Gender differences in prevention strategies and therapeutic adherence after acute myocardial infarction

GENAMI PREVENTION

Study protocol

Principal Investigator Contact Information

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SUMMARY

Background and objectives. Women with acute myocardial infarction (AMI) are less likely to receive acute treatments according to guidelines recommendations, often present worse short- and long-term outcomes, and are less likely to receive secondary prevention therapies. However, comparisons have been hampered by several differences in the epidemiology, pathophysiology and presentation of AMI between men and women, including age, comorbidities, pathophysiology, and AMI types.

While several studies have been dedicated to understand and reduce the gender gap in acute care, the role of gender on compliance with secondary prevention recommendations (pharmacological and non-pharmacological), and the factors associated with non-compliance in women are largely unknown.

The aims of the study is to compare between a cohort of women who have suffered an AMI and a comparable cohort of men:1) the proportion of 6- and 12-month adherence to the secondary cardiovascular prevention recommendations, 2) the proportion of patients with adequate control of risk factors, 3) the incidence of clinical outcomes, and 4) to study the factors associated with lower adherence (including biological, disease-related, psychosocial, and gender-related).

Design. Prospective, matched cohort study of patients hospitalized for type 1 acute myocardial infarction with significant coronary artery disease. The reference cohort will be composed of 500 women and the comparison group of 500 men with a 1:1 matching for age (±2 years) and ECG (STEMI/NSTEMI), with 1-year follow-up assessing adherence with pharmacological and non-pharmacological secondary prevention recommendations, risk factor control and clinical outcomes.

End-points. Primary end-point: composite outcome of adherence to all secondary CV prevention recommendations 12 months after discharge, including pharmacological therapies, diet, physical activity and participation in cardiac rehabilitation programs. Secondary end-points: adherence to all secondary CV prevention recommendations at 6 months, percentage of patients achieving optimal control of all individual CV risk factors, composite clinical endpoint at 12 months: all-cause death, all-cause rehospitalization, and all-cause emergency department visits, among others.

Statistical analysis. A logistic regression models will be used to evaluate differences in the primary outcome between women and men, as well as in other outcomes. All subjects will be assumed to have a fixed follow-up (12±1 month). Multivariate adjusted models will be used to address any potential confounding in the associations between sex and each of the outcomes. Covariates will be selected based on their pre-defined clinical value and the unbalances observed across groups in the univariate analyses.

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Clinical sites (25)

	C. Autónoma	Hospital	Población
1	Andalucía	Hospital Universitario Virgen Macarena	Sevilla
2	Andalucía	Hospital Universitario Virgen de la Victoria	Málaga
3	Aragón	Hospital Universitario Lozano Blesa	Zaragoza
4	Asturias	Hospital Universitario Central de Asturias	Oviedo
5	Baleares	Hospital Universitari Son Espases	Palma de Mallorca
6	C. La Mancha	Complejo Hospitalario de Toledo	Toledo
7	C. La Mancha	Complejo Hospitalario Universitario de Albacete	Albacete
8	C. León	Hospital Clínico Universitario de Salamanca	Salamanca
9	C. León	Complejo Asistencial Universitario de León	León
10	C. Madrid	Hospital Universitario Fundación Alcorcón	Alcorcón
11	C. Madrid	Hospital Universitario 12 de Octubre	Madrid
12	C. Valenciana	Hospital General Universitario de Alicante	Alicante
13	C. Valenciana	Hospital Clínico Universitario de Valencia	Valencia
14	Canarias	Hospital Universitario de Gran Canaria Dr. Negrín (*)	Las Palmas de Gran Canaria
15	Canarias	Complejo Hospitalario Universitario de Canarias, La Laguna	Tenerife
16	Cantabria	Hospital Universitario Marqués de Valdecilla	Santander
17	Cataluña	Hospital Universitario de Bellvitge	Barcelona
18	Cataluña	Hospital Universitario Vall´d Hebron	Barcelona
19	Extremadura	Hospital San Pedro de Alcántara	Cáceres
20	Galicia	Hospital Álvaro Cunqueiro de Vigo	Vigo
21	Galicia	Hospital Universitario de Santiago de Compostela	Santiago
22	Murcia	Hospital Universitario Virgen de la Arrixaca	Murcia
23	Navarra	Complejo Hospitalario de Navarra	Pamplona
24	País Vasco	Hospital Universitario de Basurto	Bilbao
25	País Vasco	Hospital Universitario de Áraba (sede Txagorritxu)	Vitoria

1. RATIONALE AND BACKGROUND

Coronary artery disease (CAD) is the leading cause of death worldwide, both in women and men,[1] mostly driven by acute coronary syndromes. Actually, CAD kills twice as many women as breast cancer.[2] In recent years there has been a decrease in the fatality rate due to CAD[3] of 31.8% (from 2006 to 2016), standing at 132.3 in men and 67.9 in women, of white race, per 100,000 inhabitants (146.5 and 85.4 for men and women, of African American race, respectively).[4] Part of this phenomenon is due to a decrease in recent years in the incidence of ST-segment elevation acute myocardial infarction (STEMI), a slight increase in the incidence of non-ST-segment elevation acute myocardial infarction (NSTEMI) and a decrease in in-hospital mortality.[5–8] However, these data are controversial, since the annual incidence of hospitalizations for AMI has increased in young people, with the greatest increase observed in young women. Also trends in mortality have changed, with increasing CAD mortality among woman and higher in-hospital mortality in young women (<45 years).[9,10] Women with AMI are undertreated and also have a greater burden of comorbidities.[11,12] Likewise, the number of hospitalizations for AMI, as well as the risk of in-hospital mortality, has been decreasing in recent years (although in-hospital mortality in women has increased slightly).[13] One other factor that explains the decrease in mortality after an AMI is the development and implementation of effective evidence-based therapies, such as coronary revascularization and pharmacological treatments. These treatments are started in the acute hospitalization phase and are continued during follow-up (secondary prevention).[14] These facts should persuade us to conduct further studies, especially in young women, to try to explain these effects.

The role of biology and gender in the pathophysiology and outcomes of AMI

There are notable differences in the susceptibility and pathophysiological mechanisms of AMI between men and women, some biologically-based but others due to environmental factors, among which, gender-specific conditions have gained interest in recent years. Men have a greater predisposition to atherothrombotic (type 1) AMI, usually presenting at younger ages. In contrast, although type 1 is the most common form of presentation in women, they

present more frequently other mechanisms of AMI (i.e. type 2 myocardial infarctions caused by spontaneous coronary artery dissection, or AMI with non-obstructive coronary artery disease —MINOCA—, i.e. coronary vasospasm or microvascular dysfunction, especially in the younger age group).[15]

Most medical treatments that demonstrated clinical benefits in AMI did so mainly in patients with type 1 AMI (antiplatelet drugs, lipid-lowering therapies, beta-blockers…).

Risk factors for atherosclerotic CAD can be classified in four major groups:

- Traditional cardiovascular risk factors. Cardiovascular risk factors are underreported in women who come to the Primary Care consultation.[16,17] This lack of diagnosis prevents specific preventive actions. Another noteworthy aspect is that while in men there has been a decrease in unhealthy lifestyle habits such as smoking, in women, especially in the younger group, it has remained stable or may even have increased.[3,18] Obesity and sedentary lifestyle are more frequent in women. Notably, the impact of metabolic risk factors such as diabetes could confer a higher cardiovascular risk in women than in men.[18]
    - Non-modifiable biological risk factors: age, sex, ethnic background, familiar history of cardiovascular disease.
    - Modifiable risk factors: hypertension, diabetes, dyslipidemia, smoking, obesity.
- Non-traditional risk factors: obstructive sleep apnea syndrome and chronic kidney disease.
- Sex-specific risk factors.[2,19–25] A number of clinical conditions unique to women that have been identified to be associated with increased risk of cardiovascular disease. Reproductive factors include early menarche, early menopause, history of miscarriages, reproductive treatments, polycystic ovary syndrome (which is closely related to metabolic syndrome and insulin resistance), gestational diabetes, number of pregnancies, breastfeeding and lactation duration, hysterectomy, hormone replacement therapy, use of hormonal contraceptives, history of pre-eclampsia, eclampsia, or pregnancy-associated hypertension [2]. Female protection against CVD is associated with sex hormone levels as the incidence and severity of CVD increases in postmenopausal

women[26] and the prevalence of CAD is greater in young women who had an oophorectomy compared to those with intact ovaries.[27] Taken together, this data has sparked much investigation into the potential of female sex hormones in conferring cardioprotection. The mechanisms that explain the association between these factors and the increase in cardiovascular risk are complex, but could be related to greater adiposity in patients who present them (i.e. polycystic ovary syndrome, early menarche), proinflammatory factors or endothelial dysfunction, among others.[23]

- Socio-economic factors: Social support acts as a protective element that reduces the impact of negative life events in people's lives.[28] Therefore, it is considered that poor social support is associated with a 1.5 to 2-fold increase in the risk of CVD, both in healthy people and in those with heart disease.[28] Low socioeconomic status is associated with increased risk of cardiovascular events, including AMI and poorer survival [29,30]. The impact of material deprivation and level of socioeconomic resources is even greater in women than in men.[31] For women, living in a deprived neighborhood may affect coronary health in a greater extent than men, especially in the younger stratum.[32]
- Psycho-social risk factors.[33] Increasing importance is given to factors such as chronic stress, anxiety disorders, depression, personality factors, economic status, sleep disorders, social isolation or childhood trauma. Depression, anxiety, anger and stress (acute, chronic) are factors that increase cardiovascular risk.[34] It is considered that there is a dose-response relationship between depression and cardiovascular events, and therefore a more severe depression also increases cardiovascular risk.[35] Anxiety is related to an increase in cardiac mortality, especially in patients with a more severe cardiovascular disease. The influence of stress on cardiovascular risk depends on the presence of acute triggers, and chronic stress.[36] Acute stress affects cardiovascular physiology, increasing the risk of arrhythmias, myocardial ischemia, and may precipitate an acute myocardial infarction.[37] Chronic stress, however, seems to influence cardiovascular disease through chronic physiological disturbances, and is linked, among others, to work stress, marital

problems, long-term caregiving to people in a situation of dependency, aspects related to the neighborhood or the economic status.[33,38] Work stress under burdensome domestic work has been strongly associated with depression in women and men [39] but there are differences in the levels of work overload reported between genders. Women reported higher levels of work overload, stress and conflict than men, which increased significantly with the number of children at home. The various stress indices reached a peak between the ages of 35 and 39. [40] The role of social, psychological and cultural factors has not been fully studied. Psychosocial factors have a greater impact on the outcomes of women who present with an AMI, especially in the younger age stratum, as they have high rates of poverty, social isolation, history of sexual abuse or childhood trauma and are often from minority groups.[41,42] Depression is present in more than half of women aged <50 years who present with an AMI, and is associated with worse outcomes.[43,44] The role of specific gender issues in the outcome of AMI has been seldom studied.[45,46]

Gender differences in acute myocardial infarction presentation and management

Women with AMI often show longer delays to diagnosis, reperfusion therapy, and a higher risk of complications, such as bleeding, cardiogenic shock or mechanical complications.[47–50] This worse prognosis has traditionally been attributed to their higher risk profile, with older age and more comorbidities.[51]

Women with AMI are less likely to receive timely reperfusion, other acute treatments, secondary prevention therapies or be referred to cardiac rehabilitation.[52,53,54,55,56] There are sex-related disparities still observed today in the care of patients with infarction that disadvantage women and that extend to three key moments: ACS diagnosis, acute treatments (including DAPT at arrival and reperfusion therapy) and secondary prevention treatments (anti -platelets, statins, renin-angiotensin system inhibitors).[57,58] Women are less commonly prescribed cardiac rehabilitation after ACS, and are particularly unlike to participate in cardiac rehabilitation programs.[59,60] As cardiac rehabilitation has

also shown benefit in women after an ACS, an effort is needed to increase utilization among women.

However, most comparisons between women and men with AMI are hampered by the major differences in the epidemiology and pathophysiology of AMI,[13] including the older age of women, their greater comorbidity (particularly, renal disease),[11] increased risk of adverse effects with therapies (i.e. bleeding)[49] and the different proportion of different AMI types (i.e. women presenting more often with type-2 AMI or with non-obstructive coronary artery disease),[15,55,61] which has therapeutic and prognostic implications. These differences need to be accounted for to improve the accuracy of comparisons and define more clearly the role of sex and gender on the management and outcomes of AMI.[46]

Gender and determinants of adherence to evidence-based therapies after AMI

Age, gender, the presence of comorbidities and polypharmacy are factors that predict adherence to secondary prevention therapies [62]. Women with AMI have been found to have differences in adherence compared with men, with lower adherence to $P2Y_{12}$ inhibitors (i.e. clopidogrel) [63] or a 10% greater probability of non-adherence to statins.[64] In a study with 148,654 patients with AMI, who had received secondary prevention measures in accordance with the clinical guidelines (loading dose of antiplatelets and chronic doses of aspirin, beta-blockers and ACE inhibitors in patients with AMI and reduced left ventricular ejection fraction, lipid-lowering drugs and medical advice smoking cessation) female gender was associated with poorer adherence on all measures [65]. However, a recent meta-analysis showed a lower adherence to lipid-lowering drugs (OR = 0.87, 95% CI 0.82-0.92) with no differences in the other three major pharmacological groups of secondary prevention (ACE inhibitors/ARA-II, beta-blockers and antiplatelets) in women post-MI,[66] but the role of the differences in age and comorbidities in these results is unknown. Regarding the adherence to non-pharmacological secondary prevention measures, registries and observational studies have observed that men are less likely to achieve blood pressure goals than women.[67] The results of the EUROASPIRE V survey also reveal that women change their healthy food habits in compliance with the recommendations, more frequently than men do.[68]

With the increasing awareness of sex disparities in cardiac care in the last years, it is possible that the sex-related differences in the prescription of secondary prevention therapies have improved. However, in the last two years, due to the COVID-19 pandemic, social disparities have increased and this may have had an unfavorable impact on women's health, increasing the gender gap. The reasons for these differences are not well known and should be explored in order to develop interventions to improve effective secondary prevention strategies tailored for women, and their outcomes.

2. HIPOTHESIS

We have the following three alternative hypotheses.
Compared with men:

- the adherence to secondary prevention strategies after AMI is lower in women, regardless of their baseline differences.
- the control of CV risk factors after AMI is poorer in women.
- The incidence of clinical outcomes and/or use of healthcare resources after AMI is higher in women.

The null hypothesis for each of the previous statements is that there is no difference between men and women for each of the outcomes. The main rationale for our alternative hypotheses is based on gender-related factors rather than on biological differences.

In addition, we hypothesize that there are gender-related factors associated with (non-) adherence to secondary prevention recommendations in women.

3. OBJECTIVES

General objective. To evaluate if there are differences in the level of adherence to recommended secondary prevention therapies (pharmacological and non-pharmacological) between women and men surviving a type 1 AMI (with obstructive CAD), its potential consequences, and the potential factors related to that difference, if present.

Specific objectives. To compare between women and men:

1) The adherence to recommended secondary prevention therapies at 6 months and 12 months measured as the
    1a. Proportion of patients adherent to all recommended pharmacological secondary prevention therapies at 6 and 12 months
    1b. Proportion of patients adherent to all recommended non-pharmacological secondary prevention therapies at 6 and 12 months
2) The relationship of the adherence with control of risk factors, clinical outcomes, and use of healthcare resources
    2a. The proportion of patients with optimal control of all cardiovascular risk factors at 6 and 12 months
    2b. The incidence of clinical outcomes at 6 and 12 months
    2c. The cumulative use of healthcare resources and cost after discharge

3) To assess the factors associated with non-adherence to recommended secondary prevention therapies, with special emphasis to socioeconomic factors and gender issues.

4. STUDY DESIGN AND RESEARCH PLAN

4.1. DESIGN.

Prospective, matched cohort study of patients hospitalized for a type 1 AMI with evidence of obstructive coronary artery disease who are discharged home alive. **Women** will be enrolled first, ideally in a consecutive manner, as they are the focus of the study. **Men** will be recruited subsequently as the comparison group, with 1:1 matching for age and ECG presentation. Matching will be performed locally, in each study site (hospital). All patients will undergo 1-year follow-up with clinical and therapeutic adherence evaluation.

Reference cohort: 500 women discharged alive after a hospitalization for a type 1 AMI with significant CAD
Comparator cohort: 500 age (±2 years) and ECG (STEMI/NSTEMI) locally matched men discharged alive after a hospitalization for a type 1 AMI with significant CAD

4.2. RECRUITMENT.

Participant centers

25 hospitals managing routinely AMIs and representing different regions from Spain will be invited to participate

Patient recruitment

All consecutive women fulfilling all inclusion criteria and without exclusion criteria surviving the index hospitalization will be invited to participate. Subsequently, men with inclusion criteria and without exclusion criteria, matched for age and ECG presentation, will be recruited.

Inclusion criteria

- Hospitalization for a type 1 AMI[69] (detection of a rise and/or fall of cTn value above the 99th percentile URL and with at least one of the followings: symptoms of acute myocardial ischemia; new ischaemic ECG changes; development of phathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion

abnormality in a patterns consistent with an ischaemic aetiology; identification of a coronary thrombus by angiography including intracoronary imaging)

- Presence of obstructive coronary artery disease (CAD)[70] (i.e. coronary artery stenosis ≥50%)
- Age >18 years. No maximal age limit applies
- Signed informed consent

Exclusion criteria

- Terminal disease (expected survival <12 months)
- Unavailable for 12-month follow-up (i.e.: living abroad, social situation…)
- Does not speak Spanish
- Major active comorbidity (severe renal or liver failure, active cancer requiring chemotherapy…), interfering with regular post-MI management

5. INITIAL EVALUATION

5.1. BASELINE CHARACTERISTICS

5.1.1. Biological factors

- Anthropological: age, sex, weight, height and body mass index.
- Sex-specific factors of women's cardiovascular risk: menarche age, number of pregnancies, gestational diabetes, early menopause, polycystic ovary syndrome, presence and number of miscarriages, use of hormonal replacement therapy (yes/no, duration), fertility treatments, use of hormonal contraceptives, history of eclampsia or pre-eclampsia, history of breast or endometrial cancer.
- Vital signs: blood pressure (SBP, DBP) and heart rate.
- Risk factors: hypertension, diabetes, hyperlipidemia, LDL, HDL, total cholesterol, triglycerides, lipoprotein(a), uric acid, tobacco and alcohol consumption, chronic alcoholism, HbA1c level, waist circumference, familiar history of premature coronary artery disease or familiar hypercholesterolemia. Pattern of food consumption and practice of physical activity (this will be measured using

questionnaire MEDAS and IPAQ which will be described in the followings sections).

- Comorbidities: prior coronary artery disease (acute or chronic coronary syndrome), prior percutaneous coronary intervention, prior CABG, prior cerebrovascular disease (transient ischemic attack, ischemic stroke), peripheral vascular disease, heart failure, chronic kidney disease, COPD, Obstructive sleep apnea/hypopnea syndrome (OSAHS), atrial fibrillation, autoimmune disorders, anemia, depression (diagnosis of major depressive disorder), anxiety (diagnosis of generalized anxiety disorder) and Charlson Comorbidity Index (CCI).[15]

5.1.2. Disease related factors

AMI features:

- Type of MI (STEMI/NSTEMI)
- Number of diseased vessels
- BARI segment responsible of AMI
- Left ventricular ejection fraction at discharge (LVEF) before discharge (typically by echocardiography)
- Killip class (on admission, “maximal”)
- In-hospital complications (heart failure, bleeding, arrhythmias, cardiogenic shock).

In-hospital management:

- Reperfusion rates and times (for STEMI)
- Patients receiving coronary angiography (for non-STEMI) and time since diagnosis to coronary angiography
- Type of coronary revascularization
- Coronary revascularization rates and completeness
- Admission to the coronary unit
- Length of hospital stay

5.1.3. Socioeconomic factors

- Social factors: ethnic group, educational level, marital status/living arrangements, role of primary caregiver and overload, country of birth, zip code.

- Economic factors: income category, employment status, type of contract (part-time or full-time), work conciliation.
- Quality of life (SF-12[16]), Spanish version.[71]

5.1.4. Psychological factors

- Anxiety and Depression (HADS [72]), Spanish version.[73]

5.1.5. Gender issues

- Domestic and care workloads and intensity, frequency and duration of care: time of care and domestic work and intensity, frequency and duration of care, as well as the distribution of care (CUIDAR-SE Questionnaire).
- Zarit Caregiver Burden Interview,[74] Spanish version[75]

5.2. SECONDARY PREVENTION RECOMMENDATIONS

5.2.1. PHARMACOLOGICAL TREATMENTS

- Secondary prevention strategies and medications (drugs)
  - Antiplatelets: Aspirin and $P2Y_{12}$ inhibitors (including type)
  - Lipid-lowering therapies (statins, ezetimibe, PCSK9)
  - RAASi
  - Betablockers
  - Glucose control medications [SGLT2 inhibitors, GLP-1 agonists…]
- Prescription pattern: Total number of daily intakes, dose of each medication, total number of medications, use of injectable drugs, past difficulties regarding type of therapy.

5.2.2. Referral To Cardiac Rehabilitation/Secondary Prevention Program

- Prescription pattern: Recommendation and scheduling to attend and participate in a structured program of cardiac rehabilitation/secondary prevention education
- Adherence to the cardiac rehabilitation program
  - Number of attended sessions divided by the number of sessions prescribed.
  - ¿Achieve goals of target heart rate? TBD

5.2.3. Diet Recommendations

Current cardiovascular prevention guidelines recommend adopting a diet based on farm products and reducing foods of animal origin, together with the following recommendations:[76]

- The consumption of saturated fats should not exceed 10% of total daily energy intake. Likewise, it is recommended to replace these with fats that contain polyunsaturated and monounsaturated fatty acids.
- Replace carbohydrates in the diet with whole grain products (with whole grain cereals).
- Trans fats should be minimized as much as possible, especially those from processed foods, whose consumption is totally discouraged.
- Reduce salt intake to <5 g per day.
- Consume 30-45 g of fiber per day, preferably from whole grain cereals.
- The intake of more than 200 grams of fruit per day (2 or 3 meals per day) is recommended.
- Eat more than 200 grams of vegetables a day (2 or 3 meals a day).
- Reduce the consumption of red meat to a total of 150-500 grams per week, especially processed meats.
- The consumption of fish is recommended 1 or 2 times a week, particularly the consumption of fish with essential fatty acids.
- Consume 30 grams of unsalted nuts per day.
- Reduce alcohol consumption to a maximum of 100 grams per week.
- The consumption of sugary drinks such as soft drinks or fruit juices is discouraged.

5.2.4. Physical Activity Recommendations

- Prescription pattern: current cardiovascular prevention guidelines recommend performing moderate-intensity physical activity for 30 minutes a day 5 or 7 days a week (a total of 150-300 minutes a

week) or performing 75 minutes of vigorous activity 1 or 2 days a week (a total of 75-150 minutes a week) for cardiovascular risk reduction [76].

5.3. OUTCOMES

All outcomes will be compared between men and women.

OUTCOME DEFINITIONS

5.3.1. Co-Primary outcomes

- **Pharmacological primary endpoint**: outcome of adherence to pharmacological therapies (MMAS-8) 12 months after discharge.
- **Non-pharmacological primary endpoint**: Composite outcome of adherence to non-pharmacological secondary CV prevention recommendations 12 months after discharge, including diet, physical activity and participation in cardiac rehabilitation programs.

Adherence will be defined as compliance with at least 80% of each of the CV prevention recommendations separately: medications, cardiac rehabilitation program, diet and physical activity. This outcome is defined as an all-or-nothing endpoint with a binary response. These outcomes are defined as an all-or-none endpoint with a binary response.

5.3.2. Secondary outcomes.

- **Pharmacological primary endpoint**: outcome of adherence to pharmacological therapies (MMAS-8) 6 months after discharge.
- **Non-pharmacological primary endpoint**: Composite outcome of adherence to non-pharmacological secondary CV prevention recommendations 6 months after discharge, including diet, physical activity and participation in cardiac rehabilitation programs.

5.3.3. Pre-defined exploratory outcomes

- Composite outcome of adherence to all secondary CV prevention recommendations 6 months after discharge (all-or-none composite outcome with a binary response)

- Percentage of patients achieving optimal (guidelines-recommended) control of all individual CV risk factors (LDL-cholesterol levels, blood pressure levels, HbA1c levels, smoking, levels of physical activity/sedentary life)
- 12-month incidence of the composite clinical endpoint: All-cause death, all-cause rehospitalization, and all-cause emergency department visits
- Use of healthcare resources at 12 months, including: days hospitalized (re-hospitalizations), number of ED visits, number of cardiac rehabilitation sessions, number of outpatient specialist visits, and number of urgent PCI procedures).
- Assessment of the main predictors of adherence with secondary prevention recommendations in women (biological, disease-related, pharmacological, socio-economic, psychological, gender)
- Composite outcome of adherence to all secondary pharmacological CV prevention recommendations 12 months after discharge, using pharmacy dispensation records.
- In addition, data on changes in dose or drug will be collected to analyze their influence on adherence.
- Evaluation of each individual components of the composite of adherence to secondary CV prevention recommendations 6 and 12 months after discharge (these recommendations will be given to all patients at discharge):
    - Pharmacological therapies
    - Diet
    - Physical activity and
    - Participation in cardiac rehabilitation programs
- Percentage of patients achieving optimal (guidelines-recommended) control of all individual CV risk factors:
    - LDL-cholesterol levels
    - Blood pressure levels
    - HbA1c levels
    - BMI
    - Smoking

- Levels of physical activity/sedentary life
- Diet

- Composite endpoint of cardiovascular death, rehospitalization, and emergency department visits for cardiovascular causes, and urgent coronary revascularization.
- Effect of delays on return to work on adherence to cardiac rehabilitation and other secondary prevention measures.

OUTCOME METRICS

- **Primary endpoint:** Composite outcome of adherence to all secondary CV prevention recommendations at 12 months after discharge. The composite is built as an all-or-nothing response to an adherence ≥80% in all prescribed components of the endpoint: pharmacological therapies (MMAS-8), diet, physical activity and participation in a cardiac rehabilitation program. Adherence will be defined as having at least 80% compliance with all CV prevention recommendations; drugs, cardiac rehabilitation program, diet and physical activity)
- Measurement of adherence to secondary prevention recommendations: At least 80% of adherence for the following prescribed recommendations at 6 and 12 months:
  - Diet recommendations
  - Physical activity recommendations
  - Drug prescriptions:
    - Aspirin for all without contraindications
    - $P2Y_{12}$ inhibitors for all, according to the time indicated at discharge (if none, use 12 months)
    - Statins / other lipid-lowering therapies for all
    - Any of the following if indicated:
      - Beta blockers (if LVEF <0.40 or HF)
      - Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (if LVEF <0.40 or HF)
      - Glucose control medications (SGLT2 inhibitors/GLP-1 agonists)

1. Measurement of adherence to pharmacological recommendations:

a) The Morinsky Medication Adherence Scale (MMAS-8).[77] A total score of all items will be calculated with a sum score ranging from 0 to 8 for adherence. MMAS-8 Score will be calculated if the respondent answers at least 6 of 8 items. MMAS is trichomized in three levels of adherence:
   - High adherence (score 8)
   - Medium adherence (score, 6 to 7)
   - Low adherence (score, <6)

b) Records of dispensations in the pharmacy: This is an indirect method to measure compliance based on evaluating the collection of the medication in the pharmacy. Patients who withdrew all medications during the year will be considered adherent. The information will be checked from the medical history that records the withdrawal of drugs from the pharmacy. This will be done for each of the secondary prevention medications to calculate adherence to each of them (aspirin, $P2Y_{12}$ inhibitors, statins, and beta blockers or ACE inhibitors).

2. Measurement of adherence to non-pharmacological recommendations:

c) Adherence to diet: to evaluate this measure, the 14-point Mediterranean Diet Adherence Screener (MEDAS) questionnaire of Schröder et al, (2011) will be used [78]. It is a 14-item questionnaire derived from the PREDIMED study (Primary Prevention Mediterranean Diet). Each item is assessed with a binary score (0 or 1) according to the diet pattern, referring to daily or weekly consumption, during the last 3 months. The score ranges between 0 and 14 points, establishing two levels of adherence:
   - Score <9: Poor adherence to the Mediterranean Diet, which requires an improvement in eating habits.
   - Score ≥9: Good adherence to the Mediterranean Diet

d) Adherence to physical activity: it will be used the International Physical Activity Questionnaire (IPAQ) (Craig, 2003) [79]. It consists of 5 questions about the frequency, duration and intensity (vigorous or moderate) of physical activity, carried out in the last week (last 7 days). It also collects the frequency and duration of the walking activity and the time that the person remains seated on a weekday. The IPAQ allows individuals to be assigned to three categories (low, medium, high)

according to the estimated energy expenditure for each activity: vigorous, 8 MET (metabolic equivalent task); moderate, 4 METs; and walking, 3.3 METs. According to the IPAQ categories, individuals who belong to the high or medium category are compliant, and those who belong to the low category are non-compliant. In addition to the classification by METs, there is the possibility of classifying individuals based on the duration, frequency and intensity of physical activity, without the need to calculate METs. These criteria included in the official guidelines published by the IPAQ Research Consortium are the following:

- Low – No activity reported or some activity reported, but not enough to meet Category 2 or 3.
- Moderate: any of the following 3 criteria
  - 3 or more days of vigorous activity of at least 20 minutes per day
  - 5 or more days of moderate-intensity activity and/or walking for at least 30 minutes per day
  - 5 or more days of any combination of moderate-intensity or vigorous-intensity walking activities, achieving a minimum of at least 600 METs/min per week.
- High: either of the following 2 criteria
  - Vigorous intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week
  - 7 or more days of any combination of walking, moderate or vigorous intensity activities that accumulate at least 3000 MET-minutes/week

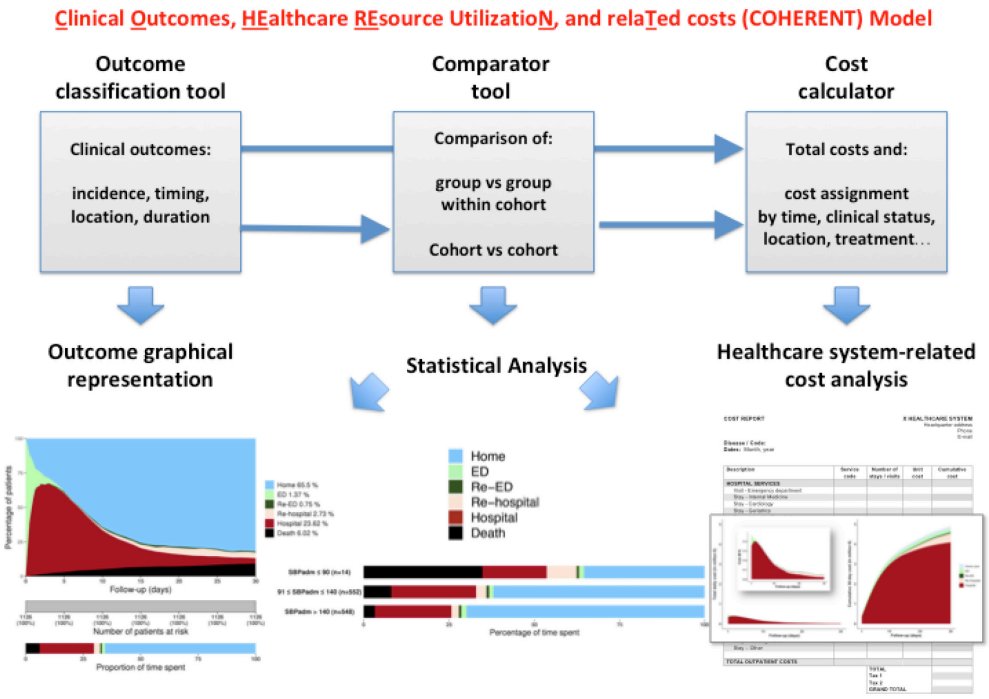
e) Cardiac rehabilitation: Attendance to all cardiac rehabilitation sessions will be collected and those who have completed at least 80% of scheduled sessions will be considered adherent. To explore its influence on cardiac rehabilitation attendance, time from discharge to return to work will be collected as an outcome.

f) Measurement of clinical endpoints:

- Major adverse cardiovascular events at 6 and 12 months, including the combined endpoint of cardiovascular mortality, nonfatal AMI, nonfatal ischemic stroke
- Cardiovascular mortality
- Hospitalizations due to cardiovascular reasons
- Emergency department visits due to cardiac causes
- Urgent revascularization
- Acute myocardial infarction

g) The independent predictors of adherence with secondary prevention recommendations in women will be estimated with adequate statistical analyses (e.g., logistic regression models)

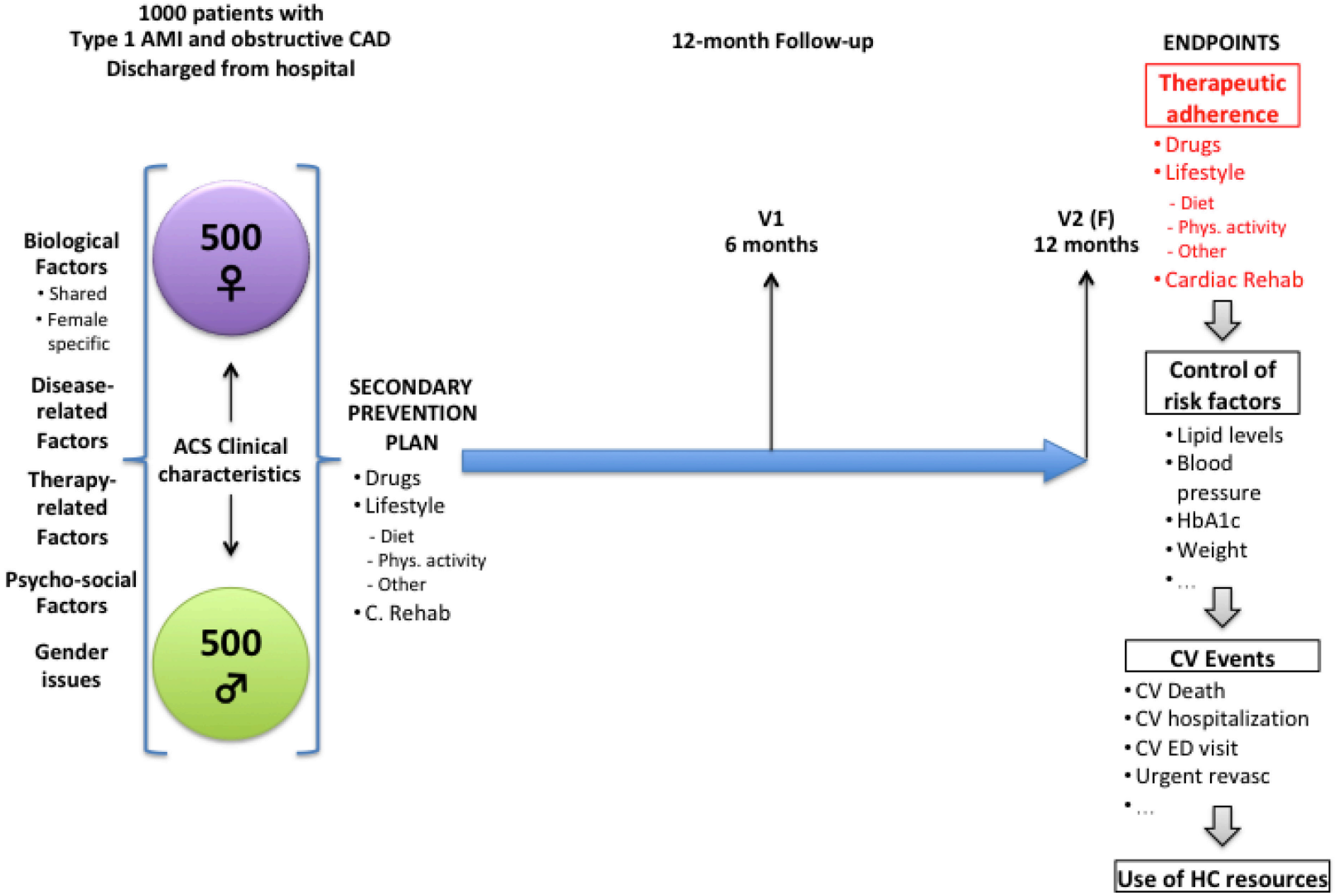
h) The use of healthcare resources will be analyzed using the COHERENT model [80].



5.4. TIMELINE

Number of Sites:	25
Site Names:	Cardiology Departments from Spanish hospitals
Study Start Date:	September-2022
Study End Date:	December-2024
Number of Subjects:	1000 (500 cases and 500 controls)
First Patient In Date:	September-2022
Last Patient Out Date:	June-2024
Enrollment Period	6 months

Figure 1. Study design and flowchart



6. STATISTICAL ANALYSIS

A minimum sample size of 820 participants (410 per group) was estimated for an expected relative difference in recommendations compliance of the all-or-none composite primary outcome of 20%. An α error of 0.05 and a β error of 0.20 were considered for the sample size. The recommendations compliance was estimated as 42% for women and 52% for men. With the consideration of 20% of lost to follow-up (discontinuations) the total sample size is 984 patients, which is rounded out to 1000 patients (500 women and 500 men). To increase regional representation and allow exploration of potential regional variability, 25 hospitals from all regions in Spain (17 Autonomous Communities) will be invited to participate.

For the description of continuous variables, mean and SD, or median and interquartile range will be used for Gaussian and non-normal distributions, respectively. For describing categorical variables, frequencies and percentages per category will be used. Categorical variables will be compared using the chi2 test, whilst continuous variables will be compared using the student *t* test.

Logistic regression models will be used to evaluate differences in binary outcomes between women and men (in hospital AMI management, post discharge MI management). All subjects will be assumed to have a fixed follow-up (12±1 month). Multivariate adjusted models will be used to address any potential confounding in the associations between sex and each of the outcomes. Covariates will be selected based on their pre-defined clinical value and the unbalances observed across groups in the univariate analyses. Linear, multinomial or ordinal regression models would be used in case of continuous, categorical, or ordinal outcomes, respectively.

In addition to the models evaluating the association between sex and outcomes, a predictive model will be conducted to set predictors for the following outcomes:

1) a composite of all preventive therapies (all-or-nothing for diet, physical activity, $P2Y_{12}$ inhibitors, statins, and beta blockers or ACE inhibitors [if prescribed at discharge]), and

2) each group of preventive interventions (drugs, cardiac rehab, diet, physical activity)

Candidate predictors are classified as biological factors (age, sex, risk factors, comorbidities), disease-related (type of MI: STEMI/NSTEMI, LVEF, number of vessels…), pharmacological factors (daily number of drugs, daily number of doses, specific drugs), socio-economic factors (zip code, education level, employment status, wages…) and specific gender issues (family responsibilities, work conciliation…). Special consideration will be given to age due to the high figures of in-hospital mortality in young women.

For women-specific analysis, female specific factors (menarche age, pregnancies, gestational diabetes, menopause…) will be considered.

We will use the *Clinical Outcomes, HEalthcare REsource UtilizatioN, and relaTed costs* (COHERENT) model to study the hospital-related healthcare resources (ED visits, specialist visits, re-hospitalizations and urgent procedures) and costs.

7. DATA MANAGEMENT PLAN PROPOSAL

According to the Ethics Principles, only patients for whom a signed informed consent is obtained will be enrolled in the study. The research project is scientifically justified and described in a detailed protocol which will be presented to and approved first by the imas12 Research Commission and Research Ethics Committee and secondly by the Research Committees of all centers. Patient data will be recorded according to common practice. A "Patient Identification Log", including personal data and the patient ID codes will be generated and securely saved in the investigators file under strict physical, digital and personal security measures, guarded by the team researchers and never shared.

Data will be generated as per protocol. Variables will be collected manually by project researchers or automatically by the electronic systems or equipment. Data files generated will be labelled appropriately and placed in suitably labelled/organised folders and sub-folders, with questionnaires, permissions, informed consents, protocol and study versions properly identified to facilitate easy finding, process automation and analysis, and reduce errors. Qualitative and quantitative data will be generated. Raw data will be analyzed and presented as tables, graphs and images in presentations and publications. The format and scale of the datasets will depend on data composition and magnitude. These will be accessible using common software facilitating access, data sharing, and long-term validity during and after the project. The research results will comply with the FAIR (Findable, Accessible, Interoperable and Reusable) principles and published in scientific journals in open access mode.

Standard protocols will be defined, optimized and implemented to obtain data in a reliable and consistent manner. The services of a CRO will be contracted to assess data consistency though a Data Monitoring plan with individual random evaluation of the patients included in this study and overall analysis of the project's key variables. In addition, the Informed Consents will be reviewed to ensure adequate compliance with current regulations on GCP in research. The project staff will be adequately trained in the protocol requirements by the CRO staff to ensure high quality results. Data generated and methods used will be scrutinized to ensure that procedures have been carried out correctly,

appropriate controls used, and all information is suitably recorded to have accurate and reliable data. These routine procedures for high quality research will facilitate positive evaluation by peer reviewers in scientific contexts and high-impact publishers.

Electronic data records will be generated, saved in one server with automated daily backups. File names/locations will be recorded in screening logs to allow electronic records to be linked to raw data. File names will have appropriately descriptive titles, including date of data generation to allow easy finding. Details of all data collected from patients will be recorded in REDCap, located in one server of the imas12 Research Institute. Additionally, regular electronic progress reports summarising the key information will be compiled by project staff. Electronic and written records will be retained for at least 10 years after the end of the project.

Access to pre-publication electronic data will be limited to the members of the research group and relevant collaborators via limited access to shared drives on the imas12 Research Institute server. Access to servers are controlled by imas12 IT staff to reduce the likelihood of malicious loss/damage. All computers used in this project will run Standard Staff Desktop with firewalls and antivirus software automatically upgraded and secure remote access to data enabled. The study team's exclusive use of the data will be made available at the time of publication, at the latest. Depending on the nature of the data, this may be made available earlier, either to interested researchers or potential new collaborators on an individual basis after prior request and review or publicly whenever needed (negative data). When research data or resources are shared with external users ahead of publication, specific written agreements will be signed by all parts to avoid misuse or external result communication/publication without the PI review and written approval of content and conditions (i.e. authorship).

All people involved in the research project will have knowledge and accreditation of international standards of Good Clinical Practice (GCP) to guarantee the safety, rights and well-being of the participants and the quality and validity of research data. All collected and stored study data will be pseudoanimized, with only a limited part of the research team will have

restricted access to the linking participants identity, in accordance with the provisions of the Organic Law 3/2018 (Dec 5, 2018), Data Protection Personal Data and Guarantee of Digital Rights, Law 14/2007 (July 3, 2007), and Biomedical Research Law 41/2002, (November 14, 2002), basic regulator of patient´s autonomy of rights and obligations regarding information and clinical documentation.

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