Association of Use of Angiotensin-converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with fall and trauma-related hospitalization among elderly patients: a nationwide population-based cohort study

PROTOCOLE DE RECHERCHE HORS RECHERCHE IMPLIQUANT LA PERSONNE HUMAINE

(Recherche sur données de l'Assurance Maladie Française)

Version n°6 du 22/02/2022

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Summary

Technical Summary

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TITLE	Association of Use of Angiotensin-converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with fall and trauma-related hospitalization among elderly patients: a nationwide population-based cohort study.
STUDY BACKGROUND	ARBs and ACE inhibitors are the most commonly prescribed antihypertensive drugs among adults in the world. They are first-line drugs for hypertension, heart failure and myocardial infarction. While large clinical trials and meta-analysis post marketing authorization showed no association between antihypertensive and fall, several observational studies on large cohorts of real-life patients have shown the opposite. Although these studies have assessed the risk of fall and trauma associated with RAS as a class, whether differences exist between ARBs and ACE inhibitors is unclear. Indeed, ARBs and ACE inhibitors have different pharmacodynamic mechanisms, which may in turn induce different antihypertensive effects. The primary mechanism of action of ARBs is to reduce AT1 receptor activation, even more effectively than ACE inhibitors. ARBs also promote higher activation of AT2 receptors, which enhances their antihypertensive action.
OBJECTIVES	**Primary:** Determine whether use of ARBs, when compared with ACE inhibitors, is associated with an increased risk of fall and trauma-related hospitalization among of 65 years and older a multivariable Cox proportional-hazards outcome models using

propensity-score matching/stratification.

Secondary:

1. Determine whether use of ARBs, when compared with ACE inhibitors, is associated with an increased risk of syncope, malaise, orthostatic hypotension, and serious outcomes (ICU hospitalizations, death) among of 65 years old and older.
2. Determine whether use of one ARB, when compared with other ARBs, is associated with an increased risk of fall and trauma-related hospitalization among of 65 years old and older.
3. Determine whether use of one ACE inhibitor, when compared with other ACE inhibitors, is associated with an increased risk of fall and trauma-related hospitalization among 65 years old and older.

Sensitivity:

1. Determine whether use of ARBs, when compared with ACE inhibitors, is associated with an increased risk of fall and trauma-related hospitalization among of 65 years and older by using a multivariable Cox proportional-hazards outcome models without propensity-score matching, only with adjustment for covariates.
2. Determine whether use of ARBs, when compared with ACE inhibitors, is associated with an increased risk of fracture-related hospitalization alone, of fall-related hospitalization alone and trauma-related hospitalization alone among of 65 years and older.
3. Determine if the risk of fall and trauma related hospitalization with ARBs or ACE inhibitors varies according to sex (female / male), age group, type of pathology (heart failure / hypertension / ischemic heart disease), type of cardiovascular prevention (primary / secondary), and finally according to the type of prescriber (cardiologist / general practitioner) among of 65 years old and older.
4. Assess whether the risk for fall or trauma-related hospitalization varies with duration of use of ARBs.

Ancillary:

1. Access the risk of "accident and injury" reports (SMQ) when compared to all other report for ARB versus ACE inhibitors in Vigibase®.

METHOD	Using the General Beneficiary Sample (EGB), we will conduct a cohort study among all patients aged 65 years and older with a first prescription for ARBs or ACE inhibitors between January 1st, 2009 and December 31st, 2019. EGB is a permanent 1/97th sample of the population from the French National Health Data (SNDS). The reference group will be ACE inhibitors and comparison group will be ARBs. We will identify patients with an incident fall or trauma-related hospitalization identified in the PMSI through the ICD-10 hospitalization. We will use propensity score (PS) to take account the potential confounding. We will use Cox proportional hazards models to estimate the hazard ratios of fall and trauma-related hospitalization associated with the use of ARBs compared with ACE inhibitors. Secondary analysis will explore whether the risk varies with duration of use, and we will assess the risk of fall and trauma-related hospitalization in each pharmacological class. We will also conduct sensitivity analyses to assess the robustness of our results. Ancyllary analysis will acces the risk of "accident and injury" reports (SMQ) when compared to all other report for ARB versus ACE inhibitors in Vigibase®.
OUTCOMES	**Primary outcome:** Occurrence of a hospitalization for fall or trauma during the follow-up. **Secondary Outcomes:** – Hospitalization for syncope or malaise during the follow-up. – Hospitalization for orthostatic hypotension during the follow-up. – Onset of death during the follow-up. – Onset of ICU hospitalization during the follow-up. – Occurrence of a hospitalization for fall (ICD-10 W06, W10, W17-19) or trauma (S00-99, T00-T14) during the follow-up for each ARB apart when compared to ACE inhibitors group. – Occurrence of a hospitalization for fall (ICD-10 W06, W10, W17-19) or trauma (S00-99, T00-T14) during the follow-up for each ACE inhibitors apart when compared to ARB group. **Sensitivity Outcomes:** – Risk of fall and trauma related hospitalization with ARBs or ACE inhibitors varies according to sex (female / male), age group, type of pathology (heart

	failure / hypertension / ischemic heart disease), type of cardiovascular prevention (primary / secondary), and finally according to the type of prescriber (cardiologist / general practitioner). – Fracture-related hospitalization alone, fall-related hospitalization alone and hospitalization alone during the follow-up. – Risk for fall or trauma-related hospitalization according to variation of duration use of ARBs **Ancillary Outcome:** – Risk of "accident and injury" reports (SMQ) when compared to all other report for ARB versus ACE inhibitors in Vigibase®.
NUMBER OF SUBJECTS NEEDED	We conservatively expect an incidence of falls of approximately 0.036 per 100 persons per years among adults >65 years newly prescribed an ARB or ACE inhibitors. With a cohort of approximately 10,000 patients with a first ARBs or ACE inhibitors prescription, including 6,300 new users of ARBs, and a conservative median follow-up time of approximately 1 years. Therefore, using a two-tailed alpha of 5% we will have over 90% power to detect a HR of 1.35.
EXPECTED IMPACT	Identify which RAS class, and in this class witch drug is associated with a lower risk of hospitalization for falls and trauma in elderly subjects. Improve the prescription of antihypertensive drugs in the elderly by physicians (general practitioner, geriatrician, and cardiologist). Reduce the risk of falls and fractures associated with the use of antihypertensive drugs in the elderly. Promote a higher quality of life for the elderly by preserving their autonomy and decrease health costs.
UNIVERISTY OF ADMINISTRATIVE REGISTRATION	**Master 2 Epidemiological and Clinical Research (Public Health)** Toulouse University III Paul Sabatier Faculty of Medicine 37, Allées Jules Guesde 31000 Toulouse – France

Protocol Information

1. Study Background

Hypertension affects nearly one in three adults in France, with a prevalence of 30.6% in 2015 (95% CI: 32.5-40.4; p=0.0001). Hypertension increased significantly with age, from 6.3% in 18-34 year-old patients to 67.8% in 65-74 years-old, and is even higher over 75 years-old. It is one of the main risk factor for cardio-neurovascular disease, nephropathy and cognitive impairment. (1) There is no longer any debate about the benefit of treating hypertension in the elderly. Treating elderly patients with hypertension reduces all-cause mortality and cardiovascular morbidity and mortality. (2)

Angiotensin II is a peptide resulting from the cleavage of angiotensin I by the angiotensin converting enzyme (ACE). Angiotensin II binds to and activates angiotensin II receptors type 1 (AT1R), responsible of vasoconstriction, fibrosis, inflammation, oxidative stress and cardiac hypertrophy and angiotensin II receptor type 2 (AT2R), responsible of vasodilatation, anti-fibrotic, anti-inflammation, reduction of oxidative stress and anti-proliferation. So, while AT1R have hypertensive effect, AT2R have antihypertensive effect. (3) ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II. Angiotensin II receptor blockers (ARBs) are AT1R antagonists. These inhibitions decrease blood pressure and increase natriuresis. The antihypertensive agents to be used as first-line agents in hypertension are either ACE inhibitors or ARBs according to the ESC/ESH-AHA guidelines for the management of hypertension. (4,5) They are also used in first line for chronic heart failure, myocardial infarction. Alternative pathways are implicated in the Renin Angiotensin System (RAS) pathway with other receptors like the AT4 receptor, MrgD and Mas receptor or enzymes like (chymases, neprilysin). (3) They appear to be collateral pathways for blood pressure control with an antihypertensive effect and are more activated when the main pathway is blocked by the ARBs or ACE inhibitors and would be involved in the efficacy and adverse effects of these drugs.

The pharmacodynamics mechanism of ARBs and ACE is at the origin of adverse effects such as hypotension, orthostatic hypotension (OH) and syncope. They are common expected adverse effects ($\geq$ 1/100 to < 1/10) of ACE inhibitors and ARBs, listed in their Summary of Product Characteristics. Those adverse events are also listed in mechanism of fall. (6-7) Falls are a major cause of morbidity and mortality among older adults. (8-9) The risk of falling increases with age, resulting in sometimes serious injuries that could lead to hospitalization, surgery or death. Falls are also a major cause of institutionalization. (10) More than 40% of admissions to nursing homes are related to falls. (11) In addition, presence of OH increases all-cause mortality and coronary event risk, independently of traditional risk factors. (12) Pharmacological therapy is a common cause of OH, particularly in older patients but the association between ARBs or ACE inhibitors and OH, syncope and fall is still being debated at the moment.

Opinions diverge and animate the scientific community. Many large clinical trials and meta-analysis post marketing authorization showed no association between antihypertensive drugs and OH, syncope and fall. They included relatively healthy participants and may not reflect the risk in older adults with multiple chronic conditions. Several groups of participants were excluded like patients with a high risk of fracture or fall or OH: moderate to severe chronic heart failure, coronaropathy, chronic kidney injury or dementia. (13-15) Such exclusions may impair the generalizability of clinical trials results. (16) Lately, a meta-analysis found no evidence of an association with antihypertensive treatment with fall, but they were associated with an increased risk of hypotension (1.97, 1.67 to 2.32, $\tau 2=0.132$, n=35), and syncope (1.28, 1.03 to 1.59, $\tau 2=0.050$, n=16). (17) However, the limited generalizability of findings from randomized controlled trials (RCTs), such as to older adults, patients with comorbidities or comedications, is one of the major drivers for the conduct of comparative effectiveness research (CER). (18) Large observational databases are often used to answer questions about comparative safety.

Several observational studies on large cohorts of real-life patients have shown the opposite. In an American crossed-sectional study with 477,516 patients of 65 (SD=13) years-old treated with antihypertensive drugs, the multivariable ORs for serious falls/syncope were 2.18 (95% CI=2.11, 2.25) for minimum SBP <110 mmHg and 1.54 (95%CI=1.43, 1.66) for mean SBP <110 mmHg compared with SBP ≥110 mmHg. (19) In another observational study including 543,572 new users of antihypertensive drugs among community-dwelling elderly, the risk of having an injurious fall during the first 45 days following antihypertensive treatment was also increased compared to falls rate in the control periods of 450 days (IRR=1.69; 95 % CI, 1.57–1.81). (20)

Although both ARBs and ACE inhibitors block the main RAS pathway and increase alternative pathway of the RAS by different mechanisms implicated in antihypertensive effect, they differ in several important aspects. ARBs reduced activation of AT1 receptors more effectively than do ACE inhibitors. ARBs permit activation of AT2 receptors, which enhances its antihypertensive action. Whether the pharmacological differences between ARBs and ACE inhibitors result in significant differences in therapeutic outcomes is an open question. (3) Opinions widely diverge and are still being discussed the scientific community. (13-15, 17, 19, 20) It remains to be determined in a real-life study, with a large proportion of older adults with multiple chronic conditions, which between ACE inhibitors and ARBs causes the most falls in subjects over 65 years of age.

Moreover, it has been shown that the blood pressure decrease differs according to the ACE inhibitors used. (21-24) These findings suggest that antihypertensive effect varies across a same pharmacological class. The risk based on the pharmacological mechanism must be different in each pharmacological class (ACE inhibitors or ARBs).

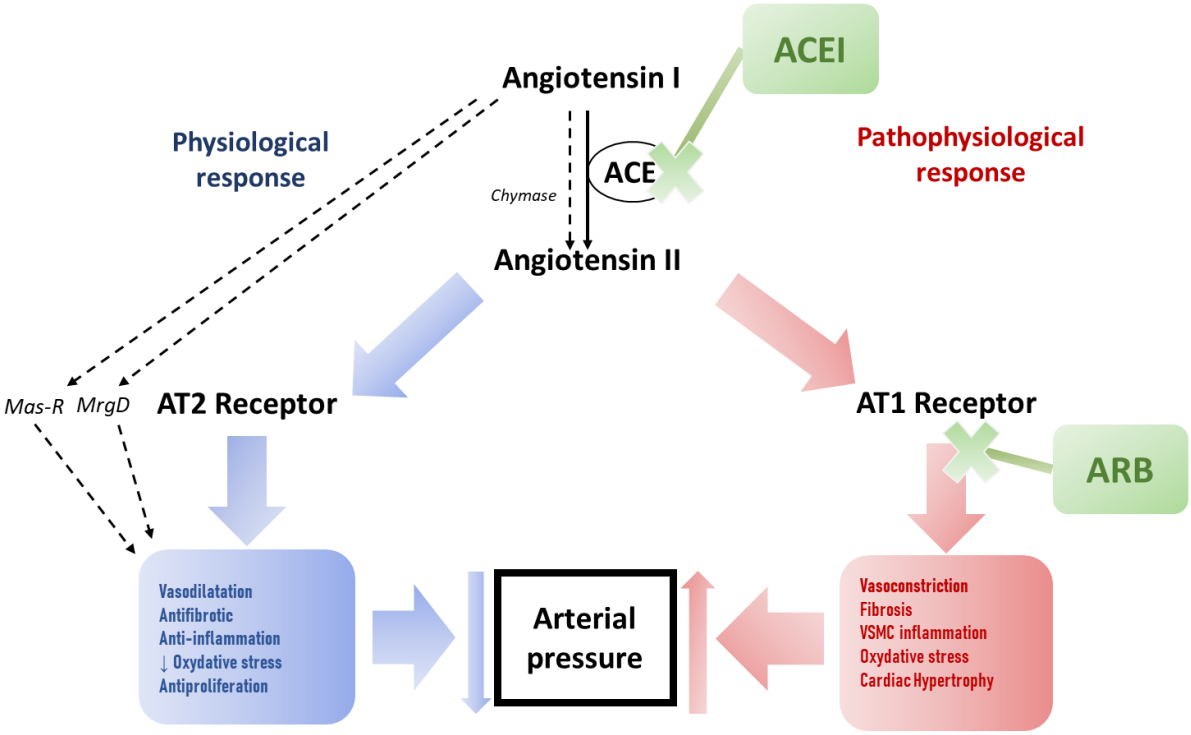

Figure 1: Schematic components of the RAS and mechanism of ACEI and ARB. The heavy arrows show the classical pathway, and the light arrows indicate alternatives pathways. RAS: Renin Angiotensin System, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin II receptor blockers. Receptors involved: AT1 receptor, AT2 receptor, Mas-R, MrgD. Enzymes involved: ACE (Angiotensin converting enzyme), chymase.

2. Hypothesis

Due to an antihypertensive effect not only by the inhibition of AT1R, but also by increasing the activation of AT2R and alternative pathways, we suggest that ARBs patients experience more fall and trauma-related hospitalizations than ACE inhibitors patients. Moreover, we suggest that the risk based on the pharmacological mechanism must be different in each pharmacological class (ACE inhibitors or ARBs).

3. Objectives

a. Primary Objective

We will conduct a population-based study to determine whether use of ARBs, when compared with ACE inhibitors, is associated with an increased risk of fall and trauma-related hospitalization among elderly patients.

b. Secondary Objectives:

Determine whether use of ARBs, when compared with ACE inhibitors, is associated with an increased risk of syncope, malaise, orthostatic hypotension, and serious outcomes (ICU hospitalizations, death) among of 65 years old and older.

Determine whether use for each ARB apart when compared to ACE inhibitors group, is associated with an increased risk of fall or trauma-related hospitalization among of 65 years old and older.

Determine whether use for each ACE inhibitors apart when compared to ARB group, is associated with an increased risk of fall or trauma-related hospitalization among 65 years old and older.

c. Ancillary Objectives:

Access the risk of "accident and injury" reports (SMQ) when compared to all other report for ARB versus ACE inhibitors in Vigibase®.

4. Method

a. Study design

Using the General Beneficiary Sample (EGB), we will conduct a cohort study among all patients aged 65 years and older with a first prescription for ARBs or ACE inhibitors between January 1st, 2009 and December 31st, 2019.

b. Data source

The General Beneficiary Sample (EGB) is a permanent sample representative of the population covered by French health care insurance. EGB is a permanent 1/97th sample of the SNIIRAM, representative in terms of age and sex, and contains data on approximately 660,000 health insurance beneficiaries. EGB collects all health insurance reimbursement services performed in the city, the Inter Regime Consummation Datamart (DCIR) as well as hospitalization data, by chaining with the Medicalization Program of the Information Systems (PMSI).

The database collects the healthcare consumption submitted for reimbursement by the individuals, as well as some administrative data: age at the time of the first dispensation, sex, insurance coverage (ALD, CMUc), date of death, origin of the prescription (hospital, outpatient). Public hospitalization records are not available. Diagnoses are coded according to the ICD-10 classification. The data have been available since 2003 for the general healthcare system, with implementation of the other healthcare systems and increasing reliability over the following years.

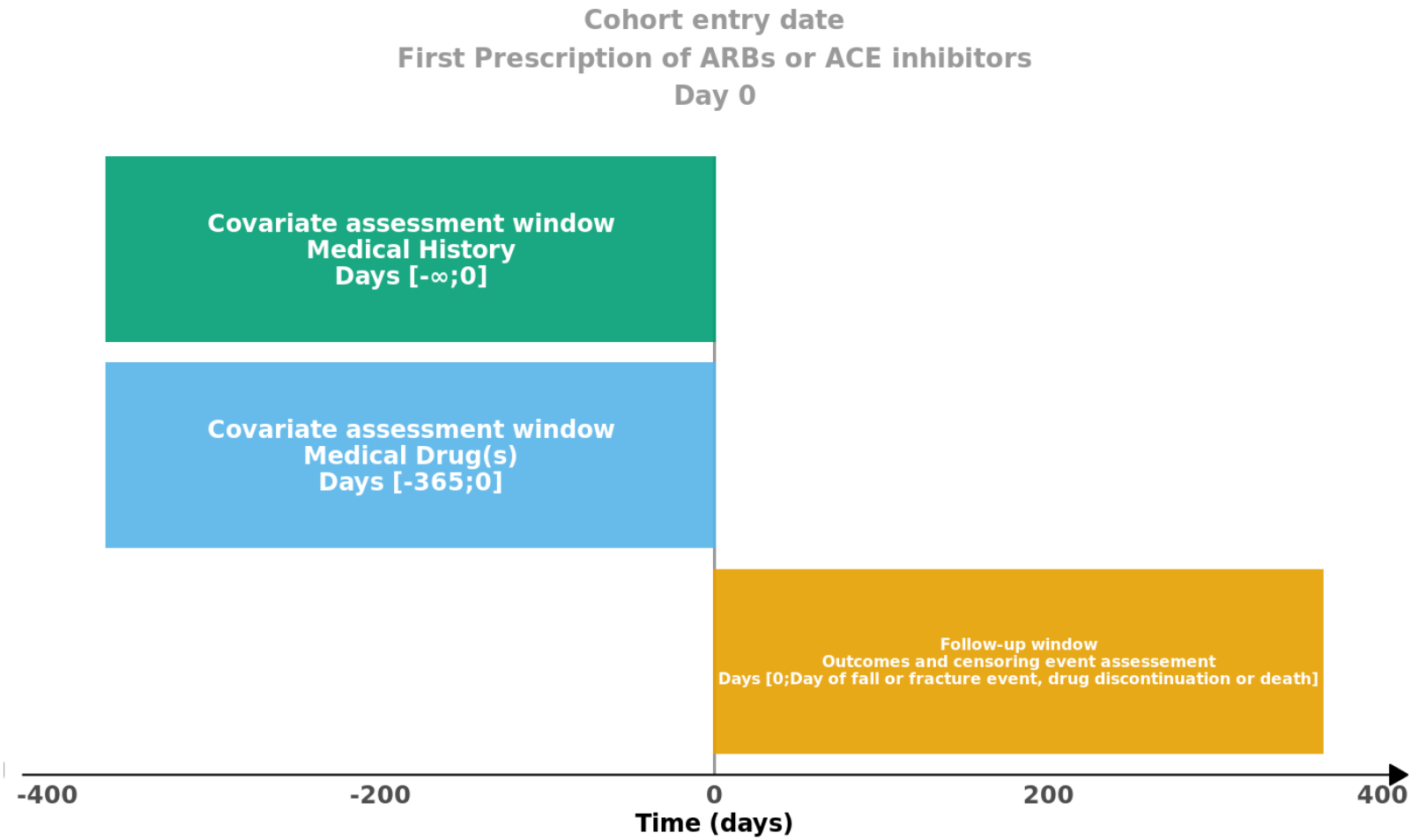

Figure 1: Study design ACEI and ARB initiators were defined patients who had no record of a RAS prescription. Among these patients, the index date was defined as the date of ACEI and ARB initiation. Baseline covariates were identified in a period prior to the index date. Study follow-up began immediately after the index date.

c. Definition of the study population

We will assemble a cohort of all patients of 65 years and over with a first prescription for an ARB or an ACE inhibitor between January 1st, 2009, and December 31st, 2019.

Cohort entry will be defined as the date of the first ARB or an ACE inhibitor prescription within the study period. Patients with less than 1 year of information in the EGB before cohort entry date and patients who have been prescribed any antihypertensive drugs (calcium channel blockers, beta-blockers, loop diuretics, thiazide diuretics, mineral-corticoid antagonists, central antihypertensive drugs, and renin inhibitors) before cohort entry will be excluded to form a cohort of new users of ARB or ACE inhibitor. Patients will not be included if there is an occurrence of a hospitalization for fall-related hospitalization (W06, W07, W10, W17-19 and R296) or trauma-related hospitalization (S00-99, T00-T14) in the year before the first incident prescription of a RAS medication. Owing to the lack of data for drug exposure during hospitalization, all periods of hospital stay will be considered as periods of exposure if the patient was in possession of drugs at the date of hospital admission.

Patients will be followed up until the date of their first outcome event, treatment discontinuation, death resulting from any cause, endpoint date of the study (one year following the first prescription) or censored upon a switch from an ARB or an ACE inhibitor to another antihypertensive drug, whichever occurs first.

d. Selection of comparison group(s)

The reference group will be ARBs and comparison group will be ACE inhibitors. The ACE inhibitors and ARBs drugs included in the main analysis will be identified in the EGB by their ATC codes, which are described in Table 1, as well as their pharmacological properties.

e. Exposures, Outcomes and Covariates

Exposures

We will use an as-treated exposure definition, where patients will be considered exposed from the date of the first dispensation and censored at the date of treatment discontinuation, switch to or add-on of another class of antihypertensive drug (calcium channel blockers, beta-blockers, loop diuretics, thiazide diuretics, mineral-corticoid antagonists, central antihypertensive drugs and renin inhibitors). Censoring will also happen if patients switch an ARB for an ACE and inversely.

The duration of an ARB or an ACE inhibitor use will be calculated from the number and duration of successive prescriptions for the same ARB or an ACE inhibitor. Patients will be considered continuously exposed if the duration of one prescription overlaps with the date of the next prescription. In the event of two non-overlapping successive prescriptions, we will allow for a grace period of 30

days to account for residual effects, refills, and delay for a fall or trauma-related hospitalization and will consider these patients still under treatment.

Outcomes

We will identify patients with an incident fall or trauma-related hospitalization identified in the PMSI through the ICD-10 hospitalization codes for fall (ICD-10 W06, W07, W10, W17-19 and R296) and for trauma (ICD-10 S00-99, T00-T14).

Primary end point:

- Occurrence of a hospitalization for fall (ICD-10 W06, W07, W10, W17-19 and R296) or trauma (ICD-10 S00-99, T00-T14) during the follow-up.

Secondary end points:

- Hospitalization for syncope (ICD-10 R55) or malaise (ICD-10 R53) during the follow-up.
- Hospitalization for orthostatic hypotension (ICD-10 I951) during the follow-up.
- Onset of ICU hospitalization for falls or trauma during the follow-up.
- Onset of death during the follow-up.
- Occurrence of a hospitalization for fall (ICD-10 W06, W07, W10, W17-19) or trauma (S00-99, T00-T14) during the follow-up for each ARB apart when compared to ACE inhibitors group.
- Occurrence of a hospitalization for fall (ICD-10 W06, W07, W10, W17-19) or trauma (S00-99, T00-T14) during the follow-up for each ACE inhibitors apart when compared to ARB group.

Sensitivity endpoint:

- Risk of fall and trauma related hospitalization with ARBs or ACE inhibitors according to sex (female / male), age group, type of pathology (heart failure / hypertension / ischemic heart disease), type of cardiovascular prevention (primary / secondary), and finally according to the type of prescriber (cardiologist / general practitioner / geriatrician).
- Risk of fracture-related hospitalization alone, fall-related hospitalization alone and trauma-related hospitalization alone during the follow-up.
- Risk for fall or trauma-related hospitalization according to variation of duration use of ARBs

Ancillary endpoint:

- Risk of "accident and injury" reports (SMQ) when compared to all other report for ARB versus ACE inhibitors in Vigibase®.

Covariates

The following covariates will be analyzed in the study. Table 3 also list the covariates, the way they will be collected and their descriptions.

Sociodemographic characteristics:

- Patient identification number
- Age
- Sex
- Year of entry in the cohort
- Comorbidities: diabetes, renal failure, cognitive disorders, polypathologies
- Cardiovascular co-prescription
- Long-term illness (ALD)

Comorbidity in year prior to cohort entry contributing to falls:

- Alzheimer's disease and other dementias
- Cerebral vascular accident
- Parkinson's disease
- Epilepsy
- Severe neurological and muscular disorders (including myopathy), severe epilepsy
- Arterial disease
- Heart failure
- Cardiac arrhythmia
- Atrioventricular block
- Osteoporosis
- Polyarthritis
- Age-related macular degeneration
- Cancer
- Alcohol dependence

Medications in year prior to cohort entry contributing to falls:

- Sedative effect: barbiturates, benzodiazepines, morphine and derivatives, anticonvulsants
- extrapyramidal syndrome: neuroleptics

- Orthostatic hypotension: calcium channel blockers, beta-blockers and diuretics, L-dopa and dopamine agonists, antidepressants
- Conduction and cardiac rhythm disorders: antiarrhythmics, especially digitalis, hypokalemic diuretics (torsade de pointe), beta-blockers

Other variables of interest:

- Cardiovascular prevention
- Origin of the prescription
- Number of consultations with a general practitioner
- Number of consultations with a specialist physician
- Category of prescriber who made the incident RAS drug prescription
- Total number of different INNs (International Nonproprietary Names)
- Charlson score
- Death
- Death during follow-up
- CMU-c

f. Data/ Statistical analysis

The extraction of data from the database will be carried out by the SAS® software V9.4M7 (SAS Institute Inc., Cary, NC, USA). A preliminary cleaning of the database (duplicates and aberrant data) will be conducted before the statistical analysis. The statistical analysis of the data will be performed using SAS® software.

Primary analysis

We will use propensity score (PS) to take account the potential confounding. Potential confounders were defined during the 365-day baseline period and will include year of cohort entry, age at cohort entry, sex, geographic region, comorbidity and medications contributing to falls and insurance type. Descriptive statistics will be used to compare baseline characteristics between patients starting ARBs and patients starting ACE inhibitors. Crude and age-and-sex-standardized incidence rates with 95% CIs of fall and trauma will be estimated based on a Poisson distribution for each exposure group.

In the primary analysis, we will use Cox proportional hazards models with PS matching/stratification to estimate the HRs with 95% CIs of fall and trauma associated with the use of ARBs compared to use of ACE inhibitors. We will also plot the weighted cumulative incidence curve of fall and trauma for each exposure group over the follow-up time.

Secondary analysis

We will conduct two secondary analyses. First, we will repeat the primary analysis to assess the risk of other serious events (death, malaise, orthostatic hypotension, hospitalization in intensive care and death associated with the use of ARBs compared to use of ACE inhibitors.

Second, we will repeat the primary analysis and calculate the incidences of falls and trauma-related hospitalization for each ARB and ACE inhibitors separately in their own pharmacological class when compared to the opposite RAS class.

Sensitivity analyses

We will perform sensitivity analyses to assess the robustness of our results. Multivariable Cox proportional-hazards outcome models without propensity-score matching or stratification will be fitted, with adjustment for covariates.

We will conduct several subgroup analyses, according to sex (female / male), age group, type of pathology (heart failure / hypertension / ischemic heart disease), type of cardiovascular prevention (primary / secondary), and finally according to the type of prescriber (cardiologist / general practitioner / geriatrician).

We will also conduct sensitivity analyses by restricting the primary outcome. We will repeat the primary analysis to assess the risk of fall alone, trauma alone, fracture alone.

Finally, we will assess whether the risk for fall or trauma-related hospitalization varies with duration of use of ARBs. Duration of use will be stratified into 3 categories approximately based on the tertiles of distribution of use in the reference group.

Ancillary analysis

We will perform a case-non-case study using Vigibase®, World Health Organization's unique global database of reported potential side effects of drugs. It is the largest such database in the world, which contains the WHO's Global Individual Case Safety Reports (ICSR), which includes over 28 million anonymous reports of Suspected adverse drug reactions (ADRs), in September 2021, reported to the WHO Uppsala Surveillance Center by national pharmacovigilance systems from over 130 countries around the world since 1968. We will use the terminology of the Medical Dictionary for Regulatory Activities (MedDRA). We will perform a description of the ADRs characteristics followed by investigation of the reporting risk using disproportionality analyses. Cases will be defined as “accident and injury” reports (Standardised MedDRA Queries – SMQ). Non-cases will be all other reports. SMQs are a unique feature of MedDRA and provide a strong tool to support safety analysis and reporting. The

SMQ topics are intended to address the important pharmacovigilance topics needed by regulatory and industry users. Drugs will be classified according to the ATC classification.

Using a case/non-case design, we will perform univariate then multivariate logistic regression to estimate the odds ratios (RORs) with their 95% confidence intervals (CIs). We will also perform sensitivity analyses to assess the robustness of our results. We will access the reporting risk of "Fracture" (HLGT), "Bone and joint injuries" (HGLT) using disproportionality analyses.

5. Number of Subjects Needed

EGB is a permanent 1/97th sample representative of the population covered by French health care insurance. According to Thalès-Cégédim data from the French National Health Authority, of all incident antihypertensive prescriptions in France in 2009 (n=933 117), 24.0% (n=224 156) were ARB alone, 13.9% (n=130 125) were ACE inhibitors alone. In 2008, according to a study from the French National Health Authority on the EGB, people over 70 years of age represented 20.79% of all people receiving a first-time antihypertensive treatment as monotherapy (25).

In our study, it appears that we could include approximately 578 patients per year with an incident prescription of ARB and 337 patients per year with an incident prescription of ACE inhibitors. Thus, we could potentially include approximately 10 065 patients included over the period 2009-2019.

We conservatively expect an incidence of falls of approximately 0.036 per 100 persons per years among adults >65 years newly prescribed an ARB or ACE inhibitors. (26) With a cohort of approximately 10,000 patients with a first ARBs or ACE inhibitors prescription, including 6,300 new users of ARBs, and a conservative median follow-up time of approximately 1 year. Therefore, using a two-tailed alpha of 5% we will have over 90% power to detect a HR of 1.35.

6. Legal Aspect

Having public service missions, the Pharmacoepidemiology team of the Clinical Investigation Center (CIC) of the Toulouse University Hospital, have permanent access to SNDS data, as specified by Decree n° 2016-1871 of December 26, 2016, and authorized by the CNIL.

As the present study falls under the qualification of non-interventional research on existing data with a change of purpose and is not part of research on the human person as defined by the so-called Jardé law, the opinion of a CPP (Committee for the Protection of Persons) is not necessary according to French legislation.

Access to the EGB data is nominative for a given study via a secure portal for people who have received the necessary training and authorizations. The data necessary for the present study are already

available and accessible through Dr François MONTASTRUC and the pharmaco-epidemiology team who are authorized to use the EGB data. Julia GUION-FIRMIN will make the necessary trainings from the CNAM to access the data.

7. Expected Impact

Falls are the leading cause of accidental death in the elderly. The economic burden of falls in the elderly on society is vast: hospitalization, surgery, loss of autonomy leading to the need for home help or institutionalization. Therefore, the evaluation of the association between risk of falls and antihypertensive drugs has been a scientific matter for many years. If it is admitted in CER studies that there is an association between falls and antihypertensive drugs, these data do not allow us to provide clear direction for the physician's prescription for elderly subjects.

With the help of our study, we want to determine the first-line antihypertensive drug for an elderly patient, as it has been done with statins. Thus, in this study, we first want to identify which RAS class is the safest to use in the geriatric population, regarding the risk of falls and trauma. Then, we want to know if in the class with the lowest risk, there is a drug that is safer than the others for elderly subjects. We will be able to obtain a better description of fractured falls under antihypertensive drugs acting on the Renin-Angiotensin-Aldosterone System.

Grounded on an interdisciplinary approach, the scientific impact of the project extends to the field of medical pharmacology, geriatrics and cardiology. We will be able to improve the prescription of antihypertensive drugs in the elderly. Thus, directions for physician prescription could be based on the results of our research on a nationwide observational cohort. Using real life data, we may be able to reduce the risk of falls and fractures associated with the use of antihypertensive drugs in the elderly. We could promote a higher quality of life for the elderly by preserving their autonomy and decrease health costs.

Provisional schedule

Date	Stages
November 2021	Submission of the initial version of the protocol for the SNDS commission.
February – March 2022	Data collection.
April – May 2022	Main statistical analyses.
May – June 2022	Secondary, additional and sensitivity statistical analyses.
April– June 2022	Critical analysis of all the results and discussions with the scientific committee.
May – June 2022	Preparation and submission of the Master II thesis.
June – July 2022	Writing and submission of the article based on this protocol, submitted to a peer-reviewed scientific journal.
After July 2022	Adjustments on the manuscript according to the comments of the scientific journal, possible additional analyses according to reviewing.
December 31, 2023	Last day of possible access to EGB data on the SNDS portal for this project.

Abbreviation

ACE: Angiotensin Converting Enzyme

ALD: Affection longue durée

ARB: Angiotensin II receptor blockers

ATC: Anatomical Therapeutic and Chemical Classification

ATR1: Angiotensin II Receptor Type 1

ATR2: Angiotensin II Receptor Type 2

CER: Comparative Effectiveness Research

CI: Confidence Interval

CIC: Clinical Investigation Center

CMUc: Couverture maladie universelle complémentaire

CNAM: Caisse Nationale d'Assurance Maladie

CNIL: Commission Nationale de l'Informatique et des Libertés

CPP: Committee for the Protection of Persons

CV : Cardiovascular

DCIR: Datamart de Consommation Inter-Régime

EGB: Echantillon Généraliste des Bénéficiaires

ESC: European Society of Cardiology

ESH: European Society of Hypertension

HAH: American Heart Association

HR: Hazard ratio

ICD: International Classification of Diseases

ICU: Intensive Care Unit

INNs: International Nonproprietary Names

IRR: Incidence rate ratio

OH: Orthostatic Hypotension

OR: Odds Ratio

PS: Propensity Score

RAS: Renin Angiotensin System

RCT: Randomized Controlled Trials

SBP: Systolic Blood Pressure

SD: Standard Deviation

SNDS: Système National des Données de Santé

SNIIRAM: Système National d'Information Inter-régimes de l'Assurance Maladie

WHO : World Health Organization

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Annexes

Table 1. List of renin-angiotensin system blockers marketed in France during the study period (2000-2020). Source: ANSM

Pharmacological class	Group (INN)	Drug	Date of marketing authorization	ATC Code
Angiotensin converting enzyme inhibitors	Benazepril	CIBACENE and generics	27/07/1990	C09AA07
	Captopril	CAPTEA, LOPRIL and generics	27/01/1987 20/02/1981	C09AA01
	Cilazapril	JUSTOR	19/09/1990	C09AA08
	Enalapril	RENITEC and generics	22/03/1984	C09AA02
	Fosinopril	FOZITEC and generics	04/03/1992	C09AA09
	Lisinopril	ZESTRIL, PRINIVIL and generics	06/10/1987	C09AA03
	Moexipril	MOEX	20/08/1996	C09AA13
	Perindopril	COVERSYL and generics	22/06/1988	C09AA04
	Quinapril	ACUITEL and generics	14/04/1989	C09AA06
	Ramipril	TRIATEC and generics	07/02/2003	C09AA05
	Trandolapril	ODRIK and generics	19/02/1992	C09AA10
	Zofenopril	ZOFENIL, TEOULA and generics	29/03/1999 30/03/2001	C09AA15
Angiotensin II receptor antagonists	Azilsartan	EDARBI, IPREZIV	07/12/2011	C09CA09
	Candesartan	ATANCAND, KENZEN and generics	23/05/2005	C09CA06
	Irbesartan	APROVEL and generics	27/08/1997	C09CA04
	Losartan	COZAAR and generics	15/02/1995	C09CA01
	Olmesartan	OLMETEC, ALTEIS	06/08/2003 29/10/2003	C09CA08
	Telmisartan	MICARDIS, PRITOR, KINZALMONO and generics	16/12/1998 11/12/1998 16/12/1998	C09CA07
	Valsartan	TAREG, NISIS and generics	31/05/2001	C09CA03

Table 2. List of ICD-10 codes associated with falls and trauma.

Code	Title
W06	Fall from a bed
W07	Fall from a chair
W10	Fall in and out of stairs and steps
W17	Other fall from one level to another
W18	Other fall on the same level
W19	Fall, unspecified
S00-S09	Traumatic head injuries
S10-S19	Traumatic neck injuries
S20-S29	Traumatic chest injuries
S30-S39	Traumatic injuries of the abdomen, lumbar spine and pelvis
S40-S49	Traumatic injuries of the shoulder and arm
S50-S59	Traumatic injuries of the elbow and forearm
S60-S69	Traumatic injuries of the wrist and hand
S70-S79	Traumatic injuries of the hip and upper leg
S80-S89	Traumatic injuries of the knee and leg
S90-S99	Traumatic injuries of the ankle and foot
T00-T07	Traumatic injuries of several parts of the body
T08-T14	Traumatic injuries of unspecified location of the trunk, limb or other body region
R296	Recurrent falls

Table 3. List of ICD-10 codes associated with fracture.

Code	Title
S02	Skull and facial bone fracture
S12	Neck fracture
S22	Rib, sternum, and dorsal spine fracture
S32	Lumbar spine and pelvis fracture
S42	Shoulder and arm fracture
S52	Forearm fracture
S62	Wrist and hand fracture
S72	Femur fracture
S82	Leg fracture, including ankle
S92	Foot fracture, except ankle

Table 4. Descriptive variables and potential adjustment variables. Exhaustive list of covariates that will be analyzed in the study, the way they will be collected and their descriptions.

Label	Mode	Description
Patient identification number		Anonymized patient identification number
Age	≥ 65 years – < 75 years ≥ 75 years – < 85 years ≥ 85years	Age at inclusion
Sex	Men Female	
Year	Quantitative variable	Year of entry into the cohort
Cardiovascular Coprescription	• Lipid-lowering • Antithrombotic • Other cardiovascular treatment	Prescription of a lipid-lowering or antithrombotic treatment (antiplatelet agents, antivitamin K, heparins) or another treatment with cardiovascular indications.
ALD	Yes No	Patient registered in the ALD regime.
Cardiovascular ALD	• Stroke • Arterial disease • Heart failure • Severe or complicated hypertension • Coronary artery disease • Atrial fibrillation and flutter • Pulmonary embolism • Atrioventricular block	Patient registered in the ALD regime for a long-term cardiovascular disease (stroke, arterial disease, heart failure, severe or complicated hypertension, coronary disease, atrial fibrillation and flutter, pulmonary embolism, atrioventricular block)

Chronic kidney disease	Yes No	Patient registered in the ALD regime for renal impairment or with a reimbursement for suppletion treatment such as renal dialysis, renal transplantation or renal transplantation follow-up.
Diabetes	Yes No	Patient registered in the ALD regime for diabetes or with reimbursement for anti-diabetic treatment.
Alzheimer's disease and other dementias	Yes No	Patient registered in the ALD regime for Alzheimer's disease and other dementias or with reimbursement for Alzheimer's disease treatment.
Polypathologies	Yes No	Patient registered in the ALD regime for polypathology
Comorbidity in year prior to cohort entry contributing to falls	Yes No	Patient registered in the ALD regime for: • Alzheimer's disease and other dementias • Cerebral vascular accident • Arterial disease • Heart failure • Parkinson's disease • Epilepsy • Severe neurological and muscular disorders (including myopathy), severe epilepsy • Osteoporosis • Cardiac arrhythmia • Polyarthritis • Atrioventricular block • Age-related macular degeneration • Cancer • Alcohol dependance
Medications in year prior to cohort entry contributing to falls	Yes No	Prescription in the year of a listed drug contributing to the risk of falls in the elderly: • sedative effect: barbiturates, benzodiazepines, morphine and derivatives, anticonvulsants

		• extrapyramidal syndrome: neuroleptics • orthostatic hypotension: calcium channel blockers, beta-blockers and diuretics, L-dopa and dopamine agonists, antidepressants • conduction and cardiac rhythm disorders: antiarrhythmics, especially digitalis, hypokalemic diuretics (torsade de pointe), beta-blockers
Cardiovascular prevention	Secondary Probable primary with major risk factor of cardiovascular disease Probable primary without major risk factor of cardiovascular disease	Cardiovascular event registered in ALD or using a CV treatment. Presence of diabetes (see above) or co-prescription of a lipid-lowering drug Patient not classified in secondary prevention or primary prevention with FDR
Origin of the prescription	Hospital Outpatient	First prescription, depending on if it comes from a health institution or a private health professional
Number of consultations with a general practitioner	Quantitative variable	Number of consultations observed during the follow-up year with a general practitioner.
Number of consultations with a specialist physician	Quantitative variable	Number of consultations observed during the follow-up year with a specialist physician.
Category of prescriber who made the prevalent RAS drug prescription	General practitioner Specialist physician	Category of physician performing the incident prescription
Total number of different INNs (International Nonproprietary Names)	≤ 4 ≥ 4	Number of INNs dispensed in the 12 months following the first prescription.

Charlson score	Low: 0 Mild: 1 – 2 Moderate: 3 – 4 Severe: ≥ 5	Score as presented by Bannay et al. for use in SNDS databases
Death	Yes No	Death between 2009 and 2019**.**
Death during follow-up	Yes No	Death occurring in the 12 months following the first prescription
CMU-c	CMUc No CMUc	Reimbursement under the french universal complementary coverage (CMUc)