Universitat Autònoma de Barcelona

Impact of medication adherence on mortality and cardiovascular morbidity: a population-based cohort study IMPACT study

Gerard Sotorra Figuerola

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IMPACT study.

PhD candidate: Gerard Sotorra Figuerola

PhD director: Dr. Maria Giner Soriano

Autonomous University of Barcelona

Department of Pharmacology, Therapeutics and Toxicology

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Signatures:

PhD director: Dr. Maria Giner Soriano

PhD tutor: Dr. Rosa María Antonijoan Arbós

PhD candidate: Gerard Sotorra Figuerola

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ABSTRACT

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, such as coronary heart disease (CHD). CHD is manifested as acute coronary syndrome (ACS), which includes several clinical entities: ST-segment elevation myocardial infarction (STEMI), non-STEMI and unstable angina. In 2016, CVD was the leading cause of mortality worldwide and it is estimated that 28% of deaths in Spain are due to CVD.

CHD management takes place in Primary Healthcare settings and it is based on population-level lifestyle changes in diet, smoking and physical activity, and effective drugs, such as antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ACEI/ARBs). Adherence to these drugs plays an essential role in secondary prevention after ACS. Despite the high evidence of pharmacological secondary prevention, several works have shown poor medication adherence.

This thesis is part of the IMPACT study, which is a population-based observational cohort study conducted with data from electronic health records from Primary Healthcare in Catalonia (Spain). This is an article-based thesis with two manuscripts related to the results of the IMPACT study.

The study population includes all individuals older than 18 with a first episode of ACS (acute myocardial infarction or unstable angina) registered in SIDIAP (Information System for Research in Primary Care) from 2009 to 2016 with at least 2 months of follow-up after the index date. The main objective is to assess the relationship between adherence to the recommended drugs (antiplatelet agents, beta-blockers, ACEI/ARBs and statins) for secondary prevention and

the clinical outcomes of cardiovascular (CV) morbidity and all-cause mortality (analysed as a composite endpoint) in patients with established CHD.

In paper 1 we describe baseline clinical characteristics and gender differences in the prescription of long-term pharmacological secondary prevention drugs. We found that women were older, had more comorbidities at baseline and received more comedication after ACS than men. We also found a strong relation in the medication prescribed between being women and older in our population. Most patients were treated with a combination of 4 or 3 recommended drugs.

In paper 2 we assess the association between the composite endpoint (major CV events [MACE] and all-cause mortality) risk and adherence to study drugs for secondary prevention by pharmacological groups and number of drugs prescribed. Overall, our results show that adherence to any recommended drug combination led to a significant reduction of the composite endpoint risk compared to nonadherence, regardless of the number of drugs prescribed. Adherence to 4 or 3 drugs prescribed was associated with a lower risk of the composite endpoint than adherence to 2 or 1 drug. Medication adherence to secondary prevention in our population was high.

The most important strengths of our study are the large number of patients included, the representativeness for the general population, complete clinical characteristics and socio-demographic data, long follow-up periods and real-world data. To our knowledge, this is the first population-based study in our setting conducted with SIDIAP (Information System for Research in Primary Care) database, which analyses prescribed drugs and medication adherence, and its association between with the risk of MACE and all-cause mortality. The

study provides high value knowledge about CVD in Catalonia, as SIDIAP captures information from approximately 5.8 million inhabitants in southern Europe.

Studies conducted with electronic health records have some limitations inherent to electronic databases, such as incompleteness, loss of follow-up, potential confounders, non-randomised data and possible selection biases, which affect all population records and may be minimised using adequate statistical methods.

Keywords

Acute coronary syndrome; medication adherence; platelet aggregation inhibitors; angiotensin-converting enzyme inhibitor; angiotensin receptor antagonist; adrenergic beta-antagonist; coronary disease; electronic health records; pharmacological secondary prevention; primary health care.

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1. LIST OF ABBREVATIONS AND ACRONYMS

Abbreviation	Full Terminology
ACE	Angiotensin converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AMI	Acute myocardial infraction
ARB	Angiotensin-receptor blockers
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidential interval
COX-1	Cyclooxygenase 1
CV	Cardiovascular
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
GPIIb/IIIa	Glycoprotein IIb/IIIa
HF	Heart failure
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HR	Hazard ratio
ICS	Catalan health institute

JMIR	Journal of Medical Internet Research
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MACE	Major cardiovascular event
MPR	Medication possession ratio
MRA	Mineralocorticoid receptor antagonist
OR	Odd ratio
PCI	Percutaneous coronary intervention
PDC	Proportion of days covered
PGH2	Prostaglandin H2
PGI2	Prostaglandin I2
PHC	Primary health care
RAAS	Renin-angiotensin-aldosterone system
SIDIAP	Information system for research in primary care
STEMI	ST-segment elevation myocardial infarction
TXA2	Thromboxane A2

2. INTRODUCTION

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, such as coronary heart disease (CHD), cerebrovascular disease and peripheral artery disease. CVD is the leading threat to global health, whether measured by mortality, morbidity or economic cost.(1,2) CHD is manifested as acute coronary syndrome (ACS), which includes several clinical entities: ST-segment elevation myocardial infarction (STEMI), non-STEMI and unstable angina.(3,4)

In 2016, CVD was the leading cause of mortality worldwide, accounting for 31% of deaths for all causes and being responsible for the largest proportion of deaths for non-communicable diseases.(5) In Spain, it is estimated that 28% of deaths are due to CVD, closely followed by cancer disease.(6) Despite this figure, the incidence of CVD death has decreased over the last decades, due to both population-level lifestyle changes in diet, smoking and physical activity, and due to the development of effective interventions to treat individuals, such as effective drugs to tackle modifiable cardiovascular (CV) risk factors.(7)

However, despite advances in prevention measures, CVD continues to be the leading cause of disability and health care expenditure. The annual rates have been stable in the last years, and progress has been made in the treatment of ACS. The impact of prevention measures is compensated by an increase in obesity and diabetes mellitus, population aging and the appearance of other comorbidities, such as renal failure.(8)

It is estimated that ACS cases will increase in Spain in the coming decades and the most significant cause will be the increase of the elderly population that will account for up to 60% of all ACS by 2049.(9)

2.1. Cardiovascular risk factors

CHD eventually results in coronary thrombosis, leading to ACS or even cardiac death. These events occur when an atherosclerotic plaque ruptures or is eroded, resulting in partial or total occlusion of the coronary tree.(10)

Although clinical practice guidelines briefly address the nonpharmacological secondary prevention measures for patients' management with CHD, arteriopathy can be prevented with changes in lifestyle and diet. These lifestyle and diet recommendations are based on dyslipidaemia management and CVD prevention.(8,11–14)

2.1.1. Diet

Some aspects of a Mediterranean-style diet are already included in clinical practice guidelines to promote healthy eating and prevent CVD since the risk of ACS in Mediterranean countries is lower than in non-Mediterranean countries in Europe. The traditional Mediterranean diet is recommended worldwide due to a cardioprotective effect and improved plasma lipid profile, and is highly effective for CV prevention.(15,16)

A large meta-analysis of randomised clinical trials in healthy adults and high CV risk adults assessed the effectiveness of a Mediterranean-style diet for the primary and secondary CVD prevention. The author concluded that despite the

large number of trials, the beneficial effects of a Mediterranean-style diet are still uncertain for both primary and secondary prevention. Nevertheless, the meta-analysis adds positive findings of several mechanisms to explain the beneficial effect of Mediterranean diet based on observational evidence.(16)

Clinical practice guidelines agree that a healthy diet reduces the risk of CVD. A diet like Mediterranean diet is recommended in these guidelines. Also, it is well known that overweight and obesity (body mass index ≥ 25 kg/m^2) are associated with higher all-cause mortality risk compared with a healthy weight. The diet recommended in clinical practice guidelines for CV prevention includes low saturated fat intake and replacing omega-3 polyunsaturated fatty acids, five portions of vegetables or fruit a day, limited alcohol consumption and fish one or two times per week. The Mediterranean diet supplemented with extra virgin olive oil or nuts reduces the incidence of serious CV events in patients at high risk of events, but without previous CVD.(15,17)

2.1.2. Smoking

Smoking promotes atherosclerosis and potentiates atherosclerotic plaque instability, because it has a considerable prothrombotic, prooxidative and proinflammatory effects. Some studies have shown a mortality benefit associated with smoking cessation, and patients with ACS who are smokers have double probability of recurrent ischemic events than non-smokers.(8,18) Smoking cessation is the most effective of all secondary prevention measures.(15)

2.1.3. Hypertension

Hypertension is a risk factor in patients with STEMI and non-STEMI and it should be kept under control. Two main strategies to control blood pressure (BP) are needed in these patients: lifestyle changes and pharmacotherapy.(19)

Clinical practice guidelines of hypertension management recommend a target BP <140/90 mmHg, regardless of the number of comorbidities and level of CV risk for almost all situations, except for example with advanced age or in patients with diabetes mellitus.(19,20) In elderly patients with a high risk level, a target of <120 mmHg may be considered.(15)

The lifestyle measures to reduce BP recommended are salt restriction, moderation of alcohol consumption, increased consumption of vegetables and fruits, weight reduction and maintaining an ideal body weight, regular physical activity and smoking cessation.(19,20)

Regarding the pharmacotherapy approach, there are five pharmacological groups recommended by clinical practice guidelines: diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB). They can be used for treatment initiation or maintenance, alone or in multiple combinations. Beta-blockers should be used in patients with a prior ACS.(19,20)

2.1.4. Dyslipidaemias

The prevalence of dyslipidaemia in Spain is around 30-40%, and is one of the most prevalent CV risk factors.(21) It is estimated that the prevalence of hypercholesterolemia in patients admitted for ACS is around 40-50%.(22,23)

Clinical practice guidelines for the management of dyslipidaemias focus on the importance of low-density lipoprotein (LDL)-cholesterol reduction to prevent CVD. The target approach to lipid management is aimed at reducing LDL-cholesterol depending on the CV risk: at a very high risk, the goal is <70 mg/dL, for high risk it is <100 mg/dL and for moderate risk it is <115mg/dL.(23–25)

Statins are recommended in all patients with acute myocardial infraction (AMI), regardless of cholesterol concentrations. The benefit of statins in secondary prevention has been unequivocally demonstrated and a high-intensity lipid-lowering treatment should be started as early as possible in all patients. Treatment with ezetimibe should be considered in patients with an intolerance to statins.(15)

All patients with established CVD should be treated during hospital admission with high-dose statins, regardless of their LDL-cholesterol values. The drug of choice is atorvastatin 40-80 mg.(8,23,26)

2.2. Pharmacological secondary prevention

Clinical practice guidelines recommend long-term therapy for ACS secondary prevention. This pharmacological therapy consists of a combination of aspirin, statins and beta-blockers, and an ACEI/ARB should also be added in all patients after ACS, unless contraindicated. Routine treatment with nitrates, calcium antagonists or mineralocorticoid receptor antagonists (MRA) is not indicated.(15,27–29) Several randomised clinical trials, meta-analyses and observational cohort studies have demonstrated improvements in survival with

this long-term therapy in high-risk patients, particularly those with established CVD.(1,30,31)

2.2.1. Antiplatelet therapy

2.2.1.1. Platelet aggregation

Platelets are blood cells that play central roles in the processes of haemostasis and inflammation. Activation of platelets is a complex interplay of adhesion and signalling biomolecules, and is necessary for effective haemostasis and adhesion of platelets to the injury. After adhesion, platelets are activated by a number of agonists such as adenosine diphosphate (ADP) and collagen present at the site of vascular injury.(32,33)

Platelet activation increases the free calcium concentration, producing structural and functional changes in these blood cells. Calcium simulates membrane phospholipase A2 activity, which liberates arachidonic acid which is then converted to prostaglandin H2 (PGH2) by the enzyme cyclooxygenase 1 (COX-1). PGH2 is metabolised to thromboxane A2 (TXA2), a potent activator of platelets, by thromboxane synthase. ADP, TXA2 and thrombin have receptors coupled to G-proteins, which activate phospholipase Cβ and phospholipase Cγ, generating diacylglycerol and inositol trisphosphate, which results increased calcium.(32,33)

The glycoprotein IIb/IIIa (GPIIb/IIIa) complex is the main adhesion molecule involved in platelet aggregation. This membrane protein binds soluble plasma fibrinogen.(33)

2.2.1.2. Mechanism of action of platelet-aggregation inhibitors

Antiplatelet drugs act on different targets in the platelet aggregation pathway summarised above. Drugs such as aspirin inhibit COX-1 irreversibly via acetylation, which is the main producer of TXA2 in platelets. Also, PGH2 and prostaglandin I2 (PGI2) are inhibited by aspirin. Lower doses (50-300 mg/day) of aspirin inhibit TXA2 more than PGI2. Consequently, aspirin produces a relevant and irreversible anti-aggregation effect over several days.(34,35)

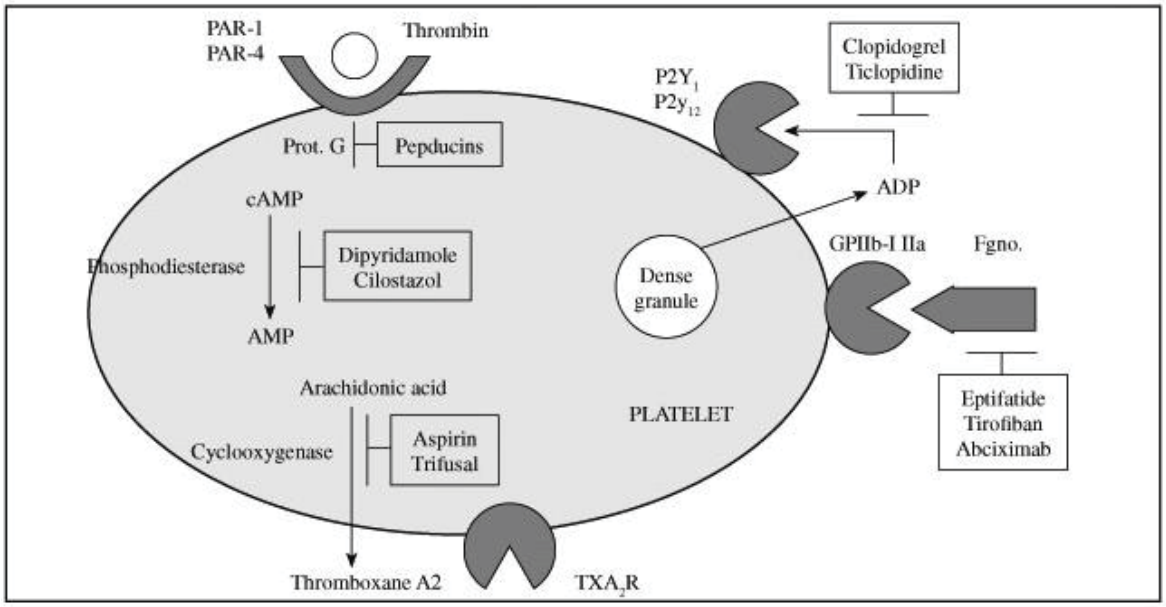
Thienopyridines (the prodrugs ticlopidine, prasugrel and clopidogrel) irreversibly inhibit the ADP-dependent mechanism in platelets. The active metabolite of clopidogrel inhibits the binding of ADP to platelet P2Y12 receptor and subsequent ADP-mediated activation of the GPIIb/IIIa complex.(35)

Ticagrelor is an orally administered direct-acting P2Y12 receptor antagonist that binds reversibly and selectively to the receptor, preventing platelet activation and aggregation.(36,37) Cangrelor also binds selectively and reversibly to the P2Y12 receptor to prevent further signalling and platelet activation, but this is administered intravenously.(38)

Other drugs, like abciximab or tirofiban, directly block the GPIIb/IIIa receptor as antagonists. Abciximab is the Fab fragment of a chimeric immunoglobulin G1 monoclonal antibody. Abciximab action results in the inhibition of platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets.(35)

Dipyridamole is a vasodilator that produces an increase in ADP, inhibiting aggregation in the cyclic guanosine monophosphate activity through phosphodiesterase inhibition.(35,39)

Figure 1. Mechanisms of action of antiplatelet drugs



Source: Alberca-de-las-Parras, FM. et al. *Rev. esp. enferm. dig.* 2015;107;5;289-306.(40)

2.2.1.3. Scientific evidence for antiplatelet therapy in secondary prevention

Aspirin is the main drug in CHD secondary prevention.(41) The alternative to aspirin is clopidogrel (75 mg), indicated for patients with aspirin intolerance or in combination with aspirin.(8,15) Aspirin's efficacy for secondary prevention has been tested in numerous clinical trials; the evidence suggests that aspirin at low doses (75-100 mg/day) offers the optimal risk/benefit ratio in patients with ACS for secondary prevention.(42) Several studies have shown that aspirin in doses ≥300mg is similar to doses of 75-100 mg/day for the prevention of major CV events; however, the major bleeding risk is higher with doses ≥300mg.(15,43,44) Aspirin long-term therapy is recommended indefinitely in all patients after ACS.(15)

A meta-analysis of randomised trials of long-term antiplatelet therapy vs. control in approximately 20,000 patients with prior AMI demonstrated a 25% reduction

in risk of recurrent vascular events (nonfatal AMI, nonfatal stroke and death) in the antiplatelet treatment group. The most widely tested dose was 75 to 325 mg of aspirin, with no evidence that higher dose aspirin or an alternative antiplatelet was more effective.(45)

Current practice guidelines recommend dual antiplatelet therapy (DAPT), i.e. a combination of aspirin and a P2Y12 inhibitor (for example, clopidogrel), for up to 12 months after percutaneous coronary intervention (PCI) and for 1 month in patients treated with fibrinolytics without subsequent PCI.(15,46)

2.2.1.4. Aspirin and P2Y12 inhibitors in DAPT for secondary prevention

Aspirin is the main drug used in secondary prevention and is complemented by P2Y12 inhibitors (e.g., clopidogrel, prasugrel or ticagrelor). Clopidogrel is a thienopyridine with an irreversible inhibitory effect on the P2Y12 ADP receptor. Several clinical trials have demonstrated the efficacy of aspirin and clopidogrel in combination compared with aspirin/placebo for 3 to 12 months in patients who have suffered unstable angina or non-STEMI.(41,45)

DAPT, a combination of aspirin and a P2Y12 inhibitor, is one of the most investigated treatments in secondary prevention. Clinical practice guidelines recommend DAPT for up to 12 months to the patients with STEMI and non-STEMI after primary PCI.(13–15,28,47)

The optimal duration of DAPT is at least 1 month in patients treated with fibrinolytics, but it should be expanded up to 12 months.(13–15,28,47) However, there is still discussion in the scientific community about the optimal duration of

DAPT in patients with CHD. The evidence shows that the risk of bleeding with DAPT is proportionally related to the duration within and beyond 1 year of treatment.(46) Extending DAPT duration beyond 12 months increases the risk of severe bleeding, without reducing mortality and ischemic events.(48) However, a recent retrospective cohort database study showed that prolonged DAPT up to 3 years after AMI was associated with a significant reduction in overall mortality and recurrent AMI.(49)

Clopidogrel is the more commonly used P2Y12 inhibitor, although prasugrel has shown favourable pharmacodynamics and clinical efficacy over clopidogrel, showing more rapid and consistent effects on receptor inhibition. Several clinical trials have shown superior ADP inhibition-induced effects of ticagrelor and prasugrel compared with clopidogrel, but with a higher bleeding risk. Despite this higher bleeding risk, prasugrel and ticagrelor appear to have a better net clinical benefit.(46,50)

In comparison with anticoagulant therapy, DAPT was superior in patients who underwent PCI in numerous clinical trials.(46)

2.2.2. Statins

2.2.2.1. Mechanism of action of statins

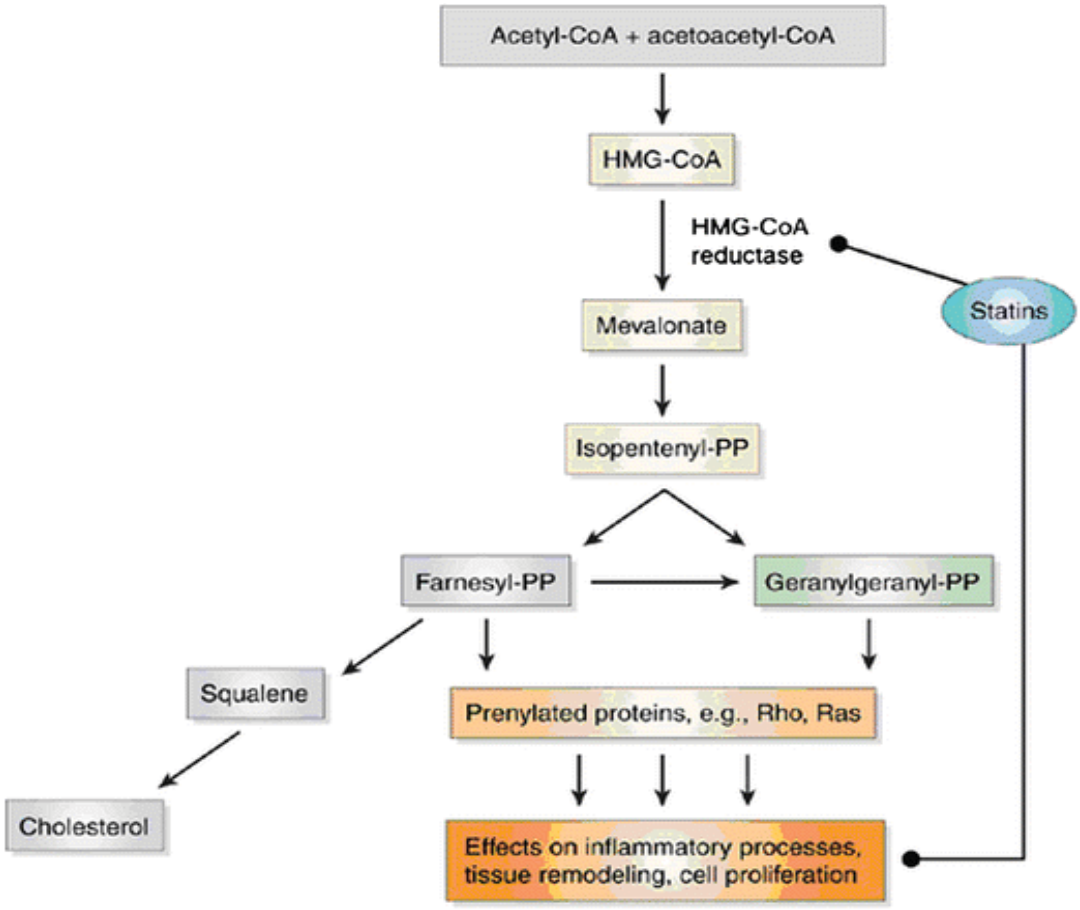
The main enzyme of cholesterol synthesis is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This enzyme catalyses the first committed step in sterol biosynthesis. Statins are structural analogues of HMG-CoA reductase and block this enzyme in the mevalonate pathway, reducing hepatic cholesterol synthesis.(23,35,51)

This reduction in intracellular cholesterol concentration leads to microsomal HMG-CoA reductase and increases the expression of LDL receptors on the surface of hepatocytes, thereby decreasing plasma LDL levels and other apoB-containing lipoproteins in the blood, such as triglyceride-rich particles. Other CV effects attributed to statins are a reduction in oxidative stress and vascular inflammation.(23,35,51)

The LDL-cholesterol reduction is dose-dependent and it is different for each statin. Atorvastatin and rosuvastatin are the strongest HMG-CoA reductase inhibitors, while in contrast simvastatin and fluvastatin are the weakest.(23,35,51) A recent meta-analysis ranked statins according their strength regarding lipid control: lovastatin was ranked as the best for reducing total cholesterol and triglycerides and fluvastatin has the best high-density lipoprotein-cholesterol increasing efficacy.(52)

Lovastatin and simvastatin are prodrugs; they are inactive lactones and must be converted to the active form in the digestive tract, opening (acid form hydroxyl beta derivates) in hydroxyl beta derivatives. The other statins are already activated when they are administered.(35)

Figure 2. Mechanism of action of statins



Source: Chatterjee, S. et al. *Curr Cardiol Rep.*2015;17;4 (53)

2.2.2.2. Scientific evidence for statin therapy in secondary prevention

The efficacy of statins to reduce CV morbidity and mortality in secondary prevention has been demonstrated in a large number of clinical trials and observational studies; these drugs are strongly recommended in clinical practice guidelines. Therapy with statins should start as early as possible after admission in all ACS patients, regardless of cholesterol concentration, and maintained as long-term therapy for secondary prevention in all patients in the absence of contraindications. The intensity of statin therapy should be

increased to high intensity in patients who are already receiving low- or moderate-intensity at ACS presentation.(13–15,23)

A large number of meta-analyses have been performed to study the efficacy and safety of statins. These showed a 10% reduction in all-cause mortality per 40 mg/dl LDL-cholesterol reduction. Also, they observed that major cardiovascular event (MACE) risk was reduced by around 23% and the risk of stroke by 17% per 40 mg/dL of LDL-cholesterol concentration reduction.(23,54) Another meta-analysis of clinical trials with more than 190,000 patients concluded that statins significantly reduced the incidence of all-cause mortality and MACE as compared to control in secondary prevention.(55)

In addition, statins have been studied in population-based studies. The effect of initiating statins for secondary prevention after first AMI in elderly patients showed improved survival and lower risk of recurrent AMI, stroke and CV and all-cause mortality and revascularisation.(56–58)

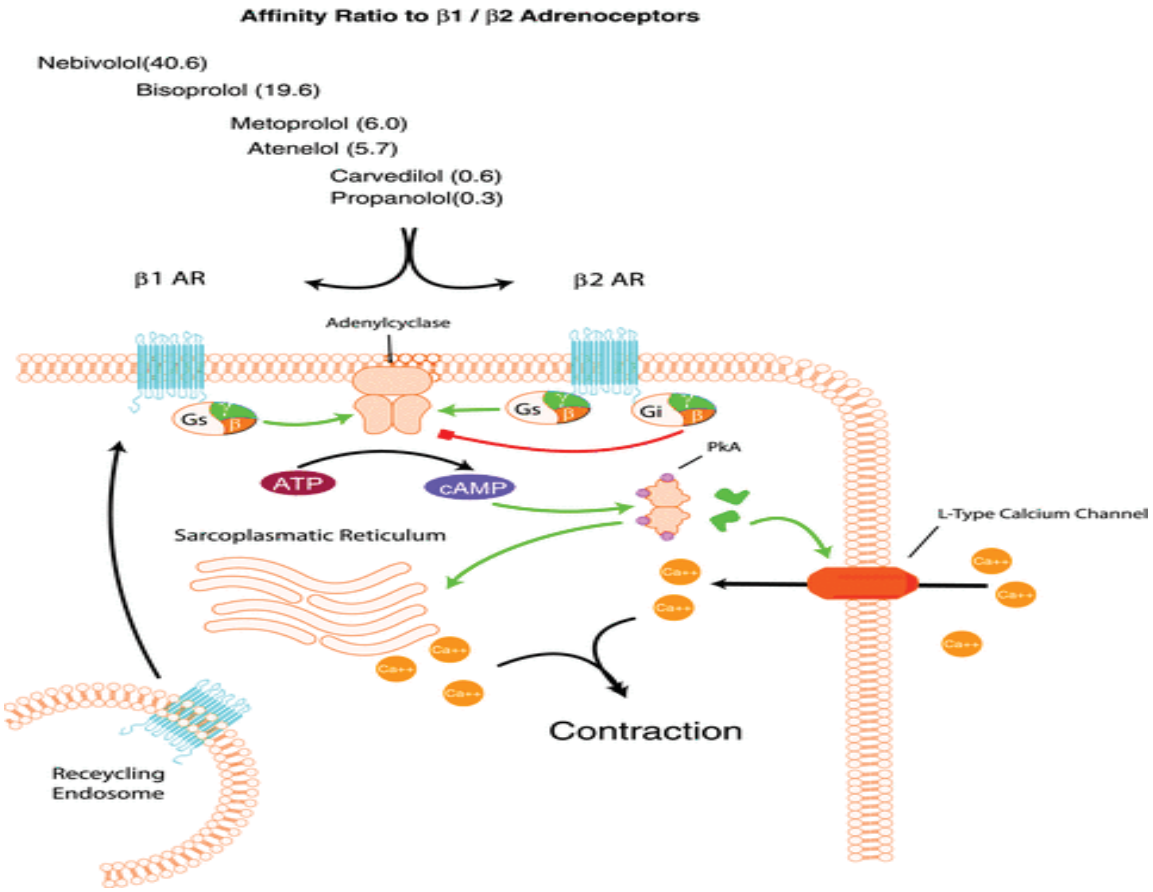
2.2.3. Beta-blockers

2.2.3.1. Mechanism of action of beta-blockers

Beta-blockers are a group of agents that are able to antagonise β-adrenergic receptors. These receptors have three subtypes (β1, β2 and β3) and belong to the G protein-coupled receptor family that are activated by catecholamines. β1 receptors are predominant in the heart, β2 in smooth muscle and β3 in adipose tissue. Beta-blocker agents occupy the receptor and reduce in a competitive manner receptor occupation by catecholamines. Beta-blockers differ in the relative affinity from β1 and β2 receptors; some of them have more affinity for

β1 over β2 (such as atenolol, betaxolol, bisoprolol, metoprolol, acebutolol, alprenolol, atenolol, celiprolol, esmolol and nebivolol) and others show the same affinity between β1 and β2 receptor (propranolol, carteolol, carvedilol, nadolol, penbutolol, pindolol, timolol, sotalol).(35)

Figure 3: Mechanism of action of beta-blockers



Source: Dennis Ladage, et al. *Cardiovascular Therapeutics*. 2013;31;2;76-83.(59)

2.2.3.2. Scientific evidence for beta-blocker therapy in secondary prevention

Several clinical trials and observational studies support the use of oral beta-blocker after ACS for secondary prevention. Clinical practice guidelines for the management with STEMI and non-STEMI recommend the routine

administration of beta-blockers in all patients, and especially in patients with reduced left ventricular function (≥40%).(13–15)

A large systemic review and meta-analysis of nearly 200,000 patients following AMI without heart failure (HF) concluded that long-term beta-blocker therapy may not constitute a significant reduction in the risk of all-cause mortality.(60) However, a recent database study with more than 28,000 patients concluded that beta-blockers therapy for ≥1 year after AMI was associated with reduced mortality (adjusted hazard ratio [HR] 0.81 (confidential interval [CI] 0.72-0.91)) compared with use of <1 year.(61) Also, Dondo et al.(62) assessed the association between the use of beta-blockers and 1-year mortality with almost 92,000 patients with AMI without HF. The authors concluded that use of beta-blockers after hospital discharge was not associated with lower risk of death at any time point up to 1 year.

Park et al.(63) in a prospective study concluded that beta-blockers prescribed at discharge after AMI were associated with a 29% reduced mortality risk (HR: 0.71; 95% 055-0.90), but beyond a year after AMI, they were not associated with reduced mortality. Another study found that being adherent to beta-blockers was associated with a 20% reduction of recurrent AMI.(64)

Although beta-blockers have been used for a long time as long-term therapy for the management of AMI, the role of beta-blockers in secondary prevention after AMI has been called into question. It is clear that additional large randomised clinical trials are necessary to clarify their role.

2.2.4. Angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers

2.2.4.1. Mechanisms of action of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers

The renin-angiotensin-aldosterone system (RAAS) regulates blood volume and systemic vascular resistance. Prorenin is secreted in an inactive form by juxtaglomerular cells in the afferent arterioles of the kidney. Prorenin is converted to renin when juxtaglomerular cells are activated due to decreased BP, beta-activation or decreased sodium levels in the distal tube. Renin is released into the circulation and interacts with angiotensinogen, which is produced in the liver. Angiotensinogen is converted into angiotensin I (inactive form) by renin and this is converted to angiotensin II (active form) by the action of endothelial angiotensin converting enzyme (ACE).(65)

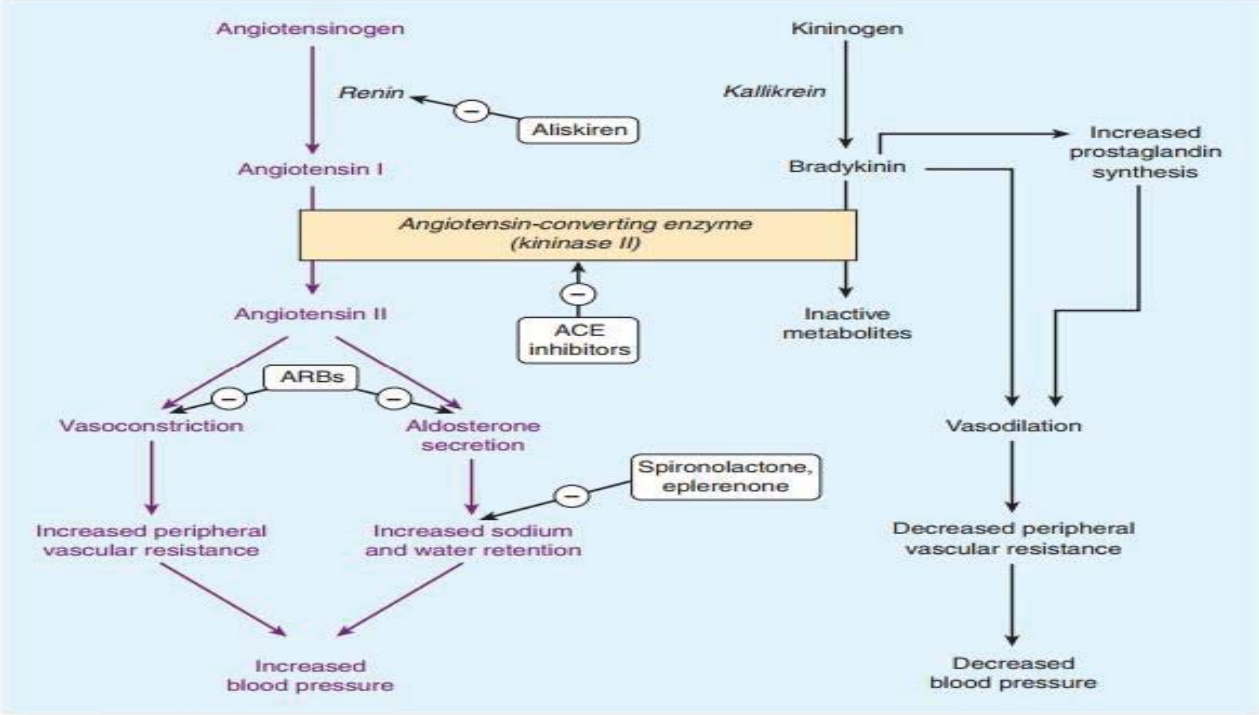
Angiotensin II acts in the kidney, arterioles and adrenal cortex by binding to angiotensin receptors. Angiotensin II has several effects, such as increased sodium reabsorption in the kidney, the release of aldosterone from the adrenal cortex, increased water intake and the release of antidiuretic hormone. Aldosterone is a steroid hormone that also increases sodium reabsorption and potassium excretion in the nephron. The effects of aldosterone take hours or days to start, but the effect of angiotensin II is much more rapid. The goal of RAAS is increase total body sodium to increase the osmolarity, total body water and vascular tone in order to increase BP.(65)

Captopril, enalapril, ramipril and other drugs of the same pharmacological group are highly specific and competitive ACEI. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and

reduced aldosterone secretion. Most of them are prodrugs, except for captopril and lisinopril, which need to be activated by metabolism, and enalapril (inactive) that is rapidly and extensively hydrolysed to enalaprilat, a potent ACEI.(35,66,67)

ARBs also interact with the RAAS and are synthetic oral angiotensin II receptor antagonists. Losartan and valsartan were the first commercialised ARB. Also, there are other ARB such as candesartan, eprosartan, irbesartan, telmisartan and olmesartan. ARBs are more selective in inhibiting the effect of angiotensin than ACEI because they do not interact with bradykinin metabolism.(35,68)

Figure 4. Mechanism of actions of ACEI/ARBs



Source: Katzung BG. *Farmacología bàsica y clínica.* 13a ed. Mc Graw Hill Education; 2016. (35)

2.2.4.2. Scientific evidence for ACEI/ARB therapy in secondary prevention

ACEIs should be considered as a long-term therapy after ACS in all patients, especially in patients who have experienced HF in the early phase or impaired left ventricular ejection fraction (LVEF) (≤40%), hypertension or diabetes. Their use in secondary prevention has been demonstrated independent of the other CV protectives therapy and the clinical benefits are greatest in patients with a high level of risk.(13,14,28)

ARBs are an alternative to ACEIs in patients who do not tolerate them, demonstrated in the VALIANT trial in which valsartan was shown to be noninferior to captopril.(13–15,28) However, a systemic review and meta-analysis performed by Lo Salvador et al.(69) with 17 studies and more than 70,000 patients concluded that the use of an ACEI was more effective in reducing total deaths and CV related deaths than an ARB in the hypertensive population. Also, two recent population-based studies found that the use of an ACEI after AMI was significantly associated with a reduced incidence of MACE, all-cause death, any repeat revascularisation, stroke and re-hospitalisation compared with the use of an ARB.(70,71)

2.2.5. Brief scientific evidence for other pharmacological groups in secondary prevention

There are other pharmacological groups recommended after ACS for secondary prevention in the current clinical practice guidelines. (13–15,28)

2.2.5.1. Ezetimibe

Ezetimibe is a selective intestinal absorption inhibitor of cholesterol and phytosterols that does not affect the absorption of fat-soluble nutrients. Ezetimibe acts on the Niemann-Pick C1-Like 1 multipass membrane protein in the intestinal lumen.(23,35)

Clinical practice guidelines have established that ezetimibe should be considered as a second line treatment in secondary prevention in patients with intolerance to statins. Ezetimibe is used in combination with a statin to achieve greater LDL-cholesterol reduction. The IMPROVE-IT clinical trial performed with more 18,000 patients compared this combination with ezetimibe 10 mg/simvastatin 40 mg and simvastatin 40 mg in monotherapy. The Kaplan-Meier event rate for the primary endpoint (CV death, hospital admission for instable angina, MI or stroke) at 7 years was 32.7% in the combination group and 34.7% for simvastatin alone (HR, 0.936; 95% CI, 0.89 to 0.99; P=0.016).(13–15,72)

Ezetimibe in combination with a statin provides an incremental reduction of 15-20% and in monotherapy reduces LDL-cholesterol by around 15-22% in hypercholesteraemic patients.(23)

2.2.5.2. Calcium channel blockers

Calcium channel blockers have shown no beneficial effect on the rate of reinfarction or death after STEMI. This pharmacological group may be useful to relieve ischemia and lower BP in patients with contraindications to beta-blockers, such as in the presence of obstructive airway disease. The use of

nifedipine showed a trend of higher mortality.(15,73) These drugs are not indicated in non-STEMI patients.(13,14,27)

2.2.5.3. Nitrates

The routine use of nitrates in STEMI and non-STEMI is not recommended. Only intravenous nitrates may be useful in the acute phase.(14,15,27,73)

2.2.5.4. Mineralocorticoid/aldosterone receptor antagonists

Eplerenone, a selective MRA, has been shown to reduce morbidity and mortality in patients with left ventricular dysfunction (≤40%) and HF or diabetes mellitus after STEMI or non-STEMI. MRA are recommended in these patients in combination with beta-blockers and ACEIs. Two clinical trials showed beneficial effects in early treatment with MRA in patients with STEMI and without HF. Further studies are needed to clarify. MRAs are contraindicated in case of renal failure or hyperkalaemia.(13–15,73)

2.3. Drug utilisation studies on recommended secondary prevention drugs after acute coronary syndrome

As mentioned above, clinical practice guidelines recommend long-term therapy with a combination of aspirin, statins and beta-blockers after ACS for secondary prevention; ACEI/ARB should be considered in all patients.(13–15,27,28,73) Several real-world data observational studies have studied the utilisation and effectiveness of this pharmacological combination after ACS.

A population-based cohort study conducted in Spain showed that, after ACS, most patients were treated with a combination of 4 drugs: 92.8% of patients were treated at least with an antiplatelet agent, 74.7% with a beta-blocker, 87.1% with a statin and 77.2% with an ACEI/ARB.(74) A similar population-based cohort study showed that 67% of patients with CVD were treated with a combination of aspirin, statin and at least one BP-lowering agent for secondary prevention.(75)

Zeymer et al.(76) in a prospective study in 9,998 survivors of AMI found that 62.6% were treated with combination of 4 drugs and 92.5% with a combination of 4-3 drugs. In contrast, a large epidemiological study in countries at various stages of economic development showed that overall 58.5% of individuals were not taking any of the 4 drugs, whereas 3.1% were taking all 4 drug types.(77)

A data chart review study with more than 2,500 patients showed that patients after STEMI are more likely to receive antiplatelets, beta-blockers, ACEI/ARBs or lipid lowering agents than non-STEMI patients.(78)

Regarding the differences in pharmacotherapy use in men and women, some population-based studies have focused on the differences between genders in pharmacological treatment received after ACS, concluding that women were less likely to be treated with the 4 drugs.(79,80) According to some studies, women were older, had more comorbidities and received more co-medication (excluding the 4 recommended drugs) after ACS than men.(79,81)

A retrospective study in Portugal assessed gender differences in receiving pharmacological therapy for secondary prevention after STEMI and non-STEMI. Among the STEMI patients, women were less likely to be discharged with DAPT

(odd ratio [OR] 0.52, 95% CI 0.29-0.91) than men, but there were no differences between genders among non-STEMI patients.(82) Also, some studies found that DAPT is less prescribed in women than men. (83,84)

Other real-world studies have studied the association between the prescription or use of 4 drugs and the risk of mortality or MACE after an ACS. Lafeber et al.(75) study found that, after a median follow-up period of five years, combination therapy (aspirin, statin and at least one BP-lowering agent) in secondary prevention was associated with a lower risk of AMI (HR 0.68, 95% CI 0.49-0.96), ischemic cerebrovascular accident (HR 0.37, 95% CI 0.16-0.84) and all-cause mortality (HR 0.69, 95% CI 0.49-0.96) compared with the absence of combination therapy.

A French population-based cohort study evaluated secondary prevention after ACS in 2,874 patients to compare the effectiveness of the combination of the 4 drugs to incomplete combinations. They concluded that the use of incomplete combinations (≤ 3 drugs) was associated with a higher risk of CV morbidity and all-cause mortality.(85) Another French database study found that the use of the combination of 4 drugs at discharge after ACS was associated with lower rates of MACE at five years, especially in high-risk patients.(86)

In the same line, another Spanish population-based study with 92,436 patients who previously had a MACE showed that those receiving the combination of an antiplatelet, a statin and an ACEI had lower mortality risk than those receiving other combinations, although medication adherence was not assessed.(87)

In another population-based study, Bezin et al.(88) assessed the risk associated with ACS recurrence or all-cause death with 3 three drugs instead of

the 4 drugs after ACS in 31,668 patients. The adjusted HR of the combination of an ACEI/ARB, an antiplatelet and a beta-blocker versus full therapy was 1.46 (95% CI: 1.33-1.60), that of the antiplatelet, beta-blocker and statin combination was 1.30 (1.17-1.43), that of the ACEI/ARB, beta-blocker a statin combination was 1.11 (0.98-1.25), and that of the antiplatelet, ACEI/ARB and statin combination was 0.99 (0.89-1.10).

A recent systematic review and meta-analysis with 21 effectiveness studies of the combination of 4 drugs compared the combination of 4 drugs to either monotherapy or no therapy. The risk ratios were 0.60 (95% CI: 0.55 to 0.66) for all-cause mortality, 0.73 (0.64 to 0.83) for AMI and 0.79 (0.68 to 0.91) for stroke. Comparing the combination of 4 drugs with 3 drugs, the risk ratio was 0.58 (0.49 to 0.69), while for 2 drugs, the risk ratio was 0.67 (0.60 to 0.76), concluding that the different groups work in an additive manner and the combination of 4 drugs is the optimal treatment.(89)

2.4. Medication adherence to secondary prevention drugs after acute coronary syndrome

Medication adherence in population-based studies can be calculated using proportion of days covered (PDC) or the medication possession ratio (MPR). PDC is an adherence medication metric, equivalent to MPR, to calculate adherence by dividing the number of days of medication supplied by the number of days of the period to be covered with the prescription issued. ESPACOMP members have developed guidelines for the reporting of

medication adherence in research studies; the final version of the guidelines was published in 2018.(90,91)

Despite the evidence that adherence to pharmacological secondary prevention after ACS is necessary to reduce CV morbidity and mortality, some studies have shown that adherence to prescribed drugs is poor for long-term drug treatment in CVD.(1,30,92) A meta-analysis with 376,162 patients showed that approximately one third of patients who suffered an AMI were not adherent to CV long-term treatment for secondary prevention. The estimated overall adherence to CV medications was 66% (95% CI 56-75) for secondary prevention long-term treatment after a median of 2 years. The adherence was higher in secondary prevention than in primary prevention (50%, 95% CI 45-56).(93)

Sanfélix-Gimeno et al.(92) assessed adherence in a Spanish population-based cohort study with 7,462 patients after ACS. Medication adherence was evaluated by estimating the PDC. Fully adherence was defined as at least 75% of treatment days covered by treatment dispensed (PDC ≥75). They found that PDC ≥75 was reached by 69.9% of patients with antiplatelets, 43.3% with beta-blockers, 45.4% with ACEI/ARBs and 58.8% with statins. 47.6% of patients reached PDC ≥75 for 3 or more drugs and 18% of patients did not reach PDC75 with any drug.

Huber et al. (94) studied medication adherence after AMI using a large health care claims database. The results of 4,349 patients showed that a high proportion of patients with low (0%-79%) MPR was observed for all drugs:

47.6% for DAPT; 23.5% for lipid-lowering drugs; 47.3% for ACEI/ARBs; and 88.1% for beta-blockers.

Different factors have been found to be related to long-term nonadherence, such as fewer comorbidities, socioeconomic factors (lower-income neighbourhoods), side effects, age, life chaos and patients who were admitted in the hospital for more than a week compared to those with shorter stays.(31,74,95)

The impact of medication adherence on secondary prevention and association with MACE or/and all-cause mortality has been assessed in several studies. One of them was a meta-analysis with 106,002 patients with stable CHD reviewing several studies with adherence to multiple agents and a single agent. They found that high adherence to 4 drugs was associated with a lower risk of all-cause mortality (risk ratio [RR] 0.56; 95% CI: 0.45-0.69) and MACE (RR 0.66; 95% CI: 0.51-0.87), as well as CV hospitalisation/AMI (RR 0.61; 95% CI: 0.45-0.82).(96)

Bansilal et al.(30) performed a cohort study of 4,015 patients who had suffered an AMI. Fully adherent patients (PDC ≥80%) to statins and ACEI/ARBs had a significantly lower rate of MACE than nonadherents (18.9% vs. 26.3%; HR 0.73; p=0.0004) and partial adherents (18.9% vs. 24.7%; HR: 0.81; p = 0.02). Another population-based study performed in France also analysed the association of 4 drug adherence (PDC ≥80%) over 30 months to reduce cardiac morbidity and mortality after AMI. The study showed that nonadherence to drugs after AMI increased mortality and readmission (HR=1.43, P<0.0001).(97)

Hamood et al.(98) showed that medication nonadherence was significantly associated with increased adjusted all-cause mortality risk for aspirin and ACEI/ARB, but not for beta-blockers. Also, Huber et al.(94) found that patients with high adherence (MPR ≥80%) to all 4 drugs had a significantly reduced risk for all-cause mortality, except for beta-blockers, and MACE.

However, other population-based studies have assessed the adherence to beta-blockers and risk of subsequent AMIs at days 31 to 365 from discharge in a self-controlled case series design. They used data from prescriptions to estimate if the patient was exposed or unexposed to beta-blockers at the time of the event. The incidence rate ratios of recurrent AMI in exposed versus unexposed period was 0.79 (95% CI 0.69 to 0.90, P=0.001). The subsequent sensitivity analyses confirmed the robustness of results.(64) Some studies suggest that beta-blockers do not improve prognosis beyond a year after ACS. (63,99,100)

A strategy to reduce poor adherence is the use of a polypill including key medications such as a statin, ACEI and aspirin. Several clinical trials have shown that the combination is well-tolerated and reduces CV risk.(15,101) Healthcare professionals should focus on poor adherence and on communication with patients about the treatment and importance of medication adherence. Also, monitoring and periodic feedback to the patients should be implemented as part of standard of care. However, this approach does not allow for dose modifications.

3. STUDY JUSTIFICATION

CVD is the leading cause of mortality and morbidity worldwide and in Europe. Despite that, it is well-known that the incidence of CVD has decreased over recent decades due to population lifestyle changes, the development of effective pharmacological treatments and medical interventions.

The improvement in morbidity and mortality associated with treatment with the drugs recommended by clinical practice guidelines (antiplatelet agents, beta-blockers, ACEI/ARBs and statins) has been widely demonstrated in patients with established CVD. Therefore, it is essential to achieve high medication adherence to these drugs to benefit from this improvement.

Despite this, several studies have shown that medication adherence to long-term treatment is poor. Therefore, it is important to assess medication adherence in these patients in order to understand its impact on the outcomes of cardiovascular morbidity and mortality in our population.

For these reasons, it is necessary to assess the association between long-term medication adherence to pharmacological secondary prevention and MACE and all-cause mortality in our population. To our knowledge, this is the first population-based study in the SIDIAP database that will provide high value knowledge about the cardiovascular disease and medication adherence in Catalonia (Spain) representing more than 5.8 million inhabitants in southern Europe.

4. STUDY HYPOTHESIS

4.1. Main hypothesis

- Patients with established CHD who adhere to drug therapy with the 4-3 recommended pharmacological groups (antiplatelet agents, beta-blockers, ACEI/ARBs and statins) for secondary prevention have a lower risk of MACE and all-cause mortality (analysed as a composite endpoint) compared with patients who do not adhere to drug therapy.

4.2. Secondary hypothesis

- Most patients are treated with 4-3 recommended pharmacological groups after first ACS. We expect to find women receiving fewer recommended drugs than men.
- We expect to find similar clinical characteristics than in previous similar studies, with some differences between genders. We expect women to be older and to have more comorbidities than men.
- A positive benefit is expected in patients who are adherent to treatment with 4-3 drugs compared with patients who are adherent to only any combination of 2 or 1 drugs.

5. STUDY OBJECTIVES

5.1. Main objective

- To assess the relationship between adherence to the 4-3 recommended pharmacological groups (antiplatelet agents, beta-blockers, ACEI/ARBs and statins) for secondary prevention and the clinical outcomes of CV morbidity and all-cause mortality (analysed as a composite endpoint) in patients with established CHD. The clinical outcomes which were included as components of the composite endpoint were all-cause mortality, ACS and ischemic stroke. (Paper 2)

5.2. Secondary objectives

- To estimate the prevalence of use of the 4 drug treatments and describe the medication prescribed and drug combinations for secondary prevention after a first episode of ACS and to assess differences between genders. (Paper 1)
- To describe baseline socio-demographic and clinical characteristics of patients after a first episode of ACS and to assess differences between genders. (Paper 1)
- To assess the incidence of the composite endpoint in patients who are adherent to treatment with 4-3 drugs compared with patients who are adherent to any combination of 2 or 1 drugs. (Paper 2)

6. METHODS AND RESULTS

This is an article-based thesis with two manuscripts related to the results of the IMPACT study:

- **Paper 1**: This paper was focused on baseline clinical characteristics and gender differences in the prescription of long-term pharmacological secondary prevention drugs.
- **Paper 2**: The second paper shows the impact of adherence to drugs for secondary prevention on mortality and CV morbidity after ACS.

6.1. Paper 1

Gerard Sotorra-Figuerola, Dan Ouchi, Ana García-Sangenís, Maria Giner-Soriano, Rosa Morros. **Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study.** Atención Primaria (accepted ref. APRIM-D-21-00119, 28th June 2021).

This article was accepted in a journal. The paper is still to be published (currently in edition). DOI: not available.

Atención Primaria

Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study.

--Borrador del manuscrito--

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Autor correspondiente:	Maria Giner-Soriano Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain. Institut Català de la Salut, Generalitat de Catalunya, Barcelona, Spain. Barcelona, SPAIN
Primer autor:	Gerard Sotorra-Figuerola, PharmD, MSc
Orden de autores:	Gerard Sotorra-Figuerola, PharmD, MSc
	Dan Ouchi, Statistician, MSc
	Ana García-Sangenís, PharmD, MSc
	Maria Giner-Soriano, PharmD, PhD
	Rosa Morros, MD, PhD
Resumen:	Abstract Objective: to describe baseline socio-demographic and clinical characteristics and drugs prescribed for secondary prevention after a first episode of ACS and to assess differences between men and women. Setting: PHC in Catalonia. Data source: SIDIAP (Information System for Research in Primary Care). Participants: patients who suffered an ACS during 2009-2016 and followed-up in PHC centres of the Catalan Health Institute in Catalonia. Interventions: not applicable. Main measures: socio-demographic and clinical characteristics at baseline: sex, age, socioeconomic index, toxic habits, comorbidities, study drugs (prescribed for cardiovascular secondary prevention: antiplatelets, betablockers, statins, drugs acting on the renin-angiotensin system) and comedications. Results: 8,071 patients included, 71.3% of them were men and 80.2% had an acute myocardial infarction. Their mean age was 65.3 and women were older than 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 comedications. Most patients were treated with a combination of four or three study drugs for secondary prevention. Men initiated more drug treatments for secondary prevention and dual antiplatelet therapy than women. Resumen Objetivos: describir las características sociodemográficas y clínicas basales y fármacos prescritos para prevención cardiovascular secundaria tras un síndrome coronario agudo (SCA). Analizar si existen diferencias entre hombres y mujeres. Emplazamiento: AP en Cataluña. Fuente de datos: SIDIAP (Sistema de Información para el Desarrollo de la Investigación en AP).

	Participantes: pacientes que hayan sufrido un primer SCA durante 2009-2016, seguidos en AP del Instituto Catalán de la Salud en Cataluña. Intervenciones: no aplica. Mediciones principales: características sociodemográficas y clínicas al inicio: sexo, edad, índice socioeconómico, hábitos tóxicos, comorbilidades, fármacos de estudio (prescritos para prevención secundaria: antiagregantes, betabloqueantes, estatinas, fármacos del sistema renina-angiotensina) y fármacos concomitantes. Resultados: se incluyeron 8 071 pacientes; 71,3% hombres y 80,2% habían sufrido infarto. La edad media era de 65,3 años y las mujeres eran mayores que los hombres. Las comorbilidades más frecuentes fueron hipertensión, dislipemia y diabetes; más comunes en mujeres. Antiagregantes (91,3%) y estatinas (85,7%) fueron los fármacos más prescritos. El uso de todas las comedicaciones era más frecuente en mujeres, excepto nitratos. La combinación de los cuatro grupos farmacológicos de estudio se prescribió a 47,7% de los pacientes incluidos y la combinación de antiagregante, betabloqueante y estatina a 18,4%. Más hombres que mujeres recibieron los fármacos recomendados. Conclusiones: las mujeres incluidas eran mayores, con más comorbilidad y mayor uso de comedicaciones. La mayoría de pacientes eran tratados con la combinación de tres o cuatro fármacos para prevención secundaria. Los hombres iniciaban más fármacos para prevención secundaria y más terapia antiagregante doble que las mujeres.
Revisores sugeridos:	
Revisores a los que se opone:	

Key points

- Most patients in our study were treated with a combination of four or three pharmacological drugs recommended for secondary prevention.
- Age, gender and most clinical characteristics were similar to prior studies analysing secondary prevention treatment after ACS.
- 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.

Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study.

Abstract

Objective: to describe baseline socio-demographic and clinical characteristics and drugs prescribed for secondary prevention after a first episode of ACS and to assess differences between men and women.

Setting: PHC in Catalonia. Data source: SIDIAP (Information System for Research in Primary Care).

Participants: patients who suffered an ACS during 2009-2016 and followed-up in PHC centres of the Catalan Health Institute in Catalonia.

Interventions: not applicable.

Main measures: socio-demographic and clinical characteristics at baseline: sex, age, socioeconomic index, toxic habits, comorbidities, study drugs (prescribed for cardiovascular secondary prevention: antiplatelets, betablockers, statins, drugs acting on the renin-angiotensin system) and comedications.

Results: 8,071 patients included, 71.3% of them were men and 80.2% had an acute myocardial infarction. Their mean age was 65.3 and women were older than 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 comedications. Most patients were treated with a combination of four or three study drugs for secondary prevention. Men initiated more drug treatments for secondary prevention and dual antiplatelet therapy than women.

Keywords: electronic health records; acute coronary syndrome; drug adherence; secondary prevention.

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Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study.

Tratamiento farmacológico después de un síndrome coronario agudo: características clínicas y diferencias de género en un estudio poblacional de cohortes.

Gerard Sotorra-Figuerola[1,2], Dan Ouchi[1,2], Ana García-Sangenís[1,2], Maria Giner-Soriano[1,2], Rosa Morros[1,3,4,5]

Gerard Sotorra-Figuerola, PharmD, MSc, ORCID 0000-0002-7284-1365

Dan Ouchi Vernet, MSc. ORCID 0000-0002-8630-152X

Ana García-Sangenís, PharmD, MSc. ORCID 0000-0002-6689-6466

Maria Giner-Soriano, PharmD, PhD. ORCID 0000-0003-3750-9233

Rosa Morros, MD, PhD. ORCID 0000-0001-6752-8748

(1) Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.
(2) Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.
(3) Institut Català de la Salut, Barcelona, Spain.
(4) Universitat Autònoma de Barcelona, Departament de Farmacologia, Terapèutica i Toxicologia, Bellaterra (Cerdanyola del Vallès), Spain.
(5) Plataforma SCReN, UICEC IDIAP Jordi Gol, Barcelona, Spain.

Autora para correspondencia

Dra. Maria Giner-Soriano
Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.
Gran Via de les Corts Catalanes 587, àtic
Barcelona, 08007
+34 934824110
mginer@idiapjgol.info

Requisitos éticos: de acuerdo con la legislación europea y española sobre confidencialidad y protección de datos ([EU] 2016/679), los datos contenidos en SIDIAP son siempre pseudonimizados. Para el cruce con la base de datos CMBD, SIDIAP utiliza un tercero para asegurar la confidencialidad.
El presente estudio sigue todas las regulaciones nacionales e internacionales: Declaración de Helsinki y Principios de Buenas Prácticas en Investigación.
El estudio fue aprobado por el Comité de Ética de Investigación del IDIAPJGol el 3 de mayo de 2017.

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Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study.

Introduction

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] Therefore, the European and American Cardiology guidelines recommend in both genders this long-term pharmacological therapy for an acute coronary syndrome (ACS) secondary prevention.[8–12]

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.[13] Sanfélix-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 described differences between men and women 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.[14–17] Some differences between genders in secondary prevention have also been described and found that women were less likely to be treated. [14–16]

This work is part of IMPACT study and the protocol has been previously published.[18]The objective of IMPACT study is to assess the impact of the four recommended drugs adherence on mortality and cardiovascular morbidity. 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 (PHC) 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 admitted in hospitals of the Catalan Health Institute during 2009-2016, followed-up in PHC. The data source is Information System for Research in Primary Care (SIDIAP)

database, which includes PHC data of more than 5.8 million people from Catalonia (approximately 80% of the Catalan population).[18]

Data source

SIDIAP database,[19] which contains pseudonymized information coming from different data sources: ECAP (electronic health records in PHC of the Catalan Health Institute, including) socio-demographic characteristics, comorbidities registered as International Classification of Disease (ICD) 10 codes (Table S1),[20] specialist referrals, clinical parameters, toxic habits (smoking and alcohol intake), sickness leave, date of death, laboratory test data; general practitioners' prescriptions and their corresponding pharmacy invoice data registered as chemical classification system (ATC) codes;[21] and the CMBD-HA (minimum basic dataset at hospital discharge),[22] which includes diagnoses at hospital discharge registered as ICD9 codes (Table S1). [23]

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 were included. The individuals lost in follow-up during the first two months have no information available in the database to be captured. *Exclusion criteria:* patients with a recorded diagnosis of a previous ischaemic stroke.

Study variables

At index date: age, gender, socioeconomic MEDEA Index,[24,25] toxic habits (smoking and alcohol), 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 socioeconomic index is a deprivation index built with the information of five cities in Spain (Barcelona, Bilbao, Madrid, Sevilla, Valencia), using the census section as the unit of analysis and 2001 census data, based on five indicators of socioeconomic position: manual workers, unemployment, temporary workers, overall insufficient education and insufficient education in young people. MEDEA is able to detect small areas with socioeconomic inequalities in large cities, allowing the study of associations between socioeconomic indicators and mortality. MEDEA is categorized in five urban quintiles, with quintile 1 (U1) corresponding to the least deprived population and quintile 5 (U5), the most deprived.[24] In order to facilitate the presentation of our results, we grouped categories U1 to U3, and U4 to U5. The rural category (R) includes municipalities with less than 10,000 inhabitants and a population density lower than 150/km^2. The use of MEDEA index has not been analysed for rural areas. Socioeconomic deprivation measured with MEDEA was associated with an increase in total mortality in urban areas of Catalonia. [25]

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 PHC, due to the length of hospital's prescriptions and the delay in the register of the dispensing in our records

Statistical analysis

Demographic and baseline characteristics of the participants were described using counts and proportions for categorical variables and for continuous variables mean with standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for skewed distributions. Univariate analysis between genders was performed by means of Pearson's Chi-square test and we compared mean or median between groups using Student's T test and Mann-Whitney U test, respectively. The analysis between groups according to the number of study drugs was performed using the ANOVA test (under equal variance assumption) for continuous variables and Pearson's Chi-square test (with continuity correction) for categorical variables.

Regarding to the missing data, we assumed that if data was missing, it meant that the patient did not had that condition.

All analyses were performed using R 3.5.1 (R Core Team, 2020. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/), 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 and 8,573 of them were excluded (Figure 1). 8,071 patients were 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, women were older 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 all significantly more common in women. Heart failure and renal impairment were also common in women (Table 1).

Antiplatelet agents (91.3%) were the most prescribed drugs, followed by statins (85.7%), beta-blockers (76.7%), and lastly, ACEI/ARBs (66.3%). More men than women received all study drugs. Nitrates were the comedication most prescribed overall after the event. The use of all comedications was significantly higher in women, except for nitrates (Table 2). The combination of four study drugs was initially prescribed in 47.7% of patients and 31.8% of total prescriptions were with three study drugs. Beta-blockers, statins and antiplatelets was the more frequent combination of three components (18.4%) (Figure 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).

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

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 (Figure 3).

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 genders and number of study drugs prescribed. 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.[26] In agreement with similar studies, we found a higher prevalence of comorbidities in women,[27–29] while men had a higher prevalence of peripheral artery disease,[30] possibly related with the higher frequency of smoking habit.

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.[15,16,26,31]

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.[32] 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 women and men was slight and not significant, probably related to higher frequency of hypertension in women in our study population, because women were older than men. These results were similar to Lafeber et al [33] and Sanfélix-Gimeno et al studies.[5] Regarding comedications, anticoagulants and diuretics were the most prescribed in women, possibly related with their higher frequency of atrial fibrillation and heart failure than in men.

Women initiated secondary prevention less frequently than men.[14–16,34–36] 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 ≤ 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.[37] 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.[38–40]

Zeymer et al[41] 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.[36,41,42]

Other author already mentioned, Lafeber et al[33] 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 ≥ one blood-pressure lowering agent(s).[33]

Aspirin and clopidogrel were the most frequently antiplatelets prescribed. Dual antiplatelet therapy was less frequently prescribed to women as described by previous studies,[42–44] probably because women were older.[45] Bisoprolol, enalapril, and losartan were the most prescribed beta-blockers with slight differences between genders. The statins most commonly prescribed overall 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. Our database has PHC's data, therefore some hospital's data is not available.

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.[46–48]

This is the first work conducted with SIDIAP database which analyses the drugs prescribed for secondary prevention of cardiovascular disease providing high value knowledge about the cardiovascular disease in Catalonia (North-East Spain), which represents more than 5,8 million inhabitants in south Europe. The results can be extrapolated to all population in Catalonia and the rest of Spain, as the health systems and population characteristics are similar.

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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

Key points

What is known on the topic o Long-term administration of aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers improve survival after an acute coronary syndrome (ACS), and it is recommended in both sexes by guidelines for secondary prevention of cardiovascular disease.
What this study contributes o We have studied a large set of ACS patients initiating secondary prevention from a cohort in SIDIAP database (Catalonia, Spain). o Women were less likely to be treated with the recommended drugs for secondary prevention.

Study outline

Figure 1 includes the study flowchart.

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

N (%)	Overall	Women	Men	P-value
	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(24,25)				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* *Missing (10.3 %)*	2320 (32.1)	335 (15.5)	1985 (39.1)	<0.001
High alcohol intake** *Missing (21.8 %)*	5 (0.1)	0 (0.0)	5 (0.1)	<0.001
BMI (kg/m2; mean, SD) *Missing (20.8 %)*	29.0 (4.7)	29.9 (5.5)	28.7 (4.3)	<0.001
BMI ≥ 30: obesity	2387 (37.4)	903 (45.1)	1484 (33.8)	<0.001
Cholesterol Total mg/dL, mean (SD) *Missing (14.8 %)*	208.00 [180.00, 235.00]	211.00 [183.00, 238.00]	206.00 [179.00, 235.00]	<0.001
Cholesterol LDL mg/dL, median (IQR, Range) *Missing (21.5 %)*	128.00 [104.00, 153.00]	128.00 [103.00, 152.00]	129.00 [104.00, 153.00]	0.510
Cholesterol HDL mg/dL, median (IQR, Range) *Missing (19.0 %)*	47.00 [40.00, 56.00]	53.00 [44.00, 62.00]	45.00 [38.00, 53.00]	<0.001
Triglycerides mg/dL, median (IQR, Range) *Missing (17.7 %)*	127.00 [94.00, 183.00]	124.00 [93.00, 178.00]	128.00 [95.00, 185.00]	<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/1.73m^2 *Missing (14.9 %)*	528 (7.6)	274 (12.8)	254 (5.4)	<0.001

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

**SIDIAP database includes three categories: current smoker, ex-smoker and non-smoker.*

*** SIDIAP includes three categories: non-consumer, occasional consumer and usual/high-risk consumer.*

Table 2. Gender 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

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.

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

N (%)	4	3	≤2	P-value
	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
Gender; women	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(24,25)				<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* *Missing (10.3 %)*	1234 (35.5)	745 (32.9)	341 (22.8)	<0.001
High alcohol intake** *Missing (21.8 %)*	3 (0.1)	1 (0.1)	1 (0.1)	<0.001
BMI (kg/m2; mean, SD) *Missing (20.8 %)*	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) *Missing (14.8 %)*	211.7 (42.7)	210.0 (42.8)	201.10 (44.4)	<0.001
Cholesterol LDL mg/dL, mean, (SD) *Missing (21.5 %)*	131.5 (35.3)	131.3 (37.6)	122.1 (36.9)	<0.001
Cholesterol HDL mg/dL, mean, (SD) *Missing (19.0 %)*	48.5 (12.8)	49.1 (13.1)	50.2 (15.0)	0.001
Triglycerides mg/dL, mean, (SD) *Missing (17.7 %)*	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/1.73m^2 *Missing (14.9 %)*	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

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; HLD-C, high density lipoprotein- cholesterol; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; R (Rural); U (Urban).

**SIDIAP database includes three categories: current smoker, ex-smoker and non-smoker.*

*** SIDIAP includes three categories: non-consumer, occasional consumer and usual/high-risk consumer.*

FIGURES legends

Figure 1. Study flowchart

Figure 1 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.

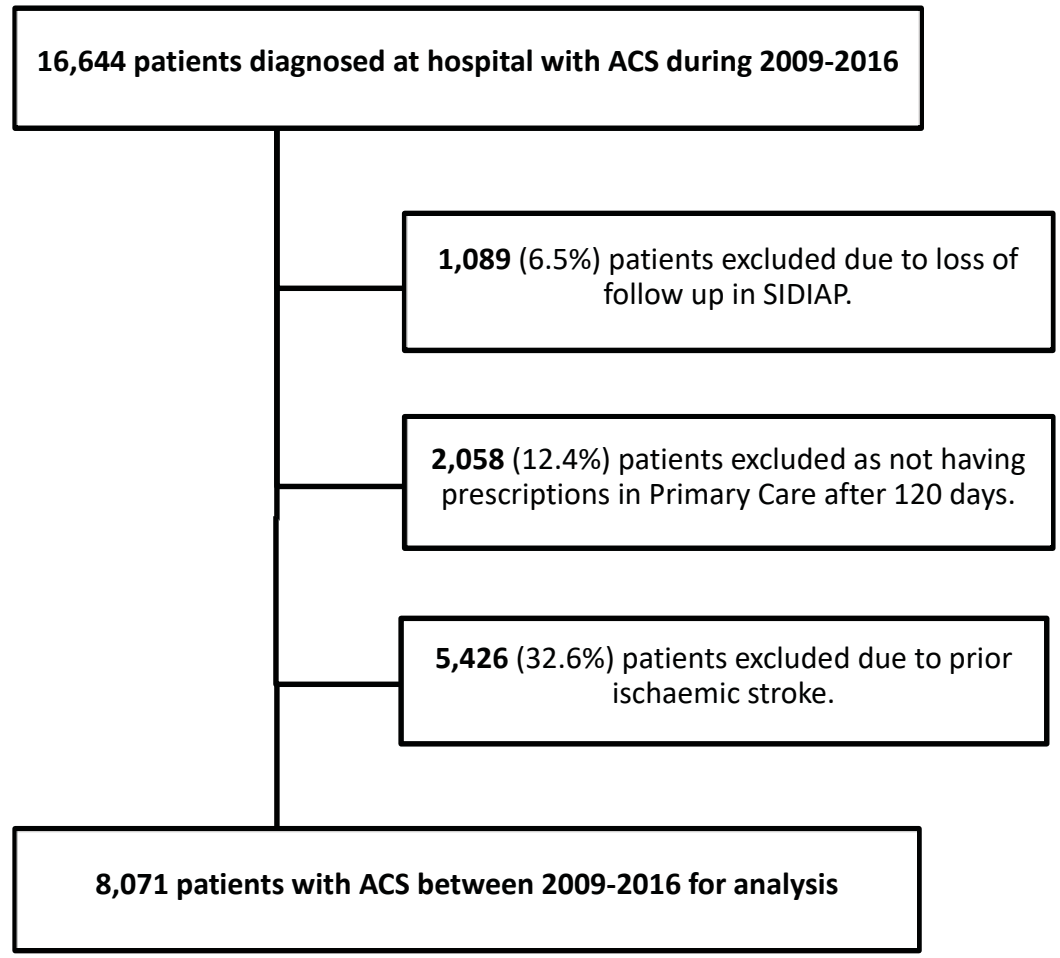
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; AntiPL, antiplatelets.

Figure 3. Drugs prescribed per gender.

Figure 3 depicts the different drugs prescribed overall, in men and women.

Distribution between genders was compared using the Chi-Square test with all p-values <0.001.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers.



	Women	Men
AMI	1,776 (76.6%)	4,699 (81.7%)
Unstable angina	542 (23.4%)	1,054 (18.3%)

Figure 2

Click here to access/download;Figure;Figure 2. Study drugs combinations_option 2.pdf

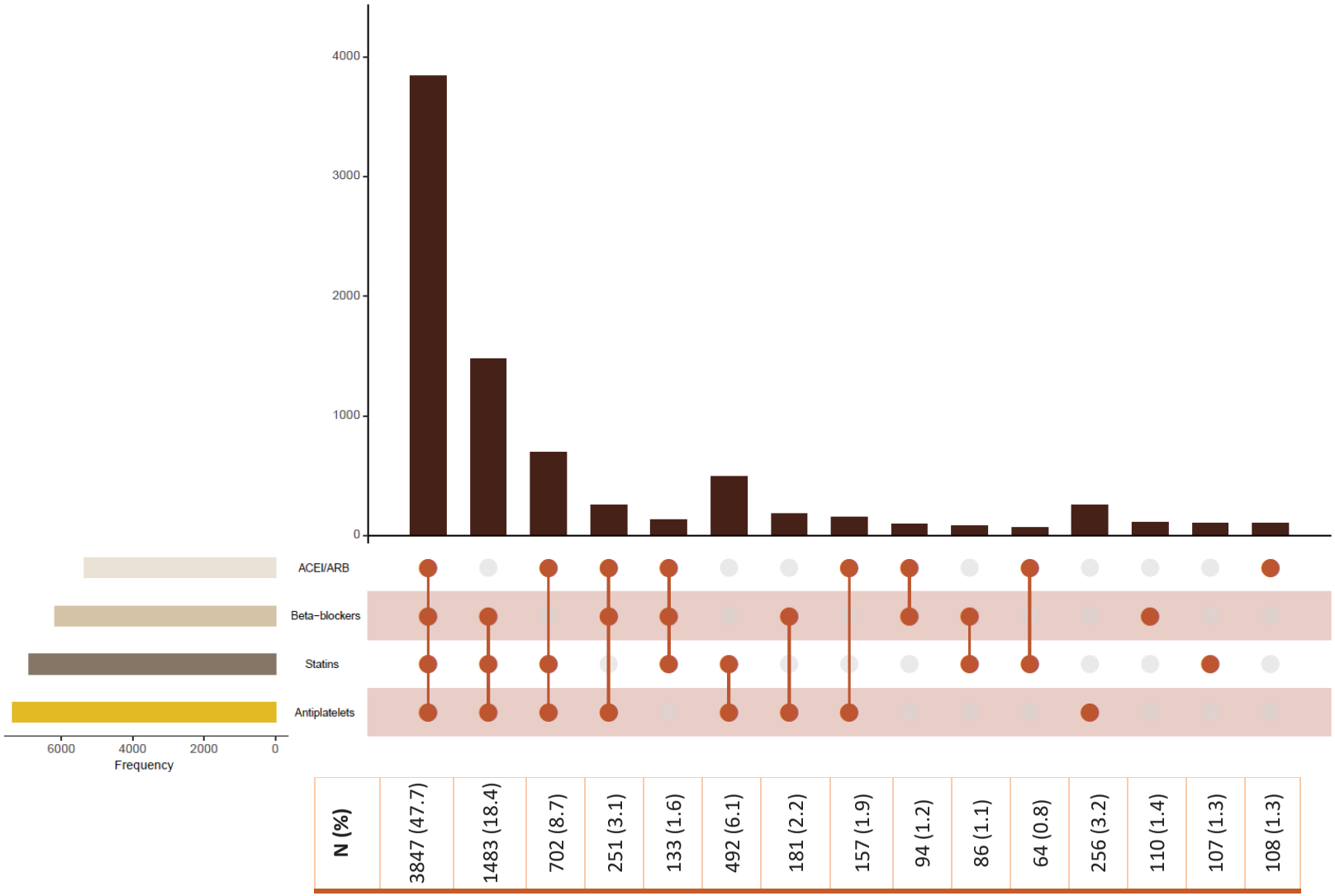


Figure 3

Appendices A

Table S1. International Classification of Disease, Nineth Revision (ICD-9) codes for endpoints of study and procedures and ICD-10 codes for comorbidities of interest or disease for exclusion

ICD-9 code	Description
411*	Unstable angina and other forms of acute coronary heart disease.
410*	Acute myocardial infarction
433*, 434*, 435*, 436*, 437*	Ischaemic stroke
ICD-10 code	**Description**
I24*, I25*	Coronary heart disease
I63*, I65*, I66*, I67.2, I67.8	Ischaemic stroke
G45	Transient cerebral ischaemic attack.
I70*, I73*, I74*	Peripheral vascular disease
E78*	Dyslipidaemia
I10*, I15*	Hypertension
E10*, E11*	Diabetes mellitus
I48	Atrial fibrillation
I50*	Heart failure
C00*-C97*	Malignancies
J40*-J44*	Chronic obstructive pulmonary disease
F30*-F39*	Depression
M05*, M06*, M15*-M19*	Arthritis (osteoarthritis or rheumatoid arthritis)
M80*, M81*	Osteoporosis
N18*	Chronic Kidney disease
B20*-B24*	Human Immunodeficiency virus
G30*, G31*	Alzheimer's disease, other dementias

Table S2. Drugs prescribed per sex.

N (%)			All	Women	Men
Antiplatelets	More used	Aspirin	7201 (51.1)	1922 (53.4)	5279 (50.3)
		Clopidrogrel	4819 (34.2)	1214 (33.7)	3605 (34.3)
		Combinations	1112 (7.9)	284 (7.9)	828 (7.9)
		Prasugrel	505 (3.6)	66 (1.8)	439 (4.2)
		Ticagrelor	428 (3.0)	104 (2.9)	324 (3.1)
	Others	Cilostazol	16 (0.1)	1 (0.03)	15 (0.1)
		Ticlopidine	9 (0.06)	5 (0.1)	4 (0.04)
		Triflusal	15 (0.11)	4 (0.1)	11 (0.1)
Statins	More used	Atorvastatin	5302 (63.8)	1361 (61.4)	3941 (64.6)
		Pravastatin	108 (1.3)	40 (1.8)	68 (1.1)
		Rosuvastatin	311 (3.7)	81 (3.7)	230 (3.8)
		Simvastatin	2502 (30.1)	705 (31.8)	1797 (29.5)
	Others	Fluvastatin	23 (0.3)	8 (0.4)	15 (0.3)
		Lovastatin	16 (0.2)	9 (0.4)	7 (0.1)
		Pitavastatin	54 (0.7)	11 (0.5)	43 (0.7)
Beta-blockers	More used	Atenolol	925 (11.9)	261 (12.1)	664 (11.9)
		Bisoprolol	5541 (71.4)	1505 (69.8)	4036 (72.1)
		Carvedilol	1100 (14.2)	321 (14.9)	779 (13.9)
		Nebivolol	139 (1.8)	49 (2.3)	90 (1.6)
	Others	Metoprolol	4 (0.05)	1 (0.05)	3 (0.05)
		Nadolol	3 (0.04)	3 (0.1)	0 (0)
		Propranolol	40 (0.5)	16 (0.7)	24 (0.4)
		Sotalol	6 (0.08)	2 (0.09)	4 (0.07)
ACEI	More used	Captopril	53 (0.9)	27 (1.6)	26 (0.6)
		Enalapril	4280 (68.6)	1217 (72.2)	3063 (67.3)
		Lisinopril	137 (2.2)	29 (1.7)	108 (2.4)
		Ramipril	1723 (27.6)	391 (23.2)	1332 (29.3)
	Others	Cilazapril	4 (0.06)	4 (0.2)	0 (0)
		Delapril	4 (0.06)	0 (0)	4 (0.09)
		Fosinopril	6 (0.09)	1 (0.06)	5 (0.1)
		Imidapril	7 (0.1)	2 (0.12)	5 (0.1)
		Perindopril	8 (0.1)	2 (0.12)	6 (0.1)
		Quinapril	3 (0.05)	1 (0.06)	2 (0.04)
		Trandolapril	12 (0.2)	12 (0.7)	0 (0)
ARB	More used	Candesartan	98 (6.2)	40 (6.0)	58 (6.3)
		Losartan	570 (35.9)	233 (35.2)	337 (36.4)
		Olmesartan	260 (16.4)	98 (14.8)	162 (17.5)
		Valsartan	458 (28.9)	198 (29.9)	260 (28.1)
	Others	Eprosartan	13 (0.8)	10 (1.5)	3 (0.3)
		Irbesartan	82 (5.2)	42 (6.3)	40 (4.3)
		Telmisartan	107 (6.8)	41 (6.2)	66 (7.1)

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

Maria Giner-Soriano <mginer@idiapjgol.info>

APRIM-D-21-00119: decisión de los editores / editorial decision

6 missatges

Atencion Primaria <em@editorialmanager.com> 28 de juny de 2021, a les 12:02
Respon: Atencion Primaria <atenprimaria@elsevier.com>
Per a: Maria Giner-Soriano <mginer@idiapjgol.info>

Apreciado/a Dr Giner-Soriano:

Es un placer comunicarle que su manuscrito "Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study." (Ref. APRIM-D-21-00119) ha sido aceptado para su publicación en la sección Original de la Atención Primaria.

Recuerde que en su momento le remitiremos las pruebas de autor en formato pdf a esta misma dirección electrónica.

Apreciamos y valoramos su contribución a Atención Primaria. Invitamos regularmente a los autores de manuscritos recientemente publicados a participar en el proceso de revisión por pares. Si aún no formaba parte del grupo de revisores de la revista, ahora se le ha añadido. Esperamos que siga participando en nuestra revista y que nos tenga en cuenta para futuros envíos.

Reciba un cordial saludo,

Josep Jiménez Villa
Editor asociado
Atención Primaria

****

Dear Dr Giner-Soriano,

We are glad to inform you that your article "Pharmacological treatment after acute coronary syndrome: baseline clinical characteristics and gender differences in a population-based cohort study." (Ref. APRIM-D-21-00119) has been accepted for its publication in Atención Primaria.

Please remember that, before publication, you will receive an e-mail with the galley proofs of your article in pdf format.

We appreciate and value your contribution to Atención Primaria. We regularly invite authors of recently published manuscript to participate in the peer review process. If you were not already part of the journal's reviewer pool, you have now been added to it. We look forward to your continued participation in our journal, and we hope you will consider us again for future submissions.

Thank you for your contribution to the journal.

Yours sincerely,

6.2. Paper 2

Sotorra-Figuerola G, Ouchi D, Giner-Soriano M, Morros R. **Impact of adherence to drugs for secondary prevention on mortality and cardiovascular morbidity: A population-based cohort study. IMPACT study**. Pharmacoepidemiol Drug Saf. 2021 May 3. doi: 10.1002/pds.5261. Epub ahead of print. PMID: 33938603.(102)

DOI: 10.1002/pds.5261.

Impact of adherence to drugs for secondary prevention on mortality and cardiovascular morbidity: A population-based cohort study. IMPACT study.

Cardiovascular impact of medication adherence.

Gerard Sotorra-Figuerola[1,2], Dan Ouchi[1,2], Maria Giner-Soriano[1,2], Rosa Morros[1,3,4,5]

[1]Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.

[2]Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.

[3]Institut Català de la Salut, Barcelona, Spain.

[4]Universitat Autònoma de Barcelona, Departament de Farmacologia, Terapèutica i Toxicologia, Bellaterra (Cerdanyola del Vallès), Spain.

[5]Plataforma SCReN, UICEC IDIAP Jordi Gol, Barcelona, Spain.

Corresponding author

Maria Giner-Soriano

PharmD, PhD

Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.

Gran Via de les Corts Catalanes 587, àtic

Barcelona, 08007

Spain

Phone: +34 934824110

Email: mginer@idiapjgol.info

Prior postings and presentations

- Gerard Sotorra-Figuerola, Dan Ouchi, Rosa Morros, Maria Giner-Soriano. **Impact of medication adherence by drug classes on mortality and cardiovascular morbidity after acute coronary syndrome in both sexes: population-based cohort study**. 36th ICPE Congress, Abstracts of the 36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Virtual, September 16-17, 2020. *Pharmacoepidemiology and Drug Safety* 2020;29(S3):1-684.
- Sotorra Figuerola G, Ouchi D, Giner-Soriano M, Garcia-Sangenís A, Pera Pujadas H, Morros R. **Acute coronary syndrome in Catalonia: baseline characteristics of patients from a SIDIAP cohort (IMPACT study)**. XXX Congreso de la Sociedad Española de Farmacología Clínica. Santander, 4-5 octubre 2018. *Basic & Clinical Pharmacology & Toxicology* 2018;123(S4):1-68(CP67).
- Giner-Soriano M, Sotorra Figuerola G, Cortés J, Pera Pujadas H, Garcia-Sangenís A, Morros R. **Impact of medication adherence on mortality and cardiovascular morbidity: protocol for a population-based cohort study**. *JMIR Res Protoc* 2018;7(3):e73. https://doi.org/10.2196/resprot.8121

Abstract

Purpose: Adherence to pharmacological therapy for secondary prevention after an acute coronary syndrome (ACS) reduces the risk of new cardiovascular events. However, several studies showed poor adherence. Our study aim was to assess the risk of a composite endpoint of major cardiovascular events (MACE) and all-cause mortality according to the adherence to these drugs in patients after an ACS in a primary health care cohort.

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. Drug adherence was evaluated through Proportion of Days Covered (PDC).

Results: We included 7152 patients and 5692 (79.6%) were adherent (PDC≥75%) to the study drugs during the first year after the event. Adherents to any combination showed a significant reduction of the composite endpoint risk (HR 0.80 [0.73-0.88]), and a significant lower probability of the composite endpoint than nonadherents for all drugs, except beta-blockers. Adherents to 2 (HR 1.2; 95% CI 1.0 -1.3) and 1 drug (HR 1.5; 95% CI 1.2-1.8) had higher composite endpoint risk compared to adherents to 4-3 drugs.

Conclusion: Adherence to any combination of recommended drugs reduced the composite endpoint risk, regardless the number of drugs prescribed. Adherence to a combination of 4-3 drugs was significantly associated with a reduced mortality risk compared with adherents to 2 or 1, but it was not significant for MACE.

Keywords

Acute coronary syndrome; coronary heart disease; electronic health records; medication adherence; primary health care; secondary prevention.

Word count

2,895 words in the main text, 250 words in the abstract, 2 tables, 4 figures, 4 supplementary tables, 2 supplementary figure.

Key points

- This is the first population-based study in our setting that assessed the relation between adherence to pharmacological secondary prevention and risk of MACE.
- Most patients were treated with a combination of 4 or 3 drugs recommended for secondary prevention. Antiplatelets and statins were the most frequent drugs prescribed.
- Adherence (PDC≥75%) to the study drugs prescribed during the first year of treatment after the event was high.
- Adherence to any combination of recommended drugs reduced the composite endpoint risk, regardless the number of recommended drugs prescribed.
- Adherence to a combination of 4-3 recommended drugs was significantly associated to lower mortality risk compared with adherents to 2 or 1.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide with 31% of all deaths, causing about one-third of all deaths in people older than 35.[1,2] However, some studies indicate a reduction in incidence of CVD over the last decades, due to population lifestyle changes and the development of effective drugs and medical interventions.[3,4] In Spain, CVD remains the leading cause of death, closely followed by cancer disease.[5]

Numerous studies have shown that long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) as pharmacological secondary prevention after acute coronary syndrome (ACS) has contributed substantially to reduce cardiovascular morbidity and mortality.[6–10] Clinical practice guidelines recommend this long-term pharmacological therapy for ACS secondary prevention, unless it is contraindicated.[11–15]

Adherence to this therapy plays an essential role in secondary prevention after ACS.[11–13,16] Despite the high evidence of pharmacological secondary prevention, several works have shown poor adherence independently of drug classes.[6,7,10,17–20]

In Spain, medication adherence was evaluated in a population-based study by estimating the Proportion of Days Covered (PDC), equivalent to Medication Possession Rate (MPR). Fully adherence was defined as PDC75 (at least 75% of treatment days were covered by treatment dispensed). PDC75 was reached by 69.9% of patients with antiplatelets agents and for statins, beta-blockers and ACEI/ARB was around 50%. Almost half of patients reached a PDC75 for three or more drug classes.[10]

The impact of medication adherence to secondary prevention has been assessed on other several population-based studies and clinical trials. Adherence was related to a lower risk of all-cause mortality and lower rates of major cardiovascular events (MACE) or hospitalization.[7,16,21] Patients with high adherence (PDC ≥ 80% or MPR ≥ 80%) to all drug classes had a significantly reduced risk for all-cause mortality and MACE.[7,20] Other study found a lower mortality risk in patients receiving antiplatelets, statins and ACEI than those receiving less than 3 drugs, but the medication adherence was not assessed.[22]

The aim of our study was to assess the risk of a composite endpoint of MACE and all-cause mortality according to the level of adherence to antiplatelet agents, beta-blockers, ACEI/ARB and statins in patients with establish CVD in a primary health care (PHC) cohort. The study protocol has already been published.[23]

Methods

Study design

The IMPACT study is a population-based observational cohort study. The study population were all individuals older than 18 with a first episode of ACS (AMI or unstable angina) registered in the Information System for Research in Primary Care (SIDIAP)[24] from 2009 to 2016 with at least two months of follow-up after the index date.[23]

The index date was defined as the date of the ACS episode registered in the Minimum Basic Dataset at Hospital Discharge (CMBD-HA)[25] of the Catalan Health Institute (ICS).

Exclusion criteria: patients with a recorded diagnosis of a previous ischaemic stroke.

Data source

SIDIAP contains pseudonymized clinical information originated from different data sources: ECAP (electronic health records in PHC of ICS registered by health professionals) which contains: socio-demographic characteristics, comorbidities registered as International Classification of Disease (ICD)-10 codes,[26] specialist referrals, clinical parameters, toxic habits, sickness leave, date of death, laboratory test data; GPs prescriptions and their corresponding pharmacy invoice data registered as chemical classification system (ATC) codes;[27] and the CMBD-HA which includes diagnoses at hospital discharge registered as ICD-9 codes.[28] The ICD-9 and ICD-10 codes used are enclosed in supplementary material (Table S1)

Variables

The variables assessed at baseline were as follows: age; sex; socioeconomic MEDEA Index;[29,30] smoking status; alcohol intake; body mass index (BMI); type of ACS event at index date (AMI, unstable angina or other forms of ACS); laboratory data (cholesterol, other lipid parameters and glomerular filtration rate); and comorbidities of interest. The ATC code definitions on the prescribed medication were described in the protocol and in Table S4.[23]

Patients were classified as exposed to the study drugs if they were prescribed any of study drugs (antiplatelets, beta-blockers, statins and ACEI/ARB) after the episode of ACS. Only patients with at least two months of follow-up in SIDIAP database after the index date were included. 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 PHC. It was used this period of time because the hospital's prescriptions are only valid for a period of two months and those prescriptions cannot be captured in SIDIAP, only GP's prescriptions are captured. Other co-medications were also assessed after the index date.

The variables assessed during follow-up were included in a composite endpoint composed by all-cause mortality, and MACE (includes: ACS and ischaemic stroke). All-cause mortality during follow-up was assessed through SIDIAP database. We had access to date of death, but the cause of death is not available in the database.

Medication adherence calculation

We obtained the information on drug exposure from the electronic prescription and the pharmacy invoice registry. The information available for each prescription is the dose, frequency of administration, start and end date. The information available for the invoice data is the number of packages dispensed of each preparation and the month and year of dispensing.

The medication adherence was evaluated determining the PDC for all study drugs prescribed to each patient during the first year after the index date. PDC is an adherence medication metric, equivalent to MPR, to calculate the adherence dividing the number of days of medication supplied by the number of days of the period to be covered with the prescription issued.[31,32]

The PDC calculation was based on the packages dispensed (days of pharmacy invoice covered) and days of supply (days of prescription covered) for each package. The patients were classified into two categories using the standard threshold of 75%: ≥75% adherents and <75% non-adherents.[7,10,23]

A statistical algorithm was created to identify the most probable drugs prescribed for each patient in the first 120 days after the index date, taking into account: time from index date, % of days prescribed, % of days dispensed and if the prescription continued active after 120 days. An example of an adherent patient analysis is included in supplementary material (Figure S1).

The adherence was estimated taking into account all treatments prescribed and dispensed for each patient during the first year after index date. When patients stopped having treatment prescribed or dispensed recorded in the database for >60 days, we considered that they discontinued treatment.

Ethics

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.

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-HA database, SIDIAP uses a trusted third party in order to ensure confidentiality when linking both data sources. The databased delivered to the research team is completely pseudonymized in order to make impossible the identification of the individuals.

The study was approved by Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol Clinical Research Ethics Committee, the reference institution for research in PHC of the ICS, at May 3, 2017.

Statistical analysis

Demographic and baseline characteristics of the participants were described using frequencies and percentages for categorical variables and mean and standard deviation for continuous variables.

We defined time to follow-up as the time between index date and the event. Patients were followed-up until censored: composite endpoint, lost to follow-up or until end of 2016.

The crude and adjusted Hazard Ratios (HR) for adherences were calculated for composite endpoint using Cox proportional hazard regressions models. Time-to-composite endpoint analysis was performed by Kaplan-Meier method and log-rank test.

Marginal structural models (MSM) were used to estimate causal effects by correcting for confounding. We estimated inverse probability weights (IPW) based on the propensity score using age, gender, comorbidities and other comedications. If needed, weights were truncated to the 5th percentile. The estimated weights were used in the proportional hazard model to correct for confounding.

All analyses were performed using R 3.5.1 under a significance level of 0.05.

Results

From 2009 to 2016, 7,152 patients with a first episode of ACS were included in IMPACT study(Figure S2). The mean age was 70.7 and 70.3% of patients were men, being women older than men (76.4 vs 68.3, $p< 0.001$). The overall mean follow-up time was

912.85 (standard deviation [SD]: 802.2) days: for adherent patients was 917.0 (SD: 798.6) days and for non-adherent was 896.7 (SD: 816.1) days, p value = 0.387. The median follow-up time was 670 days and maximum time was 2,859 days.

Overall, 5,692 (79.6%) patients were adherent (PDC≥75%) to the study drugs prescribed during the first year of treatment after the event, regardless of the number study drugs prescribed (Table S2). Antiplatelets and statins were the most frequent drug classes prescribed (88.8% and 87.8%) and with higher adherences (Table 1).

The combination of four study drugs (antiplatelet, statin, beta-blocker and ACEI/ARB) was prescribed in 47.7% of patients, being adherent 81% of them. Table 1 describes the adherence for each drug class and drugs combinations prescribed after the index date.

During the follow-up, 2,476 (34.7%) patients suffered the composite endpoint (10.0% died – all cause-mortality – and 24.7% suffered a second MACE).

Overall, Figure 1 shows the Kaplan-Meier curves of time to composite endpoint for adherent and nonadherent patients to any combination of study drugs for all follow-up period, regardless the number of drugs prescribed. Adherent patients to any drug combination showed a significant reduction of the composite endpoint risk versus nonadherents (adjusted HR 0.80 [0.73-0.88]; p value <0,0001) (Figure 1).

Regarding the adherence assessment by drug classes, the Kaplan Meier curves for the time to the composite endpoint showed that adherent patients had a significant lower probability to have a subsequent cardiovascular event or death (assessed as composite endpoint) than nonadherent patients for all drug classes (statistically non-significant for beta-blockers), regardless of number of drugs and the drug combination

prescribed. Antiplatelets (median survival probability: 2,636 days in adherents and 955 days in nonadherents, p<0.001) and statins (median survival probability: 2,637 days in adherents and 1,331 days in nonadherents, p<0.001) showed a higher difference between adherents and nonadherents than beta-blockers and ACEI/ARB (Figure 2).

Table 2 shows the risk of suffering the composite endpoint comparing adherents and nonadherents stratified by drug class, regardless of number of drugs prescribed. We found a lower composite endpoint risk in adherents compared with nonadherents for those receiving antiplatelets and statins.

Regarding the adherence to the different drug combinations, Figure 3 shows the association between medication adherence and composite endpoint risk, according to different drugs combinations (4-3 drugs, 2 drugs or 1 drug). Adherents to 2 drugs (adjusted HR 1.2; 95% CI 1.0 -1.3, p value < 0.001) and 1 drug (adjusted HR 1.5; 95% CI 1.2-1.8, p value < 0.001) had higher composite endpoint risk compared to adherents to 4-3 drugs (Figure 3 and Figure 4).

Splitting the composite endpoint in all-cause mortality and MACE, we found a significant higher risk of all-cause mortality in adherents to 1 or 2 drugs in comparison to adherents to 4-3 drugs (adjusted HR 4.2, 95% CI 3.2-5.6 and 2.0, 95% CI 1.6-2.5, p value < 0.001). Regarding to MACE risk, no statistically significant differences were found between these groups (Figure 3).

We found no statistically significant differences in being adherent or not to 4-3 drugs and the composite endpoint risk (adjusted HR 1.0, 95% CI 0.9-1.1, p value = 0.85). Adherents to 2-1 drugs had lower composite endpoint risk (adjusted HR 1.2, 95% CI 1.1-1.3, p value < 0.001) and all-cause mortality risk (adjusted HR 1.6, 95% CI 1.3-1.9, p

value < 0.001) than nonadherents to 2-1- drugs, but not for MACE subgroup (adjusted HR 1.1, 95% CI 0.96-1.2, p value = 0.17) (Table S3).

Figure 4 shows Kaplan-Meier curves of time to the composite endpoint comparing only adherent patients to 4-3, 2 and 1 study drugs. The adherent patients to 4-3 drugs (median survival probability was 2,637 days) had lower probability to composite endpoint risk than adherents to 2 drugs (median survival probability was 2,032 days) and 1 drug (median survival probability was 1,353 days).

Discussion

Our study assessed the composite endpoint (MACE and all-cause mortality) risk according to the adherence to evidenced-based medication for secondary prevention by drug class and by number of drugs prescribed in a PHC cohort based on a large health care dataset. We assessed 7,152 patients, who initiated on 4-3 drugs (82.0%), 2 drugs (11.3%) or 1 (6.7%) as a secondary prevention treatment after the first ACS. Nearly half of patients were prescribed the four drugs recommended[11–13] and 81% of them were adherent. The use of recommended drugs in our study population is in concordance with similar previous observational studies,[18,33] but was higher than other studies.[10,20,22,34,35]

We found a high number of adherents (defined as PDC ≥ 75%) in all drug classes and all drug combinations during the first year after ACS. In Sanfélix-Gimeno *et al.* study, PDC75 was reached by 69.9% of patients with antiplatelets, 43.3% with beta-blockers, 45.4% with ACEI/ARB and 58.8% with statins. 47.6% of patients reached PDC75 for three or more pharmacological groups.[10]

We found that higher adherence to drugs prescribed reduced the risk of the composite endpoint. In concordance in previous studies,[20,34] we found that the reduction of composite endpoint risk was higher for statins and antiplatelets than for beta-blockers and ACEI/ARB. Huber *et al*. reported that a good medication adherence was significantly associated with lower likelihood for mortality for all recommended drugs, except for beta-blockers. Also, the authors found that adherence to dual antiplatelet therapy, ACEI/ARB and beta-blockers was not significantly associated to lower risk of MACE.[20] However, a meta-analysis of nearly 200,000 patients concluded that there was no association between beta-blockers and all-cause mortality,[36] but in other study found that being adherent to beta-blockers was associated with a 20% reduction of recurrent AMIs.[37]

In contrast to our results, Bansilal *et al.* reported that fully adherents (PDC > 80%) to statins and ACEI/ARB had a significantly lower rate of MACE (included all-cause mortality or hospitalization for nonfatal MI; stroke; or coronary revascularization) than nonadherents (18.9% vs. 26.3%; HR 0.73; p = 0.0004) and partially adherents (18.9% vs. 24.7%; HR: 0.81; p = 0.02) groups at two years.[7]

In agreement with other studies,[22,34] we found that adherent patients to only 2 or 1 drugs had significant higher risk to composite endpoint compared with adherents to combinations of 4-3 drugs. However, splitting the composite endpoint in all-cause mortality and MACE, we found that these differences between adherents to 4-3 drugs versus adherents to 2 and 1 drugs disappeared, and were not statistically significant for MACE subgroup. Probably, these patients had higher mortality rate and worst prognosis.

In other studies where the adherence was not evaluated, users of all recommended drugs had a significant reduction of risk of all-cause mortality or MACE compared with user of 2 or 1 drugs.[9,33,35]

We did not find any statistical significant discrepancy between adherents and nonadherents to 4-3 drugs and composite endpoint risk, but our results showed a lower risk in adherents to 2 or 1 drug versus nonadherents to these combination for all-cause mortality, similar to Hamood *et al* study.[34] Our assumption to this difference was that we did not have enough sample size in the group of nonadherents to 4-3 drugs.

Finally, our findings showed that the composite endpoint risk in adherents is lower if patients were receiving 4-3 recommended drugs compared with adherents 2 or 1 drugs. We have found no studies comparing the composite endpoint risk only between adherent patients treated with combinations of 4-3, 2 and 1 recommended drugs.

Strengths and limitations

To our knowledge, this is the first population-based study in our setting that assessed the relation between adherence to pharmacological secondary prevention and risk of MACE in our population. The strengths of this study are the large number of patients included, representativeness for general population, complete socio-demographic data and long follow-up and real-world data.

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, the cause of mortality

is not available and we cannot capture hospital pharmacological treatments, which can be related with the mortality during the first weeks after the event. The individuals lost in follow-up during the first two months have no information available in the database to be captured, therefore these patients were excluded. Probably, these patients were followed in hospital, and not in PHC. SIDIAP database is a primary care database and it does not include any information registered in the hospital records.

Our data are representative of the Catalan and the Spanish population and previous studies have been published.[38–40]

Conclusions

According to our findings, the medication adherence to cardiovascular secondary prevention in our population was high. Most patients were treated with a combination of four or three drugs recommended.

Adherence to any combination of pharmacological therapy with aspirin, statins, beta-blockers, and ACEI or ARB reduced the composite endpoint risk, regardless the number of recommended drugs prescribed.

Adherence to a combination of four-three recommended drugs was significantly associated with a reduced mortality risk compared with adherents to two or one, but it was not significant for MACE.

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Tables

Table 1. Distribution of patients by drug class and number of drugs prescribed.

	Total N (%*)	Adherent N (%**)	Nonadherent N (%**)
Drug classes			
Antiplatelets	6350 (88.8)	5918 (93.2)	432 (6.8)
Statins	6279 (87.8)	5730 (91.3)	549 (8.7)
Beta-blockers	5534 (77.4)	4744 (85.7)	790 (14.3)
ACEI/ARB	5324 (74.4)	4630 (87.0)	694 (13.0)
Drug combinations			
4-3 drugs	5201 (82.0)	4226 (81.3)	975 (18.7)
2 drugs	718 (11.3)	585 (81.5)	133 (18.5)
1 drug	423 (6.7)	329 (77.8)	94 (22.2)
Total	7152 (100)	5692 (79.6)	1460 (20.4)

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers.
*Calculated from total of patients (7,152 patients). **Calculated from total of the row.

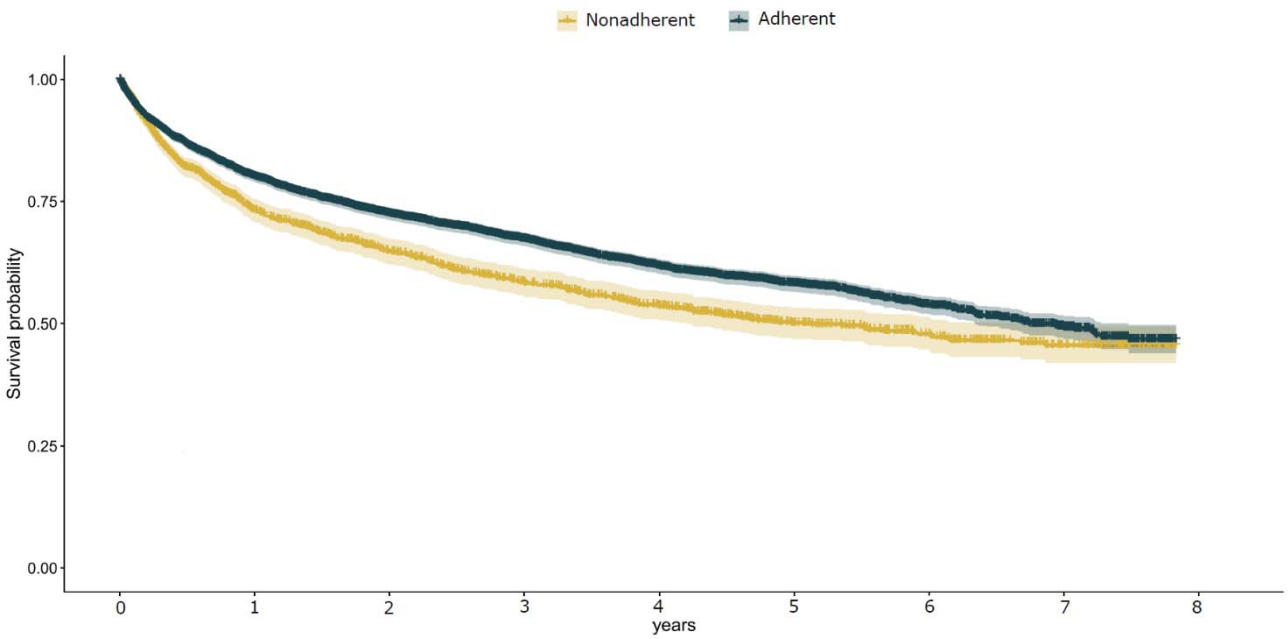
Table 2. Marginal structural model results of the adjusted association between medication adherence and composite endpoint risk by drug classes.

Drug classes	HR (95% CI)	Adjusted HR (95% CI)
Antiplatelets	0.57 (0.5-0.66)*	0.69 (0.59-0.81)*
Statins	0.62 (0.54-0.71)*	0.74 (0.64-0.86)*
Beta-blockers	0.87 (0.77-0.99)**	0.96 (0.85-1.1)**
ACEI/ARB	0.82 (0.72-0.93)**	1 (0.91-1.2)**

HR: hazard ratio; CI: confidence interval; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers. Composite endpoint includes: all-cause mortality, acute coronary syndrome and ischaemic stroke. *P value <0.001. **Statistically non-significant.

Figures

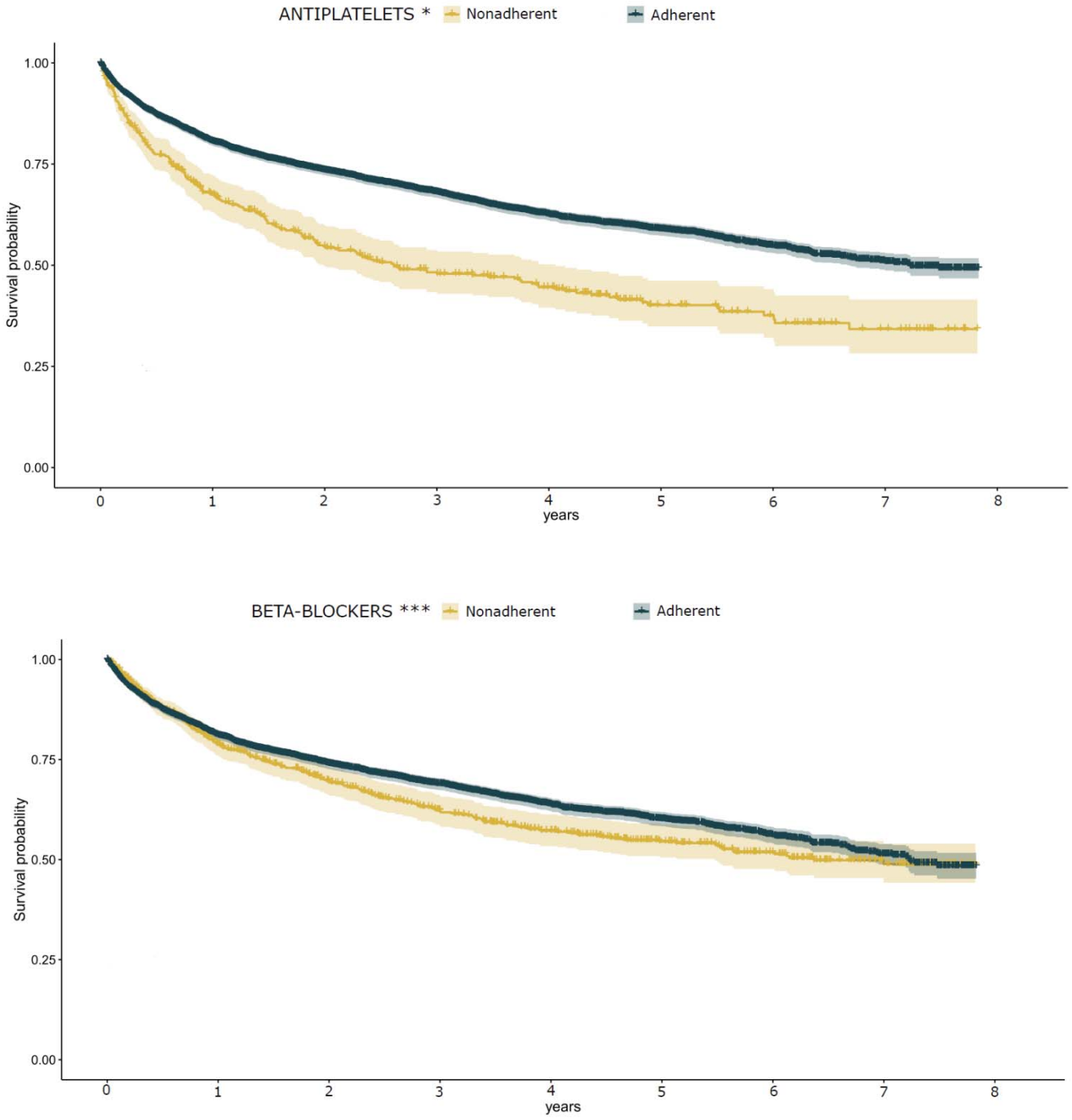
Figure 1. Kaplan-Meier curves for the composite endpoint for adherents and nonadherents in all follow-up period, regardless of number of drugs prescribed.

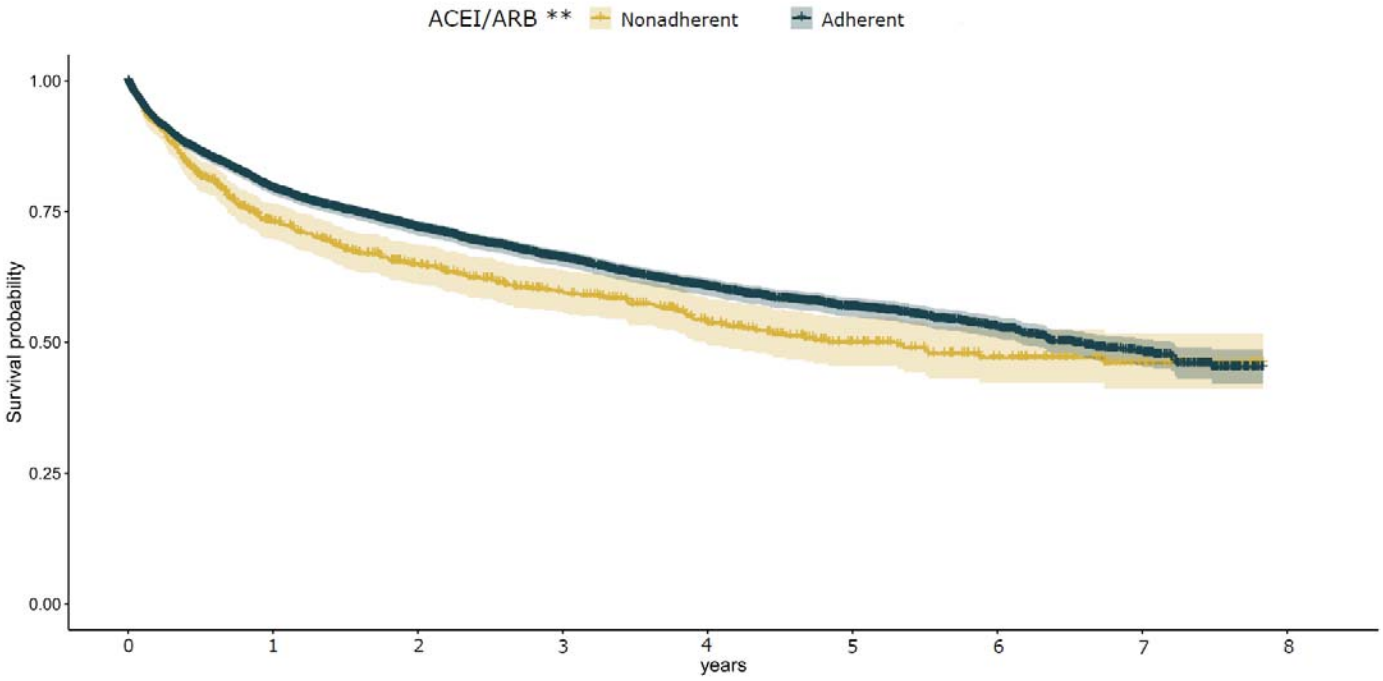


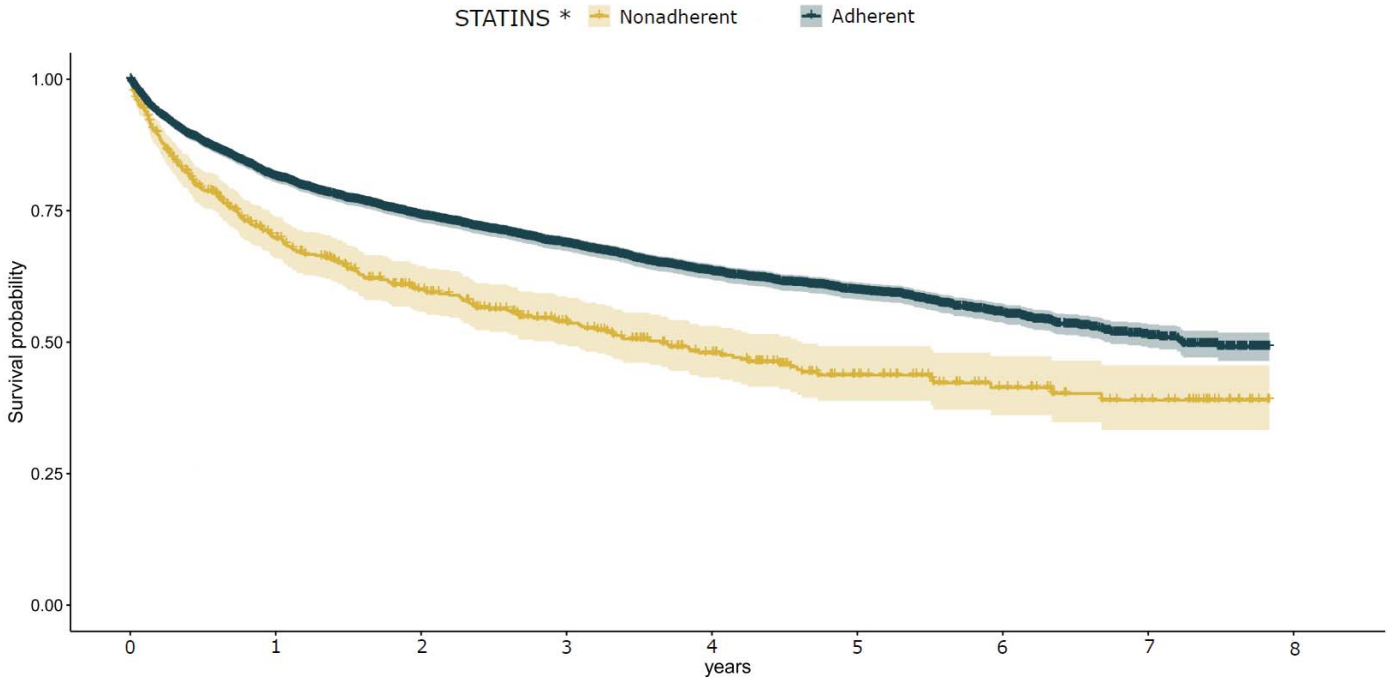
Composite endpoint: all-cause mortality and MACE (acute coronary syndrome and ischaemic stroke).

Statistically significant; P value <0.001

Figure 2. Kaplan-Meier curves for the composite endpoint comparing adherents with nonadherents by drug classes, regardless of number of drugs prescribed.



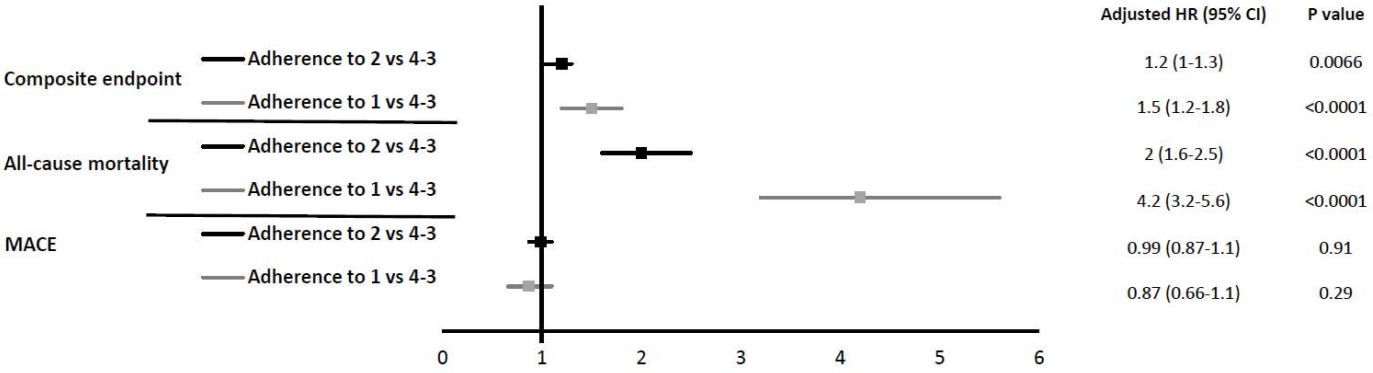




Composite endpoint: all-cause mortality and MACE (acute coronary syndrome and ischaemic stroke).

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers. Composite endpoint includes: all-cause mortality, acute coronary syndrome and ischaemic stroke. *P value <0.001; ** P Value <0.05; ***Statistically non-significant.

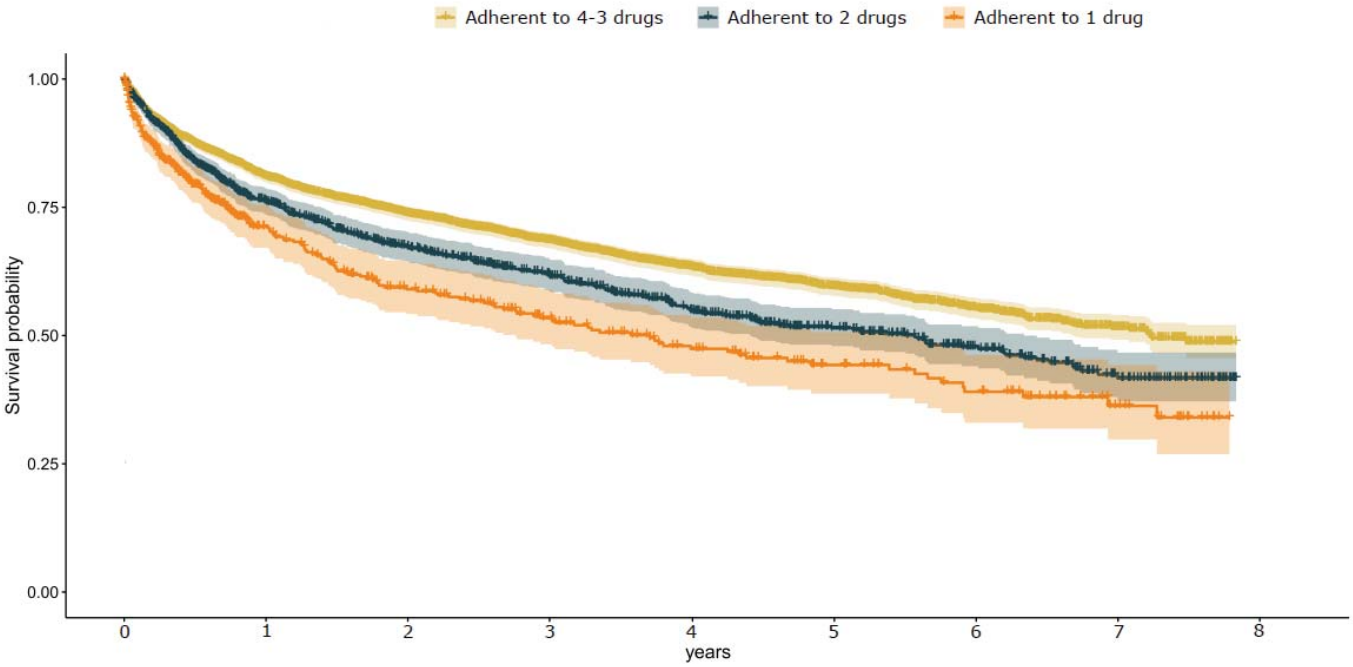
Figure 3. Forest plot of hazard ratios for the composite endpoint comparing drug combinations in adherent and nonadherent patients.



Composite endpoint: all-cause mortality and MACE (acute coronary syndrome and ischaemic stroke).

HR: hazard ratio; CI: confidence interval, ACS; acute coronary syndrome; MACE; major cardiovascular events.

Figure 4. Kaplan-Meier estimates time to the composite endpoint for adherence to a combination of 4-3 versus adherence to 2 or 1 study drugs.



Composite endpoint: all-cause mortality and MACE (acute coronary syndrome and ischaemic stroke).

Statistically significant; P value <0.001

Additional manuscript support information in Annex 1:

- Figure S1: Example of adherence analysis: adherent patient.
- Figure S2: Study flow chart.
- Table S1: International Classification of Disease, Nineth Revision (ICD-9) codes for endpoints of study and procedures and ICD-10 codes for comorbidities of interest or disease for exclusion.
- Table S2: Number of adherent and nonadherent patients for each drug combination after ACS.
- Table S3: Hazard ratios of composite endpoint comparing adherence between same drug combinations.
- Table S4: ATC codes of study drugs and comedications.

6.3. Other scientific publications

In addition, some of results were presented in two posters presented at two separate scientific conferences, one national and the other international. Additionally, the study protocol was published in the Journal of Medical Internet Research (JMIR) Research Protocols.

6.3.1. Poster 1

Sotorra Figuerola G, Ouchi D, Giner-Soriano M, Garcia-Sangenís A, Pera Pujadas H, Morros R. **Acute coronary syndrome in Catalonia: baseline characteristics of patients from a SIDIAP cohort (IMPACT study).** XXX Congreso de la Sociedad Española de Farmacología Clínica. Santander, 4-5 octubre 2018. *Basic & Clinical Pharmacology & Toxicology* 2018;123(S4):1-68(CP67). *Refer to Annex 2 (Poster).*

6.3.2. Poster 2

Gerard Sotorra-Figuerola, Dan Ouchi, Rosa Morros, Maria Giner-Soriano. **Impact of medication adherence by drug classes on mortality and cardiovascular morbidity after acute coronary syndrome in both sexes: population-based cohort study. 36th ICPE Congress, Abstracts of the 36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management**, Virtual, September 16-17, 2020. *Pharmacoepidemiology and Drug Safety* 2020;29(S3):1-684.

The poster was awarded as a Spotlight Poster. *Refer to Annex 3 (Poster).*

6.3.3. Protocol publication

Maria Giner-Soriano, Gerard Sotorra Figuerola, Jordi Cortés, Helena Pera Pujadas, Ana Garcia-Sangenis, Rosa Morros. **Impact of medication adherence on mortality and cardiovascular morbidity: protocol for a population-based cohort study.** JMIR Research Protocols 2018;7(3):e73. Doi:10.2196/resprot.8121. *Refer to Annex 4 (published protocol).*

7. DISCUSSION

This was a population-based cohort study that assessed baseline socio-demographic and clinical characteristics, prevalence of use of the 4 drugs recommended for CV secondary prevention, focusing on gender differences, and association between adherence to drugs and the risk of MACE and all-cause mortality in real world conditions of patients who had suffered an ACS.

7.1. Discussion for paper 1

In the first part of study, we assessed the baseline clinical characteristics and gender differences of 8,701 patients from primary healthcare (PHC) who suffered a first episode of ACS during 2009-2016. These patients were analysed overall, divided into genders and by number of study drugs prescribed.

The mean age of first ACS in our study was 65.3 years and 27.2% of patients were older than 75 years old. The prevalence of the most common comorbidities (hypertension, dyslipidaemia and diabetes mellitus) was similar to another previous Spanish study.(74)

Regarding the baseline clinical characteristics by gender, we found a higher percentage of men than women (71.3% men vs. 28.7% women) with ACS, similar to previous studies.(79-81,103–104) Women were older (71.1 vs. 63.0, $p<0.001$) and had more comorbidities such as hypertension, dyslipidaemia, HF, renal impairment and diabetes than men at baseline, except for peripheral artery disease, which was higher in men. Our results are in agreement with other studies that also found a higher prevalence of comorbidities in

women,(79,80,105) except for peripheral artery disease, which was also higher in men.(83)

Overall, nitrates were the comedication prescribed by far the highest, followed by the rest of comedications included with similar percentages, except for anticoagulants with much lower use, as they are not recommended for secondary prevention after ACS. The routine use of nitrates in STEMI and non-STEMI is not recommended. (13–15,27,28,73)

Also, we found that women had more comedications prescribed after the first ACS than men, as described by Ribas et al.(81) We think that this is probably because women were older at diagnosis. Anticoagulants and diuretics use was doubled in women, possibly related to their higher frequency of atrial fibrillation and HF than in men.

Most patients (91.3%) initiated treatment for secondary prevention with antiplatelets after the first ACS. Statins were the second most prescribed drug (85.7% of patients); beta-blockers (76.7% of patients) and ACEI/ARBs (66.3% of patients) were less prescribed. ACEI/ARBs might be less prescribed as they are not always recommended for all patients.(13–15,27,28,73) These results are quite similar to previous studies.(31,74,75) All study drugs were more commonly prescribed in men than in women, except for the ACEI/ARB group, which showed non-significant differences between genders, probably related to the higher frequency of hypertension in women in our study population.

Overall, aspirin and clopidogrel were the most frequently antiplatelet agents prescribed. DAPT was less frequently prescribed in women as described by previous studies,(82-84) probably because they were older at baseline.(106)

Pereira et al.(82) reported that women were less likely to be discharged with DAPT than men (OR 0.52, 95% CI 0.29-0.91). Bisoprolol, enalapril and losartan were the most prescribed beta-blockers with slight differences between genders. The most commonly prescribed statins overall were atorvastatin and simvastatin, without gender differences regarding the type of statin prescribed.

A high percentage of our overall population (79.5%) initiated treatment with a combination of 4 or 3 drugs, and almost half (47.7%) with 4 study drugs. The most common combination of 3 drugs (18.4%) was composed of an antiplatelet, a statin and a beta-blocker. Zeymer et al.(76) reported in a similar study that 92.5% of patients were treated with combination of 4-3 drugs and 62.6% with combination of 4. The combination of beta-blockers, statins and antiplatelets was also high (39.5%). However, Lafeber et al.(75) found fewer patients (67.0%) treated with the combination of an aspirin, a statin and at least one BP lowering agent.

Pereira et al.(82) reported on the number of drugs prescribed to STEMI and non-STEMI patients; the proportion of patients discharged with 3 drugs (aspirin + clopidogrel, beta-blocker and statin) was 76% and 69%, and those given 5 drugs (aspirin and clopidogrel, beta-blocker, ACEI/ARB and statin) was 61% and 48%, respectively. They concluded that the majority of younger patients (aged ≤80 years) were discharged with the recommended drugs, but only half of them received the full therapy with 5 drugs.

Women initiated secondary prevention with a combination of 4-3 drugs less frequently than men.(79,80,104,107-109) We found a higher proportion of women treated with ≤ 2 study than men. This may have occurred because women were older at first diagnosis and there is a trend to prescribe fewer

drugs to older patients,(82,108) because they have more comorbidities and comedications.(110). Therefore, this assumption could be extended to our finding that women were initiated with 4-3 drugs less frequently than men, because women were older than men when they suffered their first ACS.(111–113)

In fact, we found a strong association in the medication prescribed between being women and older in our population, probably because women had the first ACS at an older age than men. Several authors suggested that age >75 years is a potent predictor for not receiving therapy with 4 components.(76,82,108) Consequently, women had a lower probability of being treated with study drugs and a higher probability of being treated with other comedications.

7.2. Discussion for paper 2

In the second part of the study, we assessed the association between the composite endpoint (MACE and all-cause mortality) risk and adherence to study drugs for secondary prevention by pharmacological groups and number of drugs prescribed.

In this case, we included 7,152 patients; the study sample was reduced by 919 patients compared with the first study, because these patients had <60 days of follow-up in the survival analysis and they were excluded. Despite the sample size reduction, the mean age and gender distribution were similar to the first part of study.

Most of the patients were initiated on 4-3 drugs (82.0%) for secondary prevention treatment. The combination of 4 drugs was prescribed to nearly half of patients and, overall, almost 80% of patients were adherent (PDC ≥75%) to the study drug combination prescribed during the first year of treatment. The use of study drugs in our study population was higher than other previous observational studies,(74,76,87,94,98) and in concordance with other similar studies.(114,115) Also, we found higher medication adherence than another similar study.(74)

Overall, our results show that adherence to any drug combination led to a significant reduction of the composite endpoint risk compared to nonadherence, regardless of the number of drugs prescribed. However, comparing medication adherents and nonadherents by each pharmacological group, we found that adherence to prescribed drugs reduced the risk of the composite endpoint, and it was higher for statins and antiplatelets than other pharmacological groups, in concordance with previous studies.(94,98) Beta-blockers and ACEI/ARBs were also associated with a lower risk of the composite endpoint, but it was not statistically significant. Other authors reported that adherence to ACEI/ARBs and beta-blockers was not associated to lower risk of MACE or mortality.(60,94) Some recent studies indicated that beta-blockers improve 1-year prognosis after AMI, but it is not associated with reduced mortality beyond 1 year.(63,99,100) In contrast, another study found that adherence to beta-blockers was associated with a reduction of recurrent AMI.(64) Also, Bansilial et al.(30) reported that full and partially adherents (PDC >80%) to statins and ACEI/ARB had a significantly lower rate of MACE (included all-cause mortality) than nonadherents at 2 years.

Comparing adherent patients with the different number of study drugs prescribed, we found that adherence to a combination of 4-3 drugs was associated with a lower risk of having the composite endpoint compared with adherence to a combination of 2 or 1 drugs. These results were consistent with other previous studies.(87,98) However, when we split the composite endpoint in all-cause mortality and MACE, we found that these differences between groups disappeared for MACE subgroups without statistical significance. Probably, these patients had a higher mortality rate and worse prognosis. As per our knowledge, we did not find previous publications comparing these combinations and taking into account medication adherence; we only found similar studies where medication adherence was not evaluated. They reported that patients treated with all recommended drugs had a significant reduction of risk of all-cause mortality or MACE compared with patients treated with 2 or 1 drugs.(75,76,115)

We found a statistically significant lower risk of composite endpoint risk and all-cause mortality in adherents to 2 or 1drugs versus nonadherents to these combinations, similar to a study by Hamood et al.(98). However, we did not find statistically significant differences between adherent and nonadherent patients with the combination of 4-3 drugs, probably because we did not have a large enough sample size in the group of nonadherents.

Our results show that adherent patients to 4-3 drugs had a statistically significant lower composite endpoint risk compared with adherents to 2 and 1 drugs. Also, the time to the composite endpoint was shorter with 4-3 drugs than in other groups with fewer drugs. In the same line, adherents to 2 drugs had a statistically significant lower composite endpoint risk than adherents to only 1

recommended drug. However, we found no studies comparing the composite endpoint risk only between adherent patients treated with varying combinations of the recommended drugs.

8. STRENGTHS AND LIMITATIONS

The most important strengths of our study are the large number of patients included, the representativeness for the general population, complete clinical characteristics and socio-demographic data, long follow-up periods and real-world data. To our knowledge, this is the first population-based study in our setting conducted with SIDIAP (The Information System for Research in Primary Care) database, which analyses prescribed drugs and medication adherence, and its association between with the risk of MACE and all-cause mortality. The study provides high value knowledge about CVD in Catalonia (north-eastern Spain), as SIDIAP captures information from approximately 5.8 million inhabitants in southern Europe. The results can be extrapolated to the population of Catalonia, which is about 7.5 million people, approximately 12% of the Spanish population. The results can also be extrapolated to the rest of Spain, as the health systems and population characteristics are similar. The results obtained from the SIDIAP database are usually transferred to the Catalan Health Institute (ICS). ICS usually assesses the results and incorporates them into recommendations and guidelines in PHC when applicable. Studies conducted with electronic health records have some limitations inherent to electronic databases, such as incompleteness, loss of follow-up, potential confounders, non-randomised data and possible selection biases, which affect all population records and may be minimised using adequate statistical methods.

In addition, there are specific limitations in our database. Some of them are that prescriptions are not linked with diagnoses in SIDIAP database, the cause of mortality is not always available and we cannot capture hospital

pharmacological treatments, which can be related to prognosis and mortality during the first weeks after the event, or other hospital records such as the Killip-Kimbal class, LVEF, revascularisation, etc. as SIDIAP database is a PHC-based database.

Another limitation found during the study was the exclusion of patients who died in the first two months after ACS, as they had no information available in the database to be captured. Also, we excluded 2,058 patients for not having prescriptions in PHC after 120 days. These patients were likely followed in hospital, and not in PHC.

In addition, the database does not include the type of AMI, although we did not have the intention to classify by type of AMI, because clinical practice guidelines recommend the same pharmacological treatment for secondary prevention in STEMI and non-STEMI. Moreover, we did not review study drug contraindications in patients who did not have all 4 study drugs prescribed.

Despite the inherent limitations of database studies, the data in this study are supported by previous studies, and the presence of CV risk factors and outcomes has been previously validated in SIDIAP. (116–118)

9. CONCLUSIONS

1. Women were older, had more comorbidities at baseline and received more comedication after ACS than men. The proportion of men and women in our study was not balanced (28.7% women).

2. Most patients initiated treatment for secondary prevention with antiplatelets (91.3% of patients) and statins (85.7%). Beta-blockers (76.5%) and ACEI/ARBs (66.3%) were less prescribed. Most patients (79.5%) were treated with a combination of 4-3 drugs.

3. Men initiated more recommended drugs for secondary prevention after ACS than women. Men also received more DAPT therapy and atorvastatin than women.

4. Medication adherence to secondary prevention in our population was high (79.6%), regardless the number of drugs prescribed. 81.3% of patients with 4-3 drugs prescribed were adherent. Medication adherence to combinations of 2 and 1 drug was also high.

5. Adherence to a combination of 4-3 drugs was significantly associated with a reduced mortality risk compared with adherents to 2 or 1, but it was not significant for MACE.

6. Adherence to 4-3 drugs prescribed was associated with a lower risk of the composite endpoint than adherence to 2 drugs or 1 drug.

7. Adherence to any combination of pharmacological therapy with antiplatelets, statins, beta-blockers and ACEI/ARBs reduced the composite endpoint risk, regardless of the number of drugs prescribed.

10. REAL WORLD IMPLICATIONS

To our knowledge, the IMPACT study is the first population-based study in SIDIAP database that assessed the association between adherence to pharmacological secondary prevention and MACE and all-cause mortality risk in our population.

SIDIAP covers a population of more than 5.8 million people living in Catalonia (north-eastern Spain), which is about 80% of the total of 7.5 million population in Catalonia and approximately 12% of the Spanish population. The results can be extrapolated to the population of Catalonia and the rest of Spain.

Overall, we found a high number of patients with 4-3 recommended drugs prescribed for secondary prevention as well as excellent medication adherence. However, these numbers can be improved in order to ensure that all patients receive 4-3 drugs after their first ACS, unless contraindicated, because around 20% of patients are still not receiving the complete therapy recommended by clinical practice guidelines. Despite this, adherence was high in our population (around 80%), but this can also be improved if physicians, pharmacists and nurses work together and implement measures to educate patients in the importance of adherence to long-term secondary prevention treatment.

Our results and other previous studies have shown that adherence to antiplatelet medication and statins provide more CV protection in secondary prevention than beta-blockers and ACEI/ARB. However, it does not mean that beta-blockers and ACEI/ARB do not play crucial roles in secondary prevention; they are still recommended as essential drugs after ACS, and they have widely demonstrated efficacy and efficiency in secondary prevention.

Based on our results and other previous studies, it is extremely important to focus on the differences in number of drugs prescribed between genders. We found that women were older, had more comorbidities at baseline and received more comedications after the first ACS than men, but women initiated secondary prevention with recommended drugs less frequently than men. Our assumption regarding this underprescription is because women are older and have more comorbidities, although the clinical practice guidelines do recommend the same treatment for women and the older population than men at any age. It is likely that the prescription and use of drugs is different between women and men in several pathologies.

In addition, real-world data studies, in contrast to clinical trials, allow us to assess several drugs together and in real-life conditions, instead of only one drug. Therefore, the effectivity of all drugs used to treat a pathology can be studied using real-world data studies.

The applicability of this type of study allows the investigators:

- To conduct subsequent studies to assess the reluctance of prescribers to prescribe treatment according to clinical practice guidelines.
- To conduct subsequent prospective studies to improve these drug prescriptions.
- After the completion of both these studies, the results of our study should be reassessed using the same study design.
- In addition, these results obtained with SIDIAP database should assess in order to be incorporated into the recommendations and guidelines in

PHC in the ICS and other local guidelines in PHC with an equivalent population, like other regions of Spain and southern Europe.

PHC professionals (family physicians, community and PHC pharmacists, and nurses) should work together to ensure that all patients, regardless of gender, receive all the recommended drugs after the first ACS and that patients adhere to these medications.

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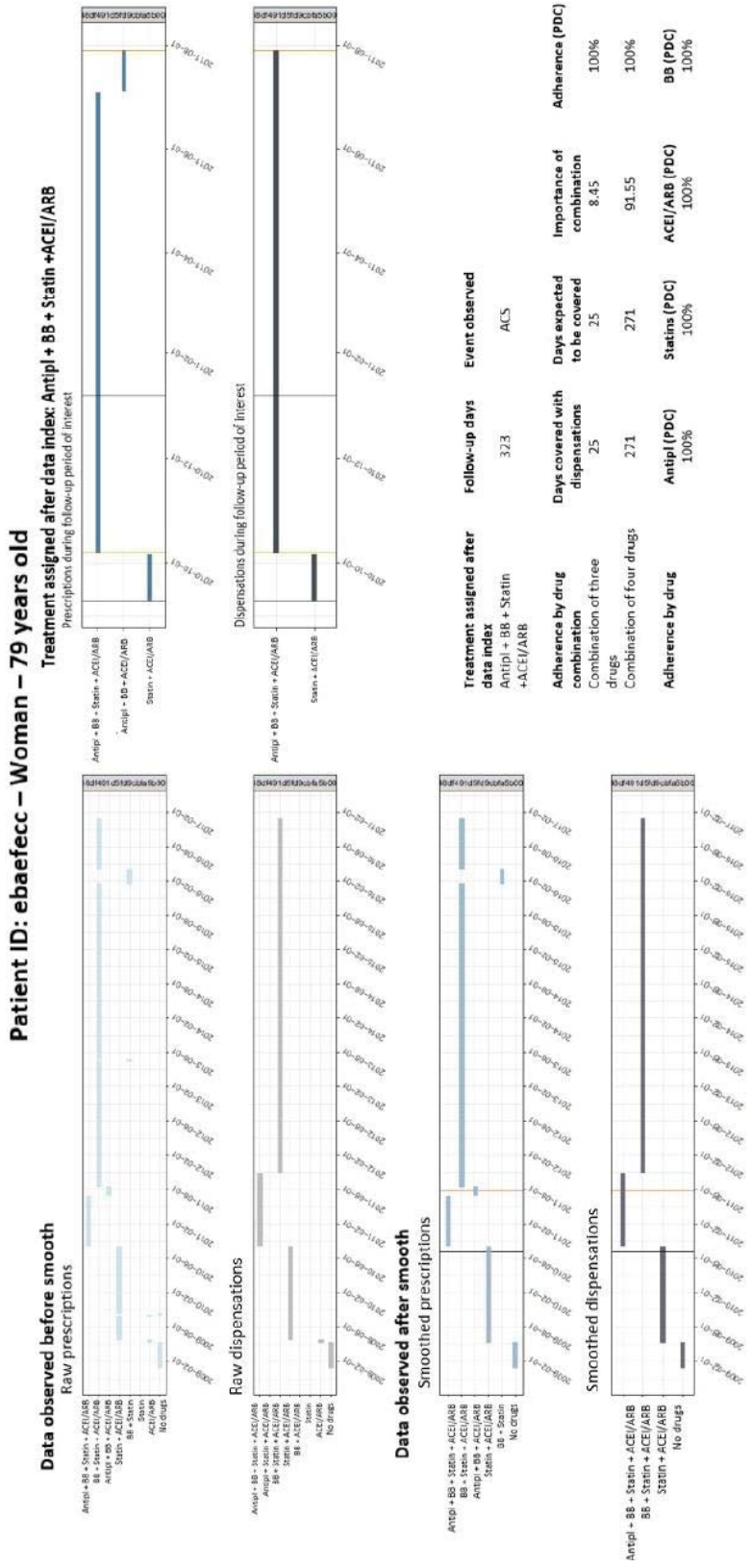
12. ANNEX 1

Sotorra-Figuerola G, Ouchi D, Giner-Soriano M, Morros R. **Impact of adherence to drugs for secondary prevention on mortality and cardiovascular morbidity: a population-based cohort study. IMPACT study**. Pharmacoepidemiol Drug Saf. 2021 May 3. doi: 10.1002/pds.5261. Epub ahead of print. PMID: 33938603.(102) (Paper 2)

Additional manuscript support information:

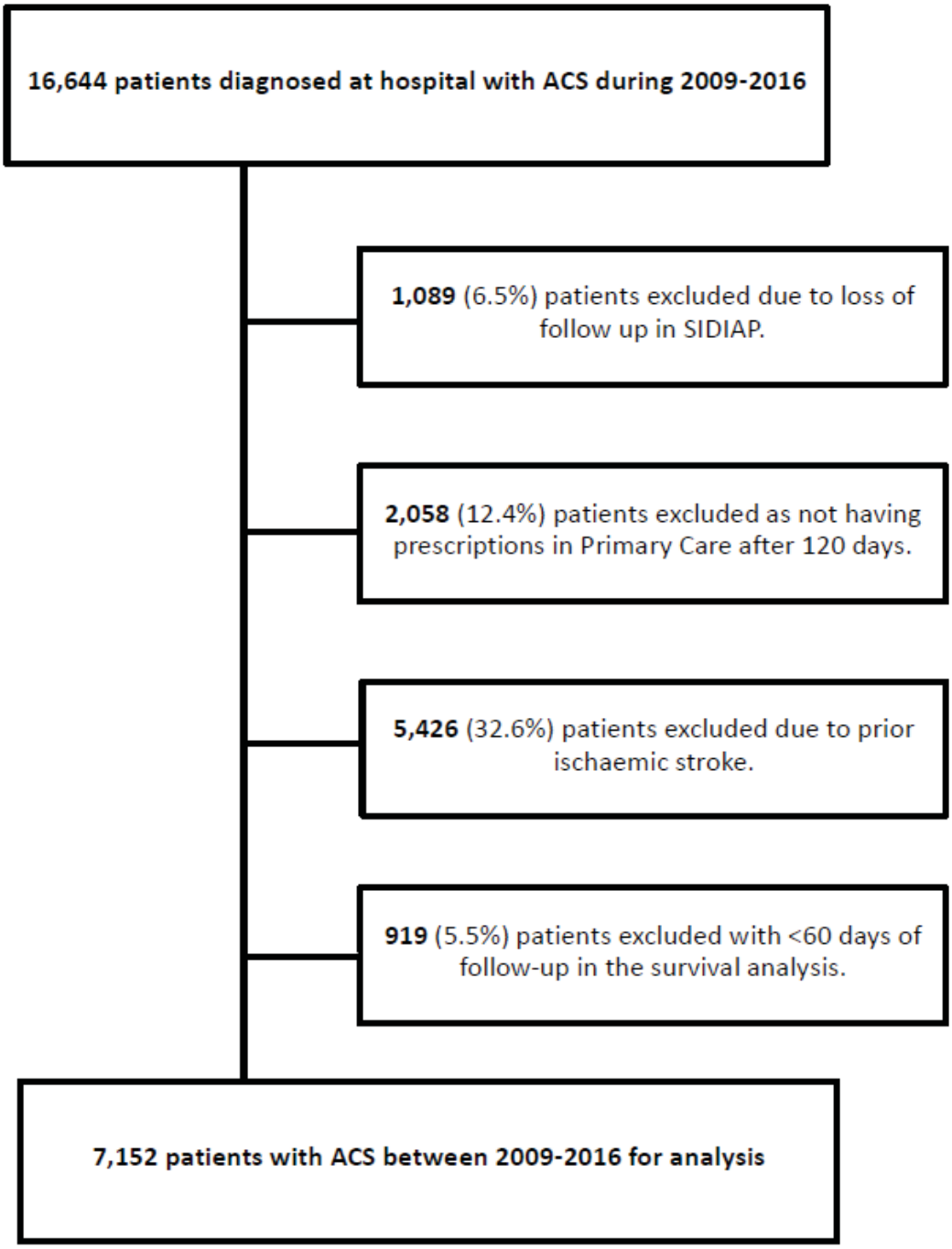
- Figure S1: Example of adherence analysis: adherent patient.
- Figure S2: Study flow chart.
- Table S1: International Classification of Disease, Nineth Revision (ICD-9) codes for endpoints of study and procedures and ICD-10 codes for comorbidities of interest or disease for exclusion.
- Table S2: Number of adherent and nonadherent patients for each drug combination after ACS.
- Table S3: Hazard ratios of composite endpoint comparing adherence between same drug combinations.
- Table S4: ATC codes of study drugs and comedications.

Figure S1: Example of adherence analysis: adherent patient.



Antipl: antiplatelets; BB: beta-blockers; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; ACS: acute coronary syndrome; PDC: proportion of days covered.

Figure S2: Study flow chart.



ACS; acute coronary syndrome. AMI; acute myocardial infarction.

Table S1: International Classification of Disease, Nineth Revision (ICD-9) codes for endpoints of study and procedures and ICD-10 codes for comorbidities of interest or disease for exclusion.

ICD-9 code	Description
411*	Unstable angina and other forms of acute coronary heart disease.
410*	Acute myocardial infarction
433*, 434*, 435*, 436*, 437*	Ischaemic stroke
ICD-10 code	**Description**
I24*, I25*	Coronary heart disease
I63*, I65*, I66*, I67.2, I67.8	Ischaemic stroke
G45	Transient cerebral ischaemic attack.
I70*, I73*, I74*	Peripheral vascular disease
E78*	Dyslipidaemia
I10*, I15*	Hypertension
E10*, E11*	Diabetes mellitus
I48	Atrial fibrillation
I50*	Heart failure
C00*-C97*	Malignancies
J40*-J44*	Chronic obstructive pulmonary disease
F30*-F39*	Depression
M05*, M06*, M15*-M19*	Arthritis (osteoarthritis or rheumatoid arthritis)
M80*, M81*	Osteoporosis
N18*	Chronic Kidney disease
B20*-B24*	Human Immunodeficiency virus
G30*, G31*	Alzheimer's disease, other dementias

Table S2: Number of adherent and nonadherent patients for each drug combination after ACS.

	Overall (%*)	Women (%**)	Men (%**)
N	7152 (100)	2122 (29.7)	5030 (70.3)
Age	**Overall (SD)**	**Women (SD)**	**Men (SD)**
Mean	70.69 (13.66)	68.27 (13.09)	76.42 (13.27)
Events by sex	**Overall (IR)**	**Women (IR)**	**Men (IR)**
No event or death	4676 (0.83)	1330 (0.24)	3346 (0.60)
Death	712 (0.13)	303 (0.05)	409 (0.07)
ACS or ischaemic stroke	1764 (0.31)	489 (0.09)	1275 (0.23)
Events by adherence	**Overall (IR)**	**Adherent (IR)**	**Non-Adherent (IR)**
Overall N (%)	7152 (100)	5739 (80.3)	1413 (19.7)
No event or death	4676 (0.83)	3842 (0.69)	834 (0.15)
Death	712 (0.12)	432 (0.08)	280 (0.05)
ACS or ischaemic stroke	1764 (0.31)	1465 (0.26)	299 (0.05)
Adherence by drug combination	**Overall (%*)**	**Adherent (%**)**	**Non-Adherent (%**)**
Antiplatelets + Statins + Beta-blockers + ACEI/ARB	3264 (45.6)	2610 (80.0)	654 (20.0)
Antiplatelets + Statins + Beta-blockers	1101 (15.4)	898 (81.6)	203 (18.4)
Antiplatelets + Statins + ACEI/ARB	637 (8.9)	522 (81.9)	115 (18.1)
Antiplatelets + Beta-blockers + ACEI/ARB	164 (2.3)	134 (81.7)	30 (18.3)
Statins + Beta-blockers + ACEI/ARB	117 (1.6)	94 (80.3)	23 (19.7)
Antiplatelets + Statins	365 (5.1)	300 (82.2)	65 (17.8)
Antiplatelets + Beta-blockers	100 (1.4)	78 (78.0)	22 (22.0)
Antiplatelets + ACEI/ARB	177 (2.5)	137 (77.4)	40 (22.6)
Beta-blockers + ACEI/ARB	124 (1.7)	99 (79.8)	25 (20.2)
Statins + Beta-blockers	82 (1.1)	60 (73.2)	22 (26.8)
Statins + ACEI/ARB	178 (2.5)	137 (77.0)	41 (23.0)
Antiplatelets	175 (2.5)	129 (73.7)	46 (26.3)
Beta-blockers	114 (1.6)	90 (78.9)	24 (21.1)
ACEI/ARB	358 (5.0)	257 (71.8)	101 (28.2)
Statins	196 (2.7)	147 (75.0)	49 (25.0)

*ACS: acute coronary syndrome; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; IR: incident rate per 100 person-year *Calculated from total of patients (7152 patients). **Calculated from total of the row.*

Table S3: Hazard ratios of composite endpoint comparing adherence between same drug combinations.

	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Composite endpoint				
Adherence to 4-3 vs nonadherence to 4-3	0.96 (0.85-1.1)	0.42	1 (0.9-1.1)	0.85
Adherence to 2-1 vs nonadherence to 2-1	1.2 (1.1-1.3)	0,00055	1.2 (1.1-1.3)	0.00025
All-cause mortality				
Adherence to 4-3 vs nonadherence to 4-3	NULL	NULL	NULL	NULL
Adherence to 2-1 vs nonadherence to 2-1	1.9 (1.60-2.2)	<0,0001	1.6 (1.3-1.9)	<0,0001
ACS or ischaemic stroke				
Adherence to 4-3 vs nonadherence to 4-3	1.1 (1-1.3)	0.051	1.2 (1-1.3)	0.03
Adherence to 2-1 vs nonadherence to 2-1	1 (0.81-1.4)	0.73	1.1 (0.96-1.2)	0.17

HR: hazard ratio; CI: confidence interval, ACS; acute coronary syndrome.

Table S4: ATC codes of study drugs and comedications.

ATC code	Description of therapeutic group
Study drugs	
B01AC	Platelet aggregation inhibitors
C07	Beta-blockers
C09A, C09B	Angiotensin-converting enzyme inhibitors
C09C, C09D	Angiotensin-receptor blockers
C10AA, C10B	Statins
Comedications	
C03	Diuretics
C02	Antihypertensive drugs
C08CA, C08D	Calcium-channel blockers
B01AA, B01AB, B01AD, B01AE, B01AF, B01AX	Anticoagulants
A10	Drugs used in diabetes
C10AB, C10AC, C10AD, C10AX	Other lipid-lowering drugs
C01A, C01B	Digoxin and antiarrhythmics
C01DA,	Nitrates
N05A	Antipsychotics
M01A, N02BA, N02BB	Non-steroidal anti-inflammatory drugs

13. ANNEX 2

POSTER: Sotorra Figuerola G, Ouchi D, Giner-Soriano M, Garcia-Sangenís A, Pera Pujadas H, Morros R. **Acute coronary syndrome in Catalonia: baseline characteristics of patients from a SIDIAP cohort (IMPACT study).** XXX Congreso de la Sociedad Española de Farmacología Clínica. Santander, 4-5 octubre 2018. *Basic & Clinical Pharmacology & Toxicology* 2018;123(S4):1-68(CP67).

XXX CONGRESO
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10/9 2018 Por el beneficio terapéutico de los pacientes
SANTANDER 3, 4 y 5 de octubre de 2018
Valdecilla
Farmacología clínica

Tratamiento para la prevención secundaria en síndrome coronario agudo. Estudio de cohortes con datos de vida real (Estudio IMPACT)

Authors: Gerard Sotorra[1,2], Dan Ouchi[1,2], Maria Giner-Soriano[1,2,3], Ana Garcia-Sangenis[1], Helena Pera Pujades[1], Rosa Morros[1,2,3]

[1]Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAPJGol), Barcelona, Spain. [2]Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain. [3]Institut Català de la Salut, Barcelona, Spain.

OBJETIVO

Describir las características basales de los pacientes con síndrome coronario agudo (SCA) y su tratamiento farmacológico prescrito para la prevención secundaria de eventos cardiovasculares.

METODOLOGÍA

Estudio de cohortes de base poblacional que incluye los pacientes adultos con un primer episodio de SCA (infarto agudo de miocardio –IAM– o angina inestable) que haya motivado el ingreso en alguno de los hospitales del Instituto Catalán de la Salud (ICS) entre 2009-2016 y que son atendidos en los centros de atención primaria (AP) del ICS. La información sociodemográfica y clínica se obtuvo de la base de datos SIDIAP (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria), que contiene información anonimizada procedente de la historia clínica informatizada de 279 centros de AP del ICS (aproximadamente 5,8 millones de personas, 80% de la población catalana) sobre: datos sociodemográficos, diagnósticos, exploraciones clínicas, hábitos tóxicos, datos de laboratorio y datos de prescripción y facturación de farmacia. Se analizó la prescripción electrónica de AP después del ingreso hospitalario y hasta los 120 días siguientes de los cuatro grupos farmacológicos recomendados en prevención secundaria en SCA: antiagregantes, betabloqueantes, estatinas y fármacos que actúan al sistema renina-angiotensina (inhibidores de la enzima conversora de angiotensina; IECA, y antagonistas de los receptores de angiotensina II; ARA II).

RESULTADOS

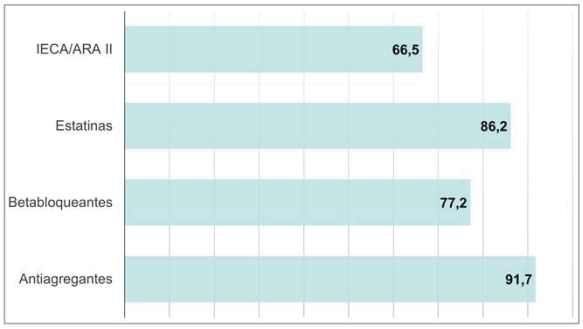
Se diagnosticaron 10.153 pacientes de un primer episodio de SCA en el periodo de estudio. Se disponía de datos de prescripción en AP para 7.877 (77,6%) pacientes. La mayoría de pacientes (91,7%) tenían prescripción de antiagregantes. Estatinas, betabloqueantes y IECA o ARA II se prescribieron en 86,2%, 77,2% y 66,5% de pacientes, respectivamente. En cuanto a la combinación recomendada de cuatro grupos, estaba prescrita en 48,3% de los pacientes, mientras que el resto de pacientes tenía prescripciones de tres, dos o un fármaco (6,7% de los pacientes solo tenían un fármaco prescrito y no se incluyen en la Figura 2).

Tabla 1. Características basales de los pacientes incluidos

Características basales	N= 10153
	n (%)
Infarto agudo de miocardio	7954 (78,3)
Sexo, mujeres	3192 (31,4)
Edad, media (DE)	65,7 (14,3)
Edad ≥ 65	5628 (55,4)
Fumadores	1247 (58,0)
IMC, media (DE)	29,0 (4,9)
Colesterol total, media (DE)	205,2 (44,6)
Comorbilidades	**n (%)**
Arteriopatía periférica	544 (5,4)
Artritis	1910 (18,8)
Cáncer	988 (9,7)
Depresión	846 (8,3)
Diabetes mellitus	2745 (27,0)
Dislipemia	4168 (41,1)
EPOC	1058 (10,4)
Enfermedad renal crónica	816 (8,0)
Fibrilación auricular	655 (6,5)
Hipertensión	5343 (52,6)
Insuficiencia cardíaca	460 (4,5)
Osteoporosis	510 (5,0)
Medicación concomitante	**n (%)**
Antagonistas de canales de calcio	1653 (16,3)
Anticoagulantes orales	893 (8,8)
AINE	2133 (21,0)
Antipsicóticos	294 (2,9)
Digoxina	446 (4,4)
Diuréticos	2309 (22,7)
Hipoglucemiantes	2491 (24,5)
Hipolipemiantes	390 (3,8)
Nitratos	3308 (32,6)

DE; desviación estándar, IMC; índice de masa corporal, EPOC; enfermedad pulmonar obstructiva crónica, AINE; antiinflamatorios no esteroideos.

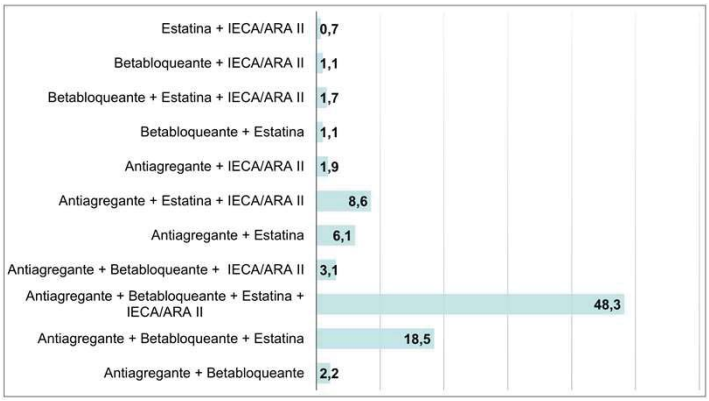
Figura 1. Población que inicia tratamiento para prevención secundaria (%)



N= 7877

IECA; inhibidores de la enzima conversora de angiotensina
ARA II; antagonistas de receptores de angiotensina II

Figura 2. Tratamientos farmacológicos combinados (%)



CONCLUSIONES

Se estudiaron 7.877 pacientes con SCA y prescripción farmacológica en AP durante el periodo de estudio. Menos de la mitad de los pacientes tenían prescripción de los cuatro grupos farmacológicos recomendados después del ingreso hospitalario. El tratamiento antiagregante fue el más prescrito para la prevención secundaria, mientras que el resto de grupos farmacológicos recomendados se prescribieron en menor grado. Respecto a los pacientes que no tienen registros de prescripción en AP, es posible que su seguimiento se lleve a cabo por el especialista hospitalario.

Los siguientes pasos de nuestro estudio serán estimar la adherencia y la persistencia al tratamiento para prevención secundaria y estudiar su relación con la incidencia de eventos cardiovasculares posteriores.

14. ANNEX 3

POSTER: Gerard Sotorra-Figuerola, Dan Ouchi, Rosa Morros, Maria Giner-Soriano. **Impact of medication adherence by drug classes on mortality and cardiovascular morbidity after acute coronary syndrome in both sexes: population-based cohort study. 36th ICPE Congress, Abstracts of the 36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management**, Virtual, September 16-17, 2020. *Pharmacoepidemiology and Drug Safety* 2020;29(S3):1-684.

Impact of medication adherence by drug classes on mortality and cardiovascular morbidity after acute coronary syndrome in both sexes: population-based cohort study.

Authors: Gerard Sotorra-Figuerola[1,2], Dan Ouchi[1,2], Rosa Morros[1,2,3], Maria Giner-Soriano[1,2,3]

[1]Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jol i Gurina (IDIAPJGol), Barcelona, Spain. [2]Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain. [3]Institut Català de la Salut, Barcelona, Spain

BACKGROUND

Long-term administration of antiplatelets, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) as a secondary prevention improves survival after an acute coronary syndrome (ACS). Adherence to these drug classes is related to reduce a cardiovascular morbidity and mortality.

OBJECTIVE

To assess the relationship between the adherences to the four study classes for secondary prevention and cardiovascular morbidity and all-cause mortality (composite endpoint) in patients after a first episode of ACS in both sexes.

METHODS

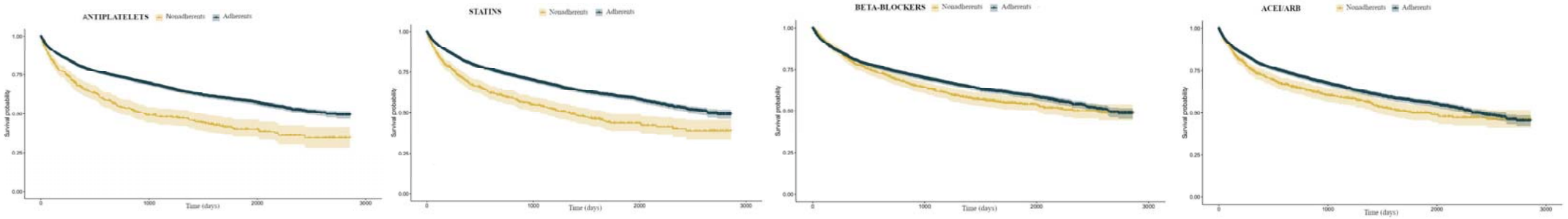
- **Design:** population-based cohort study.
- **Population**: adults admitted to hospital with a first episode of ACS during 2009-2016.
- **Study drug classes:** antiplatelets, statins, beta-blockers and ACEI/ARB.
- **Data Source:** SIDIAP (Information System for research in Primary Care) database (Catalonia, Spain).
- **Composite endpoint included**: ACS, ischaemic stroke and all-cause mortality.
- **Adherence assessment:** proportion of days covered (PDC), classifying the patients into adherents (≥85%) and nonadherents (<85%).
- **Statistical analysis:** time to composite endpoint by means of nonparametric Kaplan–Meier curves and log-rank test for group comparison.

RESULTS

Population characteristics

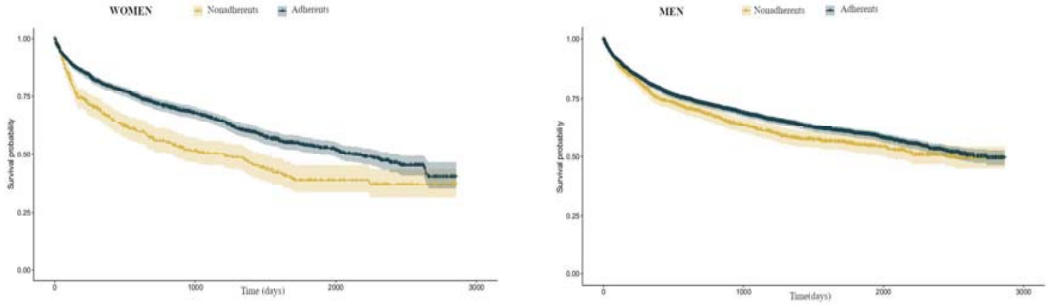
- 7,152 patients met the inclusion criteria having at least one study drug prescribed.
- 70.3% were men and the mean age was 70.7 years-old (men: 68.3; women: 76.4).
- During follow-up (median 2.5 years): 1,139 (22.6%) patients suffered a second ACS, 136 (2.7%) had an ischemic stroke and 409 (8.1%) died.

Kaplan-Meier curves: time to composite endpoint in adherents and nonadherents by drug classes.



- Adherent patients had a significant lower probability to have a subsequent cardiovascular event or death (assessed as composite endpoint) than nonadherent patients for all drug classes. The observed benefits of being adherent were higher in antiplatelets (median survival probability: 2636 days in adherents and 955 days in nonadherents, p<0.001) and statins (median survival probability: 2637 days in adherents and 1331 days in nonadherents, p<0.001).

Kaplan-Meier curves: time to composite endpoint in adherents versus nonadherents by sex, regardless the number of drugs and drug combination prescribed.



- Adherent men and women had a significant lower probability to suffer a second event or death (assessed as a composite endpoint) than nonadherent. The effect of being adherent was higher in women (median survival probability: 2115 days in adherents and 1202 days in nonadherents, p<0.001).

CONCLUSION

Adherence to study drugs after a first ACS was associated to lower probability of suffering a new cardiovascular event or death. This effect was higher for antiplatelets and statins. The differences between sexes were slight, although nonadherent women had more probability to suffer a second event or death than men, particularly, at the end of follow-up, probably because women were older.

Disclosure of funding source: *this study obtained funding for data extraction from SIDIAP database at the "6ª convocatòria d'ajuts SIDIAP" in March 2017.*

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15. ANNEX 4

PROTOCOL PUBLICATION: Maria Giner-Soriano, Gerard Sotorra Figuerola, Jordi Cortés, Helena Pera Pujadas, Ana Garcia-Sangenis, Rosa Morros. **Impact of medication adherence on mortality and cardiovascular morbidity: protocol for a population-based cohort study.** JMIR Research Protocols 2018;7(3):e73. Doi:10.2196/resprot.8121

Protocol

Impact of Medication Adherence on Mortality and Cardiovascular Morbidity: Protocol for a Population-Based Cohort Study

Maria Giner-Soriano[1,2,3*], PhD, PharmD; Gerard Sotorra Figuerola[1,4*], MSc, PharmD; Jordi Cortés[1,4,5,6*], MSc; Helena Pera Pujadas[1,4,6*], MSc, PharmD; Ana Garcia-Sangenis[1,4*], PharmD, MSc; Rosa Morros[1,2,3,6*], MD PhD

[1]Medicines Research Unit, Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Barcelona, Spain

[2]Departament de Farmacologia, Terapèutica i Toxicologia, Universitat Autònoma de Barcelona, Bellaterra, Spain

[3]Institut Català de la Salut, Barcelona, Spain

[4]Universitat Autònoma de Barcelona, Bellaterra, Spain

[5]Departament d'Estadística i Investigació Operativa, Universitat Politècnica de Catalunya, Barcelona, Spain

[6]Spanish Clinical Research Network, Unidad de Investigación Clínica y Ensayos Clínicos, Institut Universitari d'Investigació en Atenció Primària, Barcelona, Spain

[*]all authors contributed equally

Corresponding Author:
Maria Giner-Soriano, PhD, PharmD
Medicines Research Unit
Institut Universitari d'Investigació en Atenció Primària Jordi Gol
Gran Via de les Corts Catalanes 587
àtic
Barcelona, 08007
Spain
Phone: 34 934824110
Email: mginer@idiapjgol.info

Abstract

Background: Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, such as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. CVD is the leading threat to global health, whether measured by mortality, morbidity, or economic cost. Long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers improves survival in patients with stablished coronary heart disease. Nevertheless, adherence to prescribed medication is poor for long-term drug treatment.

Objective: We aim to assess the relationship between adherences to the four pharmacological groups recommended for secondary prevention and the clinical outcomes of cardiovascular morbidity and mortality in patients with established CHD according to the level of adherence to these drugs in a population of incident cases of acute coronary syndrome (ACS).

Methods: Population-based cohort study of patients with a first episode of ACS during 2006-2015 in the Information System for Research in Primary Care (SIDIAP) database. We will estimate adherence to these drugs. The primary endpoint is a composite of all-cause mortality, ACS, and ischaemic stroke. Bivariate analyses will be performed estimating odds ratios for categorical variables and mean differences for continuous variables. Hazard ratios for adherences will be calculated for outcome events using Cox proportional hazard regression models, and proportionality of hazards assumption will be tested.

Results: We expect to estimate adherence to all four study treatments, the incidence of MACE, and to analyze if this incidence is associated with the level of drug adherence.

Conclusions: We expect to find that adherent patients have a lower risk of the primary endpoints compared with nonadherent patients.

Trial Registration: This study protocol was classified as EPA-OD by the AEMPS (IJG-EST-2017-01-2017-01, 07/04/2017) and registered in the EU PAS register (EUPAS19017, 09/05/2017).

(JMIR Res Protoc 2018;7(3):e73) doi:10.2196/resprot.8121

KEYWORDS

cardiovascular diseases; coronary heart disease; acute coronary syndrome; adherence; aspirin; statins; beta-blockers; angiotensin-converting enzyme inhibitors; angiotensin-receptor blockers

Introduction

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, such as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. CVD is the leading threat to global health, whether measured by mortality, morbidity, or economic cost [1]. In 2012, it was the leading cause of mortality worldwide, accounting for 31% of an estimated 56 million deaths from all causes. Also, CVD was responsible for the largest proportion of deaths for noncommunicable diseases under the age of 70 years, 37% of 16 million deaths [2].

Despite these numbers, the incidence of CVD death has decreased dramatically over the last four decades due to both population-level lifestyle changes in diet, smoking, and physical activity, and the development of effective interventions to treat individuals. The latter includes invasive procedures and effective drugs to tackle modifiable CVD risk factors [3].

A number of randomized clinical trials, meta-analyses and cohort studies have demonstrated 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 CVD. Nevertheless, adherence to prescribed medication is poor for long-term drug treatment in CVD [1,4-6]. Different factors have been described to be related with long-term nonadherence [1,5-7].

In a recent cohort study conducted by Bansilal et al [4], 4015 patients who had suffered an acute myocardial infarction (AMI) were categorized according to their drug adherence to statin and ACEI into three categories: fully adherent (≥80% proportion of days covered [PDC]), partially adherent (40-79% PDC) or nonadherent (<40% PDC). Fully adherents had lower rates of major cardiovascular events (MACE) than partially adherents, 18.9% vs 24.7% (adjusted hazard ratio [HR] 0.81, 95% CI 0.69-0.94) and nonadherents, 18.9% vs 26.3% (HR 0.72, 95% CI 0.62-0.85).

In the cohort study conducted by Lafeber et al [8], 2706 CHD patients were included. Of them, 67% were treated with a combination of aspirin, statin, and at least one blood pressure (BP)-lowering agent for secondary prevention. After a median follow-up period of five years, the combination therapy compared with no combination showed lower rates for all events: AMI, HR 0.68 (95% CI 0.49-0.96); ischaemic stroke, HR 0.37 (95% CI 0.16-0.84); vascular mortality, HR 0.53 (95% CI 0.33-0.85); composite endpoint of the previous events, HR 0.66 (95% CI 0.49-0.88); and all-cause mortality, HR 0.69 (95% CI 0.49-0.96).

A population-based cohort study performed in Spain assessed adherence to secondary prevention drugs in a cohort of 7462 patients who survived an acute coronary syndrome (ACS) [6]. Medication adherence was evaluated by determining the PDC for each therapeutic group (antiplatelet agents, beta-blockers, ACEI or ARB, and statins) in the nine months following hospital discharge. Full adherence was defined as PDC75, at least 75% of days of the follow-up period covered by treatments dispensed. PDC75 for antiplatelet agents was reached by 5216 (69.9%) patients, for beta-blockers by 3231 (43.3%) patients, for ACEI/ARB by 3388 (45.4%) patients, and for statins by 4388 (58.8%). Only 3552 (47.6%) patients reached PDC75 for three or more therapeutic groups, whereas 1343 (18%) of patients did not reach PDC75 with any treatment. Some factors found to be related with nonadherence were older age, female sex, or copayment of drugs dispensed.

In a meta-analysis of 20 studies [9] in 376,162 patients assessing adherence to drugs for the primary or secondary prevention of a CHD event using prescription refill frequency, the estimated overall adherence to cardiovascular medications was only 57% (95% CI 50–64) after a median of 24 months, although it was superior in secondary prevention 66% (95% CI 56–75) than in primary prevention users (50%, 95% CI 45–56).

A large epidemiological study enrolled 7519 participants with established CVD from urban and rural communities in countries at various stages of economic development [10]. Use of antiplatelet drugs, beta-blockers, ACEI or ARB, and statins was assessed. Overall, 4421 (58.5%) individuals were not taking any of the four proven effective drugs, whereas 233 (3.1%) were taking all four drug types. Individuals recruited in high-income countries had had a CHD event or stroke a median of 6.0 years (interquartile range [IQR] 3.0–10.0) before inclusion. Although medication use increased in line with increase of country economic status, adherence rates in high-income countries were sparse too: 62.0% for antiplatelet drugs, 40.0% for beta-blockers, 49.8% for ACEI or ARB and 66.5% for statins.

A meta-analysis of randomised clinical trials assessed adherence to therapy comparing different dosing regimens in patients with chronic CVD.[11] The study showed that dosing regimens with once-daily administration, compared with two or more daily administrations, were associated with a significant 56% risk reduction of nonadherence to drug therapy (relative risk 0.44, 95% CI 0.35–0.54).

Due to the improvement of morbidity and mortality found with the quadruple drug therapy with antiplatelet, beta-blocker, ACEI or ARB, and statin in patients with established CVD, it is necessary to assess the long-term adherence to these drugs in the Catalan population and its relationship with cardiovascular events and mortality. Our hypothesis is patients with established CHD who adhere to drug therapy with the four recommended pharmacological groups have a lower risk of MACE and all-cause mortality compared with patients who do not adhere to drug therapy.

The main objective of our study is to assess the relationship between adherences to the four pharmacological groups recommended for secondary prevention and the clinical

outcomes of cardiovascular morbidity and mortality in patients with established CHD. The outcomes which are included as components of the composite endpoint are all-cause mortality, ACS, and ischaemic stroke. The secondary objectives are: 1) to assess the incidence of the composite endpoint in patients who are adherent to treatment with all four drugs compared with patients who are adherent to any combination of three, two or one drug, or no drug; 2) to assess the relationship between baseline sociodemographic and clinical characteristics and adherence to drug therapy; 3) to compare the number of days on sickness leave due to any cause according to adherence to drug therapy; 4) to estimate prevalence of use of the four drug treatments; and 5) to describe the posology prescribed for the four drug treatments.

Methods

Study design

The study is a population-based retrospective cohort study.

Study Period

Inclusion period was between 2006-2015. The follow-up period was up to 2016.

Study Population

The study population includes individuals ≥18 years with an incident diagnosis of ACS during the study period 2006-2015, with at least two months of follow-up in the Information System for Research in Primary Care (SIDIAP) [12] after the index date. The next patients will be excluded: pregnant women on the index date; patients with a recorded diagnosis of ischaemic stroke in the six months prior to index date; patients living in a nursing home on the index date; and patients with Alzheimer's disease or other dementias.

Case definition: patient with an incident diagnosis of ACS registered in CMBD-HA (dataset of diagnoses at hospital discharge) [13] of the Catalan Health Institute (ICS) within the period from 2006-2015. Index date definition: date of ACS episode.

Data Collection and Data Sources

Diagnoses for study inclusion and endpoints will be obtained from CMBD-HA, which contains diagnoses at hospital discharge from all ICS hospitals, coded with International Classification of Diseases, Nineth Revision (ICD-9) [14]; see Table 1.

The rest of the variables will be captured from SIDIAP, which contains anonymized clinical information of all 279 PHC centres managed by the ICS in Catalonia (North-East Spain), covering a population of more than 5.8 million patients (about 80% of the total of 7.5 million population in Catalonia). The information contained in SIDIAP is registered by PHC general practitioners (GP), nurses and administrative staff in ECAP (electronic health records in ICS): comprehensive sociodemographic information, health conditions registered as ICD10 codes [15], specialist referrals, clinical parameters, toxic habits, PHC laboratory test results, GPs prescriptions and their corresponding pharmacy invoice data registered as Anatomical, therapeutic, chemical classification system (ATC) codes [16], date of sickness leave due to any cause, and date of death. Several reports have shown that SIDIAP data is useful for epidemiological research [17-25]. SIDIAP is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database [26].

Sample Size

The sample will be all patients with a first episode of ACS registered in CMBD-HA of ICS hospitals who meet all inclusion criteria and none of the exclusion criteria during the study period. In a previous study on patients with ACS conducted with SIDIAP database (publication pending) during the period 2009-2011, there were 3415 cases of ACS for all hospitals in Catalonia. Data from CMBD-HA of ICS hospitals corresponds approximately to 30% of all hospitals. Taking into account that our study period is 2006-2015 (10 years), we estimate to find approximately 3400 cases of ACS meeting inclusion criteria for our study.

Variables

Exposure Definition

Patients will be classified as "exposed" to the study drugs (antiplatelet agents, beta-blockers, ACEI or ARB, statins) if they are prescribed any of them after the episode of ACS (up to two months after the event). The dose prescribed in ECAP will be considered the daily dose used for the patient, and the number of tablets contained in each package will cover the same number of days (see drugs of study in Table 2).

Table 1. International Classification of Diseases, Nineth Revision (ICD-9) codes for endpoints of study and procedures.

ICD-9 code	Description
411*	Unstable angina and other forms of acute coronary heart disease
410*	Acute myocardial infarction
433*, 434*, 435*, 436*, 437*	Ischaemic stroke
00.66, 36.03, 36.09, 39.50	Coronary angioplasty

Table 2. Anatomical, therapeutic, chemical classification system (ATC) codes for drugs of interest.

ATC code	Description of therapeutic group
Study drugs	
B01AC	Platelet-aggregation inhibitors
C07	Beta-blockers
C09A, C09B	Angiotensin-converting enzyme inhibitors
C09C, C09D	Angiotensin-receptor blockers
C10AA, C10B	Statins
Concomitant drugs	
C03	Diuretics
C02	Antihypertensive drugs
C08CA, C08D	Calcium-channel blockers (dihydropyridines/verapamil, diltiazem)
B01AA, B01AB, B01AD, B01AE, B01AF, B01AX	Anticoagulants
A10	Drugs used in diabetes mellitus
C10AB, C10AC, C10AD, C10AX	Other lipid-lowering drugs
C01A, C01B	Digoxin and antiarrhythmic drugs
C01DA	Nitrates
N05A	Antipsychotics
M01A, N02BA, N02BB	Non-steroidal anti-inflammatory drugs

Adherence Definition

To estimate medication adherence, we will calculate the PDC for all four study treatments during eight months of follow-up after the index date. The PDC calculation is based on the packages dispensed and days of supply for each package, considering that the number of tablets contained in one package covers the treatment necessary for 28 or 30 days, depending on the drug. The information will be obtained from the pharmacy invoice data. For the PDC calculation, the numerator is the number of packages dispensed (invoice register) during the first 8 months of follow-up, and the denominator is the period of 8 months, which is the period for the adherence measure. Based on the PDC, patient adherence to each study drug is usually classified into one of two categories using the standard threshold of 75% (≥75%: adherent, <75%: nonadherent) [6,9]. PDC=75% accounts for six packages (each one including one month of drug treatment) dispensed during eight months. We define adherent patients as those who have received at least six packages during the first eight months after the event. Finally, according to adherence to all four study drugs, patients will be classified as adherent if they get the refill for all study drugs: PDC antiplatelet ≥75% + PDC beta-blockers ≥75% + PDC ACEI/ARB ≥75% + PDC statin ≥75%.

Study Endpoints

ICD-9 codes for primary and secondary endpoints can be seen in Table 1. They will be captured from CMBD-HA database.

Primary Endpoint

The primary endpoint will be a composite endpoint of all-cause mortality, ACS and ischaemic stroke. From the index date (first episode of ACS), patients will be followed up to the end of follow-up or until a new diagnosis of any of the endpoints stated above. Patients who experience more than one endpoint during the study follow-up will be censored upon the first event of interest. Patients who do not experience any of the clinical events included in the composite endpoint during the follow-up will be censored at the last date of follow-up.

Secondary Endpoints

The secondary endpoints will be AMI, unstable angina, ischaemic stroke, all-cause mortality, overall number of days on sickness leave due to any cause and due to CVD events, prevalence of use of the four pharmacological groups of interest, posology of the four pharmacological groups of interest.

Other Variables

All the following variables will be considered as potential confounders or effect modifiers in the association between adherence to the drug therapy and risk of the composite endpoint. They will be captured from SIDIAP database:

Patient Baseline Characteristics

All sociodemographic characteristics will be measured on the index date: index year, number of visits to PHC, age, sex, MEDEA index (socioeconomic deprivation index) [27], smoking status, alcohol intake, height, weight, Body Mass Index (BMI); the information comes primarily from a codified variable. If the patient has no information, it is calculated from height and weight and physical activity.

Table 3. ICD-10 codes for comorbidities of interest or diseases for exclusion

ICD-10 code	Description
I24*, I25*	Coronary heart disease
I63*, I65*, I66*, I67.2, I67.8	Ischaemic stroke
G45	Transient cerebral ischaemic attack
I70*, I73*, I74*	Peripheral vascular disease
E78*	Dyslipidaemia
I10*, I15*	Hypertension
E10*, E11*	Diabetes mellitus
I48	Atrial fibrillation
I50*	Heart failure
C00*-C97*	Malignancies
J40*-J44*	Chronic obstructive pulmonary disease
F30*-F39*	Depression
M05*, M06*, M15*-M19*	Arthritis (osteoarthritis or rheumatoid arthritis)
M80*, M81*	Osteoporosis
N18*	Chronic kidney disease
B20*-B24*	HIV
G30*, G31*	Alzheimer's disease, other dementias

Comorbidities and Clinical Parameters

They will be measured closest to the index date: type of cardiovascular event at index date (AMI and unstable angina and other forms of ACS captured from CMBD-HA), presence of coronary angioplasty implant after the event (data source CMBD-HA), cholesterol and other lipid parameters (low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, total-cholesterol, and triglycerides), blood pressure measured (systolic and diastolic blood pressure), glycated hemoglobin, glomerular filtration rate, serum creatinine, specific comorbid conditions (see ICD-10 codes in Table 3), Charlson comorbidity index [28,29].

Concomitant Drug Use

For all patients, baseline information on other medications for CVD prescribed throughout follow-up will be captured from the pharmacy invoice (see ATC codes for drugs in Table 2).

Statistical analysis

Demographic and baseline characteristics of the participants will be described using frequencies and percentages for categorical variables and mean, standard deviation or median and interquartile range for continuous variables, as appropriate. Bivariate analyses will be performed estimating odds ratios for categorical variables and mean differences for continuous variables as well as their respective 95% CI. Multiple imputations by chained equations will be used to replace baseline missing values. Case-complete and imputed data results will be compared as a sensitivity analysis. The raw and adjusted HRs for adherences will be calculated for outcome events using Cox proportional hazard regression models, and proportionality of hazards assumption will be tested. Association analyses between adherence to study drugs, incidence of the endpoints or sick leave, and drug therapy (objectives 1, 2 and 3) will be analysed by means of generalized linear models. Objectives 4 and 5 are descriptive and they will be described using frequencies and percentages as appropriate.

Ethical Aspects and Data Confidentiality

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 protocol has been approved by Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol Clinical Research Ethics Committee, the reference institution for research in PHC of the ICS, at May 3, 2017. Regarding the data contained in the databases and according to Spanish legislation about confidentiality and data protection (Ley Orgánica 15/1999 de 13 de diciembre de Protección de Datos de Carácter Personal), data included in SIDIAP are always anonymized. Thus, it is not necessary to ask for informed consent from the participants.

Results

We expect to estimate adherence to all four study treatments, the incidence of MACE, and to analyze if this incidence is associated with the level of drug adherence. Adherence to drug treatment has shown better results in terms of risk reduction of MACE, so we expect to find that adherent patients have a lower risk of the primary endpoints in comparison with nonadherent patients.

Discussion

We expect to find that adherent patients have a lower risk of the primary endpoints in comparison with nonadherent patients.

Selection bias is a common limitation in observational studies. In order to avoid this bias, where the population with missing data differs from those with complete data, missing values for continuous variables will be imputed instead of excluding records with missing data.

Another limitation is the presence of potential confounders. To minimize confounders' effects, Cox regression models adjusted for sociodemographic characteristics and for possible confounders and predictive factors will be used.

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Conflicts of Interest

None declared.

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Abbreviations

ACEI: angiotensin-converting enzyme inhibitors
ACS: acute coronary syndrome
AEMPS: agencia Española de medicamentos y productos sanitarios
AMI: acute myocardial infarction
ARB: angiotensin-receptor blockers
ATC: anatomical, therapeutic, chemical classification system
BMI: body mass index
BP: blood pressure
CHD: coronary heart disease
CMBD-HA: conjunt mínim bàsic de dades a d'hospitalització d'aguts (minimum dataset of
CVD: cardiovascular disease
ECAP: electronic health records in PHC
ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP: general practitioner

HR: hazard ratio
ICD: International classification of diseases
ICS: Catalan Health Institute (Institut Català de la Salut)
IDIAP: Institut Universitari d'Investigació en Atenció Primària
IQR: interquartile range
MACE: major cardiovascular events
PDC: proportion of days covered
PHC: primary healthcare
SIDIAP: Information System for the Improvement of Research in Primary Care

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