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Original article

Sex differences in the management of patients with acute coronary syndrome: A population-based ecological cross-sectional study in Spain

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Abbreviations: ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

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ABSTRACT

Introduction and objectives: Despite evidence of a reduction in the incidence and mortality of acute coronary syndrome (ACS), some studies have highlighted differences in outcomes between men and women. We aimed to explore sex differences in the management and treatment of patients with ACS in Spain.
Methods: This ecological cross-sectional study combined ACS data from 10 Spanish registries (54 centres). Meta-regression analysis was performed using aggregated data of baseline characteristics, interventional procedures, treatments, and events that occurred during hospitalization and one-year follow-up.
Results: Aggregated data from 34 605 patients (75.1% men) was included. ST-segment elevation myocardial infarction was the most frequent diagnosis (58.9%) and almost 80% of patients were Killip Class I. Compared to men, women were older (mean age: 71.0 vs 63.3 years) and presented higher rates of hypertension (68.1% vs 51.7%) and diabetes (37.7% vs 26.5%). Women were also less likely to undergo percutaneous coronary interventions, revascularization surgery, and to receive drug-eluting stents during hospitalization. Regarding to antiplatelet therapy, even though indicated, 23.1% of women were not treated with $P2Y_{12}$ inhibitors (vs 14.2% of men; $P < .001$); clopidogrel was the most frequently administered agent (> 60%). Significantly higher in-hospital (5.4% vs 3.7%) and 1-year (8.2% vs 4.9%) mortality was observed among women compared to men, which was mainly attributed to cardiovascular causes.
Conclusions: Despite older age and unfavourable risk profile, female ACS patients seem to be suboptimally treated with $P2Y_{12}$ inhibitors. To reduce mortality associated with ACS, improved prevention and optimized therapeutic approaches are needed.

Influencia del sexo en el tratamiento de pacientes con síndrome coronario agudo: estudio poblacional ecológico transversal en España

Palabras clave:
Síndrome coronario agudo
Sexo
Registro
Terapia antiagregante
Inhibidores de $P2Y_{12}$

RESUMEN

Introducción y objetivos: A pesar del descenso en la incidencia y en la mortalidad por síndrome coronario agudo (SCA), algunos estudios indican discrepancias en los resultados entre varones y mujeres. Nuestro objetivo fue investigar la influencia del sexo en el tratamiento de pacientes con SCA en España.
Métodos: Estudio ecológico transversal que recogió datos de 10 registros españoles de SCA (54 centros). Se realizó un análisis de meta-regresión con datos agregados de características basales, procedimientos, tratamientos y eventos intrahospitalarios y durante un año de seguimiento.
Resultados: En 34.605 pacientes (75,1% varones), el diagnóstico más frecuente fue infarto agudo de miocardio con elevación del segmento ST (58,9%) y 80% fueron clase Killip I. Las mujeres presentaron mayor edad (media: 71.0 frente a 63.3 años), tasa de hipertensión (68,1% frente a 51,7%) y diabetes (37,7% frente a 26,5%) que los varones. El número de intervenciones coronarias percutáneas, cirugía de revascularización y uso de *stent* fármaco-activo fueron menores en las mujeres. Respecto a la terapia antiagregante, el 23,1% de mujeres no

recibieron inhibidores $P2Y_{12}$, aun estando indicado (frente a 14,2% de varones; p < 0,001); clopidogrel fue el más administrado (> 60%). La mortalidad intrahospitalaria (5,4% frente a 3,7%) y al año (8,2% frente a 4,9%) aumentó significativamente en las mujeres respecto a los varones, principalmente por causas cardiovasculares.

Conclusiones: A pesar de su mayor edad y perfil de riesgo desfavorable, las mujeres con SCA parecen estar infratratadas con inhibidores $P2Y_{12}$. Reducir la mortalidad asociada con el SCA requiere una mejor prevención y enfoques terapéuticos optimizados.

Introduction

Cardiovascular diseases are a major health problem that constitute a leading cause of morbidity and mortality for both men and women worldwide.[1] Whilst a reduction in the incidence and mortality of cardiovascular diseases has been reported in recent years,[2,3] European data indicate that it has not been equal between men and women.[4] Accordingly, several studies have reported a greater decline in acute myocardial infarction rates in male compared to female patients, who tend to present more comorbidities than their counterparts.[5,6] The older age at acute coronary syndrome (ACS) onset in women, which has been attributed to the protective role of oestrogens against coronary events before menopause,[7] could also explain the worse clinical outcomes found in some trials.[8–10] Given that atypical symptoms of ACS are encountered more often in women than in men,[5,11] this altogether contributes to misdiagnosis and delayed recognition of ischaemia.[12]

Dual antiplatelet therapy with aspirin and $P2Y_{12}$ adenosine diphosphate receptor antagonists has long been used in ACS to prevent adverse cardiovascular events or death.[13] However, novel antithrombotic therapies developed in recent years have been associated with an increased bleeding risk,[14,15] which is particularly pronounced among women.[16] In line with previous evidence,[17–19] female sex has been postulated as an independent predictor of short-term bleeding after acute myocardial infarction.[12,16,20]

Inconsistent results have been published regarding the influence of sex on ACS outcomes,[11,21–24] which may be explained by the inclusion of populations with different baseline characteristics and/or variability in the methodology used for data analysis.[25] Nonetheless, among patients with ACS, sex differences in the management of cardiovascular events and subsequent mortality rates remain a concern nowadays.[12] Thus, emphasis should be placed on improving the identification of risk factors, early diagnosis and adequate therapeutic strategies in high-risk patients.

Previous independent studies have provided information on the epidemiology, prognosis and management of ACS in Spain.[26–28] With this nationwide ecological study that collects aggregated data from ACS patients from several Spanish registries, we sought to evaluate the impact of ACS and explore sex differences associated with patient characteristics, management, and progression in a real-world setting.

Methods

Study design and objectives

Population-based ecological cross-sectional study that collected aggregated data from ten ACS patient registries across 54 centres in Spain (Table 1 and Table 1 of the supplementary data). The study population was composed of patients (men and women) hospitalized in the participant centres, who had been diagnosed with ACS (ST-segment elevation myocardial infarction [STEMI], non-ST-elevation acute myocardial infarction or unstable angina), and whose data were entered in the corresponding ACS registry. These registries included medical records of demographic data, risk factors and comorbidities, treatments, procedures, and events that occurred during hospitalization and one-year post-discharge. Inclusion or exclusion criteria were not established for the goal of this study.

Our primary objective was to identify the proportion of women with ACS who are undertreated with antiplatelet agents ($P2Y_{12}$ inhibitors). Secondary objectives were determined as male vs. female comparisons in (a) all-cause mortality, (b) cardiovascular-related mortality, (c) interventional procedures, (d) stroke and reinfarction, and (e) bleeding complications.

Study variables

Aggregated data of patient baseline characteristics, bleeding risk, interventional procedures and events were obtained from each registry and used as variables in the analysis.

Baseline characteristics included: sex, age, weight, height, type of ACS (STEMI, non-ST-elevation acute myocardial infarction or unstable angina), Killip Class (I, II, III or IV), cardiovascular risk factors (hypertension, smoking, family history of ischaemic heart disease), comorbidities (cerebrovascular accident or transient ischaemic attack, peripheral artery disease, chronic kidney disease, dyslipidaemia, anaemia, and diabetes), prior treatments, and biochemical parameters (creatinine clearance, haemoglobin and troponin). Patients' bleeding and ischaemic risk were estimated using the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA guidelines)[29] and GRACE (Global Registry of Acute Coronary Events)[30] scores, respectively.

Table 1 – Participant registries.

Registry	Centres *n*	Recruitment period	Patients *n*	Men *n* (%)	Women *n* (%)
VESA study	10	2010–2015	12 358	9707 (78.6%)	2651 (21.4%)
CARDIOCHUS registry	1	2005–2019	6799	4913 (72.3%)	1886 (27.7%)
Cardio CHUVI-ACS	1	NA	6293	4655 (74.0%)	1638 (26.0%)
SCA San Juan	1	2008–2019	2234	1651 (73.9%)	583 (26.1%)
SCAB	1	2011 and 2016	1761	1289 (73.2%)	472 (26.8%)
ACHILLES	3	2014–2015	1717	1225 (71.4%)	492 (28.6%)
SPARTA	34	2015–2016	1441	1134 (78.7%)	307 (21.3%)
IPAG-SCA	1	2013–2015	1214	924 (76.1%)	290 (23.9%)
LONGEVO-SCA	1	2016	526	322 (61.2%)	204 (38.8%)
SCA Gómez Ulla	1	2012–2019	262	166 (63.4%)	96 (36.6%)
Total	54		34 605	25 986 (75.1%)	8619 (24.9%)

Variables related to interventional procedures were catheterization, access site, percutaneous coronary intervention, drug-eluting stent, coronary revascularization surgery and revascularization. Events included all-cause and cardiovascular-related mortality, stroke, reinfarction and bleeding complications, which were measured according the standardized criteria defined by the Bleeding Academic Research Consortium (BARC) in patients receiving antithrombotic therapy, specifically BARC types 2 to 5.[31]

Statistical analysis

Patient characteristics were evaluated using absolute and relative frequencies (percentages) for categorical variables, while mean and standard deviation (SD) were used for the continuous variables. To estimate the association between sex and binary categorical variables, analysis of binary data was performed. The odds ratio (OR) was used to measure the effect. A meta-regression model was used to find potential associations between variables, determining Wilson's or Fisher's exact test and 95% confidence interval (95%CI). The statistical analysis was carried out using STATA (version 11). A level of significance of $\alpha \leq 0.05$ was considered for the aforementioned analyses.

Ethical statement

Clinical information was obtained from Spanish ACS registry databases. This study was approved by the Ethics Committee for Research with medicinal products (CEIm) of Hospital Universitario de Bellvitge (L'Hospitalet de Llobregat, Barcelona, Spain); ACS registries included were previously authorized by their corresponding research ethics committees. Given that aggregated data was used for the analysis instead of individual patient records, additional informed consent was not required.

Results

Baseline characteristics

Overall, aggregated data from 34 605 patients belonging to 54 centres and ten national registries were collected (Table 1 and Table 1 of the supplementary data). Of these, 75.1% were men and 24.9% were women, with a mean age of 63.3 ± 12.6 years and 71.0 ± 12.6 years, respectively (Table 2). The most frequent ACS in the population was STEMI (58.9%), and nearly 80% of all patients were classified into Killip Class I on admission. Among the risk factors identified, twice as many men as women were smokers (41.9% vs. 23.2%; $P < .001$), whereas women presented hypertension (68.1% vs. 51.7%; $P < .001$) and diabetes mellitus more often (37.3% vs. 26.5%; $P < .001$). In contrast, despite its low frequency, peripheral artery disease was found more often in men than women (8.3% vs. 4.6%; $P < .001$). In terms of the most frequent comorbidities affecting both sexes similarly, 46.6% of all patients had dyslipidaemia, 20.3% had anaemia and 14.9% had chronic kidney disease.

Some differences were found in previous treatments regarding the use of adenosine diphosphate receptor inhibitors and oral anticoagulants, although aspirin was administered more often overall (23.3% vs. 5.6% adenosine diphosphate receptor inhibitors vs. 5.3% oral anticoagulants) and similarly across groups. Regarding biochemical parameters, higher creatinine clearance, haemoglobin and positive troponin levels were encountered in men. Conversely, increased ischaemic and bleeding risk, as determined by the GRACE and CRUSADE scores, respectively, were found among women.

Procedures during hospitalization

Procedural characteristics are summarized in Table 3. Catheterization and radial access were performed in the vast majority of patients regardless of sex (88.0% and 87.1%, respectively). However, despite an overall frequency of 81.0%, an 11.8% difference in favour of male patients was observed for percutaneous coronary interventions. Women were also less likely to receive a drug-eluting stent (33.4% vs. 38.6%; $P < .001$) or undergo coronary revascularization surgery (3.7% vs. 11.9%; $P < .001$).

Treatment at discharge

The majority of patients (≥90%) were treated with aspirin and/or statins at discharge (Fig. 1). Frequently used medication included angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (>70% of patients), and $P2Y_{12}$ inhibitors and beta-blockers (>78% of patients). However, significant variations were encountered between

Table 2 – Baseline characteristics of patients with acute coronary syndrome stratified by sex.

	Men	Women	P	Total
Patients, n (%)	25 986 (75.1)	8619 (24.9)		34 605
Age (y), mean ± SD	63.3 ± 12.6	71.0 ± 12.5	<.001	62.2 ± 12.5
Weight (kg), mean ± SD	80.6 ± 13.9	70.0 ± 13.0	<.001	77.9 ± 13.7
Height (cm), mean ± SD	169 ± 9	157 ± 9	<.001	165 ± 9
Type of ACS, n (%)				
STEMI	15 801 (60.3)	4566 (54.4)	<.001	20 367 (58.9)
NSTEMI	8314 (32.5)	2945 (35.8)		11 259 (32.5)
Unstable angina	1810 (7.2)	814 (9.8)		2624 (7.6)
Killip Class on admission, n (%)				
Class I	20 982 (85.1)	6546 (79.4)	<.001	27 528 (79.5)
Class II	2128 (8.7)	1038 (12.5)		3166 (9.1)
Class III	691 (2.8)	339 (4.1)		1030 (3.0)
Class IV	840 (3.4)	333 (4.0)		1173 (3.4)
Cardiovascular risk factors, n (%)				
Hypertension	12 352 (51.7)	5669 (68.1)	<.001	18 021 (55.7)
n	24 030	8325		32 355
Smoking	10 470 (41.9)	1927 (23.2)	<.001	12 397 (37.3)
n	24 889	8313		33 202
Family history of ischaemic heart disease	950 (9.5)	313 (8.1)	.213	1263 (8.2)
n	11 237	4170		15 407
Comorbidities, n (%)				
CVA or TIA	1280 (5.2)	547 (6.5)	<.001	1827 (5.5)
n	24 887	8325		33 212
Peripheral artery disease	2055 (8.3)	370 (4.6)	<.001	2425 (7.3)
n	24 886	8325		33 211
Chronic kidney disease (CCr <60 mL/min)	3034 (14.3)	1160 (16.8)	<.001	4194 (14.9)
n	21 169	6905		28 074
Dyslipidaemia	8283 (46.0)	2939 (50.0)	<.001	11 222 (46.6)
n	18 200	5893		24 093
Anaemia	2123 (17.1)	1010 (22.9)	<.001	3133 (20.3)
n	11 327	4113		15 440
Diabetes	5872 (23.7)	2481 (29.8)	<.001	8353 (25.2)
n	24 886	8325		33 211
Insulin-dependent diabetes	444 (26.5)	287 (37.3)	<.001	731 (29.8)
n	1680	772		2452
Prior treatments, n (%)				
Aspirin	5723 (23.4)	1988 (24.2)	.073	7711 (23.3)
n	24 854	8300		33 154
ADP receptor inhibitors	1425 (5.8)	424 (5.1)	.021	1849 (5.6)
n	24 721	8229		32 950
Oral anticoagulants	1165 (4.9)	578 (6.9)	<.001	1743 (5.3)
n	24 421	8325		32 746
Biochemical parameters				
Creatinine clearance (mL/h), mean ± SD	84.2 ± 33.6	72.6 ± 30.1	<.001	81.1 ± 32.7
Haemoglobin (g/L), mean ± SD	14.2 ± 2.1	12.9 ± 1.7	<.001	13.8 ± 2.0
Troponin-positive, *n* (%)	11 593 (83.8)	3958 (77.0)	<.001	15 551 (81.7)
n	13 891	5138		19 029
Risk scores, mean ± SD				
GRACE score (ischaemia)	140.9 ± 38.7	151.1 ± 41.2	<.001	143.8 ± 39.3
CRUSADE score (bleeding)	22.3 ± 14.7	35.6 ± 16.1	<.001	26.0 ± 15.1

ACS, acute coronary syndrome; ADP, adenosine diphosphate; CCr, creatinine clearance; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; CVA, cerebrovascular accident (acute stroke); GRACE, Global Registry of Acute Coronary Events; NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; TIA, transient ischaemic attack (ministroke).

sexes, particularly in the case of $P2Y_{12}$ inhibitors and beta-blockers: a 7–10% difference was observed in favour of men compared to women. Overall, female patients were less likely to receive all these pharmacological treatments, with the sole exception of oral anticoagulants, which were administered to 10.4% women vs. 7.4% men ($P < .001$).

A total of 23.1% of women (95%CI, 19.6–26.8) appeared to be undertreated with $P2Y_{12}$ inhibitors despite having this

Table 3 – Interventional procedures during patient hospitalization.

Procedure	Men *n* (%)	Women *n* (%)	*P*	*n* (%)
Catheterization	22 625 (90.2)	7211 (86.5)	<.001	29 863 (88.0)
n	25 074	8337		33 438
Access				
Radial	12 618 (87.4)	4273 (86.3)	.237	16 891 (87.1)
Femoral	1655 (11.5)	587 (11.9)		2242 (11.6)
Other	163 (1.1)	91 (1.8)		254 (1.3)
n	14 436	4951		19 387
Percutaneous coronary intervention	21 058 (84.0)	6014 (72.2)	<.001	27 072 (81.0)
n	25 074	8329		33 403
Drug-eluting stent	9613 (38.6)	2741 (33.4)	<.001	12 354 (37.3)
n	24 925	8218		33 143
Coronary revascularization surgery	921 (11.9)	212 (3.7)	<.001	1124 (5.3)
n	15 412	5687		21 090
Revascularization				
Complete	6775 (59.7)	2150 (60.7)	.302	8925 (59.9)
Partial	4576 (40.3)	1392 (39.3)		5968 (40.1)
n	11 351	3542		14 893

indication (Fig. 2), showing a statistically significant difference compared to men (OR, 14.2%; 95%CI, 13.1–15.3; $P < .001$). Among $P2Y_{12}$ inhibitors, clopidogrel was used more often than ticagrelor or prasugrel irrespective of patients' sex (64.3%, 11.9% and 9.6% in treated men vs. 62.4%, 9.8% and 4.3% in treated women, respectively).

In-hospital and follow-up events

A comparative analysis of male and female patient aggregated data was performed for mortality (all-cause and cardiovascular-related), stroke, reinfarction and bleeding episodes, both during the index hospitalization and throughout the subsequent 12-month follow-up, as well as for the interventional procedures that patients underwent during hospitalization (Table 4).

Overall, an increased frequency of events was observed in female compared to male patients. Significantly higher rates of both all-cause and cardiovascular-related mortality were observed in women compared to men, both during hospitalization (OR, 1.48; 95%CI, 1.28–1.72; and OR, 1.41; 95%CI, 1.21–1.65, respectively; $P < .001$) and follow-up (OR, 1.41; 95%CI, 1.11–1.81]; $P = .005$; and OR, 1.38; 95%CI, 1.18–1.63; $P < .001$, respectively). In all cases, mortality (range: 3.7% to 8.2%) was mainly associated with cardiovascular causes (range: 3.6% to 6.0%). Moreover, interventional procedures were performed significantly less often in women than men, accounting for a 12% difference between sexes.

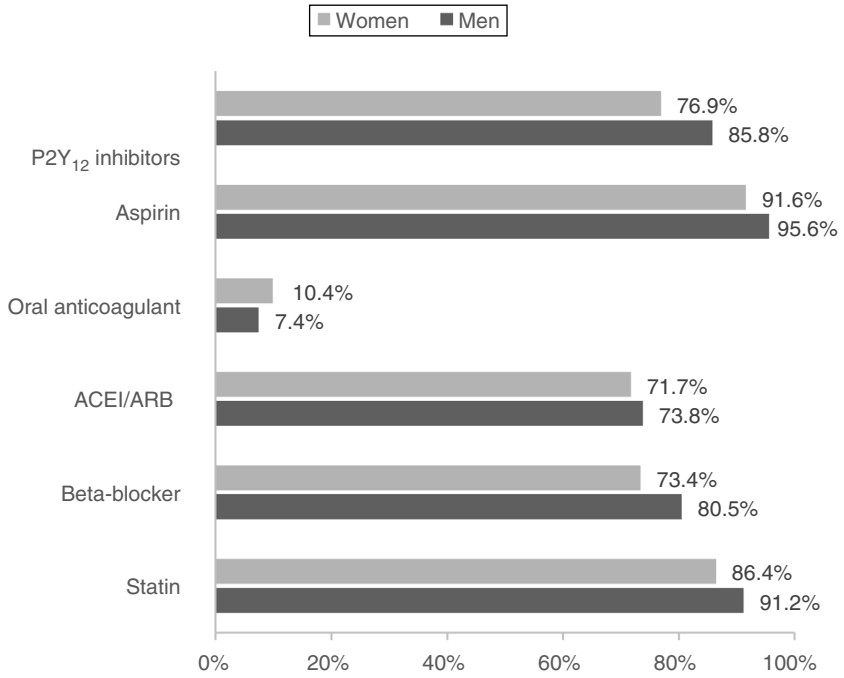
Bleeding, according to BARC 2–5, was more frequently encountered in inpatients compared to other events, such as reinfarction or stroke, regardless of sex. Whilst stroke was the lowest reported event (≤1.5%), either during hospitalization or thereafter, it occurred significantly more often among women (OR, 1.59; 95%CI, 1.19–2.14; $P = .002$; and OR, 1.43; 95%CI 1.09–1.87; $P = .009$, respectively).

Discussion

Despite the progress made using intensive therapeutic approaches in line with practice guidelines, which has led to a reduction in in-hospital mortality and associated complications,[27,32] an increase in the incidence of ACS is expected over the coming decades in Spain.[28] To the best of our knowledge, this is the first analysis carried out with ACS data from Spanish registries. We collected aggregated data from the medical records of 34 605 patients with ACS from a total of ten nationwide registries comprising 54 centres. Although an increasing incidence of non-ST-segment elevation – ACS has been previously reported in epidemiology studies,[28,33] the most frequent type of ACS among registered patients was STEMI. In line with published evidence,[5,20,34] women seemed to be older and to present an overall higher rate of risk factors and comorbidities than men. Hypertension, diabetes mellitus, heart failure and chronic kidney disease, along with older age, have been reported to be more frequent among women.[5,20,34]

Our analysis indicated that most patients (>86%) underwent catheterization and radial access during hospitalization. Radial over femoral access is recommended by the European Society of Cardiology (ECS) guidelines for coronary angiography and percutaneous coronary intervention, to minimize bleeding in patients with ACS who are treated with dual antiplatelet therapy (evidence class I, level A).[35] In contrast, our results suggest that women were less likely to undergo other cardiac procedures, such as percutaneous coronary intervention, use of drug-eluting stents and coronary revascularization surgery, which is consistent with previous evidence.[19,36,37] Although the percentage of interventional procedures appeared lower overall than recently reported in Europe,[38] which may be related to the use of old registries for our analysis, notable sex-related differences were identified.

For ACS, a dual antiplatelet therapy consisting of treatment with aspirin and $P2Y_{12}$ inhibitors clopidogrel, prasugrel or ticagrelor, is usually recommended for at least 12 months,[39,40] considering shorter durations for patients with high-risk bleeding.[41,42] Most patients (>90%) received aspirin and/or statins at discharge. $P2Y_{12}$ inhibitors and beta-blockers were also highly prescribed for ACS (>78%), although substantial differences could be observed between female and male patients. Despite the indications in current guidelines,[39,40] a significant number of women appeared undertreated with $P2Y_{12}$



	Men n (%)	Women n (%)	*P*	Total n (%)
Aspirin	22 950 (95.6%) 23 996	7258 (91.6%) 7927	< .001	30 208 (94.6%) 31 923
$P2Y_{12}$inhibitors	21 834 (85.8%) 25 433	6391 (76.8%) 8323	< .001	28 225 (83.6%) 33 756
Oral anticoagulants	1829 (7.4%) 24 854	850 (10.4%) 8196	< .001	2679 (8.1%) 33 050
ACEI/ARB	16 565 (73.8%) 22 454	5336 (71.7%) 7438	.001	21 901 (73.2%) 29 892
Beta-blockers	18 066 (80.5%) 22 453	5461 (73.4%) 7438	< .001	23 527 (78.7%) 29 891
Statins	21 626 (91.2%) 23 718	6815 (86.4%) 7887	< .001	28 441 (90.0%) 31 605

Fig. 1 – Medication at discharge by sex. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

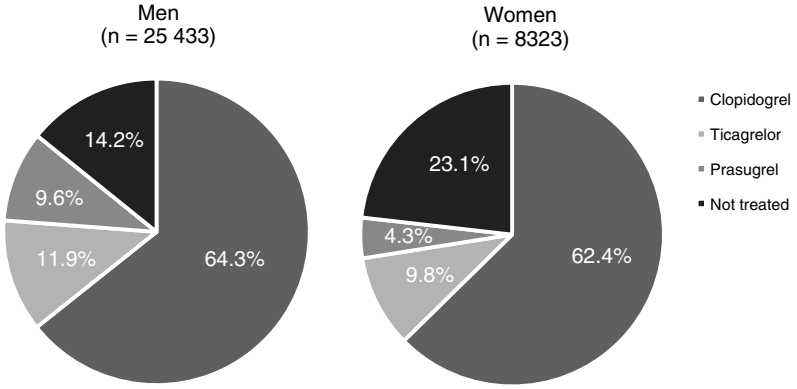


Fig. 2 – Treatment with $P2Y_{12}$ inhibitors by sex.

Table 4 – Analysis of in-hospital and 1-year follow-up events by sex.

Event	Men *n* (%)	Women *n* (%)	*P*	OR (95%CI)
Interventional procedures[a]	55 201 (59.6)	16 705 (38.3)		
n	92 598	43 656	<.001	0.91 (0.89–0.94)
Stroke				
In-hospital	155 (0.6)	80 (1.0)	.002	1.59 (1.19–2.14)
n	24 687	8133		
1-year follow-up	195 (1.0)	94 (1.5)	.009	1.43 (1.09–1.87)
n	20 472	6416		
Reinfarction				
In-hospital	387 (1.5)	156 (1.8)	.222	1.13 (0.93–1.36)
n	25 976	8608		
1-year follow-up	896 (4.2)	317 (4.7)	.429	1.06 (0.92 1.22)
n	21 462	6804		
Bleeding (BARC 2–5)[b]				
In-hospital	195 (2.9)	78 (3.3)	.455	1.11 (0.85–1.45)
n	6729	2398		
1-year follow-up	801 (11.2)	290 (11.5)	.646	1.03 (0.90–1.19)
n	7167	2526		
All-cause mortality				
In-hospital	553 (3.7)	296 (5.4)	<.001	1.48 (1.28–1.72)
n	15 050	5475		
1-year follow-up	1060 (4.9)	570 (8.2)	.005	1.41 (1.11–1.81)
n	21 658	6955		
Cardiolvascular-related mortality				
In-hospital	488 (3.6)	250 (5.0)	<.001	1.41 (1.21–1.65)
n	13 722	4980		
1-year follow-up	483 (4.1)	249 (6.0)	<.001	1.38 (1.18–1.63)
n	11 757	4164		

95%CI, 95% confidence interval; BARC, Bleeding Academic Research Consortium; OR, odds ratio.

[a] Interventional procedures included: catheterization, percutaneous coronary intervention, drug-eluting stent, and coronary revascularization surgery. Patients may have undergone one or more interventional procedures. Aggregated data of all procedures performed in the entire population is depicted; individual patient information cannot be extracted.

[b] Among the different scores utilized by the registries to measure bleeding, BARC 2–5 classification was the most frequently used in the population.

inhibitors at discharge (23.1% vs. 14.2% undertreated men). These observations are consistent with results from previous studies,[5,25,43] thereby highlighting sex-related disparities in the therapeutic management of ACS patients.

Although clopidogrel has long been used as dual antiplatelet therapy to prevent death or adverse cardiac or cerebrovascular events in patients with ACS,[13,44] the novel $P2Y_{12}$ inhibitors ticagrelor and prasugrel have shown superior efficacy.[14,15] Despite the preference for prasugrel and ticagrelor over clopidogrel in current ESC guidelines,[35] our results suggest that clopidogrel was the most frequently administered $P2Y_{12}$ inhibitor in ACS patients, regardless of sex, in Spain. This may be due to the time period when data were collected and the inclusion of aggregated data collected by the individual registries before the establishment of current ECS guidelines, but it could also underscore a failure to prescribe novel antiplatelet agents in our setting. The significantly higher rate of anaemia among women compared to men might have also led to the prescription of more conservative antiplatelet therapies.

Given its association with worse outcomes and mortality rates, bleeding constitutes the most frequent non-ischaemic complication in ACS patients.[34] Moreover, the novel antiplatelet therapies that have emerged in recent years have been linked to an increased risk of bleeding in these patients.[14,15] Some studies have described female sex as an independent predictor of non-surgery related bleeding.[17,18,39,45,46] Likewise, an increased bleeding risk, according to the CRUSADE score, was observed in women compared to men in our study. However, this observation did not translate into a statistically significant difference in terms of the number of bleeding events, either during hospitalization or thereafter. While the incidence of bleeding events from discharge to the end of follow-up was in line with the literature,[34] a lower number of in-hospital events, likely due to misregistration and subsequent underestimation, was observed among the ACS population in this study.

Overall, a higher frequency of in-hospital and follow-up events were encountered in women with ACS compared to men, with significantly increased all-cause and cardiovascular-related mortality. Whilst these rates seemed lower than those reported in a recent study of women with STEMI (16.9%) and non-ST-elevation acute myocardial infarction (11.7%) during hospitalization,[20] our results support the association between sex and unfavourable outcome in ACS.[5,17,18,34,39,45,46] In contrast, no sex-related differences were

observed in the frequency of reinfarction or bleeding during follow-up in this patient population. Regarding the risk of ischaemia, which was significantly higher among women at baseline, some studies have reported an increased long-term risk compared to bleeding in patients with prior myocardial infarction treated with $P2Y_{12}$ inhibitors.[47,48] Hence, given the importance of both bleeding and ischaemic events in the patient's prognosis, emphasis should be placed on individual risk assessments in order to adopt preventive strategies and more adequate therapeutic approaches.[34,41,42]

Limitations

Our study has certain limitations that should be taken into consideration, as they could explain the aforementioned discrepancies with previous publications. First, although we have attempted to homogenize data from the ten registries, heterogeneity cannot be completely ruled out. Registries included in this study differed in patient inclusion criteria, particularly for the time of inclusion, which may have partially biased some of the results (e.g. the use of drug-eluting stents and the extremely low percentage of patients using newer and more potent $P2Y_{12}$ inhibitors, as well as the higher proportion of STEMI cases in our population compared to literature). Second, given the observational nature of this study, inherent differences may be found in some of the variables evaluated. Since individualized patient data could not be analyzed, it is not possible to examine the causality of events. Third, patients may have presented certain clinical features, experienced events (i.e. in-hospital mortality) or undergone interventional procedures that have not been documented. While mortality and reinfarction are variables that could be easily extracted from electronic medical records, some events, such as mild or minor bleeding, are not always reported by the patient or properly recorded. Moreover, the use of different scores hindered data analysis of some variables, such as bleeding complications. The limitations addressed herein may serve to improve data collection on ACS in Spain, which should be driven by an increased effort to register these cases, along with standardization of patient evaluation criteria.

Conclusions

The results of this ecological cross-sectional study suggest that 23.1% of women with ACS may be undertreated with $P2Y_{12}$ inhibitors in Spain. Despite current recommendations in clinical practice guidelines on the use of ticagrelor or prasugrel as first-line therapy for ACS, clopidogrel appeared to be the most frequently used antiplatelet agent, regardless of sex. Older age and unfavourable risk profile of women could be associated with increased mortality rates, both during hospitalization and at follow-up. Thus, emphasis should be placed on improved ACS prevention strategies and optimized therapeutic approaches in women. Growing awareness of sex differences in the management and importance of adherence to appropriate treatments are needed to improve both ischaemic and bleeding outcomes in female and male patients with ACS.

What is known about the subject?

- ACS is a major cause of mortality and morbidity in men and women, with the incidence expected to increase in the coming years.
- Women with ACS usually are older at onset, and present atypical symptoms and unfavourable risk profile. Higher mortality rates and bleeding complications have been reported in female compared to male patients.
- Although the available evidence is mixed, sex-related differences in the management and treatment of ACS could explain women's poorer clinical outcomes.

Does it contribute anything new?

- This ecological cross-sectional study included aggregated data from 34 605 patients (75% men) from 10 ACS registries and 54 centres in Spain.
- A trend towards a greater burden of risk factors, more comorbidities and bleeding risk was observed in women.
- Despite being indicated, over 23% of women were not treated with $P2Y_{12}$ inhibitors at discharge. Clopidogrel was the $P2Y_{12}$ antagonist most often administered.
- Women seemed less likely to undergo interventional procedures. Mortality and stroke were significantly more frequent in female patients, both during hospitalization and follow-up.

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Conflicts of interest

J.M. Ruiz-Nodar has received honoraria for lectures from AstraZeneca, Biosensor, Boston Scientific, Medtronic and Terumo. J.L. Ferreiro has received honoraria for lectures from Eli Lilly and Company, Daiichi Sankyo, AstraZeneca, Roche Diagnostics, Pfizer, Abbott Laboratories, Boehringer Ingelheim and Bristol-Myers Squibb, consulting fees from AstraZeneca, Eli Lilly, Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb, and research grants from AstraZeneca. A. Cordero has received honoraria from lectures and consulting fees from AstraZeneca and AMGEN, honoraria for lectures from Bristol-Myers Squibb, and consulting fees from Ferrer Internacional. V. Bertomeu-González has received honoraria from lectures from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Pfizer, LivaNova, Sanofi, and Ferrer Internacional. F. Marín Ortuño has received research grants from Fundación para la Investigación de la Región de Murcia (FFIS) and AstraZeneca, and honoraria from Daiichi

Sankyo, Boehringer-Ingelheim and Pfizer-BMS. M. Almendro-Delia has received honoraria for lectures from Eli Lilly and Company, Daiichi Sankyo, Ferrer International, AstraZeneca, Pfizer, Boehringer Ingelheim, Bayer Hispania, and Bristol-Myers Squibb, consulting fees from AstraZeneca, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Bayer Hispania, and research grants from AstraZeneca. A. Valls-Serral has received honoraria for lectures and/or consulting from Novartis, AstraZeneca and Boehringer Ingelheim. A. Cequier has received research grants from Abbott Laboratories, Biosensors, Boston Scientific, Medtronic, Biomenco, Cordis, Orbus Neich, and the Spanish Society of Cardiology (SEC), and honoraria from Abbott Laboratories, Biosensors, Medtronic, Ferrer International, Terumo, AstraZeneca and Biotronik.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rccl.2020.10.009.

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