



Impact of comorbidities in the decision of using invasive management in elderly patients with NSTEMI

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ABSTRACT

Introduction and objectives: The presence of comorbidities in elderly patients with non-ST-segment elevation acute coronary syndrome worsens its prognosis. The objective of the study was to analyze the impact of the burden of comorbidities in the decision of using invasive management in these patients.

Methods: A total of 7211 patients > 70 years old from 11 Spanish registries were included. Individual data were analyzed in a common database. We assessed the presence of 6 comorbidities and their association with coronary angiography during admission.

Results: The mean age was 79 ± 6 years and the mean CRACE score was 150 ± 21 points. A total of 1179 patients (16%) were treated conservatively. The presence of each comorbidity was associated with less invasive management (adjusted for predictive clinical variables): cerebrovascular disease (OR, 0.78; 95%CI, 0.64-0.95; $P = .01$), anemia (OR, 0.64; 95%CI, 0.54-0.76; $P < .0001$), chronic kidney disease (OR, 0.65; 95%CI, 0.56-0.75; $P < .0001$), peripheral arterial disease (OR, 0.79; 95%CI, 0.65-0.96; $P = .02$), chronic lung disease (OR, 0.85; 95%CI, 0.71-0.99; $P = .05$), and diabetes mellitus (OR, 0.85; 95%CI, 0.74-0.98; $P < .03$). The increase in the number of comorbidities (comorbidity burden) was associated with a reduction in coronary angiographies after adjusting for the GRACE score: 1 comorbidity (OR, 0.66; 95%CI, 0.54-0.81), 2 comorbidities (OR, 0.55; 95%CI, 0.45-0.69), 3 comorbidities (OR, 0.37; 95%CI, 0.29-0.47), 4 comorbidities (OR, 0.33; 95%CI, 0.24-0.45), ≥ 5 comorbidities (OR, 0.21; 95%CI, 0.12-0.36); all P values < .0001 compared to 0.

Conclusions: The number of coronary angiographies performed drops as the number of comorbidities increases in elderly patients with non-ST-segment elevation acute coronary syndrome. More studies are still needed to know what the best management of these patients should be.

Keywords: Comorbidities. Elderly. Acute coronary syndrome. Coronary angiography.

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Influencia de las comorbilidades en la decisión del tratamiento invasivo en ancianos con SCASEST

RESUMEN

Introducción y objetivos: La comorbilidad en ancianos con síndrome coronario agudo sin elevación del segmento ST empeora el pronóstico. El objetivo fue analizar la influencia de la carga de comorbilidad en la decisión del tratamiento invasivo en ancianos con SCASEST.

Métodos: Se incluyeron 7.211 pacientes mayores de 70 años procedentes de 11 registros españoles. Los datos se analizaron en una base de datos conjunta. Se evaluó la presencia de 6 enfermedades simultáneas y su asociación con la realización de coronariografía durante el ingreso.

Resultados: La edad media fue de 79 ± 6 años y la puntuación GRACE media fue de 150 ± 21 puntos. Fueron tratados de manera conservadora 1.179 pacientes (16%). La presencia de cada enfermedad se asoció con un menor abordaje invasivo (ajustado por variables clínicas predictivas): enfermedad cerebrovascular (*odds ratio* [OR] = 0,78; intervalo de confianza del 95% [IC95%], 0,64-0,95; $p = 0,01$), anemia (OR = 0,64; IC95%, 0,54-0,76; $p < 0,0001$), insuficiencia renal (OR = 0,65; IC95%, 0,56-0,75; $p < 0,0001$), arteriopatía periférica (OR = 0,79; IC95%, 0,65-0,96; $p = 0,02$), enfermedad pulmonar crónica (OR = 0,85; IC95%, 0,71-0,99; $p = 0,05$) y diabetes mellitus (OR = 0,85; IC95%, 0,74-0,98; $p = 0,03$). Asimismo, el aumento del número de enfermedades (carga de comorbilidad) se asoció con menor realización de coronariografías, ajustado por la escala GRACE: 1 enfermedad (OR = 0,66; IC95%, 0,54-0,81); 2 (OR = 0,55; IC95%, 0,45-0,69); 3 (OR = 0,37; IC95%, 0,29-0,47); 4 (OR = 0,33; IC95%, 0,24-0,45); ≥ 5 (OR = 0,21; IC95%, 0,12-0,36); todos $p < 0,0001$, en comparación con ninguna enfermedad.

Conclusiones: Conforme aumenta la comorbilidad disminuye la realización de coronariografías en ancianos con síndrome coronario agudo sin elevación del segmento ST. Se necesitan estudios que investiguen la mejor estrategia diagnóstico-terapéutica en estos pacientes.

Palabras clave: Comorbilidad. Ancianos. Síndrome coronario agudo. Coronariografía.

Abbreviations

ACS: acute coronary syndrome. **DM:** diabetes mellitus. **NSTEACS:** non-ST-segment elevation acute coronary syndrome.

INTRODUCTION

Population ageing leads to an increase in the number of elderly patients who suffer non-ST-segment elevation acute coronary syndrome (NSTEACS). This population group, that has been misrepresented in large studies, has a great comorbidity burden that increases with age¹ and an important impact on prognosis.²⁻⁴ The ideal therapeutic strategy for the management of these patients is still unknown. The benefit of an invasive strategy in elderly patients with NSTEACS and comorbidities is still unclear.⁵⁻⁹ In general, elderly patients with comorbidities undergo fewer coronary angiographies despite their worse prognosis.¹⁰ This clinical practice—apparently in contrast with the recommendations published in the clinical practice guidelines¹¹—seems to be based on the perception of a scarce benefit due to the worse intrinsic prognosis associated with comorbidities.

In this study the data of 11 Spanish NSTEACS registries were collected to set up a common database with over 7000 elderly patients with NSTEACS. In this preliminary analysis, the objective was to study the impact of comorbidities on the decision to go with invasive approach.

METHODS

Study design

The study was conducted from 11 cohorts of Spanish registries of patients with NSTEACS (annex).^{2,12-20} All cases were included in a single database of patients with chest pain and a diagnosis of NSTEACS, > 70 years of age and with, at least, a 1-year follow-up.

The anthropometric and social-demographic data, main cardiovascular risk factors, and analytical and hemodynamic data at admission or during hospitalization were registered.

Patients were treated according to each center routine clinical practice and the decision to treat the NSTEACS invasively, with or without a coronary angiography, was left to the discretion of the treating physician. The 6-month mortality GRACE risk score was determined in all the patients.²¹

A total of 6 conditions that proved to have a higher prognostic impact on elderly patients hospitalized due to acute coronary syndrome (ACS) in a previous study were included:²² renal failure (glomerular filtration rate < 60 mL/min/1.73 m²), anemia (hemoglobin levels < 11 g/dL), diabetes mellitus (DM), cerebrovascular disease, peripheral arterial disease, and chronic pulmonary disease.

Endpoints

The study primary endpoint was to assess how the presence of comorbidities impacted the decision to perform a coronary angiography during admission.

Statistical analysis

Categorical variables were expressed as absolute values (percentages) and compared using the unpaired Student *t* test or the ANOVA. The continuous ones were expressed as mean \pm standard deviation and compared using the chi-square test.

Initially, the correlation between each disease and the performance of a coronary angiography through univariable analysis were assessed. Then, a first binary logistics regression model was conducted including the 6 conditions and the clinical variables associated with the performance of the coronary angiography in the univariable analysis. The odds ratio (OR) and the 95% confidence intervals (95%CI) were estimated. Afterwards, patients were classified according to their comorbidity burden, defined by the number of concomitant conditions (from 0 to 6). A second logistics regression model was conducted where comorbidity burden was adjusted for the predictive clinical variables in the previous analysis. Finally, a third logistics regression model was conducted where the comorbidity burden was adjusted based on the GRACE risk score. Differences were considered statistically significant with *P* values < .05

RESULTS

A total of 7211 patients with a mean age of 79 ± 6 years were included; 62% were males. Table 1 shows the population baseline characteristics. The prevalence of comorbidities was DM in 2874 patients (40%), chronic kidney disease in 3070 patients (42.6%), anemia in 1025 (14.2%), peripheral arterial disease in 1006 (14%), chronic pulmonary disease in 1161 (16%), and previous stroke in 831 (11.5%).

During admission 6032 patients (84%) underwent a coronary angiography. A total of 4339 patients (60%) were revascularized: 3848 (53%) of them through percutaneous coronary intervention and 491 (7%) through surgery. Patients on conservative management (1179, 16%) were predominantly women with higher scores in the GRACE score, and a past medical history of infarction or heart failure. Conversely, smoking and high levels of troponins or ST-segment depressions on the electrocardiogram performed at admission and a previous percutaneous coronary intervention were associated with a higher invasive approach (table 1). The GRACE risk score was lower in patients who underwent catheterization (147 ± 19 vs 159 ± 21 ; *P* = .0001).

The presence of each of the 6 conditions studied was associated with fewer coronary angiographies performed: chronic kidney disease, 60.7% vs 39% (*P* = .0001); anemia, 23.2% vs 12.5% (*P* = .0001); DM, 44.3% vs 39% (*P* = .0001); cerebrovascular disease, 15.8% vs 10.7% (*P* = .0001); peripheral arterial disease, 16.6% vs 13.4% (*p* = .04); and chronic pulmonary disease, 17.8% vs 15.8% (*P* = .08) (table 1).

In the multivariable analysis adjusted for the main cardiovascular risk factors and clinical variables that were statistically significant in the univariable analysis, the 6 conditions associated with a lower probability of an indication for coronary angiography were: cerebrovascular disease, OR, 0.78 (IC95%, 0.64-0.95; *P* = .01); anemia, OR, 0.64 (IC95%, 0.54-0.76; *P* < .0001); chronic kidney disease, OR, 0.65 (IC95%, 0.56-0.75; *P* < .0001); peripheral arterial disease, OR, 0.79 (IC95%, 0.65-0.96; *P* = .02); chronic pulmonary disease, OR, 0.85 (IC95%, 0.71-0.99; *P* = .05); and DM, OR, 0.85 (IC95%, 0.74-0.98; *P* = .03). Table 2 shows the clinical variables associated with the indication for coronary angiography.

Comorbidity burden was defined as the number of present conditions (from 0 to 6). This was their distribution: 0 conditions, *N* = 1891 (26%); 1 condition, *N* = 2413 (33.5%); 2 conditions, *N* = 1638 (22.7%); 3 conditions, *N* = 879 (12.2%); 4 conditions, *N* = 314 (4.4%); and 5 or 6 conditions, *N* = 76 (1.1%). The analysis of the comorbidity burden adjusted for the clinical variables associated with the indication for coronary angiography showed a negative correlation between the number of conditions and the probability to perform a coronary angiography: 1 condition, OR, 0.66 (95%CI,

Table 1. Differences in the baseline characteristics based on the therapeutic approach

	All N = 7211	Conservative approach N = 1179 (16)	Invasive approach N = 6032 (84)	<i>P</i>
Age (years)	79 ± 6	82 ± 6	78 ± 5	.001
Males	4441 (61.6)	597 (50.6)	3844 (63.7)	.0001
Smoking	621 (8.6)	72 (6.1)	549 (9.1)	.0001
Hypertension	5723 (79.4)	943 (80)	4780 (79.2)	.58
Dyslipidemia	4262 (59)	609 (51.7)	3653 (60.6)	.0001
Previous myocardial infarction	1682 (23.3)	371 (31.7)	1308 (21.7)	.0001
Previous percutaneous coronary intervention	1334 (19)	175 (14.8)	1159 (19.2)	.0001
Previous coronary surgery	573 (7.9)	104 (8.8)	469 (7.8)	.24
Previous heart failure	641 (8.9)	198 (16.8)	443 (7.3)	.0001
Killip ≥ 2	1889 (26.2)	463 (39.3)	1426 (23.6)	.0001
ST-segment depression	2638 (36.6)	396 (33.6)	2242 (37.2)	.02
High troponin levels	5319 (73.7)	920 (78)	4399 (73)	.001
Left ventricular ejection fraction (%)	54 ± 11	54 ± 12	55 ± 11	.03
GRACE	150 ± 21	159 ± 21	147 ± 19	.0001
Comorbidities				
Anemia	1025 (14.2)	273 (23.2)	752 (12.5)	.0001
Peripheral arterial disease	1006 (14)	196 (16.6)	810 (13.4)	.04
Chronic pulmonary disease	1161 (16.1)	210 (17.8)	951 (15.8)	.08
Diabetes mellitus	2874 (39.9)	522 (44.3)	2352 (39)	.0001
Cerebrovascular disease	831 (11.5)	186 (15.8)	645 (10.7)	.0001
Chronic kidney disease	3070 (42.6)	716 (60.7)	2354 (39)	.0001

Data are expressed as no. (%) or mean ± standard deviation.

0.54-0.81); 2 conditions, OR, 0.55 (95%CI, 0.45-0.69); 3 conditions, OR, 0.37 (95%CI, 0.29-0.46); 4 conditions, OR, 0.32 (95%CI, 0.23-0.45); and 5 or 6 conditions, OR, 0.21 (95%CI, 0.12-0.37); All *P* values < .0001 compared to no condition.

With more conditions, higher GRACE risk scores (table 3). The negative correlation between the comorbidity burden and the performance of the coronary angiography was kept after adjusting for the GRACE risk score. Figure 1 shows that with more conditions, the probability to perform a coronary angiography increased too (figure 1A) despite the higher risk posed by higher GRACE risk scores (figure 1B, table 3).

DISCUSSION

The main findings of our study were: a) the 6 conditions studied (cerebrovascular disease, anemia, chronic kidney disease,

Table 2. Results: multivariable analysis for the indication of a coronary angiography

Variable	OR	95%CI	P
Age (years)	0.89	0.88-0.91	.0001
Males	1.48	1.28-1.71	.0001
Dyslipidemia	1.44	1.26-1.66	.0001
Previous myocardial infarction	0.46	0.39-0.54	.0001
Previous heart failure	0.68	0.56-0.84	.0001
Previous percutaneous coronary intervention	1.91	1.55-2.34	.0001
Killip ≥ 2	0.68	0.56-0.80	.0001
ST-segment depression	1.44	1.25-1.66	.0001
Left ventricular ejection fraction (by 5%)	0.98	0.98-0.99	.001
Anemia	0.64	0.54-0.76	.0001
Peripheral artery disease	0.79	0.65-0.96	.02
Chronic pulmonary disease	0.85	0.71-0.99	.05
Diabetes mellitus	0.85	0.74-0.98	.03
Cerebrovascular disease	0.78	0.64-0.95	.01
Chronic kidney disease	0.65	0.56-0.75	.0001

95%CI: 95% confidence interval; OR: odds ratio.

Table 3. Distribution of comorbidity burden and the score obtained in the GRACE risk score ($P < .0001$ for the tendency)

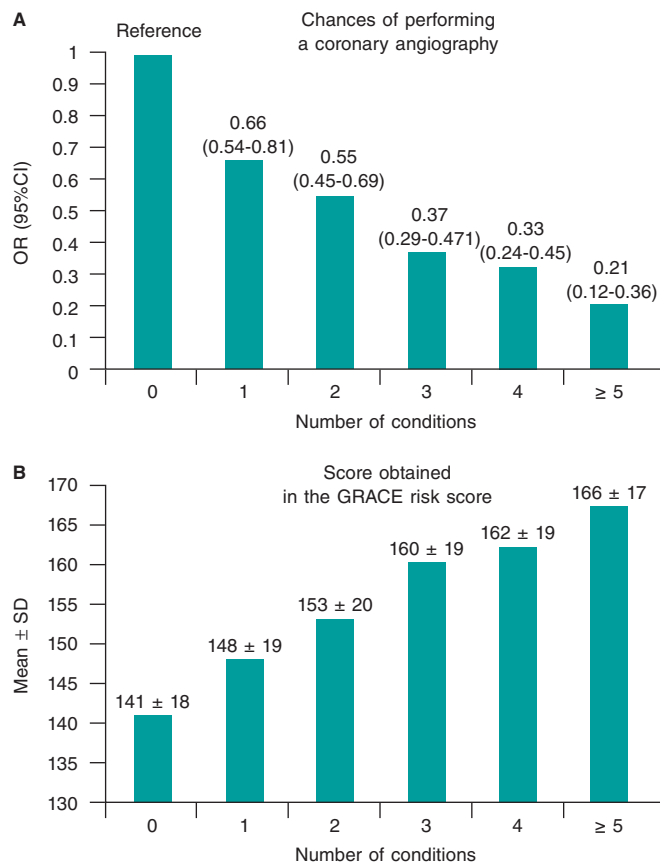
Conditions	N = 7211	GRACE risk score
0	1891 (26)	141 \pm 18
1	2413 (33.5)	148 \pm 19
2	1638 (22.7)	153 \pm 20
3	879 (12.2)	160 \pm 19
4	314 (4.4)	162 \pm 19
≥ 5	76 (1.1)	166 \pm 17

Data are expressed as no. (%) or mean \pm standard deviation.

peripheral arterial disease, chronic pulmonary disease, and DM) were independently associated with a lower probability to use the invasive approach; b) with higher comorbidity burdens, considered as the number of concomitant conditions, lower chances of performing coronary angiographies.

There is a high prevalence of comorbidities in elderly patients with NSTEMACS that greatly impacts prognosis in the short and mid-term.^{2,4} The Charlson index is the most commonly used tool to assess comorbidities.^{23,24} However, the analysis of the 6 conditions studied (chronic kidney disease, anemia, DM, cerebrovascular disease, peripheral arterial disease, and chronic pulmonary disease) has proven to be a useful risk stratification tool and have great predictive discriminatory capabilities that are similar to the Charlson index.²²

Comorbidity burden is very important for the in-hospital management of NSTEMACS.^{2,3,6,9,10} Although the optimal therapeutic strategy for the

**Figure 1. A:** chances of undergoing a coronary angiography based on the number of concomitant conditions. The odds ratio (OR) with a 95% confidence interval (95%CI) can be seen. Analysis adjusted for the GRACE risk score. **B:** Representation of the correlation between comorbidity burden and the GRACE risk score. The mean \pm standard deviation (SD) of the GRACE risk score can be seen.

management of elderly patients with NSTEMACS is still unknown, several studies show certain benefits with revascularization.^{5,7,8,25-30}

Our study shows that with higher comorbidity burdens, lower chances of undergoing coronary angiographies. This may be due to the fact that comorbidities are seen as contraindications for the invasive approach.¹⁰ However, the risk of suffering an acute myocardial infarction according to the GRACE risk score increases parallel to the number of concomitant conditions. Actually, these may be the patients who would benefit the most from an invasive approach.^{31,32}

The presence of each one of these 6 conditions was independently associated with fewer invasive approaches. On the one hand, cerebrovascular disease and peripheral arterial disease are responsible for a greater spread of atherosclerotic disease.³³ Anemia has proven to be a powerful predictor of mortality in the ACS setting;³⁴⁻³⁶ we used the 11 g/dL threshold as the cut-off value that had the greatest impact on mortality in former studies.³⁴ Its specific weight in the decision to administer conservative treatment may be justified by its clear association with the occurrence of hemorrhagic events in the ACS setting.³⁷ Chronic kidney disease is an expression of a greater spread of cardiovascular disease and is independently associated with more mortality after an ACS. There is a linear correlation between the risk of death due to cardiovascular causes and lower glomerular filtration rates.^{17,38} DM is a powerful predictor of mortality, and not only due to cardiovascular causes. There is a clear correlation between DM and major adverse cardiovascular events, and these are

patients at very high risk.³⁹ Chronic pulmonary disease is associated with a worse short-term prognosis after an acute myocardial infarction. Also, in the management of NSTEMI it is associated with diagnostic delays, fewer invasive approaches, and a lower use of drugs for secondary prevention purposes.⁴⁰

In the multivariable analysis, age, previous acute myocardial infarctions, previous heart failure, Killip class ≥ 2 at admission, and a reduced ejection fraction were associated with fewer invasive approaches. Elderly patients receive fewer evidence-based therapies. The older the age, the lower the rate of performing coronary angiographies.⁴¹ On top of age, a past medical history of infarction, heart failure, a reduced ejection fraction, and scores ≥ 2 in the Killip classification are important aspects in the prognosis of ACS that, in general, translate into a worse ventricular function. Paradoxically, our findings suggest that the higher the risk, the lower the chances of performing a coronary angiography. Actually, these findings are consistent with former studies published.^{10,42} It is possible that the perception of fewer benefits from revascularization or higher risk in the revascularization procedures may explain these results.² On the other hand, male sex, dyslipidemia, previous percutaneous coronary interventions, and ST-segment depressions at admission were associated with more invasive approaches. Several studies suggest that women undergo fewer invasive approaches compared to men despite the mortality benefits seen.⁴³ Previous angioplasties, ST-segment depressions, and dyslipidemia are probably interpreted as ischemic risk factors, which may explain their association with a higher frequency of invasive approaches.^{20,28,44}

Limitations

The main limitation of our study is that it is an observational registry with its corresponding selection bias and differences in the management of patients depending on the different centers involved. On the other hand, although the multivariable model was adjusted for percutaneous coronary intervention or previous coronary surgeries, it was not adjusted for previous coronary angiographies. It is possible that the previous knowledge of the coronary anatomy impacted the decision to perform fewer coronary angiographies in patients at higher risk.

CONCLUSIONS

The presence of comorbidities greatly impacts the therapeutic decision in elderly patients with ACS. With more conditions, higher GRACE risk scores, and lower chances of indicating a coronary angiography.

This paradox of higher-risk and more conservative treatment justifies conducting new studies to determine the benefits of the invasive strategy in elderly patients with NSTEMI and comorbidities to establish the best therapeutic decision.

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CONFLICTS OF INTEREST

J. Sanchis is an associate editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. J. Núñez has received funding from Novartis, Vitor Pharma, and Boehringer Ingelheim, and a grant from Astra Zeneca and Vitor Pharma. J.A. Barrabés has received

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WHAT IS KNOWN ABOUT THE TOPIC?

- Elderly patients with NSTEMI have a higher comorbidity burden. Concomitant conditions are associated with worse prognosis. Elderly patients with comorbidities undergo fewer coronary angiographies despite their worse prognosis, which is in sharp contrast with the recommendations published in the clinical practice guidelines.

WHAT DOES THIS STUDY ADD?

- This analysis of a multicenter registry shows the correlation between comorbidity burden and invasive therapeutic approach in elderly patients with NSTEMI. With more concomitant conditions, higher GRACE risk scores, but lower chances of indicating a coronary angiography.

ANNEX. Registries included in the study.

Hospital Clínico Universitario, Valencia²

Hospital Universitario Joan XXIII, Tarragona¹²

Hospital Universitario de Bellvitge, Barcelona¹³

Hospital Ramón y Cajal, Madrid¹⁴

Hospital Universitario de San Juan, Alicante¹⁵

LONGEVO multicenter registry¹⁶

ACHILLES multicenter registry¹⁷

Hospital Álvaro Cunqueiro, Vigo¹⁸

Hospital Clínico Universitario, Santiago de Compostela¹⁹

Hospital Universitario Vall d'Hebron, Barcelona²⁰

Hospital Universitario de La Princesa, Madrid*

*Unpublished data.

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