Early invasive strategy in non-ST-segment elevation acute coronary syndrome. The paradox continues

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KEYWORDS
Acute coronary syndrome;
Angioplasty;
Registries;
Cohort study

Abstract
Objective: Observational studies have reported a paradoxical inverse relationship between the use of an early invasive strategy (EIS) and the risk of events in patients with non-ST-segment elevation acute coronary syndrome (NSTE ACS). The study objectives are: (1) to examine the association between baseline risk in patients with NSTE ACS and the use of EIS; and (2) to identify some of the factors independently associated to the use of EIS.
Design: Retrospective cohort study.
Setting: Intensive care units participating in the SEMICYUC ARIAM Registry.
Patients: Consecutive patients admitted with a diagnosis of NSTE-ACS within 48 h of evolution between the months of April and July 2010.
Interventions: None.
Main outcomes: Coronary angiography with or without angioplasty within 72 h, risk stratification using the GRACE scale.
Results: We analyzed 543 patients with NSTE-ACS, of which 194 were of low risk, 170 intermediate risk and 179 high risk. The EIS was used in 62.4% of the patients at low risk, in 60.2% of those with intermediate risk, and in 49.7% of those at high risk (p for tendency 0.0144). The EIS was used preferentially in patients with low severity and comorbidity. In the logistic regression model, EIS was independently associated to the availability of a catheterization laboratory (OR 2.22 [95%CI 1.55–3.19]), the presence of ST changes on ECG (OR 1.80 [1.23–2.64]), or the existence of a low risk of bleeding (OR 0.76 [0.66–0.88]). Conversely, EIS was less prevalent in patients with diabetes (OR 0.60 [0.41–0.88]) or tachycardia upon admission (OR 0.54 [0.36–0.82]).

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Uso de la estrategia invasiva precoz en el síndrome coronario agudo sin elevación de ST. La paradoja continua

Resumen

Objetivo: Algunos estudios observacionales han comunicado una paradojica menor utilización de la estrategia invasiva precoz (EIP) en los pacientes con síndrome coronario agudo sin elevación de ST (SCASEST) de alto riesgo. Los objetivos del estudio son: (1) Examinar la asociación entre el riesgo basal de los pacientes con SCASEST y el uso de una estrategia invasiva precoz (EIP) en la práctica clínica actual; (2) Identificar algunos de los factores asociados de forma independiente con el uso de EIP.

Diseño: Estudio de cohortes retrospectivo

Ámbito: Unidades de cuidados intensivos participantes en el registro ARIAM-SEMICYUC.

Pacientes: Pacientes consecutivos ingresados con diagnóstico de SCASEST de menos de 48 horas de evolución entre los meses de abril-julio de 2010.

Intervenciones: Ninguna.

Variables principales: Realización de coronariografía con o sin angioplastia en las primeras 72 horas, estratificación del riesgo mediante la escala GRACE.

Resultados: Se analizaron 543 pacientes con SCASEST, de los cuales 194 eran de bajo riesgo, 170 de riesgo intermedio y 179 de riesgo alto. La EIP se utilizó en el 62,4% de los pacientes de bajo riesgo, el 60,2% de los de riesgo intermedio y el 49,7% de los de riesgo alto (p para la tendencia 0,0144). La EIP se utilizó de forma preferente en pacientes con baja gravedad y comorbilidad. En el modelo de regresión logística, la EIP se asoció de forma directa con la disponibilidad de laboratorio de hemodinámica (OR 2,22, [intervalo de confianza al 95% 1,55 a 3,19]), la presencia de cambios de ST en el ECG (OR 1,80 [1,23 a 2,64]) y la existencia de un bajo riesgo hemorrágico (OR 0,76 [0,66 a 0,88]). Por el contrario, la EIP se asoció de forma negativa con la presencia de diabetes (OR 0,60 [0,41 a 0,88]) o de taquicardia al ingreso (OR 0,54 [0,36 a 0,82]).

Conclusiones: En el año 2010, persiste una menor utilización relativa de la EIP en los pacientes de alto riesgo, debido en parte al mayor riesgo hemorrágico de estos pacientes.

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Introduction

Based on the existing scientific evidence, the main clinical practice guides recommend an early invasive strategy (EIS) in patients with medium-high risk non-ST-segment elevation acute coronary syndrome (NSTE ACS). However, some registry-based studies have documented a paradoxically lesser utilization of early invasive strategies in high risk patients. The ARIAM-SEMICYUC study offers an opportunity to re-examine this problem based on the recent Spanish data.

The objectives of the present study are: (1) to describe the use of EIS in relation to the baseline risk of patients with NSTE ACS admitted to intensive care units (ICUs); and (2) to identify the independent predictors of the application of EIS in patients admitted due to NSTE ACS.

Methods

Patients

The ARIAM-SEMICYUC project is a voluntary registry of patients with acute coronary syndrome (ACS) admitted to ICUs in Spain and Andorra. At present, trimestral surveying is made, including all the consecutive patients admitted during the time period.

The present study includes the patients admitted with a diagnosis of NSTE ACS with an evolution of at least 48h from symptoms onset, and covering the period between 1 April and 15 July 2010.

During this period, a total of 43 hospitals participated in the survey (see Annex 1), with the inclusion of 1379 patients, of which 665 were admitted with a diagnosis of NSTE ACS. The GRACE score was available in 570 of these patients.

Variables

The primary outcome variable of the study was cardiac catheterization (with or without intervention) in the first 72h after admission.

The patients were stratified according to the risk of suffering major cardiac events, based on the GRACE risk score upon admission, using the cutoff points (low, medium and high risk) pre-established in the literature.

In addition to the risk level, a retrospective analysis was made of different variables available in the registry, such
as the baseline clinical–demographic parameters, patient
treatment and evolution, and possible catheterization pre-
dictors previously described in the literature. Bleeding risk 
was quantified by means of an ad hoc index based on 
the number of independent predictors of major bleeding 
contemplated by the GRACE15,16 categorized as high or 
low risk according to the presence of some or no risk 
factor.

Statistical analysis

The descriptive analysis comprised the calculation of pro-
portions (in the case of categorical variables) and medians, 
with the corresponding interquartile range (in the case of 
continuous variables).

The contrasting of hypotheses referred to proportions 
was carried out using the χ² test (or the χ² test for 
trends). In the case of quantitative variables, contrast-
ing was based on the Mann–Whitney U-test (comparisons 
between 2 groups), the Kruskal–Wallis test (3 or more 
groups) or the Cuzick test (trends in 3 or more groups). All 
contrasts were two-sided, with an alpha level of significance 
of 5%.

With the purpose of identifying independent predictors 
of early catheterization, the variables found in the univari-
ate analysis to be associated to the adoption of EIS with 
p < 0.10 were entered in a multiple logistic regression 
model, adopting a backwards stepwise analytical strategy in 
which the least significant variable was eliminated in each 
step. Finally, the association between each of the predictor 
variables and the implementation of EIS was evaluated by 
calculating the adjusted odds ratios (ORs) and their corre-
sponding 95% confidence intervals (CI).

Results

The profile of the patients, stratified according to GRACE 
risk level, was consistent with that of other registries6,9,11 
(Table 1). The high risk group was characterized by older 
age, a greater proportion of women, increased comorbid-
ity (diabetes, previous infarction, renal failure), the existence 
of heart failure upon admission, a high baseline bleeding 
risk, and increased mortality.

Regarding the drug treatment administered from symp-
toms onset and during admission to the ICU (Table 2), the 
patients at high risk were less often treated with statins and 
beta-blockers, with no other significant differences among 
the three risk levels. Likewise, risk level was directly cor-
related to the use of noninvasive mechanical ventilation, 
with a negative association to the adoption of EIS—though 
the differences failed to reach statistical significance.

The variables associated to the implementation of EIS 
are summarized in Table 3. Basically, the group of patients 
with NSTE ACS subjected to early invasive treatment were 
younger, with a lesser prevalence of diabetes and of heart 
failure upon admission, a lesser bleeding risk, and were 
admitted to a hospital with the availability of a hemody-
namics laboratory.

The logistic regression analysis (Table 4) identified the 
availability of a hemodynamics laboratory, the presence of 
ST-segment changes, the absence of diabetes, the absence 
of tachycardia upon admission, and the existence of low 
bleeding risk as independent predictors of the use of an inva-
sive treatment strategy. Previous coronaryangiography was 
not independently correlated to the adoption of EIS (adjusted 
OR 0.77, 95% CI 0.50–1.21), and did not act as an effect 
modifier of the association between the GRACE level and 
the implementation of EIS (interaction p-value = 0.8425). 
On replacing heart rate with the Killip class, the presence 
of class >1 was found to be significantly associated to 
a lesser utilization of invasive strategies (OR 0.64, 95% CI 
0.42–0.96).

Discussion

The results of the present study confirm the inverse relation-
ship between the risk of events and the use of an EIS in NSTE 
ACS, detected in previous studies.6,8–11,17,18 At first sight this 
is paradoxical, since it would indicate that the patients who 
could benefit most from such treatment are precisely the 
individuals in which it is least used.6–12

The reasons for this paradoxical situation have not been 
fully clarified. Given the greater proportion of women and 
elderly people in the high risk stratum, the hypo-
thesis of lesser therapeutic effort could be considered in 
these individuals.7,17,19,20 However, in our study there were 
no other indications of inequalities in therapeutic effort 
according to the risk stratum involved (Table 2), and neither 
age nor gender were found to be independently associated 
to the implementation of EIS.

Given the increased frequency of prior coronaryangiog-
raphy in the patients at high risk, we must consider the 
possibility that improved prior knowledge of the coronary 
anatomy could have favored the use of a conservative strat-
ey in these patients. However, in the multivariate analysis, 
antecedents of coronaryangiography did not act as an effect 
modifier (interaction p-value = 0.8425), and were not inde-
pendently associated to the implementation of EIS (adjusted 
p-value = 0.2501).

The dose-response association between bleeding risk and 
the adoption of EIS is an important finding in this study, sug-
uggesting that the lesser utilization of EIS in the patients with 
high GRACE scores is at least partly due to the increased 
bleeding risk of these patients. Form this perspective, the 
existence of a certain dissociation between the guides 
designed in reference to ideal patients, with a single dis-
ease) and actual clinical practice (individual patients with 
comorbidities) could be understandable. However, this argu-
ment loses strength on considering the radial access—much 
less susceptible to bleeding phenomena than the femoral 
access.21–25

The scant utilization of an early invasive strategy in 
diabetic patients, reported in many studies,6,7,9,18 is 
more difficult to explain. Clinicians may presume the 
existence of multiple vessel disease not amenable to 
revascularization in diabetic individuals, and therefore an 
unfavorable risk-benefit ratio in such cases. However, this 
explanation does not fit well with the repeatedly demon-
strated benefits derived from coronary intervention in 
diabetics.27–29

The association between tachycardia upon admission 
(an indicator of heart failure) and scant interventional
| Table 1 | Profile of the patients with NSTEMI ACS according to baseline risk. |
|-----------------|-------------------|-------------------|-------------------|
|                | Total             | GRACE             | p-Value for the trend |
|                | Low (≤ 108)       | Medium (109–140)  | High (≥ 141)       |
| Age: median (P25–P75) | 67 (57.77)        | 54 (47.5, 60.5)   | 69 (63.76)        | 77 (72.81) | <0.0001 |
| Females: (%)  | 138/502 (27.5)    | 30/181 (16.6)     | 49/163 (30.1)     | 59/158 (37.3) | <0.0001 |
| Antecedents   |                   |                   |                   |
| Active smoker (%) | 140/543 (26.8)    | 100/194 (51.6)    | 25/170 (14.7)     | 15/179 (8.4) | <0.0001 |
| Hypertension (%) | 281/543 (51.8)    | 99/194 (51.0)     | 82/170 (48.2)     | 100/179 (55.9) | 0.3641 |
| Diabetes (%)   | 353/543 (65.0)    | 102/194 (52.6)    | 113/170 (66.5)    | 138/179 (77.1) | <0.0001 |
| Angina (%)     | 177/543 (32.6)    | 43/194 (22.2)     | 49/170 (28.8)     | 85/179 (47.5) | <0.0001 |
| Active smoker (%) | 108/543 (19.9)    | 26/194 (13.4)     | 40/170 (23.5)     | 42/179 (23.5) | 0.0138 |
| Previous infarction (%) | 121/543 (22.3)  | 30/194 (15.5)     | 35/170 (20.6)     | 56/179 (31.3) | 0.0003 |
| Previous coronary surgery (%) | 114/543 (21.0)  | 27/194 (13.9)     | 36/170 (21.2)     | 51/179 (28.5) | 0.0006 |
| Previous heart failure (%) | 29/543 (5.3)    | 3/194 (1.6)       | 3/170 (1.8)       | 19/179 (10.6) | 0.0032 |
| Stroke (%)     | 34/543 (6.3)      | 9/194 (4.6)       | 8/170 (4.7)       | 17/179 (9.5) | 0.0562 |
| Peripheral arterial disease (%) | 37/543 (6.8)    | 6/194 (3.1)       | 13/170 (7.7)      | 18/179 (10.1) | 0.0075 |
| Chronic renal failure (%) | 33/543 (6.1)    | 2/194 (1.0)       | 4/170 (2.4)       | 27/179 (15.1) | <0.0001 |
| Presentation   |                   |                   |                   |
| Cardiac arrest (%) | 8/543 (1.5)        | 2/194 (1.0)       | 1/170 (0.6)       | 5/179 (2.8) | 0.1664 |
| Heart rate: median (P25–P75) | 78 (66.90)        | 74.5 (64.84)      | 74 (65.90)        | 85 (70.102) | <0.0001 |
| Systolic BP upon admission in ICU median (P25–P75) | 140 (120.160) | 149.5 (130.170) | 140 (121.160) | 130 (110.149) | <0.0001 |
| Killip (%)     |                   |                   |                   |
| I              | 400/543 (73.7)    | 184/194 (94.9)    | 152/170 (89.4)    | 64/179 (35.8) |
| II             | 100/543 (18.4)    | 10/194 (5.2)      | 16/170 (9.4)      | 74/179 (41.3) |
| III–IV         | 43/543 (7.9)      | 0/194 (0.0)       | 2/170 (1.2)       | 41/179 (22.9) |
| Creatinine upon admission: median (P25–P75) | 1.0 (0.8. 1.24) | 0.96 (0.8. 1.1)  | 0.96 (0.8. 1.2)  | 1.15 (0.9. 1.7) | 0.3875 |
| High bleeding risk (%) | 340/543 (62.6)    | 55/194 (28.4)     | 123/170 (72.4)    | 162/179 (90.5) | <0.0001 |
| ST-segment depression (%) | 285/540 (52.8)  | 74/192 (38.5)     | 85/169 (50.3)     | 126/179 (70.4) | <0.0001 |
| Troponin elevation (%) | 467/525 (89.0) | 158/186 (84.9) | 143/166 (89.2) | 161/173 (93.1) | 0.0142 |
| Availability of hemodynamics (%) | 235/543 (43.3) | 89/194 (45.9) | 72/170 (42.4) | 74/179 (41.3) | 0.3741 |
| Discharge from ICU |                   |                   |                   |
| Death          | 13/543 (2.4)      | 0/177 (0.0)       | 1/159 (0.6)       | 10/157 (6.4) | <0.0001 |
| Voluntary discharge | 3/543 (0.5)    | 0/177 (0.0)       | 0/159 (0.0)       | 2/157 (1.3) | 0.135 |
| Other hospital | 36/543 (6.7)      | 13/177 (7.3)      | 8/159 (5.0)       | 9/157 (5.7) | 0.5236 |
| Ward           | 491/543 (90.4)    | 164/177 (92.7)    | 150/159 (94.3)    | 136/157 (86.6) | 0.0585 |
Table 2 Drug treatment and diagnostic-therapeutic procedures according to baseline risk during admission to the Intensive Care Unit.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>GRACE Low (&lt;108)</th>
<th>GRACE Medium (109–140)</th>
<th>GRACE High (≥141)</th>
<th>p-Value for the trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin in the first 24h (%)</td>
<td>489/543 (90.1)</td>
<td>179/194 (92.3)</td>
<td>153/170 (90.0)</td>
<td>157/179 (87.7)</td>
<td>0.1419</td>
</tr>
<tr>
<td>Clopidogrel (%)</td>
<td>471/543 (86.7)</td>
<td>171/194 (88.1)</td>
<td>148/170 (87.1)</td>
<td>152/179 (84.9)</td>
<td>0.3607</td>
</tr>
<tr>
<td>Non-fractionated heparin (%)</td>
<td>23/543 (4.2)</td>
<td>8/194 (4.1)</td>
<td>10/170 (5.9)</td>
<td>5/179 (2.8)</td>
<td>0.5434</td>
</tr>
<tr>
<td>LMWH (%)</td>
<td>318/543 (58.6)</td>
<td>117/194 (60.3)</td>
<td>98/170 (57.7)</td>
<td>103/179 (57.5)</td>
<td>0.5837</td>
</tr>
<tr>
<td>Fondaparinux (%)</td>
<td>94/543 (17.3)</td>
<td>36/194 (18.6)</td>
<td>31/170 (18.2)</td>
<td>27/179 (15.1)</td>
<td>0.381</td>
</tr>
<tr>
<td>AG IIb/IIIa (%)</td>
<td>96/543 (17.7)</td>
<td>37/194 (19.1)</td>
<td>36/170 (21.2)</td>
<td>23/179 (12.9)</td>
<td>0.1236</td>
</tr>
<tr>
<td>ACEIs/ARA (%)</td>
<td>304/543 (56.0)</td>
<td>107/194 (55.2)</td>
<td>98/170 (57.7)</td>
<td>99/179 (55.3)</td>
<td>0.9669</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>277/543 (51.0)</td>
<td>113/194 (58.3)</td>
<td>87/170 (51.2)</td>
<td>77/179 (43.0)</td>
<td>0.0033</td>
</tr>
<tr>
<td>Beta-blockers (excluding contraindication) (%)</td>
<td>276/476 (58.0)</td>
<td>113/178 (63.5)</td>
<td>87/154 (56.5)</td>
<td>76/144 (52.8)</td>
<td>0.0504</td>
</tr>
<tr>
<td>Calcium antagonists (%)</td>
<td>53/543 (9.8)</td>
<td>16/194 (8.3)</td>
<td>17/170 (10.0)</td>
<td>20/179 (11.2)</td>
<td>0.3406</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>445/543 (82.0)</td>
<td>166/194 (85.6)</td>
<td>144/170 (84.7)</td>
<td>135/179 (75.4)</td>
<td>0.0118</td>
</tr>
<tr>
<td>Catheterization &lt;72 h (%)</td>
<td>313/543 (57.6)</td>
<td>121/194 (62.4)</td>
<td>103/170 (60.2)</td>
<td>89/179 (49.7)</td>
<td>0.0144</td>
</tr>
<tr>
<td>CVS (including transfers) (%)</td>
<td>25/543 (4.6)</td>
<td>10/194 (5.2)</td>
<td>9/170 (5.3)</td>
<td>6/179 (3.4)</td>
<td>0.4137</td>
</tr>
<tr>
<td>Early PCI (%)</td>
<td>161/543 (29.7)</td>
<td>62/194 (32.0)</td>
<td>53/170 (31.2)</td>
<td>46/179 (25.7)</td>
<td>0.1905</td>
</tr>
<tr>
<td>Invasive MV (%)</td>
<td>9/543 (1.7)</td>
<td>3/194 (1.6)</td>
<td>0/170 (0.0)</td>
<td>6/179 (3.4)</td>
<td>0.1878</td>
</tr>
<tr>
<td>Noninvasive MV (%)</td>
<td>10/543 (1.8)</td>
<td>1/194 (0.5)</td>
<td>0/170 (0.0)</td>
<td>9/179 (5.0)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Echocardiogram (%)</td>
<td>187/543 (34.4)</td>
<td>66/194 (34.0)</td>
<td>49/170 (28.8)</td>
<td>72/179 (40.2)</td>
<td>0.2239</td>
</tr>
</tbody>
</table>

AG IIb/IIIa: glycoprotein IIb/IIIa antagonists; CVS: cardiovascular surgery; LMWH: low molecular weight heparin; PCI: percutaneous coronary intervention; ACEIs/ARA: angiotensin converting enzyme inhibitors/aldosterone receptor antagonists; MV: mechanical ventilation.

practices is less well known. This association possible may be attributable to chance (type I error). However, the negative association between a Killip class of >1 and the implementation of an early invasive strategy suggests that the association is real. Alternatively, difficulties in transferring unstable patients (within or between hospital centers) to the hemodynamics laboratory, or limitations of therapeutic effort, may possibly contribute to lesser utilization of invasive strategies in these patients.

Table 3 Profile of the patients with/without catheterization in the first 72h (known predictors of catheterization in NSTE ACS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No early catheterization</th>
<th>EIS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (4 categories)</td>
<td>70 (61.78)</td>
<td>65 (54.75)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Females (%)</td>
<td>86/257 (33.5)</td>
<td>83/349 (23.8)</td>
<td>0.0086</td>
</tr>
<tr>
<td>Hospital with hemodynamics (%)</td>
<td>81/257 (31.5)</td>
<td>181/349 (51.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bleeding risk factors</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>0 (%)</td>
<td>70/257 (27.2)</td>
<td>158/349 (45.4)</td>
<td></td>
</tr>
<tr>
<td>1 (%)</td>
<td>68/257 (26.5)</td>
<td>81/349 (23.2)</td>
<td></td>
</tr>
<tr>
<td>2 (%)</td>
<td>61/257 (23.7)</td>
<td>68/349 (19.5)</td>
<td></td>
</tr>
<tr>
<td>3+ (%)</td>
<td>58/257 (22.6)</td>
<td>42/349 (42.0)</td>
<td></td>
</tr>
<tr>
<td>Previous heart failure (%)</td>
<td>26/256 (10.2)</td>
<td>13/349 (3.8)</td>
<td>0.0016</td>
</tr>
<tr>
<td>History of renal failure</td>
<td>21/256 (8.2)</td>
<td>16/349 (4.6)</td>
<td>0.0693</td>
</tr>
<tr>
<td>Initial heart rate</td>
<td>80 (68.96.5)</td>
<td>76 (65.89)</td>
<td>0.0325</td>
</tr>
<tr>
<td>Initial Killip class &gt;1 (%)</td>
<td>94/256 (36.7)</td>
<td>77/349 (22.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ST changes (%)</td>
<td>143/233 (61.4)</td>
<td>232/337 (68.8)</td>
<td>0.0646</td>
</tr>
<tr>
<td>Troponin elevation (%)</td>
<td>167/244 (68.4)</td>
<td>224/328 (68.3)</td>
<td>0.9696</td>
</tr>
<tr>
<td>Previous coronaryography (%)</td>
<td>64/256(25)</td>
<td>63/347 (18.2)</td>
<td>0.0416</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>17/256 (6.6)</td>
<td>19/347 (5.5)</td>
<td>0.5506</td>
</tr>
<tr>
<td>Previous infarction (%)</td>
<td>70/256 (27.3)</td>
<td>67/347 (19.3)</td>
<td>0.0199</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>106/256 (41.4)</td>
<td>97/347 (28.0)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Invasive strategy in NSTE ACS
In conclusion, there is a tendency to concentrate the utilization of EIS among patients with NSTE ACS exhibiting scant comorbidity. This paradoxical situation is still far from being resolved. Clinicians therefore should carefully revise the risk-benefit relationship of interventionism in their patients, particularly among diabetics, patients with heart failure, and patients at high bleeding risk.  

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**Conflicts of interest**

The authors declare no conflicts of interest.

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Invasive strategy in NSTE ACS

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