Association Between Exposure to Effervescent Paracetamol and Hospitalization for Acute Heart Failure: A Case-Crossover Study

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Conflict of interest disclosure

None to declare.

Data availability

The data that support the findings of this study are available from third party (data owner). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of third party.

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ABSTRACT:

We investigated whether effervescent paracetamol, as an important source of non-dietary sodium and fluid load, is associated with a transient increase in the risk of hospitalization for acute heart failure (AHF). We conducted a unidirectional case-crossover study using data from the 1/97th representative sample from the French healthcare database. Subjects aged 18 years or more, hospitalized for AHF during the 2014-2016 period were included. Exposure to effervescent paracetamol was compared between a risk period (i.e. 15 days immediately prior to admission for AHF) and three earlier 15-day control periods, to test a possible trigger effect of effervescent paracetamol intake on AHF. Adjusted odds ratios (aOR) were estimated with a conditional logistic regression. We identified 4,301 patients hospitalized for AHF. We found that 5.7% of AHF subjects were exposed to effervescent paracetamol during the risk period, as compared with 4.1% during the control periods (aOR 1.56 [$CI_{95\%}$: 1.27 – 1.90], $p < 0.001$). This association was also found in the subgroup of subjects with hypertension (aOR 1.45 [$CI_{95\%}$: 1.13 – 1.87], $p = 0.004$, n = 2,648) and in the subgroup of subjects aged 83 years or more (aOR 1.70 [$CI_{95\%}$: 1.28 – 2.24], $p < 0.001$, n = 2,238). A similar analysis, considering exposure to non-effervescent paracetamol, did not support the existence of an indication bias likely to explain the association observed for effervescent paracetamol. This study suggests an association between effervescent paracetamol and admission for AHF and should be confirmed with other complementary study designs.

Key words: pharmacoepidemiology, adverse drug reaction, quality use of medicines, medication safety, drug safety

INTRODUCTION:

Many factors have been associated with the decompensation of chronic heart failure (CHF), including episodes of tachyarrhythmia or infection, excessive rise in blood pressure or non-adherence to drug therapy or to controlled salt and fluid intake [1–3]. Additionally, many drugs have been identified as possible triggering factors of acute heart failure (AHF), including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, negative inotropic substances or cardiotoxic cancer treatments [1,2]. In 2016, the American Heart Association published a list of drugs which are recognized or suspected to cause or exacerbate heart failure [4]. These recommendations highlighted the risk associated with exposure to sodium-containing drugs among heart failure patients. This miscellaneous group of drugs includes intravenous sodium chloride, intravenous antibiotics, effervescent tablets, and some specific non-effervescent oral formulation. To date, the iatrogenic risk associated with exposure to such high-

sodium containing drugs has been poorly evaluated [5], particularly among heart failure patients, and is based on the recommendation for restricting dietary sodium intake in CHF patients, from 1.5g/day to 3g/day, depending on the guideline considered, the type and severity of heart failure [2,6]. Beside the non-dietary sodium load, effervescent tablets are also associated with a significant fluid intake (required for drug administration), whereas restriction of fluid intake is generally recommended for patients with more severe congestive symptoms. A large nested case-control study found that patients diagnosed for incident non-fatal myocardial infarction, incident non-fatal stroke, or who died for a vascular cause, were more likely to be prescribed such high-sodium containing drugs [7]. Additionally, a crossover randomized trial found that exposure to 3g effervescent paracetamol per day, in a group of hypertensive subjects, was associated with a significant rise in blood pressure assessed by 24-hour ambulatory blood pressure measurement, as compared to a control period of exposure to 3g non-effervescent paracetamol [8]. We found that exposure to effervescent tablet is frequent in a large health check-up population in France [9], with 26.9% of the subjects declaring the use of at least one effervescent tablet during the last 30-day period. In this study, 7.3% of the subjects declared a consumption of at least 2-3 effervescent tablets per week during the last 30-day period. We did not find difference in exposure between normo- and hypertensive subjects, questioning the possibility of a large utilization of such drugs in high-risk populations, especially CHF patients. In France, 18 million boxes of effervescent paracetamol have been refunded by the healthcare insurance system in 2017, for 66.7 million inhabitants [10].

In the context of a triggering effect of an excessive sodium intake on AHF onset, and of the high sodium content of effervescent tablets of paracetamol, the aim of this study was to evaluate whether exposure to effervescent paracetamol, as a source of non-dietary sodium load and fluid intake, could be associated with hospitalization for decompensated heart failure.

METHODS:

Results of the study are reported according to the RECORD-PE guidelines[11].

Ethics

The EGB database contains only anonymized data and its access is legally authorized without having to consult with the national data protection agency (CNIL). The study protocol was submitted to the appropriate INSERM and CNAMTS entities, as legally required. In addition, an ethics committee approved the study protocol (registration number N°2018-06-02). The need for patient informed consent was waived because of the anonymous nature of the data.

Data sources

This study used health administrative data retrieved from the French National Health Insurance sample (EGB: Échantillon Généraliste des Bénéficiaires). EGB is a permanent 1/97th representative sample of the nationwide healthcare insurance database (Système National d'Information Inter-régimes de l'Assurance Maladie, SNIIRAM) and includes data from more than 660,000 individuals in 2014. SNIIRAM, and by extension EGB, is linked to the national hospital database (Programme de Médicalisation des Systèmes d'Information, PMSI) [12,13].

Study design

We performed a unidirectional case-crossover analysis [14]. In this study design (a self-controlled design derived from the case-control study), only patients with AHF are included (i.e. no control group of subjects without AHF is used), and each subject acts as his or her own control, at different time points (or periods) prior to the AHF episode (see **Figure 1**). In this study design, if exposure is more frequent during the risk period, as compared to control periods, exposure is suspected to trigger AHF. A triggering factor is associated with a case-crossover odds ratio (OR) > 1, and a preventive (or deterrent) factor with a case-crossover OR < 1.

This design allows controlling for time-invariant confounding factors which are not retrievable from EGB database (i.e. genetics, race, eating behaviors including salt consumption, substance abuse). To exclude a possible intrinsic effect of paracetamol on heart failure (since paracetamol per se might have a possible pro-hypertensive effect [15]), and to prevent confounding by indication (paracetamol might be prescribed for causes potentially triggering heart failure decompensation, such as infection), a similar analysis was performed with exposure to non-effervescent paracetamol as an active comparator.

As the temporal trend of the rate of effervescent paracetamol refunding remained stable throughout the control periods, we did not perform any case-time control analysis (see **Figure S1**).

This design is well suited in the case of intermittent treatments such as pain relief medications, which is the case in our study.

Identification of patients hospitalized for AHF

Patient admissions for AHF were retrieved from the EGB using a validated identification algorithm [16]. We included all patients, aged 18 years or more, admitted in a medical, surgical and obstetrical department during the considered year for heart failure (International Classification of Diseases ICD-10 code I50 as a main diagnosis), or for an acute complication of heart failure with an associated or related code I50. Acute complications considered were: hypertensive heart disease with heart failure (I11.0), hypertensive heart and chronic kidney disease with heart failure and kidney disease (I13.0), hypertensive heart and chronic kidney disease with heart failure and with renal disease (I13.2), hypertensive heart and chronic kidney disease with heart failure, not specified (I13.9), chronic passive congestion of liver (K76.1) or pulmonary edema (J81) during the considered year. The study period was between 01-01-2014 and 31-12-2016. For a patient with multiple hospital admissions during the study period, only the first hospital stay was selected in the analysis.

Exposure assessment

Drug exposure (to effervescent paracetamol in the main analyses, and to non-effervescent paracetamol and NSAIDs in complementary analyses) was assessed during four periods: a risk period (15-day period just before the hospital admission for AHF), and three control periods (30 to 45 days, 60 to 75 days and 90 to 105 days before admission for AHF) (**Figure 1**). Exposure during risk and control periods was defined with at least one reimbursement of the drug during the period. This binary definition of the exposure status corresponds to the extended analysis method described by Greenland [17,18] which has been recently applied to French National Healthcare database to conduct case-crossover analysis [19,20]. Medications were identified using the Presentation Identifying Code 13 (CIP-13, the list of CIP-13 codes used for data extraction is given in **Table S1**). For paracetamol (effervescent and non-effervescent), each reimbursement was expressed as an equivalent paracetamol Defined Daily Dose (DDD), calculated by multiplying the number of boxes by the number of tablets per boxes, and by the dosage in paracetamol of each tablet. This result was divided by 3,000 mg (corresponding to the DDD of paracetamol, according to the World Health Organization [21]). A high exposure group was defined by a total DDD above the median (DDD of all exposures retrieved during both risk and control periods); and a low exposure group when the total DDD was below this median.

Three case-crossover analyses were performed: effervescent paracetamol (main analysis), non-effervescent paracetamol (active comparator, to test a possible indication bias) and NSAIDs (positive control). Dose-response analyses are also reported for effervescent and non-effervescent paracetamol.

Confounding and descriptive variables

Confounding and descriptive variables were retrieved from the EGB database, either with a recorded chronic condition (Affection Longue Durée, ALD, a system which allows the reimbursement of healthcare expenditures associated with a list of specific medical conditions, including hypertension, peripheral vascular disease, or diabetes), or with a corresponding hospital discharge diagnosis, in the 3 calendar years preceding the hospital stay for AHF.

Sensitivity and complementary analyses

In order to test the robustness of the results, we performed a similar analysis, using alternative definition for the windows of exposure: the risk period was extended to the 30-day period just before hospital admission for AHF, and the three prior control periods were between 60 to 90 days before admission for control 1, 120 to 150 days before admission for control 2 and 180 to 210 days before admission for control 3. Finally, we performed additional analysis restricted to patient with history of hypertension, and in older subjects (i.e. with age equal to or over median age of the whole sample of AHF subjects), which are factors associated with increased salt sensitivity of blood pressure (15-day exposure periods, one reimbursement per period for the later complementary analysis).

Statistical analysis

Continuous data are presented as median and interquartile range. Categorical data are summarized with number and percentage. To evaluate the risk increase of hospitalization for AHF among subjects taking effervescent paracetamol, we used a case-crossover analysis, in which only cases admitted for AHF were included (no control group of subjects who were not admitted for AHF matched with AHF cases). In the sample of AHF subjects, exposure to effervescent paracetamol was assessed during the 15-day period just before AHF admission, and during three prior 15-day control periods (see **Figure 1**).

Adjusted case-crossover odds ratios were estimated using a conditional logistic regression model, stratified on individuals. In this model, the outcome was the period (1 = risk period or 0 = control period), whereas drug exposure status (see Exposure assessment above) was the independent risk factor [22]. Only subjects with discordant exposure status (i.e. exposed during risk period and unexposed during control periods, or exposed during control periods and unexposed during risk period) were used to estimate the case-crossover odds ratios.

Statistical significance was defined as p-value < 0.05 (two-sided). All analyses were performed using the R Core Team. R Foundation for Statistical Computing, Vienna Austria, version 3.4.4). For

conditional logistic regression analysis, the Survival R package (version 3.2.7) was used [23]. More information about the implementation of case-crossover design in R is available in a recent paper [24].

RESULTS:

A total of 4,305 subjects were retrieved from the EGB database between 01-01-2014 and 31-12-2016 with a first episode of hospitalization for AHF. Four subjects aged < 18 years were excluded. We finally included 4,301 patients in the analysis (flowchart of the study is given in **Figure 2**), corresponding to 4,301 risk periods and 12,903 control periods. The median age was 83.0 years (interquartile range: 75 – 88) and 53.4% were women. History of hypertension was found in 61.6% of subjects, and history of diabetes in 34.3%. Patient characteristics are reported in **Table 1**.

Patterns of drug utilization in the 30-days period before admission for AHF

More than half of heart failure subjects (50.5%) were treated with diuretics in the 30-day period before the first hospitalization for HF. Furthermore 9.0% of AHF subjects had a reimbursement of effervescent paracetamol during this period. Utilization of non-effervescent paracetamol was markedly higher, with 34.6% of subjects with at least one reimbursement. Concomitant exposure to diuretics and effervescent paracetamol was found in 5.2%, and concomitant exposure to effervescent paracetamol and angiotensin-converting enzyme (ACE) inhibitors in 3.4% (see **Table 1**).

Case-crossover analysis

In AHF subjects, exposure to effervescent paracetamol was more frequent during the risk period (5.7%) as compared with 4.1% during control periods (see **Table 2**). Results of the case-crossover analysis are reported in **Table 3.** The associated adjusted case-crossover aOR was 1.56 [95% Confidence interval $CI_{95\%}$: 1.27 – 1.90]) with no evidence for a dose-effect relationship, with an aOR 1.66 [$CI_{95\%}$: 1.31 – 2.11] and 1.39 [$CI_{95\%}$: 1.02 – 1.90] in the low and high exposure groups, respectively. **Table S2** shows the distribution of concordant and discordant matched pairs for the presence or absence of effervescent refunding during the case and control periods.

Association between period and exposure to non-effervescent paracetamol just missed significance in the main analysis, with an aOR of 1.11 [$CI_{95\%}$: 0.99 – 1.24] whereas this association marginally reached significance only in the low exposure group (aOR 1.16 [$CI_{95\%}$: 1.01 – 1.32]).

Finally, we found a positive association which did not reach significance between exposure to NSAIDs and study period (aOR 1.25 [$CI_{95\%}$: 0.92 – 1.70]).

Sensitivity and complementary analysis

In the 30-day time windows sensitivity analysis, the association of AHF with effervescent paracetamol remained significant with an aOR 1.24 [$CI_{95\%}$: 1.04 – 1.47], and a stronger association in the high exposure group (aOR 1.95 [$CI_{95\%}$: 1.52 – 2.51]). This association was also positive and significant in the non-effervescent paracetamol analysis (aOR 1.21 [$CI_{95\%}$: 1.09 – 1.33]). For NSAIDs, the association was positive, though non-significant (aOR of 1.26 [$CI_{95\%}$: 0.99 – 1.60]), consistent with the principle analysis (see **Table S3**).

In the subgroup of subjects with history of hypertension, the association was stronger while considering exposure to effervescent paracetamol (aOR 1.45 [$CI_{95\%}$: 1.13 – 1.87]) as compared with exposure to non-effervescent paracetamol (aOR 1.18 [$CI_{95\%}$: 1.03 – 1.36]), with, again, no evidence for a dose-relationship effect. In the subgroup of hypertensive subjects, association between NSAIDs exposure and period was significant (aOR 1.50 [$CI_{95\%}$: 1.01 – 2.19]). Concordant results were found in the analysis in subjects aged 83 years or more, with a positive relationship in the effervescent paracetamol analyses (aOR 1.70 [$CI_{95\%}$: 1.28 – 2.24]), and no relationship in the non-effervescent paracetamol analyses (aOR 1.03 [$CI_{95\%}$: 0.88 – 1.20]). Exposure to NSAIDs and study period were positively associated, but non-significantly (aOR 1.27, [$CI_{95\%}$: 0.78 – 2.08]) (see **Table 3**).

DISCUSSION:

This case-crossover study found a positive association between effervescent paracetamol exposure and hospitalization for decompensated heart failure (aOR 1.56 [$CI_{95\%}$: 1.27 – 1.90]), notably in older patients and those with history of hypertension.

Major validity conditions for using this design were verified: exposure to effervescent or non-effervescent paracetamol and to NSAIDs can be transient, AHF is a rare abrupt-onset event. Minor validity assumptions were also verified: the opportunity of being exposed is expected to be the same during the case and control periods. Even though we did not find any time trend in effervescent paracetamol in the 20-month period preceding admission for AHF, such time-trend was clearly observed for non-effervescent paracetamol with a continuous decreasing rate of exposure to non-effervescent paracetamol in the months preceding admission (see **Figure S1**). This time trend may have contributed to the positive association observed in the sensitivity analysis with a broader time

window of 30 days which increases the uncertainty in the timing of exposure [25]. No time trend was found for NSAIDs rate of exposure (see **Figure S2**).

Major interests of using case-crossover design is the control for important unmeasured or unmeasurable confounders, such as genotype associated with salt-sensitive phenotype, ethnicity or, to a lesser extent, consumption of dietary sodium [26], which are cofounder generally not controlled for in cohort or case-control studies based on large medico-administrative databases.

Biological hypothesis that can explain such association include the rise in blood pressure, and the interference with diuretic therapy efficacy with the non-dietary sodium load. Benitez-Camps *et al*. found, in a randomized crossover trial that the magnitude of elevation of systolic blood pressure associated with exposure to 3g/day of effervescent paracetamol among hypertensive subjects was ~ 4.0 mmHg [8]. Such effect size could be sufficient to trigger an AHF episode, particularly in older individuals in whom left ventricular compliance is decreased. Additionally, excessive drug induced Sodium intake may negatively interfere with diuretic therapy efficacy, notably for loop diuretics, since excessive sodium intake may induce a natriuresis without contracting the extracellular fluid volume in CHF patients, leading to diuretic resistance [27]. Finally, iatrogenic fluid intake associated with effervescent paracetamol might increase the risk of congestive symptoms and cardiac decompensation in more severe patients.

Classification bias related to effervescent and non-effervescent paracetamol exposure through self-medication with over-the-counter (OTC) paracetamol, an information not retrievable from EGB database, is limited in this context. Indeed, OTC use of paracetamol among chronic heart failure patients is expected to be marginal, since the ALD system in France allows the free refunding of prescribed drugs considered to be related to a list of chronic conditions, including heart failure or several rheumatologic conditions. Additionally, we previously showed in a French sample of 1,043 subjects, that participants exposed to effervescent tablets through self-medication had an estimated drug-induced sodium intake in the past 30-day period substantially lower than subjects exposed through a medical prescription (2.2 ± 2.7g and 11.3 ± 14.5g, respectively, $p < 0.001$) [9]. This reflects the fact that subjects who have a reimbursement of paracetamol are more likely to take the medication on a regular basis.

Absence of indication bias was convincingly demonstrated in our study, by performing the same analysis with non-effervescent paracetamol as an active comparator, notably in the subgroup of older subjects, where we found an OR of 1.70 for effervescent paracetamol and 1.03 for non-effervescent. Protopathic bias is not expected to be a pitfall in our analysis, since first symptoms of cardiac decompensation (i.e. dyspnea, weight gain, edema and fatigue) are not usual indications for paracetamol use.

Absence of dose-effect relationship in our study can be related with the central hypothesis for using reimbursement data as a proxy for drug exposure with large electronic healthcare databases [28]. This approximation may be difficult to apply in the case of intermittent exposure, and particularly in the case of paracetamol, since multiple behaviors can be associated with paracetamol acquisition: over prescription by the general practitioner and/or over dispensing by the pharmacist, potentially associated with the will for the patient to create a stock of drug at home (since paracetamol can be a useful drug for a myriad of clinical conditions). More generally, these results highlight the limitation of using refunding data to study dose-response relationship in case of drugs associated with intermittent pattern of exposure, due to the important uncertainty associated with the phenomenon of attrition between dispensing and actual ingestion [29].

We found a positive association between exposure to NSAIDs and hospitalization for AHF, which failed to reach significance in the main analysis, but which was significant among hypertensive subjects. These results are in concordance with the literature in terms of direction and relatively modest amplitude of association, in particular with results from the Rotterdam cohort [30] and from other studies [31,32]. The higher risk observed in the subgroup of hypertensive subjects was expected, since NSAIDs increase blood pressure through prostaglandin inhibition in the kidneys[33].

We found that frequency of exposure to effervescent paracetamol was high 30 days before hospital admission for heart failure decompensation. This could suggest that existing recommendations have had a limited impact on the healthcare professionals, particularly community pharmacists, since the preference for an effervescent formulation is usually expressed by the patient at the time of dispensing, and not explicitly indicated explicitly as such on medical prescriptions. Given the mean age of the heart failure sample (median 83 years, corresponding to the cutoff used in the subgroup analysis), many reasons could explain the preference for the effervescent formulation: it reduces the risk of pulmonary inhalation in high-risk patients (e.g. with neurological disorders or dementia), it allows an increase of fluid intake in dehydrated elderly subjects, and it eases administration of the medication in subjects with dysphagia or swallowing difficulties. A study of oral solid medicines preference among older adults, using the *Medicines Acceptability Questionnaire* [34] showed that effervescent tablets were the most acceptable formulations, in both dysphagic and non-dysphagic older subjects [35]. In all these clinical situations, sodium-free alternatives are available, such as orodispersible tablet or powder for oral solution.

Limitations of the study:

The first limitation related to the use of medico-administrative databases is the absence or inaccuracy of coding (discharge and associated diagnosis), particularly, due to the absence of specific ICD-10

codes specifically identifying type or severity of heart failure. Thus, we were not able to focus our analyses on patients with more severe congestive symptoms, who are more likely to experience detrimental iatrogenic consequences of liquid and sodium loads. A second limitation is found in the process of attrition in which drugs that are dispensed are not necessarily ingested by patient. The absence of information about self-medication and drug adherence can introduce a residual classification bias, which can reduce the power of the analysis. Finally, as for all observational studies, no formal causal relationship can be established between related factors, and additional analyses with complementary study designs are required for risk confirmation.

CONCLUSION:

We found that approximately one heart failure patients over ten had a reimbursement of effervescent paracetamol 30 days before hospitalization. We found a positive association between exposure to effervescent paracetamol and hospitalization for AHF, notably among hypertensive and older subjects. Given the existence of paracetamol in multiple sodium-free formulations, including formulations suitable for patients with swallowing difficulties (i.e. orodispersible tablets or powder for liquid solution), our data suggest that the use of effervescent paracetamol should be ~~strongly~~ discouraged among heart failure patients.

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Table 1. Characteristics of the patients included in the case-crossover study.

Characteristics	**n (%) of total population (n = 4,301)**
Female	2,298 (53.4)
Male	2,003 (46.6)

Age in years, median (Q1 - Q3)	83 (75 - 88)
Medical history, n (%)	
Hypertension	2,648 (61.6)
Diabetes	1,475 (34.3)
Peripheral artery disease	1,036 (24.1)
Stroke	736 (17.1)
Coronary artery disease or myocardial infarction	435 (10.1)
Osteoarticular pain	277 (6.4)
Parkinson, Alzheimer or other dementia	370 (8.9)
Drug reimbursement during the 30-day period preceding HF admission, n (%)	
Effervescent paracetamol	388 (9.0)
Non-effervescent paracetamol	1,489 (34.6)
Diuretics	2,174 (50.5)
Effervescent paracetamol + diuretics	225 (5.2)
NSAID	130 (3.0)
Beta-blocking agent	1,677 (39.0)
ACE inhibitors	1,397 (32.5)
Effervescent paracetamol + ACE inhibitors	148 (3.4)

ACE: angiotensin converting enzyme inhibitor, HF: heart failure, NSAID: non-steroidal anti-inflammatory drugs.

Table 2. Exposure to effervescent paracetamol according to period of inclusion of 4,301 subjects admitted for AHF included in case crossover study, 2014-2016.

Periods	n (%)
Case periods (n = 4,301)	
Non-exposure	4,055 (94.3)
Total exposure	246 (5.7)
Low exposure	155 (3.6)
High exposure	91 (2.1)
Control periods (n = 12,903*)	
Non-exposure	12,370 (95.9)
Total exposure	533 (4.1)
Low exposure	318 (2.5)
High exposure	215 (1.7)

***** *This number of control periods corresponds to 3 control periods per AHF subjects included (i.e. 4,301).*

AHF: Acute Heart Failure.

Table 3: Association between exposure to effervescent paracetamol and admission for AHF in the case-crossover study, 2014-2016.

	15-day time windows [a] **(n = 4,301)**		***15-day time windows*** [a] ***Hypertension subgroup*** **(n = 2,648)**		***15-day time windows*** [a] ***Age ≥ 83 years subgroup*** [b] **(n = 2,238)**	
Drug exposure	**Odds ratio ($CI_{95\%}$)**	**p-value**	**Odds ratio ($CI_{95\%}$)**	**p-value**	**Odds ratio ($CI_{95\%}$)**	**p-value**
Non-exposure	1.0		1.0		1.0	

Effervescent paracetamol						
Total exposure	1.56 (1.27 – 1.90)	< 0.001	1.45 (1.13 – 1.87)	0.004	1.70 (1.28 – 2.24)	< 0.001
Low exposure	1.66 (1.31 – 2.11)	< 0.001	1.54 (1.14 – 2.10)	0.005	1.96 (1.40 – 2.74)	< 0.001
High exposure	1.39 (1.02 – 1.90)	0.04	1.31 (0.90 – 1.92)	0.2	1.35 (0.89 – 2.05)	0.2
Non-effervescent paracetamol						
Total exposure	1.11 (0.99 – 1.24)	0.07	1.18 (1.03 – 1.36)	0.02	1.03 (0.88 – 1.20)	0.7
Low exposure	1.16 (1.01 – 1.32)	0.03	1.23 (1.05 – 1.45)	0.01	1.01 (0.84 – 1.22)	0.9
High exposure	1.03 (0.88 – 1.21)	0.7	1.11 (0.92 – 1.35)	0.3	1.05 (0.86 – 1.30)	0.6
Non-steroidal anti-inflammatory drugs (NSAIDs)						
Total exposure	1.25 (0.92 – 1.70)	0.1	1.50 (1.01 – 2.19)	0.04	1.27 (0.78 – 2.08)	0.3

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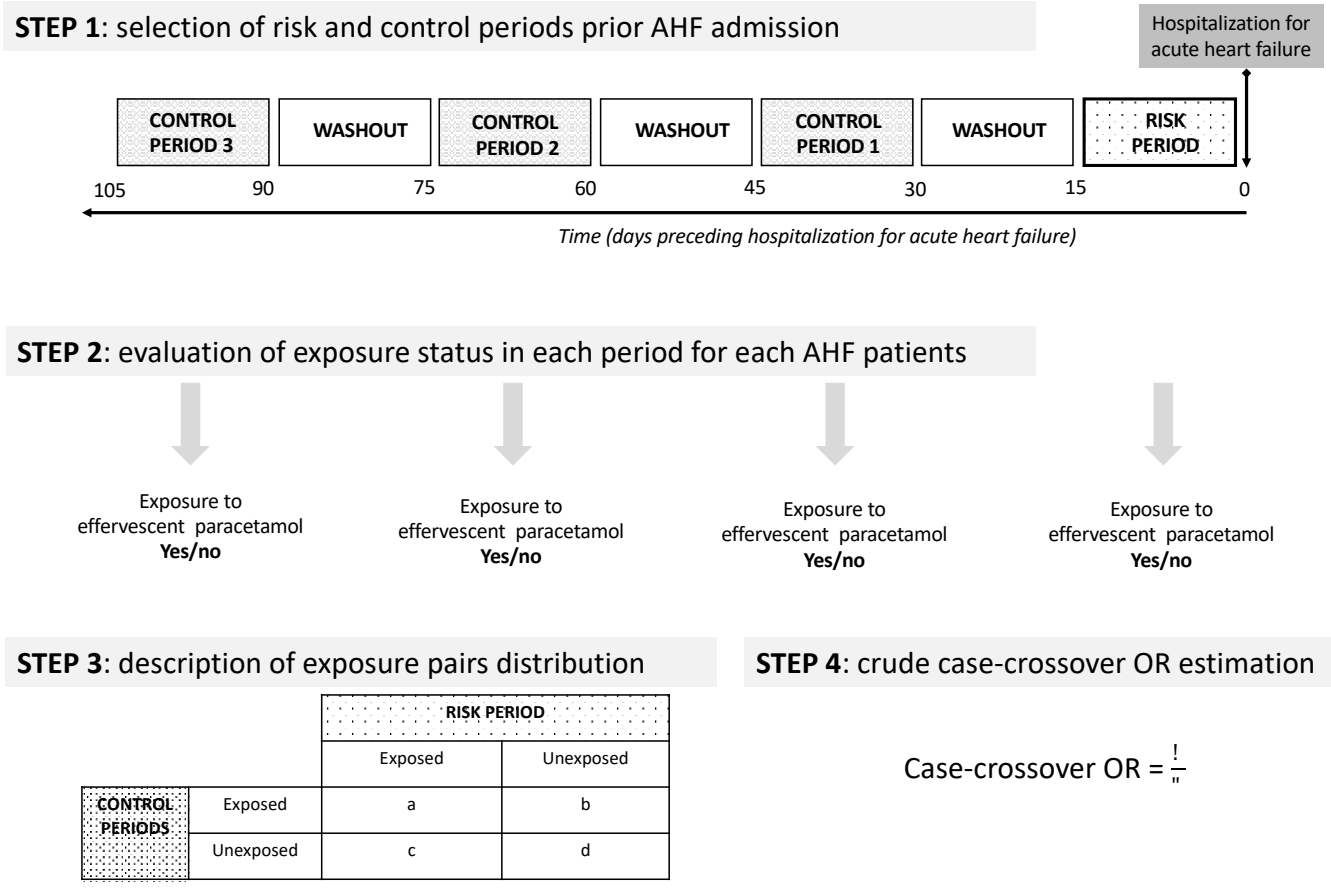
AHF: Acute Heart Failure, CI: confidence interval, OR: Odds ratio, NSAIDs: non-steroidal anti-inflammatory drugs,

[a] *Adjusted for: co-prescription of diuretics, ACE inhibitor and corticosteroids inflammatory drugs.*

[b] *Cut-off corresponding to the median age of the 4,301AHF subjects.*

FIGURE LEGENDS:



AHF: Acute Heart Failure, OR: Odds Ratio.

Figure 1. **Implementation of the case-crossover analyses**. STEP 1: definition of the time frame of case (n = 1) and control periods (n = 3) before admission for acute heart failure, STEP 2: evaluation of the exposure status in each of the four periods, STEP 3: description of exposure pairs distribution between risk and control periods, STEP 4: crude case-crossover OR estimation (adjusted case-crossover odds ratio is obtained after confounding adjustment with a conditional logistic regression). Similar analysis was performed considering non-effervescent paracetamol as an active comparator in risk and control periods, and oral NSAIDs as a positive control.

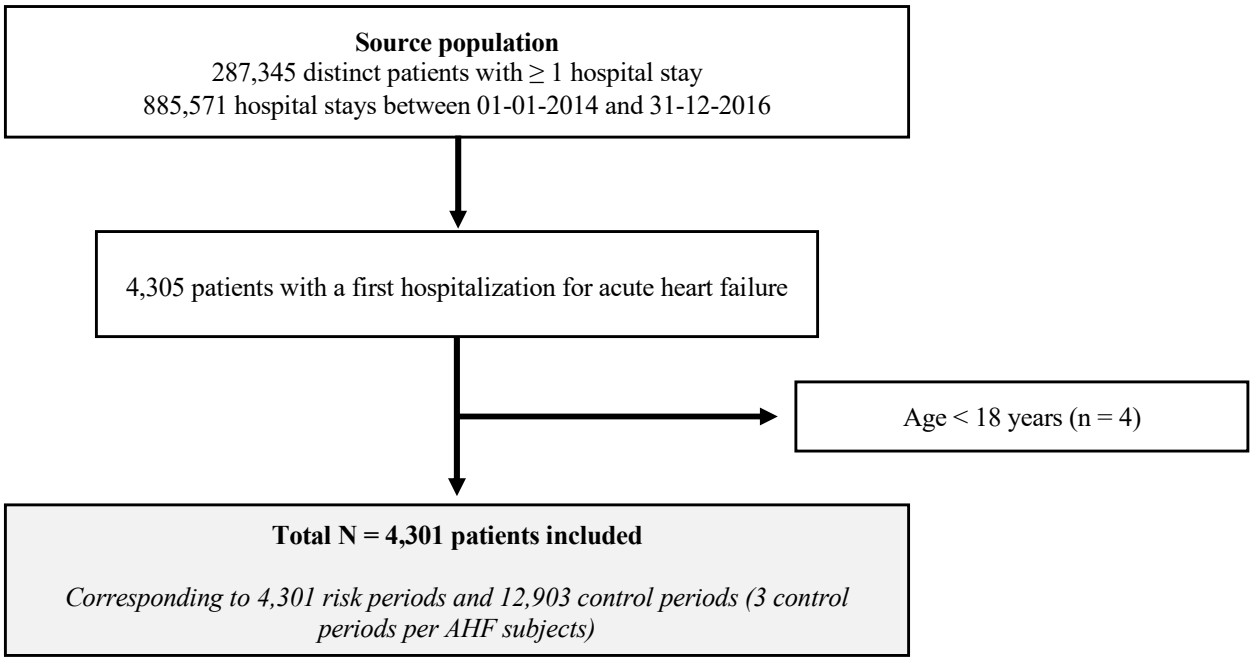


Figure 2: Flowchart of the study.