USE OF DRUGS ACTING ON RENIN-ANGIOTENSIN SYSTEM (RAS) AND RISK OF COVID-19: A CASE-POPULATION STUDY

Protocol code: SRAA-COVID19

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(This is an on-going study and the list of participating hospitals and investigators could be subjected to modifications)

ABSTRACT

The coronavirus SARS-CoV-2 uses the protein ACE2 (angiotensin converting enzyme 2) as the receptor binding domain for its protein S (spike) to gain entry into cells and replicate. Blockers of the renin-angiotensin system (RAS) have been reported to upregulate the expression of ACE2 and this observation has raised the hypothesis that the use of these drugs could facilitate COVID-19 infection and/or make it more serious. Yet, the epidemiological evidence is lacking. The aim of this project is to carry out a quick case-population study using patients admitted to hospital with a diagnosis of COVID-19 as cases and a random sample of patients from a primary care database as the control series matched with cases for exact age, sex, and month-day (10 controls per case). Information on comorbidities and drugs used in the last month (current use) will be extracted from the clinical records in both cases and controls. We will examine the association of COVID-19 with the current use of RAS blockers as compared to non-use and as compared to current use of other antihypertensive drugs by computing the adjusted Odds Ratio through a conditional logistic regression model. The feasibility of selecting a secondary series of COVID-19+ cases who were not admitted to hospital (milder cases) will be assessed.

1. BACKGROUND

It has been reported that the coronavirus SARS-CoV-2, the agent causing the COVID-19 pandemic, uses the angiotensin-converting enzyme 2 (ACE2), present in epithelial cells of the lungs, intestine, kidney and blood vessels, as the receptor binding domain for its spike protein (1), similarly to the coronavirus involved in the SARS epidemic 2002-2003 (2), but with a 10 to 20-fold higher affinity (3). This way SARS-CoV-2 invades host cells to replicate.

The protein ACE2 presents a high homology with angiotensin converting enzyme (ACE), key in the regulation of blood pressure (4). ACE cleaves angiotensin I to generate angiotensin II which acts on the receptor AT1 to promote vasoconstriction. Also, angiotensin II increases the production of aldosterone, which favors the renal reabsorption of sodium and water, leading both effects to raise blood pressure. On the contrary, ACE2 inactivates angiotensin II and increases the generation of angiotensin 1-7, a peptide with a strong vasodilator activity which serves to the homeostasis of the renin-angiotensin system (RAS) (4).

In some animal studies, RAS blockers (angiotensin converting enzyme inhibitors, ACEI or angiotensin receptor blockers, ARBs) have shown to increase the expression of ACE2 (5,6,7), although other studies did not find any increase (8). Human studies also offer inconsistent findings with some showing an increase of soluble ACE2 with some RAS blockers (9), while others did not (10,11). If RAS blockers upregulate the expression of ACE2 in cell membranes, it might be conceivable that the use of these drugs could facilitate or aggravate COVID-19 infection.

In a recent study carried out in Chinese population aimed to explore risk factors of in-hospital death in patients with COVID-19, the authors identified in the univariate analysis several factors, including age, hypertension, diabetes and coronary heart disease (12), though in the multivariate analysis only remained significant age and coronary heart disease. It is well-known that all these factors are associated with a high use of RAS blockers. Such finding, along with the aforementioned ACE2 upregulation, has fueled the hypothesis that the use of RAS blockers, particularly ACEI, could facilitate the COVID infection or make it more serious (13, 14). Some authors, instead, have proposed angiotensin II receptor blockers (ARB) as a preventive factor, or even a therapy, for COVID-19 infection for its potential to reduce lung injury (15). As if this conundrum were not enough, some authors have speculated that the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may aggravate the infection by mechanisms not well explained yet (16). All these drugs are ones of the most widely used worldwide and, although, many scientific societies and drug regulatory agencies have recommended continuing treatment with ACEI/ARB due to the lack of evidence (17, 18, 19), we urgently need pharmaco-epidemiological studies to shed some light on this issue of high social impact.

2. OBJECTIVES:

2.1. General objective:

To assess the association of RAS blockers and NSAIDs with hospital admission due to COVID-19 infection adjusted for age, sex, and cardiovascular risk factors.

2.2. Specific objectives:

- To assess whether the current use of RAS blockers was or not associated with COVID-19 cases admitted to hospital as compared to non-use of any antihypertensive drug adjusted for age, sex, and cardiovascular risk factors

- To assess whether the current use of RAS blockers was or not associated with COVID-19 cases admitted to hospital as compared to the current use of "other antihypertensive drugs", adjusted for age, sex, and cardiovascular risk factors

- To assess whether the association of RAS blockers or NSAIDs with hospital admissions due to COVID-19 is modified by sex, age and background cardiovascular risk.

- To assess whether the association of RAS blockers or NSAIDs with hospital admissions due to COVID-19 was greater among patients in more serious condition (resulting in ICU admission or death).

3. SCIENTIFIC COMMITTEE

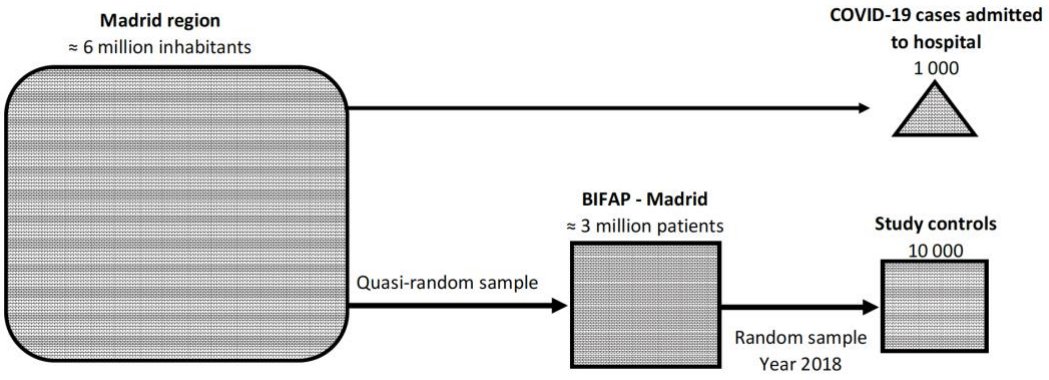
The PIs of the different participating hospitals will make up the Scientific Committee of the Project. Their main function will be to deliberate about decisions regarding the progress of the project, logistics, results and publications. Such deliberations will be carried out by email or teleconference, while face-to-face meetings are not possible.

4. METHODS

4.1. Design and study subjects: A case-population study (20) will be carried out including as cases all patients aged 18 years or older with a diagnosis of COVID-19 (confirmed when possible with a positive test for SARS-CoV-2) who were admitted to hospital and as controls a random sample of subjects extracted from the database BIFAP (the last available year), and then matched to cases by sex, age (exact), Autonomous Community (Madrid) and date (day and month; year will be 2020 for cases and 2018 for controls) (figure 1). We will use a risk set sampling method. Also, the feasibility to get information from a secondary series of cases made up for patients COVID-19 positive who were not admitted to hospital will be explored (this series could be also be used as a secondary "control" group). For cases the index date will be considered the one of the hospital admission due to COVID-19. For the secondary series of cases, index date will be the date of the admission at the Emergency Service.

4.2. Sources of information: Information of cases will be retrieved from the medical records of the participating hospitals, as well as from the electronic medical records of primary care accessed through the "HORUS" application (a viewer of the primary care records). The information from population controls will be extracted through the database BIFAP, owned by the Spanish Medicines Agency. BIFAP obtains the information from the primary care clinical records, the same source accessed through HORUS. For less serious cases not admitted to hospital we will use the information available in the hospital emergency service and HORUS.

Figure 1. The case-population approach. *Study Design. Seven hospitals of Madrid Region participate in the registry of COVID-19 cases admitted to hospital. BIFAP is a primary health care database which includes 12 million patients, around 3 million from Madrid Region (BIFAP-Madrid), and is considered fairly representative of Madrid general population (although technically speaking is not a purely random sample). Control series is a purely random sample from BIFAP-Madrid conditioned by the matching variables (year 2018). All in all, both cases and controls arise from the same source population (20).*



4.3. Study period: All patients fulfilling inclusion criteria will be included since the beginning of the outbreak in Madrid until 31 March, 2020. The study period could be extended depending on the available number of cases.

4.5. Data collection: The local PIs will get a list of patients diagnosed of COVID-19 identified by the clinical record number. All variables included in the case report form (CRF; see Appendix I for variables description and codebook) will be extracted from the medical records (section 4.2). Subjects in the study will be labelled with an alphanumeric code constructed as follows; in first place, the acronym of the hospital name (i.e. HUPA, which stands for "Hospital Universitario Príncipe de Asturias") and, in second place, a consecutive number (i.e. HUPA1, HUPA2 and so on). All CRFs without the clinical record number will be sent on a weekly basis to the coordinating center. The clinical history number will only be used locally to link the study code with the subject, in case of further verification of information was needed. The coordinating center will perform data quality control of all CRFs received.

4.6. Outcomes (dependent variables):

- Hospital admission due to COVID-19
- Hospital admission to the intensive care unit (ICU) due to COVID-19
- In-hospital death after admission due to COVID-19
- Admission to ICU or in-hospital death (combined)

4.7. Independent Variables

4.7.1. Exposure variables

- Use of angiotensin converting enzyme inhibitors (ACEI) within the month prior to hospital admission (current users).
- Use of angiotensin receptor blockers (ARB) within the month prior to hospital admission (current users).
- Use of aldosterone antagonists (AA) within the month prior to hospital admission (current users).
- Use of any of the above-mentioned RAS blockers (combined) (current users)
- Use of "Other antihypertensive drugs" within the month prior to hospital admission (current users), including calcium channel blockers (CCBs), diuretics, beta-blocking agents (BBA) and alpha-adrenoreceptor antagonists (alpha-blockers)
- Use of non-steroidal anti-inflammatory drugs (NSAID) within the month prior to hospital admission (current users).

We define *current use* of the drug(s) of interest when there was a recording of a prescription lasting up to the month prior to the index date; otherwise it will be defined as *non-use.*

For the comparison of current use of "RAS blockers" with the current use of "other antihypertensive drugs", we will generate a variable with the following mutually exclusive categories: Non-use of any anti-hypertensive drug, current use of "RAS blockers" and current use of "other antihypertensive drugs" (excluding from this category patients who were also current users of ACEIs, ARBs, or AAs). Depending on the analysis, we set "non-use of any antihypertensive drugs", or "current use of other antihypertensive drugs" as the reference category. Subsequently, we will disaggregate the category "current use of RAS blockers" into their different pharmacological subgroups: ACEIs, ARBs (excluding patients who were also current users of ACEIs), AAs (excluding patients who were also current users of ACEIs or ARBs).

When the numbers permit, we will separate "current use of RAS blockers" in two subgroups: 1) monotherapy; and 2) combinations (among them or with other antihypertensive drugs, in fixed-dose combinations or concomitantly used as separate medicinal products).

The ATC codes of different drugs and/or pharmacological subgroups can be found in Appendix I.

The date of first prescription of the current treatment episode will also be extracted in order to estimate the continuous duration of treatment. Then, duration will be categorized as follows: ≤1 month, >1 month-1 year, > 1 year. The daily dose of main drugs of interest will also be extracted and categorized as low-intermediate and high, according to their respective SmPCs.

4.7.2. Covariates (potential confounding factors)

In addition to sociodemographic variables, we will consider the presence of the following co-morbidities at index date: antecedents of hypertension, diabetes, dyslipidemia, ischemic heart disease, atrial fibrillation, heart failure, thromboembolic disease, cerebrovascular accident, asthma, chronic obstructive pulmonary disease (COPD), chronic renal failure and cancer. Also, we extracted information on the current use of the following drugs: oral anticoagulants, antiplatelet drugs, glucose-lowering drugs (oral and insulin), statins, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (see Appendix I). We will also explore the validity to extract information on use of paracetamol and metamizole. These drugs are often prescribed on demand, and without an interview to patients, it may be hard to get valid information from clinical records (this may also occur with some NSAIDs, such ibuprofen).

4.8. Statistical analysis:

Descriptive analysis: The features of cases and controls will be compared. We expect large differences in comorbidity distribution, as cases are patients admitted to hospital and controls are subjects extracted from the underlying population. According to available data from Italy, 74% of COVID-19 positive cases who died presented hypertension and a high prevalence of other comorbidities (21). Consequently, confounding by indication may reveal hard to control for, as RAS blockers are used for comorbidities that may condition the admission to hospital and thus be strongly associated to cases. In order to minimize this problem, we will compare the current use of RAS blockers (as a whole and each different subgroups) with the current use of any "other antihypertensive drug" (calcium-channel blockers, beta-blockers, alpha-blockers, and diuretics).

Main analysis: Crude odds ratios (ORs) and their 95% confidence intervals (CIs) will be computed through univariate conditional logistic regression to assess the association of current use of RAS blockers with the outcome of interest as compared to non-use and as compared to other antihypertensive drugs. After that, we built a multivariate model including the aforementioned comorbidities and comedications all at once.

If the number of cases do not permit to adjust for all covariates we looked for, we will construct different models removing covariates from it based on subject matter knowledge. Finally, we will select the one with the best trade-off between the goodness of fit and complexity. For some stratified analyses, it could be more convenient to use

unconditional logistic regression (in that case, the matching variables will be included in the model).

Effect modification: Stratified analysis will be performed to assess the potential interaction of the main exposure variables with age, sex and background cardiovascular risk, defined as high, intermediate and low. When numbers were small, only two categories were used collapsing intermediate with high or low. The statistical interaction will be assessed by comparing the AORs of different strata using the test of Altman and Bland (22).

Sample size: Data of all subjects from the participating hospitals will be collected consecutively. 10 controls extracted from BIFAP will be taken for each case. Simulations for sample size calculation considering different scenarios (with standard alpha error = 0.05 and beta error = 0.20) resulted as follows (using OpenEpi sample size for unmatched case-control studies; https://www.openepi.com/SampleSize/SSCC.htm):

OR	**Prevalence of use (%)**	**Cases**	**Controls**
≥1.5	5	918	9172
	10	499	4987
	15	363	3624
	20	298	2973
	30	240	2396
≥2.0	5	277	2763
	10	154	1540
	15	115	1146
	20	97	962
	30	81	809

According to the data available in BIFAP (in 2015), the prevalence of use of the different RAS blockers in the general population older than 40 years are: ACEI (13.2%), ARB (13.9%), AA (1%), All (27.1%).

To compute the association of ACEI or ARB use and the outcomes separately with an OR of at least 1.5, it would be necessary to include around 500 cases with their respective matched controls (5000). In case of a lower prevalence of use of the drugs of interest (5%) it would be necessary to include 1000 cases and 10,000 matched controls. The latter is selected as the sample size to be reached, unless the Scientific Committee decides to interrupt the study earlier[a].

Intermediate analyses: Intermediate analyses will be performed at different points along the study when the number of cases included are: 100, 500 and 750. At these points, matched controls will be extracted from BIFAP. Based on the results obtained,

[a] The calculations of sample size have been carried out for unmatched case-control studies The statistical advisors have calculated a slightly lower sample for a matched case-control study (871 cases and 8710 controls)

the Scientific Committee will deliberate about the need to continue with the data collection.

Sensitivity analysis: The control series arise from 2018, the last available year in BIFAP, while cases arise from 2020. Thus, in case of a secular trend in the use prevalence of antihypertensive drugs, the exposure among controls would be underestimated and, as a result, the AOR of antihypertensive drugs would be overestimated. To correct for this potential problem, we will examine the trends of use prevalence of different antihypertensive subgroups in BIFAP (people >40 years old) over the period 2010-2018 and forecast the prevalence of use for 2020. According to previous studies it is expected a ratio 2020/2018 ranging from 1.05 to 1.10. This factor will be used to correct the AOR associated with current use of RAS blockers as compared to non-use (dividing the AOR obtained in the model by such factor). In the comparison of current use of RAS blockers with current use of other antihypertensive drugs no correction is deemed necessary, as it is expected that the secular trends will be similar in both subgroups.

All statistical analyses will be performed using the statistical software STATA/SE v.15 (StataCorp LLC, College Station, TX. USA. 2017).

5. LIMITATIONS

Limitations of the study are those of any observational study. There may be a residual confounding due to unmeasured confounders. The study has been designed to assure that population controls come from the same source population as cases. However, we cannot ignore that we will use different data sources for cases (hospital records and primary care records through HORUS) and for controls (BIFAP, which only includes primary care records). Of note, both HORUS and BIFAP access to the same primary care data. In none of the data sources there is a systematic registry of over-the-counter (OTC) medications, so for drugs partially dispensed OTC (e.g. paracetamol, ibuprofen) an important misclassification of the exposure is expected, although this error would affect both cases and controls (non-differential). Finally, it is necessary to consider the current situation of national emergency and the hard work conditions of healthcare professionals; all this may have an impact on the quality of the information recorded in the field. For this reason, and in order to make the study feasible, we have reduced the number of variables for which we are extracting information.

6. ETHICS

The ethics committee (CEIm) of the University Hospital “Príncipe de Asturias” has evaluated the study protocol and issued a favorable opinion on March 18, 2020. The study protocol has also been classified as a post-authorization study with medicines of human use with other design different than prospective (EPA-OD) by the Spanish Agency for Medicines and Medical Devices (AEMPS) on March 18, 2020. Such classification is valid for the entire country. The clinical record number (CRN) is unique for each subject and thus is considered as personal data. The CRN is required to access the medical records, but once information is extracted, a consecutive alpha-numeric code ("study

id") will be assigned to each patient, so that the identification of the subject will be protected. The CRN will remain locally linked to the "study id" in a cross-list that will be kept under the custody of the PI of each center. Only authorized members of the research team and thus subjected to a duty of secrecy will access to the medical records to extract the data. Due to the high number of patients, the urgency of the situation and the dissociation of personal data, the CEIm granted a waiver for the informed consent of patients, according to the Spanish law. The study will comply with the provisions of the current legislation on research with human medicines and medical devices (Order SAS 3470/2009, Royal Decree 1090/2015, Law 14/2007 of Biomedical Research and Organic Law 3/2018 of data protection), as well as the ethical principles of the 2013 Declaration of Helsinki.

Prior to access to BIFAP data, the approval of the study protocol from the BIFAP Scientific Committee (AEMPS) has been requested.

7. RESULTS COMMUNICATION AND PUBLICATIONS

Both preliminary and final results will be released first to the PIs of the project and, then a report with those results will be submitted to the AEMPS. The coordinator researcher of the study and all the PIs conducting the study are at the disposal of the AEMPS to collaborate as scientific advisors for the decision-making process, when considered appropriate. The final results will be submitted for publication in scientific journals including all the researchers participating (PIs and collaborators) as co-authors. The coordinator researcher will inform the AEMPS about the publication of the results and will also send the manuscript at least one week in advance before submission for publication.

8. ANTICIPATED RESULTS

The results of the study will allow us to obtain epidemiological evidence about the possible association between the use of RAS blockers or NSAIDs and the risk of developing COVID-19 requiring hospital admission. It is estimated that 30% of the Spanish population over 40 years of age have exposure to RAS blockers and that 15% regularly take NSAIDs, so the consequences of stopping these treatments must be seriously considered. There may be other research groups in Spain and around the world pursuing the same objectives, so it will be important to assess the consistency of the different results obtained.

We expect to have the first interim results with 100 cases and 1000 controls in late March. The rest of interim results and final report will be available in April.

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Appendix I: table of sociodemographic, co-morbidities and co-medication variables

FEATURE	CODE	TYPE	VALUES	OBSERVATIONS
Code	Id	Alphanumeric	XXXX1, XXXX2, XXXXn	Hospital name acronym plus a consecutive number
Hospital	hospital	Nominal		The acronym of the participating hospital name (i.e. HUPA, for Hospital Universitario Príncipe de Asturias)
NHC	-	-	-	A cross-list will be created with the "Id" so it will be removed from the CRF. Researchers of each hospital must remove this variable before sending the data to the coordinating hospital.
Date of birth	dob	Date	dd/mm/yyyy	Date of birth of patients
Sex	sex	Nominal	0: Female 1: Male	
Age at diagnosis	age	Quantitative	18 to n	In years
Date of hospital admission	date_ad	Date	dd/mm/yyyy	
Evolution of the disease	evolution	Nominal	0: admitted to the current hospital 1: transferred to another hospital	
Hospital of transfer	hosp_trans	Nominal	string	Fill in just in case the patient was transferred to another hospital.
Date of transfer	date_trans	Date	dd/mm/yyyy	Fill in just in case the patient was transferred to another hospital.
Hospital of origin	hosp_orig	Nominal	string	Fill in just in case the patient was transferred to another hospital.
Date of SARS-coV-2 positive test	date_test	Date	dd/mm/yyyy	Date of first positive test
Date of COVID-10 clinical suspicion	date_susp	Date	dd/mm/yyyy	Date of first COVID-19 suspicion
ICU	icu	Nominal	0:no 1: yes	Patient admitted to intensive care unit
Date of admission in ICU	date_icu	Date	dd/mm/yyyy	
Clinical criteria for ICU admission	icu_crit	Nominal	0: no 1: yes	Fill in if patients meeting criteria for ICU admission finally were not admitted due to lack of box availability in ICU.
Outcome	outcome	Nominal	0: In process 1: Discharge 2: Death	

Date of outcome	date_outcome	Date	dd/mm/yyyy	
History of hypertension	aht	Nominal	0:no 1: yes	
History of diabetes	diabetes	Nominal	0:no 1: yes	Type 1 or Type 2
Obesity	obesity	Nominal	0:no 1: yes	Defined as BMI>30kg/m^2
History of dyslipidemia	dyslip	Nominal	0: no 1: yes	
History of acute myocardial infarction / angina pectoris/ ischemic heart disease	ami	Nominal	0:no 1: yes	
History of heart failure	h_fail	Nominal	0:no 1: yes	
History of atrial fibrillation	af	Nominal	0:no 1: yes	
History of deep venous thrombosis	dvt	Nominal	0:no 1: yes	
History of stroke	stroke	Nominal	0:no 1: yes	
History of chronic obstructive pulmonary disease	copd	Nominal	0:no 1: yes	
History of asthma	asthma	Nominal	0:no 1: yes	
History of cancer	cancer_prev	Nominal	0:no 1: yes	
Current cancer	cancer_curr	Nominal	0:no 1: yes	
History of chronic kidney disease	ckd	Nominal	0:no 1: yes	
Other diseases (ie. Immune system or others)	dis_others	Nominal	String	
Angiotensin converting enzyme inhibitors (ACEi) ATC: C09A, C09B	acei	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
ACEi, active principle	acei_ap	Nominal	String	
ACEi, daily dose	acei_dd	Quantitative	n	mg/day
ACEi, date of first prescription	acei_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Angiotensin receptor blockers (ARB) ATC: C09C, C09D	arb	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
ARB, active principle	arb_ap	Nominal	String	
ARB, daily dose	arb_dd	Quantitative	n	mg/day
ARB, date of first prescription	Arb_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Aldosterone antagonists (AA) ATC: C03DA	aa	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
AA, active principle	aa_ap	Nominal	String	

AA, daily dose	aa_dd	Quantitative	n	mg/day
AA, date of first prescription	aa_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Aliskiren ATC: C09X	alisk	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
Sacubitril ATC: C09DX04	sacubi	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
Calcium channel blockers (including diltiazem and verapamil) ATC: C08, C09BB10, C09BB02, C09BB12, C09BB06, C09BB05, C09BB03, C09DB01, C09DB02, C01DB04, C09DX01, C09DX03, C09DX06 C09XA53, C09XA54, C10BX03, C10BX07, C10BX09, C10BX11, C10BX14	cab	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
CaB, active principle	cab_pa	Nominal	String	
CaB, date of first prescription	Cab_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Diuretics ATC: C03A, C03B, C03C, C03DB, C03E, C03X	diur	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
Diuretics, active principle	diur_ap	Nominal	String	
Diuretics, date of first prescription	diur_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Beta-blockers (BB) ATC: C07A	bb	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
BB, active principle	bb_ap	Nominal	String	
BB, date of first prescription	bb_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Alpha-blockers (AB) ATC: C02CA	alpha	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
AB, active principle	alpha_ap	Nominal	String	
AB, date of first prescription	alpha_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Oral anticoagulants (OAC) ATC: B01AA, B01AE, B01AF,	oac		0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
OAC, active principle	oac_pa	Nominal	String	
Antiplatelet drugs ATC: B01AC	antiplat		0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
Antiplatelet drugs, active principle	antiplat_ap	Nominal	String	

Non-steroidal anti-inflammatory drugs (NSAIDs) ATC: M01AA, M01AB, M01AC, M01AE, M01AG, M01AH, M01AX01, M01AX02, M01AX04, M01AX07, M01AX13, M01AX14, M01AX17, M01AX18, M01AX22, M01AX23, M01AX24, M01AX26, M01AX68	nsaid	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
NSAID, active principle	nsaid_ap	Nominal	String	
NSAID, daily dose	nsaid_dd	Quantitative	n	mg/day
NSAID, date of first prescription	nsaid_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Corticosteroids for systemic use ATC: H02A, H02B	cortic	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
Cortic., active principle	cortic_ap	Nominal	String	
Cortic, daily dose	cortic_dd	Quantitative	n	mg/day
Cortic, date of first prescription	cortic_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Acetaminophen ATC: N02BE01, N02BE51, N02BE71, N02AA59, N02AJ01, N02AJ06, N02AJ13, N02AJ17 M03BA52, M03BX55,	aceta	Nominal	0:no 1: yes	Fill in if the patient was treated in the past month prior to diagnosis
Acetaminophen, date of first prescription	aceta_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Metamizole ATC: N02BB02, N02BB52, N02BB91, A03DB04	meta	Nominal	0:no 1: yes	Fill in if the patient was treated in the last month prior to diagnosis
Metamizole, date of first prescription	meta_fpd	Date	dd/mm/yyyy	Date of treatment initiation
Statins ATC: C10AA, C10BA, C10BX	stat	Nominal	0:no 1: yes	Fill in if the patient was treated in the last month prior to diagnosis
Ezetimibe ATC: C10AX09, C10BA05, C10BA06, C10BA02	ezetim	Nominal	0:no 1: yes	Fill in if the patient was treated in the last month prior to diagnosis
Oral glucose lowering drugs (OGLD) ATC: A10B	ogld	Nominal	0:no 1: yes	Fill in if the patient was treated in the last month prior to diagnosis
OGLD, active principle (including combinations)	ogld_ap	Nominal	String	When used in combination, include all active principles
Insulin ATC: A10A	insulin	Nominal	0:no 1: yes	Fill in if the patient was treated in the last month prior to diagnosis