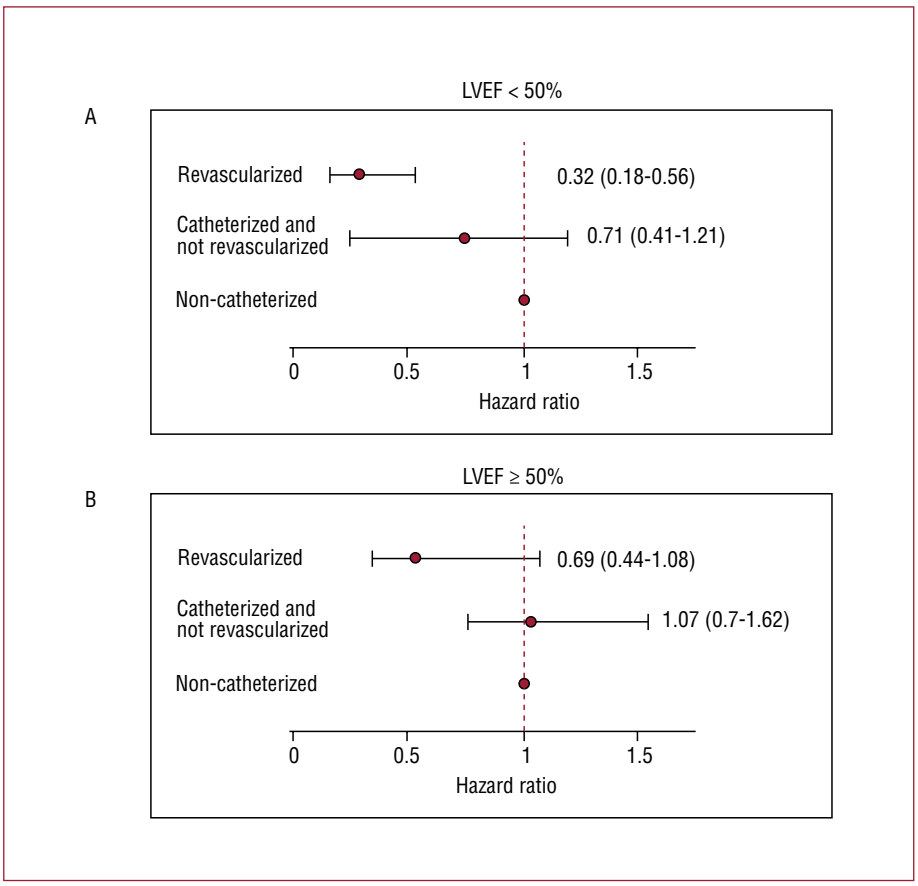

Figure 2. Prognostic effect attributable to coronary angiography or revascularization procedures depending on the presence of systolic dysfunction in patients with NSTEACS. A: patients with systolic dysfunction. B: patients with preserved systolic function. Multivariate analysis adjusted by the propensity index (individual probability of being catheterized), for TIMI risk score, accompanying comorbidity (Charlson index), elevated serum creatinine levels and Killip class >I at admission.

RIS has been associated with a striking reduction in the risk of major adverse events in recently published observational studies.[5-9] These studies included population subgroups classically under-represented in clinical trials (patients with heart failure, women, patients of advanced age, and patients with high comorbidity, among others). Despite the plethora of studies investigating the prognostic influence of an RIS on NSTEACS, the information available on this issue in patients with SD and NSTEACS is very limited.

Most clinical trials do not provide data related to LVEF,[16-18] but when provided, the data are predominantly normal although the percentage of patients with SD is not specified.[27-28] Only the ICTUS study reported that a marginal 14% of the study population presented an LVEF <35%.[19] Despite the precautions taken when interpreting the analysis by population subgroups, most studies present their results grouped according to the classic variables (age, sex, diabetes, electrocardiographic alterations, and elevated biomarkers, among others); however, the absence of prognostic information related to the patients with SD is striking. Thus, only the old VANQWISH study reported that in the subgroup of patients with SD, no benefit attributable to an RIS was found, although neither the percentage of patients with SD nor the cutoff points used to define it were specified.[27]

The LVEF has not always been measured in observational studies,[5,8,20] and thus it has not been routinely included as a prognostic variable. Furthermore, despite the fact that numerous studies investigating chronic ischemic heart disease have highlighted the benefit of revascularization in patients with SD,[29] such studies are more than just scarce within the area of NSTEACS; in fact, there are none. In view of our results, we suggest that one of the possible differences that may explain the prognostic differences between randomized and observational studies resides, at least partly, in the fact that the proportion of patients with SD included in the observational studies was much higher than that in controlled studies.

Biological Plausibility of Our Findings

It is well known that LVEF is one of the more relevant independent predictors in patients with ACS.[10-12] Within the area of chronic ischemic heart

disease, a large body of evidence has indicated that ischemic patients with depressed LVEF and predicted recovery (using noninvasive myocardial viability testing) constitute a high-risk group in whom revascularization improves survival.[29-30] However, in NSTEACS, the evidence in this regard is very limited, although certain observations suggest it. Plein et al reported that regional wall-motion abnormalities in patients with NSTEACS showed good diagnostic yield in predicting significant coronary artery disease on angiography.[31] In a series of 601 patients assessed by magnetic resonance imaging for acute chest pain of possible coronary origin, Bodí et al demonstrated that the joint presence of inducible ischemia and regional wall-motion abnormalities identified the subgroup of patients who would obtain the greatest benefit from revascularization in terms of reducing the risk of cardiovascular episodes.[32] Recently, in a series of 13 707 patients with ACS in the GRACE registry, Steg et al reported that revascularized patients in Killip class >I presented a 50% reduction in mortality at 6 months compared to nonvascularized patients with CHF.[20] As expected, in the patients for whom LVEF values were available (69%) in this series, the percentage of subjects in Killip class >I and with an LVEF ≤40% was 48.7% compared to only 20% of patients without CHF.

Thus, and on the basis of the ischemic cascade,[33] we suggest that the presence of SD in patients with NSTEACS identifies patients with greater and more severe coronary disease and, therefore, those who would obtain greater benefit from coronary revascularization.

Clinical Implications

Even though the current clinical practice guidelines recommend measuring the LVEF in the first hours of NSTEACS,[1-2] data from large registries, such as the GRACE[20] and CRUSADE[5] registries, show that the measurement of LVEF is not routine. Similarly, the current risk assessment scales used more frequently do not include the presence of SD among their components. In view of our results, we believe that its rapid determination would add another step to risk stratification, identifying the patients who would obtain more benefit from an early RIS.

Limitations

Although these results are robust, there are a number of limitations that should be mentioned: *a)* the proportion of revascularized patients was less than that in large randomized studies; nevertheless, it is worth taking into account that our registry included consecutive unselected patients. Furthermore, the percentages of revascularization were similar to or even higher than those presented in other contemporary national and international observational studies[5,20,34]; *b)* we cannot rule out the possibility that our results could have been affected by residual confounding factors or, more importantly, by the lack of adjustment for known but unavailable covariates; *c)* the present results were obtained in a single center, which could limit, at least partly, the extrapolation of our results to other contexts; *d)* the limited number of patients with severe LVEF depression (LVEF≤35%) impedes our understanding of the true prognostic impact of coronary angiograph/revascularization in this subgroup; *e)* during the inclusion and follow-up periods the treatment guidelines underwent substantial changes, and thus we cannot rule out that this may have acted as a residual confounding factor that could have affected the present results; and *f)* given that systolic function was not routinely determined in early death, our data can only be extrapolated to patients who survived the hospital phase.

CONCLUSIONS

In patients with high-risk NSTEACS, the routine identification of patients with SD may be very useful for identifying those individuals who would benefit, in terms of long-term death or myocardial infarction, from routine coronary angiography. Future randomized studies are needed to confirm the present results.

REFERENCES

1. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007;28:1598-660.
2. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction. J Am Coll Cardiol. 2007;50:1-157.
3. Qayyum R, Khalid MR, Adomaityte J, Papadakos SP, Messineo FC. Systematic Review: Comparing Routine and Selective Invasive Strategies for the Acute Coronary Syndrome. Ann Intern Med. 2008;148:186-96.
4. Núñez J, Sanchis J, Bodí V. Estrategia de revascularización invasiva en el síndrome coronario agudo sin elevación del segmento ST. El debate continúa. Med Clin. 2009;18:717-23.
5. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA. 2004;292:2096-104.
6. Bodí V, Sanchís J, Llácer A, Fácila L, Núñez J, Pellicer M, et al. Estrategia invasiva en el síndrome coronario agudo sin elevación del segmento ST. De los grandes estudios al mundo real. Rev Esp Cardiol. 2004;57:1143-50.

7. Núñez J, Sanchis J, Núñez E, Bodi V, Bertomeu-González V, Bosch MJ, et al. Prognosis differences between routine invasive and conservative strategies for the management of high-risk, non-ST segment acute coronary syndromes: experience from two consecutive periods in a single center. Eur J Intern Med. 2007;18:409-16.
8. Bauer T, Koeth O, Jünger C, Heer T, Wienbergen H, Gitt A, et al. Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. Eur Heart J. 2007;28:2873-8.
9. Sanchis J, Bertomeu V, Bodi V, Núñez J, Lauwers C, Ruiz-Nodar JM, et al. Estrategia invasiva en pacientes con diabetes avanzada y síndrome coronario agudo sin elevación del segmento ST. Hallazgos angiográficos y evolución clínica. Resultados del estudio PREDICAR. Rev Esp Cardiol. 2006;59:321-8.
10. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moyé LA, Dagenais GR, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation. 1994;89:68-75.
11. Batalla A. The importance of the left ventricular ejection fraction in the prognosis of early-onset coronary disease. Int J Cardiol. 2000;75:293-4.
12. Bodí V, Sanchis J, Llácer A, Fácila L, Núñez J, Pellicer M, et al. Indicadores pronósticos en el síndrome coronario agudo sin elevación del segmento ST. Rev Esp Cardiol. 2005;58:198-216.
13. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284:835-42.
14. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation. 2000;101:2557–67.
15. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004;291:2727–33.
16. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet. 2002;360:743-51.
17. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001;344:1879-87.
18. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet. 2000;356:9-16.
19. de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, et al. Early invasive versus selectively invasive management for acute coronary síndromes. N Engl J Med. 2005;353:1095-104.
20. Steg PG, Kerner A, van de Werf F, López-Sendón J, Gore JM, Fitzgerald G, et al. Impact of In-Hospital Revascularization on Survival in Patients With Non–ST-Elevation Acute Coronary Syndrome and Congestive Heart Failure. Circulation. 2008;118:1163-71.
21. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261:884-8.
22. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. Eur Heart J. 1991;12:315-321.
23. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2002;23:1809-40.
24. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J. 2000; 21:1502-13.
25. Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V. Principles for modeling propensity scores in medical research: a systematic literature review. Pharmacoepidemiol Drug Saf. 2004;13:841-53.
26. Núñez JE, Núñez E, Fácila L, Bertomeu V, Llàcer A, Bodí V, et al. Papel del índice de Charlson en el pronóstico a 30 días y 1 año tras un infarto agudo de miocardio. Rev Esp Cardiol. 2004;57:842-9.
27. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med. 1998;338:1785-92.
28. TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994;89:1545-56.
29. Allman K, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: A meta-analysis. J Am Coll Cardiol. 2002; 39:1151-8.
30. Camici PG. Hibernation and heart failure. Heart 2004; 90: 141-3.
31. Plein S, Greenwood JP, Ridgway JP, Cranny G, Ball SG, Sivananthan MU. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. J Am Coll Cardiol. 2004;44:2173-81.
32. Bodi V, Sanchis J, Lopez-Lereu MP, Nunez J, Mainar L, Monmeneu JV, et al. Prognostic and therapeutic implications of dipyridamole stress cardiovascular magnetic resonance on the basis of the ischemic cascade. Heart. 2009;95:49-55.
33. Nesto RW, Kowalchuk GJ. The ischemic cascade: Temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol. 1987; 59:23-30.
34. Ferreira-González I, Permanyer-Miralda G, Marrugat J, Heras M, Cuñat J, Civeira E, et al. Estudio MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado). Resultados globales. Rev Esp Cardiol. 2008;61:803-16.