Pharmacological Treatment After Acute Coronary Syndrome: Baseline Clinical Characteristics and Sex Differences in a Population-Based Cohort Study.

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Abstract

Background: Cardiovascular disease remains the most common cause of death worldwide. Some differences between sexes in secondary prevention pharmacological therapies after an acute coronary syndrome (ACS) have been described, being women less likely to be treated. The aim was to describe baseline socio-demographic and clinical characteristics and drugs prescribed for secondary prevention after a first episode of ACS in a Primary Health Care cohort population in Catalonia (Spain) and to assess differences between sexes.

Methods: Population-based observational cohort study of patients with a first episode of ACS during 2009-2016. Data source: Information System for Research in Primary Care (SIDIAP) database.

Results: There were 8,071 patients included, 71.3% of them were men and 80.2% had an acute myocardial infarction (AMI). Their mean age was 65.3, being older the women than the men. The most frequent comorbidities were hypertension, dyslipidaemia and diabetes and they were more common in women. Antiplatelets (91.3%) and statins (85.7%) were the study drugs most prescribed. The uses of all comedications were significantly higher in women, except for nitrates. The combination of four study groups was initially prescribed in 47.7% of patients and combination of beta-blockers, statins and antiplatelets was prescribed in 18.4%. More men than women received all recommended pharmacological groups.

Conclusion: Women were older, had more comorbidities and received more comedication. Most patients were treated with a combination of four or three study drugs for secondary prevention. Men initiated more treatments for secondary prevention and dual antiplatelet therapy than women.

Background

Cardiovascular disease remains the most common cause of death worldwide, 31.5% of all deaths and 45% for non-communicable disease deaths in Europe.[1, 2] Despite these numbers, the incidence of cardiovascular disease has decreased over the last four decades, due to population-level lifestyle changes and the development of effective interventions to treat individuals and invasive procedures and effective drugs to tackle modifiable risk factors.[3]

Several randomized clinical trials, meta-analyses and cohort studies have shown that long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) improve survival in high risk patients, particularly those with established cardiovascular disease.[4–7] In the same alignment, the European Society Cardiology guidelines recommend in both sexes this long-term pharmacological therapy for an acute coronary syndrome (ACS) secondary prevention.[8–10]

Several population-based studies have analysed the pharmacological secondary prevention in the real-world practice. In Lafeber et al. study, 67% of patients with cardiovascular disease were treated with a

combination of aspirin, statin and at least one blood pressure-lowering agent for secondary prevention. [11] Sanflix-Gimeno et al. showed that after an ACS 92.8% of patients were treated with an antiplatelet, 74.7% with beta-blocker, 87.1% with statins and 77.2% with an ACEI or ARB.[5]

Some population-based studies have analysed differences between sexes in clinical characteristics and pharmacological treatment received after ACS. Women have been reported to be older than men and have greater comorbidities, such as hypertension, diabetes and dyslipidaemia.[12–15] Some differences between sexes in secondary prevention have also been described, being women less likely to be treated. [12–14]

This work is part of IMPACT study and the protocol has been previously published.[16] This study aims to describe the baseline socio-demographic and clinical characteristics and the medication prescribed for secondary prevention after a first episode of ACS in a Primary Health Care cohort in Catalonia (Spain) and to assess differences in these characteristics between women and men.

Methods

Study design

Population-based observational cohort study of patients with a first episode of ACS during 2009–2016. [16]

Data source

Information System for Research in Primary Care (SIDIAP) database,[17] which contains pseudonymized information coming from different data sources: ECAP (electronic health records in Primary Health Care of the Catalan Health Institute, including) socio-demographic characteristics, comorbidities registered as International Classification of Disease (ICD) 10 codes,[18] specialist referrals, clinical parameters, toxic habits, sickness leave, date of death, laboratory test data; general practitioners' prescriptions and their corresponding pharmacy invoice data registered as chemical classification system (ATC) codes;[19] and the CMBD-HA (minimum basic dataset at hospital discharge),[20] which includes diagnoses at hospital discharge registered as ICD9 codes. [21]

Study Population

All adults with a first episode of ACS (acute myocardial infarction (AMI) or unstable angina) registered in CMBD-HA from 2009–2016 with at least two months of follow-up in SIDIAP after the index date.

Exclusion criteria

patients with a recorded diagnosis of a previous ischaemic stroke.

Study Variables

At index date: age, sex, socioeconomic MEDEA Index,[22, 23] toxic habits, body mass index (BMI), type of ACS event (AMI, unstable angina or other forms of ACS), laboratory data (cholesterol, other lipid parameters and glomerular filtration rate), and comorbidities of interest. MEDEA is a deprivation index based on five indicators of socio-economic position, defined by the census tracks of Barcelona, Bilbao, Madrid, Sevilla and Valencia and explain more than 75% of their variability. The higher this is, the worse the deprivation is, and it allows analysing health inequalities. It also shows differences by sex and size of the city, and tends to be sensitive to differences between urban (U) and rural (R) areas.

The study drugs were those recommended for secondary prevention: antiplatelets, beta-blockers, statins and ACEI/ARB. Study drugs prescribed after the ACS event and other concomitant drugs were collected after the index date. The initiation of exposure to the study drugs was defined according to the drugs firstly prescribed during the period spanning from index day to 120 days after the event in order to capture all prescriptions in Primary Health Care.

Statistical analysis

Demographic and baseline characteristics of the participants were described using frequencies and percentages for categorical variables and mean, standard deviation for continuous variables. Univariate analysis of comparison between genders was performed by means of Student's t-test or Pearson's Chi-square tests as appropriate, while in the analysis between groups according to the number of study drugs we used the ANOVA test. All analyses were performed using R 3.5.1 under a significance level of 0.05.

Results

There were 16,644 patients admitted to hospital with a first episode of ACS from 2009 to 2016, 8,573 were excluded (Fig. 1) and 8,071 included, 71.3% of them were men and 80.2% had an AMI (men: 81.7%; women: 76.6%). Their mean age was 65.3, being older women than men (71.1 vs 63.0, $p < 0.001$), and 45.1% older than 75. The most frequent comorbidities were hypertension, dyslipidaemia and diabetes and they were more common in women. Heart failure and renal impairment were also common in women (Table 1).

Table 1
Sex differences in socio-demographic characteristics, laboratory data and comorbidities.

N (%)	Overall	Women	Men	P-value
Sex	8071	2318 (28.7)	5753 (71.3)	
Acute myocardial infarction	6475 (80.2)	1776 (76.6)	4699 (81.7)	< 0.001
Unstable angina	1596 (19.8)	542 (23.4)	1054 (18.3)	< 0.001
Age in years, mean (SD)	65.3 (13.6)	71.1 (13.1)	63.0 (13.0)	< 0.001
median (IQR, Range)	71.0 (22, 82)	80.0 (21, 82)	68.0 (19, 73)	< 0.001
> 75 years	2198 (27.2)	1046 (45.1)	1152 (20.0)	< 0.001
MEDEA[22, 23]				0.009
R	1427 (17.7)	386 (16.7)	1041 (18.1)	
U1-3	3366 (41.7)	924 (39.9)	2442 (42.5)	
U4-5	2785 (34.5)	851 (36.7)	1934 (33.6)	
Smokers	2320 (32.1)	335 (15.5)	1985 (39.1)	< 0.001
<i>Missing (10.3%)</i>				
High alcohol intake	5 (0.1)	0 (0.0)	5 (0.1)	< 0.001
<i>Missing (21.8%)</i>				
BMI (kg/m ² ; mean, SD)	29.0 (4.7)	29.9 (5.5)	28.7 (4.3)	< 0.001
<i>Missing (20.8%)</i>				
BMI ≥ 30: obesity	2387 (37.4)	903 (45.1)	1484 (33.8)	< 0.001
Cholesterol Total mg/dL, mean (SD)	208.9 (43.3)	211.78 (42.03)	207.63 (43.80)	< 0.001
<i>Missing (14.8%)</i>				
Cholesterol LDL mg/dL, mean (SD)	129.4 (36.6)	129.1 (36.3)	129.6 (36.7)	0.582
<i>Missing (21.5%)</i>				

P-value from Pearson's Chi-square test (categorical variables) and t-test (numeric variables) comparing women versus men. BMI, body mass index; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; R (Rural); U (Urban).

N (%)	Overall	Women	Men	P-value
Cholesterol HDL mg/dL, mean (SD) <i>Missing (19.0%)</i>	49.0 (13.4)	54.2 (14.2)	46.7 (12.3)	< 0.001
Triglycerides mg/dL, mean (SD) <i>Missing (17.7%)</i>	154.7 (104.2)	147.5 (90.7)	158.1 (109.7)	< 0.001
Diabetes mellitus	2169 (26.9)	743 (32.1)	1426 (24.8)	< 0.001
Dyslipidaemia	3450 (42.7)	1134 (48.9)	2316 (40.3)	< 0.001
Heart failure	296 (3.7)	159 (6.9)	137 (2.4)	< 0.001
Hypertension	4294 (53.2)	1540 (66.4)	2754 (47.9)	< 0.001
Peripheral artery disease	385 (4.8)	90 (3.9)	295 (5.1)	0.021
Renal impairment; eGFR < 45 ml/min/1.73 m ² <i>Missing (14.9%)</i>	528 (7.6)	274 (12.8)	254 (5.4)	< 0.001
<i>P-value from Pearson's Chi-square test (categorical variables) and t-test (numeric variables) comparing women versus men. BMI, body mass index; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; R (Rural); U (Urban).</i>				

Table 2 describes the drugs prescribed for secondary prevention. Antiplatelets (91.3%) and statins (85.7%) were the most prescribed in both sexes. More men than women received all study drugs. Nitrates were the comedication most prescribed in both sexes after the event. The uses of all comedications were significantly higher in women, except for nitrates.

Table 2
Sex differences in population that initiate treatment for secondary prevention: study drugs and
comedications after the event.

N (%)	Overall	Women	Men	P-value
Study drugs				
Antiplatelets	7369 (91.3)	1998 (86.4)	5371 (93.3)	< 0.001
Statins	6914 (85.7)	1864 (80.5)	5050 (87.8)	< 0.001
Beta-blockers	6185 (76.7)	1675 (72.4)	4510 (78.4)	< 0.001
ACEI/ARB	5356 (66.3)	1505 (65.1)	3851 (66.9)	0.2223
Comedications				
Anticoagulants	602 (7.5)	260 (11.2)	342 (5.9)	< 0.001
Calcium channel-blockers	1309 (16.2)	471 (20.3)	838 (14.6)	< 0.001
Diuretics	1754 (21.7)	792 (34.2)	962 (16.7)	< 0.001
Drug used in diabetes mellitus	1997 (24.7)	679 (29.3)	1318 (22.9)	< 0.001
NSAID	1627 (20.2)	655 (28.3)	972 (16.9)	< 0.001
Nitrates	3005 (37.2)	811 (35.0)	2194 (38.1)	0.009
<i>P-value from Pearson's Chi-square test comparing women versus men. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; NSAID, non-steroidal anti-inflammatory drugs.</i>				

The combination of four study drugs was initially prescribed in 47.7% of patients. Beta-blockers, statins and antiplatelets was the more frequent combination of three components (18.4%) (Fig. 2). More men were treated with the combination of four (2,879 [50.0%] vs 968 [41.8%], $p < 0.001$) and with the most frequent combination of three drugs: antiplatelets, statins and beta-blockers (1115 [19.4%] vs 368 [15.9%]; $p < 0.001$); and antiplatelets, statins and ACEI/ARB (492 [8.6] vs 210 [9.1], $p = 0.491$).

Patients with AMI significantly received four study drugs more frequently (86%) than other combination of three (79.2%) or $\leq$ two study drugs (68.3%, $p < 0.001$). More women initiated $\leq$ two study drugs (38.9%) than three (27.5%) or four (25.2%). Patients receiving $\leq$ two study drugs were older (68.9 years). There were more patients treated with other comedications after the event in the group of $\leq$ two study drugs than the other combinations (Table 3).

Table 3
Socio-demographic characteristics, laboratory data, comorbidities and comedications stratified by study drugs number.

N (%)	4	3	≤ 2	P-value
Study drugs number	3847 (47.7)	2569 (31.8)	1655 (20.5)	
Acute myocardial infarction	3310 (86.0)	2035 (79.2)	1130 (68.3)	< 0.001
Unstable angina	537 (14.0)	534 (20.8)	525 (31.7)	< 0.001
Sex; Female	968 (25.2)	706 (27.5)	644 (38.9)	< 0.001
Age in years, mean (SD)	63.9 (13.0)	65.2 (13.6)	68.9 (14.4)	< 0.001
> 75 years	869 (22.6)	695 (27.1)	634 (38.3)	< 0.001
MEDEA[22, 23]				< 0.001
R	683 (17.8)	412 (16.1)	332 (20.1)	
U1-3	1638 (42.6)	1056 (41.2)	672 (40.6)	
U4-5	1335 (34.7)	929 (36.2)	521 (31.5)	
Smokers <i>Missing (10.3%)</i>	1234 (35.5)	745 (32.9)	341 (22.8)	< 0.001
High alcohol intake <i>Missing (21.8%)</i>	3 (0.1)	1 (0.1)	1 (0.1)	< 0.001
BMI (kg/m ² ; mean, SD) <i>Missing (20.8%)</i>	29.3 (4.7)	28.8 (4.7)	28.7 (4.9)	< 0.001
BMI ≥ 30: obesity	1194 (39.3)	712 (35.8)	481 (35.3)	< 0.001
Cholesterol Total mg/dL, mean, (SD) <i>Missing (14.8%)</i>	211.7 (42.7)	210.0 (42.8)	201.10 (44.4)	< 0.001

P-value from ANOVA test comparing samples with 4, 3 or 2 – 1 drugs of interest. ACH, acute coronary heart disease; BMI, body mass index; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein- cholesterol; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; R (Rural); U (Urban).

N (%)	4	3	≤ 2	P-value
Cholesterol LDL mg/dL, mean, (SD) <i>Missing (21.5%)</i>	131.5 (35.3)	131.3 (37.6)	122.1 (36.9)	< 0.001
Cholesterol HDL mg/dL, mean, (SD) <i>Missing (19.0%)</i>	48.5 (12.8)	49.1 (13.1)	50.2 (15.0)	0.001
Triglycerides mg/dL, mean, (SD) <i>Missing (17.7%)</i>	159.5 (108.5)	154.00 (102.9)	145.1 (95.4)	< 0.001
Diabetes mellitus	1077 (28.0)	640 (24.9)	452 (27.3)	0.022
Dyslipidaemia	1686 (43.8)	1108 (43.1)	656 (39.6)	0.014
Heart failure	75 (1.9)	92 (3.6)	129 (7.8)	< 0.001
Hypertension	2189 (56.9)	1230 (47.9)	875 (52.9)	< 0.001
Peripheral artery disease	164 (4.3)	120 (4.7)	101 (6.1)	0.013
Renal impairment; eGFR < 45 ml/min/1.73 m ² <i>Missing (14.9%)</i>	156 (4.8)	179 (8.3)	193 (13.3)	< 0.001
Comedications after the event				
Anticoagulants	188 (4.9)	170 (6.6)	244 (14.7)	< 0.001
Calcium channel-blockers	541 (14.1)	405 (15.8)	363 (21.9)	< 0.001
Diuretics	748 (19.4)	510 (19.9)	496 (30.0)	< 0.001
Drug used in diabetes mellitus	1008 (26.2)	577 (22.5)	412 (24.9)	0.003
NSAID	734 (19.1)	538 (20.9)	355 (21.5)	0.065
Nitrates	1544 (40.1)	940 (36.6)	521 (31.5)	< 0.001
<i>P-value from ANOVA test comparing samples with 4, 3 or 2 – 1 drugs of interest. ACH, acute coronary heart disease; BMI, body mass index; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein- cholesterol; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; R (Rural); U (Urban).</i>				

Figure 3 represents the different drugs prescribed overall, in men and women. Men received dual antiplatelet therapy more frequently than women; the most used antiplatelets were aspirin and

clopidogrel. The most prescribed beta-blocker was bisoprolol both in men and women. Atorvastatin was the most prescribed statin for all patients. Enalapril and ramipril were the most used ACEI, being ramipril more frequent in men. Losartan is the most prescribed ARB, followed by valsartan and olmesartan (Fig. 3 and Table S1).

Discussion

We report baseline socio-demographic and clinical characteristics of 8,701 patients from a Primary Health Care cohort who had a first ACS. Patients' characteristics have been analysed overall, divided into sexes and number of study drugs prescribed. With regard to socio-demographic characteristics, the proportion of men and women in our study is not balanced (28.7% of women) and it is similar to previous studies.[13, 14, 24, 25]

We found that women were older, had greater comorbidity at baseline and received more comedications after the study event than men, probably because they were older when had the first ACS, as described in a similar cohort by Ribas et al.[25] In agreement with similar studies, we found a higher prevalence of comorbidities in women,[26–28] while men had a higher prevalence of peripheral artery disease,[29] possibly related with the higher frequency of smoking habit.

Most patients in our study (91.3%) initiated treatment for secondary prevention with antiplatelets after the first ACS, mainly with dual antiplatelet therapy, as recommended by guidelines. [8–10] Statins were the second drug more prescribed (85.7% of patients) and beta-blockers and ACEI/ARB were less prescribed. All patients with established cardiovascular disease should be treated during hospital admission and after discharge with statins, regardless of their cholesterol values.[30] ACEI/ARB might be less prescribed as they are not always recommended for all patients, they should be considered in all ST-Elevation Myocardial Infarction patients. [8–10] All study drugs were more commonly prescribed in men than women, except for ACEI/ARB, that difference between sexes was slight and not significant, probably related to higher frequency of HTA in women in our study population, because women were older than men. These results were similar to Lafeber et al [31] and Sanflix-Gimeno et al studies.[5] Regarding comedications, anticoagulants and diuretics were the most prescribed in women, possibly related with higher frequency of heart failure and renal impairment, being loop diuretics the group most commonly prescribed.

Women initiated secondary prevention less frequently than men.[12–14, 32–34] Nevertheless, the majority of our population (79.5%) initiated treatment with three or four drugs combined, and almost half (47.7%) with four study drugs, although we found more women treated with $\leq$ two study drugs than with three or four. This may perhaps occur because physicians prescribed fewer drugs to older patients who were multimorbid and polymedicated.[35] Probably, the same assumption could be extended to our finding found for women and the number of drugs prescribed, because men usually suffer ACS at an earlier age.[36–38]

Zeymer et al[39] conducted an observational prospective study including 9,998 patients with ACS from June 2000 until December 2002. They reported that patients receiving four drugs were younger and patient's characteristics according to the number of drugs prescribed were similar to our population. They found higher percentage (92.5%) with combination of four or three components and 62.6% with combination of four. The combination of beta-blockers, statins and antiplatelets was also high (39.5%). Also, they suggested that age > 75 years old is a potent predictor for not receiving therapy with four components.[34, 39, 40]

Other author already mentioned, Lafeber et al[31] conducted an observational prospective cohort study of 2,706 recently diagnosed patients clinically manifest coronary artery disease between January 1996 and February 2010. They found fewer patients (67.0%) treated with the combination of aspirin, a statin and $\geq$ one blood-pressure lowering agent(s).[31]

Aspirin and clopidogrel were the most frequently antiplatelets prescribed. Dual antiplatelet therapy was less frequently prescribed to women as described by previous studies,[40–42] probably because women were older.[43] Bisoprolol, enalapril, and losartan were the most prescribed beta-blockers with slight differences between sexes. The statins most commonly prescribed in both sexes were atorvastatin and simvastatin, probably because they are the statins with more experience of use

We found a strong relation in the medication prescribed between being women and older in our population, probably because women had the first ACS in older age than men. Consequently, women had lower probability to be treated with study drugs and higher probability to be treated with other comedications.

This study has some limitations inherent to electronic database studies, such as data incompleteness, loss of follow-up of patients suffering an ACS, potential confounders, non-randomised data and possible selection biases. Other limitation is that prescriptions are not linked with diagnoses in SIDIAP database. On the other hand, the strengths of our study are the large number of patients included, representativeness for the general population, complete socio-demographic and health records, long follow-up periods and real-world data. Our data is supported by previous studies and the presence of cardiovascular risk factors and outcomes has been previously validated in SIDIAP.[44–46]

This is the first work conducted with SIDIAP database which analyses the drugs prescribed for secondary prevention of cardiovascular disease. The IMPACT study is ongoing and the next step is to assess the relationship between adherence to the four pharmacological groups recommended for secondary prevention and the clinical outcomes of cardiovascular morbidity and mortality in these patients.

Conclusion

We described a large set of ACS patients initiating treatment with the drugs recommended for secondary prevention. Age, gender and most clinical characteristics were similar to prior studies.

Women were older, had more comorbidity and received more comedication after the ACS. Men initiated more drugs for secondary prevention than women. In addition, men received more dual antiplatelet therapy and atorvastatin than women.

Most patients were treated with a combination of four or three pharmacological drugs recommended for secondary prevention.

Abbreviations

ACEI

angiotensin converting enzyme inhibitors

ACS

acute coronary syndrome

AMI

acute myocardial infarction

ARB

angiotensin receptor blockers

ATC

chemical classification system

BMI

body mass index

CMBD-HA

minimum basic dataset at hospital discharge

ECAP

electronic health records in Primary Health Care of the Catalan Health Institute

ICD

international classification of disease

MEDEA

socioeconomic index

R

rural

SIDIAP

information system for research in primary care

U

urban

Declarations

Ethics approval and consent to participate:

According to European and Spanish legislation about confidentiality and data protection (Regulation [EU] 2016/679), the data contained in databases are always pseudonymized.

For the linkage with CMBD database, SIDIAP uses a trusted third party in order to ensure confidentiality when linking both data sources.

The present study follows national and international regulations: Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and Good Research Practice principles and guidelines.

The study was approved by Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAPJGol) Clinical Research Ethics Committee, the reference institution for research in Primary Health Care of the Catalan Health Institute, at May 3, 2017.

Consent for participation: The consent to participate is not applicable for this study, as the data are anonymized, proceeding from the electronic health records. This applies for all SIDIAP studies, which are approved by IDIAPJGol Clinical Research Ethics Committee.

Consent to publish: Not applicable.

Availability of data and material, including statistical code: The datasets are available at request to the corresponding author.

Competing interests: The authors declare they do not have conflict of interest.

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Author's contributions: MGS and RM designed the study and elaborated the study protocol. MGS, RM and GSF conducted the operativization of the variables. DO conducted the statistical analyses. All authors participated in the results interpretation. GSF wrote the manuscript. All authors reviewed the manuscript. This article is part of the article compendium for the PhD thesis of GSF.

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Figures

Figure 1

Study flowchart includes the flowchart of patient's inclusion and exclusion for the study. ACS; acute coronary syndrome. AMI; acute myocardial infarction.

Figure 2

Study drugs combinations This figure depicts N and % of patients initiating any possible combination of the drugs used for secondary prevention. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; AntiPL, antiplatelets.

Figure 3

Drugs prescribed per sex. Figure 3 depicts the different drugs prescribed overall, in men and women ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

Supplementary Files

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- [TableS1.Drugs prescribed per sex Supplementary materials.odt](#)