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

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Table of contents

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1. Abstract

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. In 2012, it was the leading cause of mortality worldwide, accounting for 31% of an estimated 56 million deaths from all causes. Long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) improve survival in high risk CHD patients. Nevertheless, adherence to prescribed medication is poor for long-term drug treatment in CVD.

In this cohort study we aim to assess the risk of major cardiovascular events and all-cause mortality according to the level of adherence to antiplatelet agents, beta-blockers, ACEI or ARB, and statins, in a population of incident cases of CHD, defined as patients with a first episode of acute coronary syndrome (ACS).

The main objective of the 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.

This is a population-based retrospective cohort study of patients with a first episode of ACS registered in CMBD-HA of the ICS from 2006 to 2015.

We will estimate adherence to antiplatelet agents, beta-blockers, ACEI or ARB, and statins. The primary endpoints of the study are a composite endpoint including: all-cause mortality, ACS and ischaemic stroke; and the first of these three events.

We expect to find that adherent patients would have a lower risk of the primary endpoints compared with non-adherent patients.

2. Keywords

Cardiovascular disease, myocardial infarction, coronary syndrome, medication adherence, secondary prevention, electronic health records, ischaemic stroke, all-cause mortality, drug exposure

3. 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.[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 non-communicable 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 non-adherence.[1,5–7]

In a recent cohort study conducted by Bansilal et al. 4,015 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 non-adherent (<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% confidence interval [CI] 0.69-0.94) and non-adherents, 18.9% vs 26.3% (HR 0.72, 95% CI 0.62-0.85).[4]

In the cohort study conducted by Lafeber et al. 2,706 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 (CI95% 0.49-0.96); ischaemic stroke, HR 0.37 (CI95% 0.16-0.84); vascular mortality, HR 0.53 (CI95% 0.33-0.85); composite endpoint of the previous events, HR 0.66 (CI95% 0.49-0.88); and all-cause mortality, HR 0.69 (CI95% 0.49-0.96).

A population-based cohort study performed in Spain assessed adherence to secondary prevention drugs in a cohort of 7,462 patients who survived an acute coronary syndrome (ACS). 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. Fully 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 69.9% of patients, for beta-blockers by 43.3% of patients, for ACEI/ARB by 45.4% of patients, and for statins by 58.8%. Only 47.6% of patients reached PDC75 for three or more therapeutic groups, whereas 18% of patients did not reach PDC75 with any treatment. Some factors found to be related with non-adherence were: older age, female sex or copayment.[6]

In a meta-analysis of 20 studies 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).[8]

A large epidemiological study enrolled 7,519 participants with established CVD from urban and rural communities in countries at various stages of economic development. Use of antiplatelet drugs, beta-blockers, ACEI or ARB and statins was assessed.

Overall, 58.5% of individuals were not taking any of the four proven effective drugs, whereas 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.[9]

A meta-analysis of randomised clinical trials assessed adherence to therapy comparing different dosing regimens in patients with chronic CVD. 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 non-adherence to drug therapy (relative risk [RR] 0.44, 95% CI 0.35–0.54).[10]

4. Justification and hypothesis of the study

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 our population and its relationship with cardiovascular events and mortality.

In this cohort study we aim to assess the risk of MACE and all-cause mortality according to the level of adherence to antiplatelet agents, beta-blockers, ACEI or ARB, and statins, in a population of incident cases of ischaemic heart disease, defined as patients with a first episode of ACS, including AMI and other forms of ACS.

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.

5. Objectives of the study

5.1. Main objective

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.

5.2. Secondary objectives

- 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.
- To assess the relationship between baseline socio-demographic and clinical characteristics and adherence to drug therapy.
- To compare the number of days on sickness leave due to any cause according to adherence to drug therapy.
- To estimate prevalence of use of the four drug treatments.
- To describe the posology prescribed for the four drug treatments.

6. Methods

6.1. Study design

Population-based retrospective cohort study.

6.2. Study period

- Inclusion period: 2006-2015.
- Follow-up period: up to 2016.

6.3. Study population

All adult patients from SIDIAP population who have a first episode of ACS (AMI or unstable angina, see ICD9 codes in Annex II) registered in CMBD-HA (minimum basic dataset at hospital discharge)[11] of the Catalan Health Institute (ICS).

6.3.1. Inclusion criteria

- Individuals ≥ 18 years with an incident diagnosis of ACS during the study period 2006-2015.
- Patients with at least two months of follow-up in SIDIAP after the index date.

6.3.2. Exclusion criteria

- 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.
- Patients with Alzheimer's disease or other dementias.

6.3.3. Case definition

Patient with an incident diagnosis of ACS registered in CMBD-HA of the ICS within the period from 2006-2015.

6.3.4. Index date definition

Date of ACS episode registered in CMBD-HA of the ICS.

6.4. Data collection and data sources

Diagnoses for study inclusion and endpoints will be obtained from CMBD-HA,[11] which contains diagnoses at hospital discharge from all ICS hospitals, coded with ICD-9.[12]

The rest of the variables will be captured from SIDIAP (Information System for the Improvement of Research in Primary Care),[13] 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 socio-demographic information, health conditions registered as ICD10 codes,[14] specialist referrals, clinical parameters, toxic habits, PHC laboratory test results, GPs prescriptions and their corresponding pharmacy invoice data registered as ATC codes,[15] date of sickness leave due to any cause, and date of death.

Several reports have shown that SIDIAP data is useful for epidemiological research.[16–24] SIDIAP is listed under the ENCePP resources database.[25]

6.5. Sample size

The sample size 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, project “Riesgo cardiovascular en pacientes con osteoartritis: estudio de casos y controles”), during the period 2009-2011, there were 3,415 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 3,400 cases of ACS meeting inclusion criteria for our study.

6.6. Variables

6.6.1. Exposure definition

Patients will be classified as “exposed” to the study drugs 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. ATC codes for study drugs are included in Annex I.

- **Antiplatelet agents**. One or two antiplatelets might be prescribed.
- **Beta-blockers**
- **ACEI or ARB.** In the case of ACEI or ARB combination products, the dose of ACEI or ARB will be also considered the daily dose used for the patient.
- **Statins**

6.6.2. 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 cover 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.
- 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%: non-adherent).[6,8]

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%.

6.6.3. Study endpoints

Primary endpoints

- Composite endpoint including: all-cause mortality, ACS and ischaemic stroke.

- First event of these three events: all-cause mortality, ACS or 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; e.g. a patient with an ischaemic stroke who later dies will be censored at the date of the diagnosis of the ischaemic stroke.

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

- 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.

The ICD-9 codes can be found in Annex II.

6.6.4. 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.

Patient baseline characteristics

All socio-demographic characteristics will be measured on the index date:

- Index year
- Number of visits to PHC

- Age
- Sex
- MEDEA index (socioeconomic deprivation index)[26]
- 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.
- Physical activity

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, see annex II)
- Presence of coronary angioplasty implant after the event (data source CMBD-HA, see annex II)
- Cholesterol and other lipid parameters: LDL-C, HDL-C, total-C and triglycerides.
- Blood pressure measured: systolic and diastolic blood pressure.
- HbA1c.
- Glomerular filtration rate (GFR)
- Serum creatinine
- Specific comorbid conditions (see ICD-10 codes in annex III):
    - Dyslipidaemia
    - Hypertension
    - Diabetes mellitus
    - Diabetic retinopathy
    - Atrial fibrillation
    - Heart failure
    - Peripheral artery disease
    - Cancer
    - Chronic obstructive pulmonary disease
    - Depression
    - Arthritis (osteoarthritis or rheumatoid arthritis)
    - Osteoporosis
    - Chronic kidney disease

    - Ischaemic stroke or transient ischaemic attack more than 6 months before the index date
    - Human immunodeficiency virus (HIV)
- Charlson comorbidity index[27,28]

Concomitant drug use

For all patients, baseline information on other medications for CVD prescribed throughout follow-up will be captured from the pharmacy invoice. The following classes of drugs will be considered (see ATC codes in annex I):

- Diuretics and their combinations (eplerenone will be used as a factor for adjustment, as it is recommended in addition to the quadruple therapy in those patients who had an AMI and have symptoms and/or signs of heart failure and left ventricular systolic disfunction)
- Other antihypertensive drugs
- Calcium channel blockers and their combinations
- Anticoagulant agents
- Drugs used in diabetes
- Other lipid-lowering drugs
- Antiarrhythmic drugs
- Nitrates
- Antipsychotic drugs
- Non-steroidal anti-inflammatory drugs (NSAID)
- Second antiplatelet prescribed (in some cases of ACS, a second antiplatelet has been recommended)

6.7. 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 using the Chi-square test for categorical variables and t-Student test or Mann-Whitney U test for continuous variables, according to their distribution.

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.

7. 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 will be evaluated for IDIAP Jordi Gol Clinical Research Ethics Committee, the reference institution for research in PHC of the ICS.

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.

8. Strenghts and limitations

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. The presence of cardiovascular risk factors and outcomes has been previously validated in SIDIAP.[22]

A limitation of cohort studies conducted with electronic health records are missing data. In order to avoid selection bias, where the population with missing data somehow differs from those with complete data, missing values for continuous variables will be imputed instead of excluding records with missing data.

Another limitation of this type of studies is the presence of potential confounders. To minimize confounders' effects, Cox regression models adjusted for socio-demographic characteristics and for possible confounders and predictive factors will be used. Other confounders such as physical activity, diet habits and the reasons for the GP's therapeutic choices are not available in SIDIAP, so they remain as study limitations.

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10. Annexes

10.1. Annex I: ATC codes for drugs of interest

ATC code[15]	
STUDY DRUGS	
B01AC	Platelet-aggregation inhibitors
C07	Beta-blockers
C09A, C09B	Angiotensin-converting enzyme inhibitors (ACEI)
C09C, C09D	Angiotensin-receptor blockers (ARB)
C10AA, C10B	Statins
CONCOMITANT DRUGS	
C03	Diuretics
C02	Antihypertensive drugs
C08CA, C08D	Calcium-channel blockers (dihidropyridines / 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	NSAID

10.2. Annex II: ICD-9 codes for endpoints of study and procedures

ICD-9 code[12]	
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

10.3. Annex III: ICD-10 codes for comorbidities of interest or diseases for exclusion

ICD-10 code[14]	
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

10.4. Annex IV: List of 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
CEI	Comité ético de investigación
CHD	Coronary heart disease
CI	Confidence interval
CMBD-HA	Minimum set of data at hospital discharge (conjunt mínim bàsic de dades a d'hospitalització d'aguts)
CVD	Cardiovascular disease
DDD	Daily defined dose
ECAP	Electronic health records in PHC
ENCePP	European network of centres for Pharmacoepidemiology and Pharmacovigilance
GFR	Glomerular filtration rate
GP	General practitioner
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein-cholesterol
HIV	Humane immunodeficiency virus
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
LDL-C	Low density lipoprotein-cholesterol
MACE	Major cardiovascular events
NSAID	Non-steroidal anti-inflammatory drugs
PDC	Proportion of days covered
PHC	Primary healthcare
ReEC	Registro español de estudios clínicos
RR	Relative risk
SIDIAP	Information system for the improvement of research in primary care
Total-C	Total-cholesterol