



Cardiovascular risk associated with otc-strenght nonsteroidal anti-inflammatory drugs and paracetamol

Thi Thanh Mai Duong

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THÈSE PRÉSENTÉE
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Sociétés, Politique, Santé Publique

Par Thi Thanh Mai DUONG

**RISQUES CARDIOVASCULAIRES ASSOCIÉS AUX
ANTI-INFLAMMATOIRES NON STERODIENS À DOSE
ANTALGIQUE ET AU PARACÉTAMOL**

Sous la direction de : Nicholas MOORE

Version 27.09

Soutenue le 4 Octobre 2016

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND
PARACETAMOL**

Under the supervision of Nicholas MOORE

Defended on October 4th 2016

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Abstract

Title: Cardiovascular (CV) risks associated with over-the-counter strength non-steroidal anti-inflammatory drugs (OTC NSAIDs) and paracetamol

Background

There is little data about the CV safety of Paracetamol (P) and OTC NSAIDs.

Objectives

Describe usage patterns, to evaluate and compare the risk of acute coronary syndrome (ACS) associated with P and OTC-Strength ibuprofen (OSI).

Methods

Drug utilisation, self-controlled cohort (SCC), propensity score- (PS) matched cohort, nested case-control (NCC) studies were conducted in the *Echantillon Généraliste Bénéficiaires* (EGB). Studies included P and OSI treatment episodes in adults in 2009-2014. Risks were quantified by event rate ratios (ERRs) or hazard ratio (HRs) with 95% CI.

Results

Use of OSI and P concerning mostly young persons for short durations.

The SCC studies included 316265 OSI and 1025877 P episodes in 168407 and 342494 users. In low-dose aspirin (LDA) users (3.5% OSI and 5% P episodes), ACS risk increased after OSI dispensing (ERR 1.52 [1.07-2.16]) but decreased after P (HR 0.39 [0.32-0.47]). In LDA nonusers, ACS risk increased after P (1.32 [1.16-1.49]), but not after OSI (1.22 [0.63-2.36]).

In the PS-matched study (mean age 45), there was no difference between P and OSI over the total follow-up (HR 0.97 [0.71-1.32]), despite a higher increase with OSI in the first 2 weeks (1.75 [1.08-2.82]).

In the NCC study (mean age 67), the risk increased with P but not with OSI (P: 1.36 [1.23-1.50]; OSI: 1.16 [0.78-1.72]).

Conclusion

ACS risk associated with OSI or P vary according to LDA use and age. For OSI, ACS risk increased only in LDA users. Conversely, for P, ACS risk increased only in LDA nonusers. In young LDA

nonusers, there was no difference between OSI and P (PS-matched study). In older patients (NCC study), P appeared to be associated with a higher risk.

Keywords: Acute coronary syndrome, myocardial infarction, OTC ibuprofen, OTC NSAIDs, paracetamol

Résumé

Titre : Risques cardiovasculaires (CV) associés aux anti-inflammatoires non stéroïdiens (AINS) à dose antalgique et au paracétamol

Contexte

Il y a très peu de données sur l'utilisation et la sécurité CV du paracétamol et des AINS à faible dose en l'automédication.

Objectifs

établir les caractéristiques des utilisateurs, évaluer et comparer le risque de syndrome coronarien aigu (SCA), associé au paracétamol (P) et à l'ibuprofène à dose antalgique (IDA).

Méthodes

Etudes d'utilisation, études de cohorte auto-contrôlées (*self-controlled cohort* - SCC), étude de cohorte appariée sur le score de propension et étude cas-témoin nichée (CTN) ont été réalisées dans l'Echantillon Généraliste Bénéficiaires (EGB) en incluant les épisodes de traitement d'IDA et de P chez les adultes entre 2009 et 2014. Des risques de SCA ont été estimés par les rapports de taux d'événement (RTE) ou les hazard ratios (HRs) avec l'IC à 95%.

Résultats

L'utilisation d'OSI et de P concerne surtout des jeunes pour des courtes durées de traitement.

Les études SCC ont inclu 316265 et 1025877 épisodes d'IDA et P respectivement chez 168407 et 342494 utilisateurs. Chez les utilisateurs d'aspirine à faible dose (AFD) (3,5% et 5,3% des épisodes d'IDA et de P), le risque de SCA a augmenté après la dispensation d'IDA (RTE 1,52 [1,07 à 2,16]) mais diminué après la dispensation de P (HR 0,39 [0,32 à 0,47]). Chez les non-utilisateurs d'AFD (96,5% d'IDA et 94,7% de P), le risque de SCA n'a augmenté qu'après P (1,32 [1,16 à 1,49]).

Dans l'étude de cohorte appariée (âge moyen 45 ans), il n'y avait pas de différence entre le P et l'IDA sur la durée totale du suivi (HR 0,97 [0,71 à 1,32]), en dépit d'une augmentation plus élevée avec l'IDA dans les 2 premières semaines (1,75 [1,08 à 2,82]).

Dans l'étude CTN (âge moyen 67), le risque n'a augmenté qu'avec P, pas avec l'IDA (P : 1,36 [1,23 à 1,50]; IDA : 1,16 [0,78 à 1,72]).

Conclusion

Le risque de SCA associé à l'IDA ou au P varie en fonction du statut d'utilisation d'AFD et de l'âge. Pour l'IDA, le risque n'a augmenté que chez les utilisateurs d'AFD. Au contraire, pour P, le risque a augmenté seulement chez les non-utilisateurs d'AFD. Chez les jeunes non-utilisateurs d'AFD, il n'y avait pas de différence entre l'IDA et le P (étude de cohorte apparié). Chez les patients âgés (étude CTN), P semble être associé à un risque plus élevé.

Mots clés : paracétamol, ibuprofène, faible dose, infarctus du myocarde, syndrome coronarien aigu

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List of abbreviations

ACCEs	Acute Cerebrovascular and Cardiovascular Events
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
ADRs	Adverse Drug Reactions
AEs	Adverse Events
aHR	adjusted Hazard Ratio
ALD	Affection de Longue Durée
ALF	Acute Liver Failure
AMI	Acute Myocardial Infarction
ARBs	Angiotensin II Receptor Antagonists
AUC	Area Under the Curve
BIFAP	Base de datos Informatizada para la Investigación Epidemiológica en Atención Primaria
BP	Blood Pressure
CHD	Coronary Heart Disease
CI	Confidence Interval
CMUc	Couverture Médicale Universelle complémentaire
CNAMTS	La Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés
CNS	Central Nervous System
COX	Cyclo-oxygenase
CP	Paracetamol in Combination
CPRD	Clinical Practice Research Datalink
CSF	Cerebrospinal Fluid
CV	Cardiovascular
CYP 450	Cytochrome P450
DDD	Defined Daily Dose
DMARDs	Disease-Modifying Antirheumatic Drugs
DNPR	Danish National Patient Registry
DRS	Disease Risk Score

EGB	Echantillon Généraliste de Bénéficiaires
EMA	European Medicines Agency
EPhMRA	The Anatomical Classification of Pharmaceutical Products
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	Gastrointestinal
GPRD	General Practice Research Database
GPRD	General Practitioner
HR	Hazard Ratio
ICD-10-CM	The International Classification of Diseases, Tenth Revision
ICD-9-CM	The International Classification of Diseases, Ninth Revision
IDS	Institut des Données de Santé
INSEE	Institut National de la Statistique et des Etudes Economiques
IR	Incidence Rate
IRR	Incidence Rate Ratio
LDA	Low-Dose Aspirin
MI	Myocardial Infarction
MPR	Medication Possession Ratio
MSA	Régime des agriculteurs
NHIRD	National Health Institute Research Database
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NSAID	Non-steroidal antiInflammatory drugs
OA	Osteoarthritis
OR	Odds Ratio
OSI	OTC-Strength Ibuprofen
OTC	Over-the-counter
OXMIS	Oxford Medical Information Systems
PG	Prostaglandins
PM	Person-Month
POM	Prescription Only Medicines

PPV	Positive Predictive Value
PS	Propensity Score
PSI	Prescription-Strength Ibuprofen
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RR	Relative Risk
RSI	Régime des indépendants
SALT	Study of Acute Liver Transplantation
SBP	Systolic Blood Pressure
SCC	Self-Controlled Cohort
SCCS	Self-Controlled Case Series
SNIRAM	Système National d'Informations Inter-régimes de l'Assurance Maladie
SP	Single-ingredient Paracetamol
THIN	The Health Improvement Network
TIA	Transient Ischemic Attack
TX	Thromboxane
UGIB	Upper Gastrointestinal Bleeding
UK	United Kingdom
USA	United States of America
VIGOR	Vioxx Gastrointestinal Outcomes Research
VISTA	The Virtual International Stroke Trials Archive
VKA	Vitamin K antagonist

Thesis structure

This thesis manuscript includes 6 Chapters.

CHAPTER I is the overview of over-the-counter (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, from their mechanism of action, to their efficacy and safety.

CHAPTER II is the literature review of published studies on the risks associated of the two groups of drugs. The review of OTC NSAIDs focuses on the dose and duration relationship of each individual OTC NSAIDs: ibuprofen, diclofenac and naproxen. The review of paracetamol focuses on different condition of use and different cardiovascular outcomes.

In CHAPTER III, we explain methodological approaches to study the cardiovascular safety of paracetamol and low-dose (OTC) NSAIDs, from the selection of data sources to study design and methods to control bias.

CHAPTER IV presents our descriptive studies, which aim to describe the usage pattern of OTC-Strength NSAIDs and paracetamol in France.

In CHAPTER V, we present our analytic studies to evaluate the cardiovascular risk associated with OTC-Strength NSAIDs and paracetamol. This chapter includes 3 sections: Section 1 presents the two self-controlled cohort studies to evaluate the cardiovascular safety of OTC-Strength NSAIDs and paracetamol; Section 2 presents a propensity score matched cohort study to compare the cardiovascular risk of OTC-Strength ibuprofen with paracetamol; Section 3 presents the nested case-control studies to evaluate the risk of acute coronary syndrome associated with paracetamol, OTC- and Prescription-Strength NSAIDs.

CHAPTER VI presents general discussions and conclusions about the subject, as well as implications of public health and the research perspectives.

CHAPTER I – Overview of over-the-counter non-steroidal anti-inflammatory drugs and paracetamol

1. Over-the-counter non-steroidal anti-inflammatory drugs (OTC NSAIDs)

1.1. Introduction of OTC NSAIDs into the market

Historically, anti-inflammatory drugs had their origins in the discovery of an extract from willow bark and leaves with the fascinating ability to treat fever and inflammation by the Greek physician Hippocrates. Later in the 17th century, the active ingredient of willow bark salicin was identified in Europe. Later, acetyl-salicylic acid (Aspirin) was introduced into the market by Bayer in 1899. (1) Ibuprofen was the next NSAID discovered by a team led by Stewart Adams and the patent application was filed in 1961. (2) In 1983-1984, it became the first NSAID (other than aspirin) available over-the-counter (OTC) in the United Kingdom (U.K) and the United States (U.S). Since then, ibuprofen has become one of the most widely used analgesic-antipyretic- anti-inflammatory drugs.

In 1990's, Needleman, Simmons and Herschman's discovered the inducible isoform of the enzyme cyclo-oxygenase (COX), later identified as COX-2.(3–5) This discovery led to the hypothesis that there are two COX enzyme systems controlling the production of prostanoids (prostaglandins (PGs) and thromboxane (TxA₂)); COX-1, which produces PGs and TxA₂ that regulate gastrointestinal (GI), renal, vascular and other physiological functions, and COX-2, which regulates the production of PGs involved in inflammation, pain and fever. (6–8) In December 1998, G.D. Searle and Pfizer (now Pfizer Inc) launched celecoxib (Celebrex®), the first selective COX-2 inhibitor. (9) Shortly thereafter, rofecoxib, another selective COX-2 inhibitor, was approved by the FDA in May 1999, and was marketed under the brand names Vioxx, Ceoxx, and Ceeoxx. (10) Both rofecoxib and celecoxib were 'blockbuster' drugs by 2001, boasting \$2.6 billion and \$3.1 billion in sales respectively that year, according to the pharmaceutical consulting firm Scott-Levin. Data showed that selective COX-2 inhibitors induced significantly fewer GI ulcers than non-selective COX-2 inhibitors. (11–16)

Despite of the enormous success of the “coxibs”, concerns were raised regarding their adverse cardiovascular (CV) events. The first study hinting at trouble was the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, (15) in which the risk of nonfatal myocardial infarction (MI), nonfatal stroke, and death from any vascular event were higher in the rofecoxib group than in the naproxen comparator group. In contrast, the CLASS trial, (16) found no significant difference between the treatment groups in the incidence of major cardiovascular events. This difference in rates of CV events could be a drug-class specific effect, or due to the differences in the study patients such as the use of aspirin by some patients in CLASS but not in VIGOR, or the nature of the nonselective NSAIDs used in the two trials. Subsequently, Mukherjee D *et al.* (17) reevaluated the CV risk question by reviewing the two major randomized trials VIGOR and CLASS and all the complementary data submitted to the Food and Drug Administration (FDA). The time to CV adverse event analysis in the VIGOR Trial showed a relative risk of 2.38 (95% confidence interval (CI) 1.39 to 4.00) compared to the naproxen controls. Solomon *et al.* (18) found that current rofecoxib use was associated with an elevated relative risk of acute myocardial infarction (AMI) compared with celecoxib use and no NSAID use. Dosages of rofecoxib >25 mg were associated with a higher risk than dosages < or =25 mg. The risk was elevated in the first 90 days of use but not thereafter. (18) The hypothesis proposed was that selective COX-2 inhibitors may tip the natural balance between prothrombotic thromboxane A₂ (TxA₂) and antithrombotic prostacyclin (PGI₂) potentially increasing the possibility of a thrombotic CV events. (18–20) In September 2004, Vioxx® (rofecoxib) was withdrawn from the worldwide market. This event raised the question of the CV safety of the entire class of COX-2 inhibitors. (21) (22) In 2005, the FDA and the European Medicines Agency (EMA) requested that Pfizer withdraw valdecoxib (Bextra®) from the market with regard to CV safety and serious skin reactions. (23) (24) So far, celecoxib (Celebrex®) and etoricoxib (Arcoxia®) are the two coxibs commercially available in France. Concerns remain concerning the relative cardiovascular safety of NSAIDs other than these first two so-called coxibs.

Ibuprofen, the first non-aspirin NSAID (25) available OTC, has now been licensed in 27 European and 55 non-European countries, making a total of 82 countries worldwide. In contrast to some other NSAIDs, ibuprofen has never had its licence revoked or suspended for reasons relating to safety or other factors concerned with the use of this drug. (26) The OTC maximum dosage of ibuprofen is 1200 mg per day, compared to the prescription dose of 1200

to 3600 mg. (25) (26) In France, ibuprofen is available over the counter both at 200 or 400mg dose-strength (20 tablets per box vs. 30 tablets for prescription-only dose-strength). OTC ibuprofen represents approximately 93% of all OTC NSAIDs market. (27)

After ibuprofen, naproxen sodium was also approved for OTC use in 1994 in the USA, under the trade name Aleve®. The single approved dose is 220 mg (200mg naproxen and 20g sodium), maximum OTC dosage 660mg/day in 10 days for pain. Now, naproxen sodium is approved over the counter at the dose of 220mg in many countries.

Diclofenac is only available by prescription in the U.S and other countries at doses upwards of 50 mg per unit, but in some countries lower dose 25mg and 12.5mg tablets are available OTC. 25mg diclofenac tablet use to be available OTC in the U.S but was withdrawn because of safety and efficacy reasons. From January 15th, 2015, oral diclofenac potassium tablets 12.5 and 25 mg have been withdrawn from use as an OTC painkiller in the U.K because of a small risk of heart problems. (28) In France, diclofenac is available OTC under the brand name Voltaren Dolo® (diclofenac potassium 12.5mg) and Voltaren Dolo® forte 25 mg. Ketoprofen was available over-the-counter in the United States in the form of 12.5 mg coated tablets (Orudis KT and Actron), but this form has been discontinued. It is available by prescription as 50, 75, 100, 150, and 200 mg capsules. (29) The OTC formulation of ketoprofen in France is 12.5 mg tablets for treatment of mild-to-moderate pain and dysmenorrhea.

1.2. Mechanism of action

The NSAIDs group includes approximately 200 active products from about 20 chemically different groups. The mechanism of action of NSAIDs is proposed as the inhibition of the activity of the cyclooxygenase (COX) enzyme. (30,31) This would limit the production of proinflammatory prostaglandins at a site of injury. Given this, NSAIDs have been used by scientists for the last 25 years to dissect the critical role that both the COX enzyme and the eicosanoids derived from this pathway have in normal and abnormal physiologic states.

The chemistry of the eicosanoid biosynthetic pathway is well known. PGs are formed by the oxidative cyclization of the central 5 carbons within 20 carbon polyunsaturated fatty acids. (32)

The key regulatory enzyme of this pathway is COX, which catalyzes the conversion of arachidonic acid to PGG₂ and PGH₂. PGH₂ is subsequently converted to a variety of eicosanoids that include PGE₂, PGD₂, PGF₂α, PGI₂, and TXA₂. The array of PGs produced varies depending on the downstream enzymatic machinery present in a particular cell type. For example, endothelial cells primarily produce PGI₂, whereas platelets mainly produce TXA₂. (33,34) All NSAIDs in clinical use have been shown to inhibit COX, leading to a marked decrease in PG synthesis. (35)

PGs are present in a wide variety of human tissues. (32) PGs not only play a central role in inflammation, but also regulate other critical physiological responses. In humans, PGs are involved in diverse functions, including blood clotting, ovulation, initiation of labor, bone metabolism, nerve growth and development, wound healing, kidney function, blood vessel tone, and immune responses. (36)

Cyclo-Oxygenase exists in two isoforms, COX-1 and COX-2. COX-1 is referred to as a “constitutive isoform”, and is considered to be expressed in most tissues under basal conditions. In contrast, COX-2 is referred to as an “inducible isoform”, which is believed to be undetectable in most normal tissues, but can be up-regulated during various conditions, many of them pathological. When the two isoforms were first discovered, COX-1 inhibition by NSAIDs was supposed to be associated with gastrointestinal (GI) and renal toxicity, while COX-2 inhibition has beneficial anti-inflammatory, analgesic, and antipyretic effects. (31)(37) Later on, increasing evidence showed that COX-2 also plays a physiological role in several body functions and that, conversely, COX-1 may also be induced at sites of inflammation. (38)(39)

Analgesic effects

There are two main types of pain, nociceptive and neuropathic pain. Nociceptive pain is a response associated with tissue injury from pathologic processes in an intact nervous system, where the intensity of pain is proportionate to the injury, and serves as a protective mechanism for the patient. Neuropathic pain, on the other hand, is due to dysfunction or injury to the nervous system that produces disproportionate pain to the stimulus and does not serve a protective and biologically useful function. (40) This differentiation is important because nociceptive pain responds to opioids and NSAIDs, while neuropathic pain responds better to antiepileptic drugs and tricyclic antidepressants. (41–43)

NSAIDs usually normalise the increased pain threshold associated with inflammation rather than elevate a normal pain threshold. (44) The antinociceptive effect of NSAIDs is mainly due to their common property of inhibiting COX involved in the formation of PGs. PGs are potent hyperalgesic mediators which modulate multiple sites along the nociceptive pathway and enhance both transduction (peripheral sensitizing effect) and transmission (central sensitizing effect) of nociceptive information. Inhibition of the formation of PGs at peripheral and central sites by NSAIDs thus leads to the normalisation of the increased pain threshold associated with inflammation. (44) In addition, some NSAIDs inhibit the lipoxygenase pathway, (45) which may itself result in the production of algogenic metabolites. Interference with G-protein-mediated signal transduction by NSAIDs may form the basis of an analgesic mechanism unrelated to inhibition of prostaglandin synthesis, which may explain the effectiveness of these agents against headache. (46) A mechanism involving inhibition of excitatory amino acids or N-methyl-D-aspartate receptor activation has also been proposed. (47)

Though NSAIDs have an analgesic effect independent of anti-inflammatory activity, the anti-inflammatory component also contributes to the relief of pain, especially in chronic or acute inflammatory conditions. (48)

Antiinflammatory effect

Prostaglandins are produced in the inflamed tissues, and treatment with NSAIDs inhibits the production of prostaglandins and down-regulates inflammation-related pathological symptoms such as pain and swelling. During inflammation, COX-1 mRNA, protein and activity levels do not change, but COX-2 levels increase dramatically, and, as a result, PGs production increases. Moreover, when COX-2 specific inhibitors are administered, PGs production and subsequent inflammation are significantly reduced. These data have led to the conclusion that COX-2 is involved in inflammation, whereas COX-1 is not. (49)

During the inflammation process, COX-1 is thought to contribute to “resolution”. In experimental mesangioproliferative glomerulonephritis COX-1 is expressed in glomeruli during the repair period. (50) In the process of ulcer healing, the COX-1 specific inhibitors as well as the COX-2 specific ones delay healing. These results implicate the role of COX-1 in the resolution, but not the progression of inflammation. The COX-2 gene is particularly responsive to mediators of inflammation. (51–53) In inflammation-related cells, the membrane bound

type of PGE synthase (mPGE2 synthase) is also induced by these cytokines. (54) The large amount of PGE2 produced at the inflammation site by the coupling of COX-2 and mPGE2 synthase may be involved in the progression of inflammation. Drugs with a more favourable COX-2: COX-1 activity ratios (such as celecoxib, rofecoxib, meloxicam, nimesulide) have potent anti-inflammatory activity and fewer side-effects on the stomach and kidney than agents with a less favourable COX-2: COX-1 activity ratio (such as aspirin, indomethacin, and ibuprofen, piroxicam). (55)

Antipyretic effect

Antipyretic activity of NSAIDs results from inhibition of prostaglandin E2 (PGE2) synthesis in circumventricular organs in and near the preoptic hypothalamic area. (56) Infections, tissue damage, inflammation, graft rejection, malignancies, and other disease states enhance the formation of cytokines that increase PGE2 production. PGE2 triggers the hypothalamus to promote increases in heat generation and decreases in heat loss. In these conditions, NSAIDs are potent antipyretic agents.

1.3. Pharmacokinetics properties

Absorption

NSAIDs are most often administered orally, but they are also administered topically, intraocularly, intravenously, intramuscularly and rectally. Conventional tablets, sustained release preparations, creams, gels, suppositories and eye drops are all commercially available. Although most NSAIDs are weak acids and can be absorbed via the stomach, the large surface area of the small intestine makes this the major absorptive site for orally administered NSAIDs. The absorption of NSAIDs from the GI tract has been well reviewed. (57)

Concomitant administration of NSAIDs with food or antacids may in some cases lead to delayed or even reduced absorption. (58) The effects of other drugs and food may be greater in the short term compared with long term NSAID administration. (59) GI dysfunction may be increased in the elderly, but since NSAIDs are absorbed via passive diffusion they are not significantly affected. In addition, some disease states such as Crohn's, diverticular disease and ulcerative colitis can affect both drug transit time and absorption. (59) Absorption may also

influence the pharmacokinetics of NSAID enantiomers that undergo inversion. (60) (R)-Ibuprofen undergoes a unidirectional inversion to (S)-ibuprofen that appears to depend on the rate of drug absorption. A significant positive correlation between the time to peak plasma concentration (t_{max}) and the S:R concentration ratio of ibuprofen has been observed. (60) Greater S:R area under the curve (AUC) ratios in individuals with longer t_{max} values also support the correlation between absorption rate and ibuprofen enantiomer inversion.

Plasma Distribution

The majority of NSAIDs share several physical properties in common: they are weakly acidic, lipophilic and bound extensively (>90%) to plasma albumin. (61) (62) Hence, only a small portion of the circulating drug in plasma exists in the unbound form. As unbound drug is generally considered responsible for pharmacological effects, the extent of binding of NSAIDs to plasma proteins is an important determinant of their dispositions and actions.

NSAIDs compete for binding sites with other highly plasma protein-bound drugs. If binding sites are occupied by other drugs, the plasma concentration of free and active NSAID increases at least transiently. The free plasma fraction of an NSAID may also be increased in various pathophysiological conditions (i.e. patients with secondary hypoalbuminaemia associated with active rheumatoid arthritis). (63) Aspirin decreases the plasma concentrations of many other NSAIDs, although the clinical significance of this is uncertain. The most important interactions with NSAIDs are those involving the oral anticoagulants and oral hypoglycaemic agents, though not all NSAIDs have been found to interact with these drugs.

Synovial Fluid (SF) distribution

The synovium is the most likely primary site of action for NSAIDs in rheumatoid arthritis, so synovial fluid NSAID concentrations are of clinical relevance. Some NSAIDs may become sequestered preferentially in the synovial fluid of inflamed joints, although there is large variability depending on the NSAID and the administration schedule. (64) The onset and duration of action of NSAIDs are often more accurately related to their concentration in synovial fluid rather than in plasma. NSAIDs can be divided into two groups according to their pharmacokinetic behaviour. (64) The first type comprises those NSAIDs with short or intermediate plasma elimination half-life (e.g. salicylates, ibuprofen, indomethacin, diclofenac).

Their concentration in synovial fluid may exceed those in plasma. The second group includes NSAIDs with a long plasma elimination half-life (e.g. phenylbutazone, piroxicam, meloxicam). (65) The concentrations of these drugs in synovial fluid are lower than in plasma.

In spite of the extensive data on the concentrations of the various NSAIDs at peripheral sites, the extent to which these correlate with the peripheral antinociceptive response has not been assessed in detail. The required frequency of NSAID administration cannot always be predicted from plasma half-lives. Twice daily administration of ibuprofen, ketoprofen, diclofenac or indomethacin is equally effective as more frequent administration. (66)

Central nervous system (CNS) distribution

The major pharmacokinetic determinant of the antinociceptive action is the extent of their distribution to central and peripheral sites. (67) The joints of the body are major peripheral sites of action of NSAIDs in rheumatic patients and the degree of uptake into synovial fluid is of considerable clinical interest. In contrast to the pharmacokinetics of NSAIDs in peripheral sites, only few data on concentration of NSAIDs in central nervous system (CNS) in humans are available. Bannwarth *et al.* have shown that indomethacin given intramuscularly rapidly crosses the blood–brain barrier and can be detected in cerebrospinal fluid (CSF) 0.5 h after administration. (68) Similar findings have been reported following the intramuscular administration of ketoprofen. (69) In the case of orally administered ibuprofen, CSF concentrations rise rapidly and can exceed the unbound plasma levels of the drug within 90 min. (70) In case intravenous injection, ibuprofen penetrates the CSF readily, with peak concentrations attained 30 to 40 minutes after intravenous injection of a 10 mg/kg dose. (71) The analgesia produced by these drugs may show a more marked central component than other NSAIDs.

Elimination and metabolism

Most NSAIDs are metabolised by hepatic oxidation, hepatic conjugation, or both. The metabolites of some NSAIDs are active (i.e. aspirin, diclofenac and oxaprozin). Other NSAIDs, such as nabumetone and sulindac, are prodrugs whose metabolites are responsible for the pharmacodynamic effects of the drug. NSAID plasma elimination half-lives vary widely from 0.25 to 70 hours. Differences in plasma elimination also determine administration frequency.

First-pass hepatic clearance of NSAIDs is limited by blood flow delivering the drug to the liver, the rate of degradation by hepatic enzymes and the rate of excretion in bile. Usually enzymatic degradation is slower than hepatic blood flow delivering the drug, making the former the rate-limiting step in NSAID elimination. The plasma clearance of an NSAID is therefore the product of its unbound concentration and enzymatic degradation.

Some NSAIDs undergo enterohepatic recirculation. Some experimental evidence identifies biliary excretion as important in the pathogenesis of NSAID enteropathy, whereas other data suggest major systemic contributions in NSAID enteropathy. (72) Several NSAIDs (i.e. aspirin, nabumetone) that do not undergo enterohepatic recirculation have all been found to induce enteropathy. (73)

1.4. Indication and efficacy of NSAIDs

Osteoarthritis and Rheumatoid Arthritis

Osteoarthritis (OA) and rheumatoid arthritis (RA) cause chronic pain, which may involve nociceptive as well as non-nociceptive components, including neuropathic components, due to peripheral inflammation and central sensitization. The use of NSAIDs is ubiquitous in rheumatology because of their effectiveness as anti-inflammatory and analgesic agents.

Although OA is not primarily an inflammatory disorder, NSAIDs are moderately effective at relieving pain and the muscle stiffness associated with OA. A meta-analysis of published randomized placebo-controlled trials concluded that NSAIDs, including coxib, can reduce pain and functional disability in knee OA better than placebo (effect size – ES: 0.32, 95% CI: 0.24–0.39, and 0.29, 95% CI: 0.18–0.40, respectively). However, the current analysis did not support the long-term use of NSAIDs for this condition. (74) The magnitude of treatment effect estimates varied greatly across different NSAIDs and doses. (75) The European League Against Rheumatism (EULAR) and The American College of Rheumatology both recommend that NSAIDs, at the lowest effective dose, should be added or substituted for hip/knee/hand OA treatment in patients who respond inadequately to paracetamol. (76–78) EULAR recommendations for the management of early arthritis states that symptomatic patients presenting with early arthritis should therefore be treated with NSAIDs after careful evaluation of gastrointestinal, renal, and cardiovascular status. (79)

Early use of disease-modifying anti-rheumatic drugs (DMARDs) in RA patients is of high importance. (80)(81) The British Society for Rheumatology guideline for long-term RA management recommends a stepped approach with NSAIDs co-prescribed with a proton pump inhibitor in the short term. (82) The National Institute for Health and Care Excellence (NICE) guideline suggests analgesics (for example paracetamol, codeine or compound analgesics [=fixed-dose combinations]) to potentially reduce the need for long-term NSAID or COX-2 inhibitor treatment. (83)

Although paracetamol has long been thought to be a more favourable painkiller than NSAIDs in the treatment of chronic pain, NSAIDs have a superior efficacy according to the meta-analysis by Zhang *et al.* (84) In this meta-analysis, the clinical response rate was higher with NSAIDs than with paracetamol (RR = 1.24, 95% confidence interval (CI) 1.08 to 1.41), and the number of patients who preferred NSAIDs was more than twice the number of those preferring paracetamol (RR = 2.46, 95% CI 1.51 to 4.12). Preference for NSAIDs over paracetamol was also confirmed by a survey including 1,799 patients with OA, RA, and fibromyalgia, in which over 60% found paracetamol to be much less effective or somewhat less effective. (85) A meta-analysis found that NSAIDs were statistically superior in reducing rest and walking pain compared with acetaminophen for symptomatic osteoarthritis. (86) The therapeutic efficacy of the COX-2–selective inhibitors and traditional high-dose nonselective NSAIDs appears to be roughly comparable in patients with OA and RA. (87)

OA and RA are the indications of choice for potent prescription NSAIDs used for long-term control of inflammatory symptoms. These are often the COX-2 preferring drugs or non-selective drugs associated with gastro-protective agents. A recent network meta-analysis has found that the drugs most effective for long-term relief of OA symptoms were etoricoxib, diclofenac, and rofecoxib, (75) in relation with their superior potency to inhibit COX-2 at high prescription doses.

Other painful conditions

In addition to chronic use in the diseases discussed above, NSAIDs are used for the relief of short-term painful conditions, or for exacerbations of these chronic diseases (e.g., OA flares). This is the preferred realm of the low-dose NSAIDs, when the symptoms are more related to acute pain or fever than to inflammation. In these circumstances, both COX-1 and COX-2 are

involved and the selective COX2 inhibitors have less interest compared to the classical non-selective NSAIDs. These conditions are invoked by over 70% of all NSAIDs users. These painful conditions can encompass a whole range of painful states affecting all organ systems and all ages of patients, and are particularly indicated when inflammation is a significant contributor to the painful state. In addition to acute (e.g., traumatic) or chronic (OA, RA, SA) musculoskeletal symptoms, the efficacy of NSAIDs has been also documented in gout, dysmenorrhea, dental pain, headache/migraine and acute sore throat/tonsillitis, as well as flu symptoms and fever. (88–96)

Numerically, though these acute indications represent a minority of all the NSAIDs used, because of the short-term use of small quantities of the drugs, they represent the vast majority of users. In addition, whereas chronic users are usually medically monitored for these and other diseases, short-term users of low doses of NSAIDs often do so in an OTC context without medical supervision. It is therefore important to try to quantify the actual risks of these usage pattern, to avoid taking unnecessary risks on the one hand or withholding useful drugs on the other.

Factors influencing the efficacy of NSAIDs

Individual NSAIDs do differ in their analgesic efficacy. However, there is a controversy about the relative efficacy of NSAIDs when compared with each other. Some authors have stated that there is little difference in the analgesic efficacy between the different types of NSAIDs. (97) Recent data has shown that individual NSAIDs do differ in their analgesic efficacy. The Oxford pain group has constructed the Oxford League Table for analgesics in acute pain by giving each analgesic a number to grade its efficacy. (98) Traditional NSAIDs, such as ibuprofen, diclofenac and naproxen, and COX-2 inhibitors, such as rofecoxib, valdecoxib and lumiracoxib, top the league table. By comparison, other analgesics such as aspirin 600 mg and acetaminophen 1000 mg (number needed to treat (NNT) of 4.4 and 3.8, respectively) are significantly less effective than 10 mg intramuscular morphine.

As a group, NSAIDs are excellent analgesics and are even more efficacious than intramuscular morphine for acute pain. However, it should be noted that the evidence for the efficacy of NSAIDs comes mainly from the study of acute pain conditions. There is still a controversy as to which NSAID is better in chronic pain conditions. In clinical experience there is also a patient-

specific preference for this or that NSAID, which may vary over time. The availability of different NSAIDs is therefore important for patient management.

The formulation of certain NSAIDs can have a profound effect on their efficacy. Certain formulations of NSAIDs may enhance onset of analgesia and efficacy. For example, Ibuprofen sodium dihydrate provides faster and more efficacious pain relief during the first hour after intake when compared to a conventional ibuprofen acid formulation. (99) The median time to clinically meaningful relief of pain was shorter after solubilized ibuprofen 400 mg than after acetaminophen 1000 mg. (100) A Cochrane review of ibuprofen in acute pain suggested that rapidly absorbed formulations of salts, or features to speed absorption, provided better analgesia than standard ibuprofen as the free acid. 200-mg fast-acting ibuprofen (number needed to treat 2.1; 95% CI 1.9-2.4) was as effective as 400 mg standard ibuprofen (number needed to treat 2.4; 95% CI 2.2-2.5), with faster onset of analgesia. (101) The solubilized potassium liquigel formulation of ibuprofen is available over-the-counter worldwide. Another example is diclofenac sodium softgel, which has also been shown to provide a very rapid onset of analgesic activity and prolonged analgesic duration compared with conventional diclofenac potassium or placebo.(102–104)

Indication and efficacy of non-prescription (OTC) NSAIDs

While prescription NSAIDs are mainly used for musculoskeletal pain and inflammation in conditions such as RA or OA, lower, over-the-counter (OTC) doses of NSAIDs are effective for short-term relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, common cold, muscular aches, and arthritis flares. (105)

These results come from randomized controlled trials done under medical supervision, which may be different from results in OTC-driven use in real-life. However, it may be surmised that the painful events not leading to medical consultation (and inclusion in the trial) would be less intense, and therefore even more amenable to pain relief.

Diclofenac

N. Moore reviewed the efficacy and safety of low-dose diclofenac potassium developed for OTC use.(106) The efficacy of diclofenac potassium 12.5mg tablets in conditions suitable for treatment with OTC medication, for example, acute lower back pain, headache, acute pain

after dental extraction, symptoms of cold and influenza (including fever), and dysmenorrhoea was demonstrated in thirteen randomised, double-blind trials with both placebo and active controls. A single dose of diclofenac potassium 12.5mg is the lowest recommended effective dose. A two-tablet single dose of 25mg is at least as effective as ibuprofen 400mg. A flexible dosing regimen of an initial two tablets followed by one or two tablets up to a total daily dose of 75 mg is as effective as ibuprofen used in comparable fashion up to a total daily dose of 1200 mg.

Naproxen

A pooled analysis of 5 trials was performed to compare the efficacy and safety of OTC doses of naproxen (400 mg) and naproxen/naproxen sodium (200/220 mg) with acetaminophen (1000 mg), ibuprofen (200 mg), and placebo in the treatment of primary dysmenorrhea. (107) Naproxen 400 mg and 200 mg provided greater pain relief than both acetaminophen and ibuprofen at 6 hours after administration, as could be expected from a drug with a longer half-life. Both doses of naproxen had higher scores than placebo for symptom relief and drug preference.

In two identical multicentre, randomized, double-blind, placebo-controlled, multidose, parallel-design studies, (108) analgesic efficacy and safety of non-prescription doses of naproxen sodium were compared to ibuprofen 1200 mg, or placebo in the treatment of OA of the knee. OTC doses of naproxen sodium (440/660 mg) and ibuprofen (1200 mg) effectively relieve pain in patients with mild to moderate OA of the knee. Naproxen sodium provided more effective pain relief for most variables compared with placebo, and for night pain compared with ibuprofen. Efficacy was combined with good safety and tolerability.

Ibuprofen

The OTC daily dosage of ibuprofen is 1,200 mg. The IPSO study (109) shows that, for the treatment of OA pain, ibuprofen 400 mg at a single and multiple dose (1200 mg/day) for 14 days is more effective than paracetamol, either as a single dose of 1000 mg or a multiple dose (3000 mg/day). More specifically, pain intensity decreased from the first day and was significantly lower in the ibuprofen group than in the paracetamol group ($p<0.05$). The ibuprofen group improved significantly functional disability of the patient over 2 weeks

compared with the paracetamol group for each of the subscales: stiffness ($p<0.002$), pain ($p<0.001$), physical function ($p<0.002$).

OTC ibuprofen is also very effective in controlling fever both in adults and in children. A meta-analysis found a superior efficacy of ibuprofen (5-10 mg/kg) for treating children's pain or fever compared to paracetamol (10-15 mg/kg). Those two treatments have similar efficacy for relieving moderate to severe pain. (110)

For treatment of tension-type headache and migraine, ibuprofen is often a preferred drug among the OTC analgesics. A recent evidence-based consensus report rated ibuprofen 400 mg as a drug of first choice for self-treatment of tension-type headache and migraine attacks with or without aura, along with acetylsalicylic acid (aspirin) (900–1,000 mg), diclofenac (25 mg for headache alone), naratriptan (2.5 mg), paracetamol (1,000 mg), and phenazone (1,000 mg), as well as various fixed combinations of some of these drugs. (111) A systematic review of clinical trials found that both ibuprofen 200 and 400 mg are effective in reducing headache intensity and rendering patients pain-free at 2 hours. (90)

In postoperative dental pain, liquigel ibuprofen 400 mg provided faster relief and superior overall efficacy compared with ketoprofen 25 mg, acetaminophen 1000 mg, and placebo. (112) In another study, ibuprofen liquigel 200 and 400 mg were more efficacious than acetaminophen 1000 mg in patients experiencing moderate or severe pain after surgical removal of impacted third molars during the first 2 hours. An overview of published Cochrane reviews for efficacy of OTC pain killers using data from acute postoperative pain, found that fast acting formulations of ibuprofen 200 mg and 400 mg had better efficacy than paracetamol and aspirin at various doses (additional beneficial outcome -NNT value 2.1 [1.9-2.4] and 2.1 [1.9 to 2.3] ibuprofen 200 and 400 mg respectively). (113)

Ibuprofen combinations with paracetamol and caffeine also show high efficacy in pain relief. Among OTC analgesic available in the UK, Australia, Canada, and the USA, combinations of ibuprofen plus paracetamol may be a more effective analgesic according to the overview of Cochrane reviews. (113) Ibuprofen 400mg plus paracetamol 1000mg had the lowest NNT values (1.5 [1.4-1.7]), followed by ibuprofen 200mg plus paracetamol 500mg (1.6 [1.5-1.8]). Those two combinations had better analgesic effect than ibuprofen acid alone. It's important

to note that this overview used data from acute postoperative pain, which only reflect short term use of OTC painkillers.

Ketoprofen

Oral OTC dosage of ketoprofen are 75 mg daily, or tablet 12.5 or 25 mg. In acute postoperative pain, dexketoprofen, the pure S(+)-enantiomer of ketoprofen, at dosage forms 12.5 mg and 25 mg showed an inferior efficacy to OTC ibuprofen with the number needed to treat for an additional beneficial outcome value of 3.6 (2.8 to 5.0) and 3.2 (2.6 to 4.1) respectively.

However, dexketoprofen 25 mg had better efficacy than naproxen 200 mg and paracetamol and aspirin at all doses. (113) A comparison of dexketoprofen, trometamol, ketoprofen, and placebo in postoperative dental pain showed that dexketoprofen 25 and 50mg mg produced an analgesic effect within 30 min of administration and their effect persisted for 6h while ketoprofen 50 mg produced a level of analgesia similar to those of the higher doses of dexketoprofen trometamol 50 mg, but it had a slower onset. (114) In another study, ketoprofen 12.5 mg and 25 mg having a faster onset than ibuprofen 200 mg in the treatment of postoperative dental pain. However, the duration of effect was generally shorter. (115)

In the treatment of tension headache, ketoprofen 12.5 mg proved to be significantly superior to placebo for pain relief. (116) The data suggest a dose response for ketoprofen 12.5 mg and 25 mg. Ketoprofen 25 mg demonstrated a more rapid onset of analgesia compared to paracetamol 1000 mg, and patients' global assessment rated ketoprofen 25 mg higher than paracetamol 1000 mg.

In the management of fever, data showed that ketoprofen 0.5 mg/kg appeared to be equivalent to the standard antipyretic doses of the reference products ibuprofen 5 mg/kg and paracetamol 15 mg/kg. Ketoprofen at the 0.5 mg/kg dose should be an effective option for symptomatic management of fever in children. (117)

1.5. Safety of NSAIDs at OTC dosages

When assessing the safety profile of NSAIDs, it is important to distinguish between prescription and OTC use, especially since many adverse drug reactions (ADRs) are dose related.

Prescription users typically use high-dose NSAIDs for prolonged periods (118) and are

monitored for ADRs on a regular basis by health care providers. In contrast, although risks are generally lower with occasional use of OTC NSAIDs (118), users of these products are not routinely monitored by a health care provider and may be at risk of unrecognized ADRs. (119) However in many cases the patient will stop the drug spontaneously when the desired effect has been obtained, before adverse events have had the time to develop, or be recognized. In addition, although a majority of consumers use OTC NSAIDs as per labeled instructions, a small proportion may exceed recommended doses, (120) likely resulting in the intake of prescription-level doses, the risks of which are well-known. In countries with well-developed medical systems, unrecognized events would most often be minor or limited. Significant events would lead to medical or health care services intervention.

ADRs associated with NSAIDs primarily manifest in gastrointestinal, cardiovascular and renal sites. Although the literature on safety of NSAID therapy is extensive, the risk profiles of OTC and prescription dosing are seldom separated. Epidemiological studies mostly capture prescription NSAIDs because their use is recorded in insurance claims database or electronic medical records. In our literature review, we use the cut-off daily dosages of 1,200 mg for ibuprofen, 500 mg for naproxen, 75 mg for ketoprofen and 75 mg for diclofenac to separate the OTC use from prescription use.

Gastro-intestinal toxicity

The mechanisms responsible for NSAID-induced ulcerative lesions of the GI tract are multiple. (121–123) NSAIDs injure the gut by causing topical injury to the mucosa and by systemic effects associated with mucosal prostaglandin depletion from COX inhibition. (124) Platelet inhibition has also been considered to be a key mechanism of bleeding of lesions of the GI tract; however the systemic effects of NSAIDs appear to have a predominant role. (124)

Data from three retrospective case-control studies (125) showed that at OTC dosage, ibuprofen had the lowest odds ratio (OR) for development of GI bleeding versus diclofenac or naproxen (Table 1). This meta-analysis also evaluated the impact of duration of use on GI bleeding risk and found a higher increase in short-term users (who took a non-aspirin NSAID in the week before the bleed, but not in the 2–4 weeks before that) compared to continuing users (who took a non-aspirin NSAID in the week before the bleed and in the 2–4 weeks before that), and recent users (who took a non-aspirin NSAID in the 2–4 weeks before the bleed but

not in the week before the bleed): OR 11.7 [6.5–21.0], 5.6 [4.6–7.0], 3.2 [2.1–5.1] respectively. These findings are consistent with depletion of susceptibles, where long-term users have more chance of not having had an adverse event.

Lewis *et al.* (126) in their case-control study found no association of infrequent use (1–3 days in the index week) of OTC NSAIDs with serious upper GI toxicity (OR 0.67 [0.43–1.06]), but the association was significant when OTC NSAIDs were used 4–7 days in the index week (OR 1.83 [1.14–2.95]).

Five other studies also reported the lowest relative risk (RR) of a GI bleeding-related event for OTC dose-strength ibuprofen (Table 1).

The Paracetamol, Aspirin, and Ibuprofen New Tolerability (PAIN) study was a randomized double-blind clinical trial in 8,677 patients, that assessed the frequency of significant adverse events (AEs) associated with OTC analgesics in patients with acute pain. (127) As expected, rates of GI AEs were significantly lower in patients receiving OTC doses of ibuprofen versus aspirin (4.0% vs 7.1%; $P=0.001$), and interestingly, ibuprofen was noted to produce significantly fewer overall GI AEs vs acetaminophen (5.3%; $P=0.025$). (127) The PAIN study also identified numerous factors associated with increased risk of AEs, including female sex, older age, height <160 cm, use of the analgesic for musculoskeletal pain (vs menstrual cramps, sore throat, toothache, or fever), concomitant use of prohibited medications, and increasing number of concomitant medications. (127)

Table 1. Relative risks of GI bleeding-related events associated with OTC dose-strength NSAID compared to non-use

Study	Population	Outcome	Drugs	Dose/frequency	RR/OR (95%CI)
Lewis <i>et al.</i> 2002 (125)	England,	GI bleeds	Ibuprofen	< 1200 mg/d	1.1 [0.6-2.0]
	Scotland,		Diclofenac	< 75mg	2.2 [0.8-5.8]
	Sweden		Naproxen	< 500 mg	4.8 [1.3-18.1]
Mellemkjaer <i>et al.</i> 2002 (128)	Denmark	UGIB	Ibuprofen	< 1000 mg/d	2.10 [1.1-3.7]
			Ibuprofen	1000 - 1999 mg/d	3.58 [2.4-5.1]
			Naproxen	< 700 mg/d	3.26 [1.2-7.1]

Study	Population	Outcome	Drugs	Dose/frequency	RR/OR (95%CI)
Wang <i>et al.</i> 2002 (129)	Scotland	UGIB or perforation	Ibuprofen	≤ 1200 mg/d	0.90 [0.41-1.56]
Biskupiak <i>et al.</i> 2006 (130)	U.S	Perforations, ulcers and bleeds	Ibuprofen Naproxen	200 mg dose-strength 220 mg dose-strength	1.38 [1.07-1.78] 1.54 [1.04-2.28]
Griffin <i>et al.</i> 1991 (131)	U.S	Peptic ulcer		1200 mg/d	2.3 [1.8-3.0]
Blot and McLaughlin 2000 (132)	U.S	GI bleeding	Ibuprofen	≤ 600 mg/d 601–1200 mg/d	1.8 [0.8-4.1] 3.5 [1.2–10.7]

GI, gastrointestinal; UGIB, upper gastrointestinal bleed

Cardiovascular toxicity

The CV events associated with the use of non-aspirin NSAIDs is an important clinical issue which led to the withdrawal from the market of rofecoxib (15) and valdecoxib (23). However, both observational studies and meta-analyses of data derived from randomized clinical trials showed that traditional NSAIDs, such as diclofenac, were also associated with an increased CV risk. (133)(134)

The most plausible mechanism underlying the CV risk of NSAIDs (both coxibs and traditional NSAIDs) might be the imbalance between COX-1 and COX-2 inhibition. On one hand, COX-1 is involved in platelet synthesis of the pro-aggregant and vasoconstrictor thromboxane, and its irreversible inhibition by aspirin is the basis of low-dose aspirin's antiplatelet effect. (135–139) On the contrary, constitutive COX-1 and COX-2 in the arterial wall and endothelium are involved in the synthesis of the anti-aggregant and vasodilating prostacyclin. Balanced inhibition of both COX isoforms is neutral. Preferential inhibition of COX-1 creates an imbalance in favour of prostacyclin with an anti-aggregant effect that is cardioprotective. This is the proposed reason for which naproxen, which inhibits COX-1 more than COX-2, seems less involved in this thrombotic risk. (134,137,140–143) Predominant inhibition of COX-2 would reduce prostacyclin production without affecting thromboxane, resulting in a net pro-

thrombotic or pro-aggregant and vasoconstrictive effect. If this were the mechanism, then the effect would be apparent from the first intake of the drug, it would be clearly dose-dependent, and the cumulative probability of a thrombotic event would be proportional to the intensity and duration of COX-2 inhibition. This is however not consistent with the results of the APPRoVE study which led to the withdrawal of Rofecoxib, where rofecoxib differentiated from placebo after about 3 years of treatment.

A second explanation proposed, which is not exclusive of the first, is that of a long-term consequence of the renal effects of COX-2 inhibition resulting in small but significant increases in blood pressure. (144–147) Increased blood pressure over time would alter the arterial wall structure and increase the risk of atherosclerotic plaques resulting in increased risk of coronary thrombosis. The use of NSAIDs would be just a risk factor for hypertension and secondary vascular disease. Since the thrombosis is the result of these risk factors, the delay between the use of the drugs and the appearance of the event would be long. In addition, this effect would be cumulative over time, and would be related to duration of treatment and dose.

Whatever the mechanism by which NSAIDs might affect the risk of thrombosis, both are pharmacological, dose- and duration-dependent, and both depend also upon concomitant risk factors, including age and indication for the use of the drug. It may be noted that though absolute risk depends on the patient's background risk, the relative risk associated with NSAIDs is approximately the same whatever the initial level of risk. (148) (149)

Since most users of non-prescription NSAIDs are using them at low-dose, short-term, and they would be younger patients, with fewer concomitant medications and risk factors, (148)(118) the preferable mechanism of the CV risk of OTC NSAIDs is the imbalance between COX-1 and COX-2 inhibition. This mechanism predicts an apparent risk of thrombotic event after the first intake of OTC NSAIDs. The effect would be dose-dependent and proportional to the intensity and duration of COX-2 inhibition.

The review of studies reporting on the CV risk of low-dose NSAIDs will be presented in
CHAPTER II.

Renal toxicity

All NSAIDs can alter renal function by inhibiting COX-1 (which regulates renal hemodynamics and glomerular filtration) and/or COX-2 (which mediates salt and water excretion) expressed in the kidneys.(150) Uncommon, but concerning, renal syndromes caused by nonselective NSAIDs include sodium retention, peripheral edema, increased BP and weight, congestive heart failure (rare), hyperkalemia, and acute renal failure. (150) NSAIDs may lessen response to diuretics and worsen renal insufficiency associated with use of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs). (150) Risk factors include preexisting severe hepatic or renal dysfunction, nephrotic syndrome with high-level proteinuria, older age, diabetes, hypertension, and congestive heart failure, renal stress (e.g. dehydration) from exercise in hot environments. (150–153)

Randomized controlled trials have found no increased risk for renal failure in children taking ibuprofen for fever. (154) (155) Some case studies have reported renal failure in children taking OTC ibuprofen; dehydration may have been a contributing factor. (156) (157) There have also been cases reported of transient renal failure among children with cystic fibrosis who were concurrently treated with ibuprofen and intravenous aminoglycosides. (158) A nested case-control analysis of new prescription NSAID users over 65 years of age in Quebec, Canada found that risk of renal failure was increased with current new use of NSAIDs (rate ratio: 2.05; 95% CI: 1.61–2.60), including naproxen (rate ratio: 2.42; 95% CI: 1.52–3.85). (159) Indeed, OTC ibuprofen in general has been shown to have a low risk of renal AEs. In a case-control study of Tennessee Medicaid recipients, (160) OTC ibuprofen doses were not associated with increased risk for acute renal failure; however, the risk increased dose dependently (adjusted ORs: 0.94 [95% CI: 0.58–1.51], 1.89 [1.34–2.67], and 2.32 [1.45–3.71] at ≤ 1200 , 1200–2400, and ≥ 2400 mg/d, respectively). Overall, these studies suggest that OTC ibuprofen is a low risk factor for developing acute or chronic renal conditions. However, the drugs should be taken at low-dose with precaution in elderly individuals or those with compromised renal function.

Potential drug interactions that might contribute to cardiovascular risk

Interaction of NSAIDs with some drugs, such as antihypertensive antithrombotic agents might contribute to the cardiovascular risk by reducing the effect of those drugs.

Antihypertensives

Concomitant use of NSAIDs and antihypertensives is common. Efficacy of medications that act on renal prostaglandins (eg, furosemide) or modify their effects (eg, other diuretics or ACEIs) may be reduced, resulting in increases in blood pressure (BP) with NSAID coadministration because of inhibition of renal prostaglandins and increased fluid retention. (150)

Some trials found increased risk of drug/drug interactions when prescription-strength NSAIDs and antihypertensives were coadministered over a period of multiple weeks. (161,162) Other trials found no significant effect on BP when OTC doses of ibuprofen or naproxen (146) or prescription-dose ibuprofen (163,164) were combined with antihypertensives.

A recent post hoc analysis of an randomized controlled trial (RCT) (165) comparing the effects of lumiracoxib (a prescription COX-2 inhibitor; 100 mg/d) with prescription ibuprofen (1,800 mg/d) in OA patients with hypertension controlled on stable doses of antihypertensive medication(s) observed small but consistent increases of 2.2 mmHg overall versus baseline in 24-hour mean systolic BP (SBP) in the ibuprofen-treated group. The greatest increases occurred when ibuprofen was combined with ARBs (SBP increase 4.6 mmHg) or ACEIs (SBP increase of 3.7 mmHg). A small increase in SBP was found when combined with β -blocker (2.8 mmHg) or calcium channel blocker (1.8 mmHg).

In an RCT of prescription-strength ibuprofen (1,600 mg/d) plus propranolol, no significant increase in BP was found. (166) Calcium channel blockers such as verapamil and amlodipine do not appear to be associated with clinically significant interactions with NSAIDs. (146,167) These results are expected from the mechanisms of action of both drug families. (146)

Given the clear dose- and duration-response relationship between ibuprofen use and adverse drug reactions (ADRs) in general (154) and the very small increase in BP observed with prescription-strength NSAIDs, short-term OTC ibuprofen and antihypertensives interaction would most likely have only a minor effect on BP. Chronic use of higher doses of NSAIDs with antihypertensive might cause concerns.

Aspirin

Coadministration of aspirin and most NSAIDs (other than diclofenac and ketorolac) can lead to pharmacodynamic drug/drug interactions resulting from competition for access to the acetylation site of platelet-expressed COX-1. (139,168,169) NSAID-driven reversible, transient inhibition of platelet aggregation blocks aspirin's irreversible inhibition, thereby potentially allowing clot formation. (139) This NSAID-driven effect on aspirin is of particular concern in individuals at high CV risk who take low-dose aspirin daily to reduce the risk of a thrombotic event. (139,169)

However, the interactions of NSAIDs and aspirin are still controversial, according to observational studies.

A case-control study (N=5,208, including 1,055 cases of first nonfatal MI and 4,153 community controls) found that patients taking daily prophylactic aspirin plus ibuprofen four or more times/week (doses not reported) had double the risk of an MI compared with aspirin-only users, although the difference was not statistically significant (OR: 2.03; 95% CI: 0.60–6.84), whereas the OR for MI with infrequent use (less than four times/week) of ibuprofen plus daily aspirin was 0.60 (95% CI: 0.21–1.66). (170) MacDonald and Wei also indicated that concomitant aspirin and ibuprofen could increase the possibility of experiencing CV events and all-cause mortality. (171)

Other studies suggest that risk for a CV event may actually be reduced with concomitant aspirin and ibuprofen. In a single-center, retrospective analysis, patients prescribed aspirin (typically 325 mg/d) and ibuprofen (mean 1,947 mg/d) (n=3,859) experienced about 40% fewer MIs than those prescribed aspirin alone (n=10,239; rate ratio: 0.61; 95% CI: 0.50–0.73; P<0.001). (172) A retrospective study (N=42,611, including 8,688 cases with MI and 33,923 controls) found that patients prescribed aspirin and any NSAID (doses not assessed for either treatment) had a lower risk for MI than those who did not take aspirin and/or NSAIDs (OR: 0.74; 95% CI: 0.57–0.97). In addition, individuals taking ibuprofen plus aspirin in this study had a lower OR for MI (OR: 0.69; 95% CI: 0.42–1.15) than did those taking aspirin with an NSAID other than ibuprofen (OR: 0.76; 95% CI: 0.56–1.04). (173)

The FDA recommends taking ibuprofen ≥ 8 hours before or ≥ 30 minutes after immediate-release (not enteric-coated) aspirin to reduce the likelihood of a potential interaction on platelet function. (174)

2. Paracetamol (acetaminophen)

1.1. History of paracetamol

The painkilling properties of paracetamol were discovered by accident when a similar molecule (acetanilide) was added to a patient's prescription in France in 1886. The physicians found that acetanilide produced marked fever reduction in one of their patients who, along with intestinal parasites, had a febrile disease. But since acetanilide is toxic in moderate doses, chemists modified its structure to try to find a compound that was less harmful but which still retained the analgesic properties. Harmon Northrop Morse had synthesized successfully paracetamol at Johns Hopkins University in 1877, (175) but it was not until 1887 that clinical pharmacologist Joseph von Mering tried paracetamol on patients. (176) Paracetamol is the active metabolite of phenacetin and acetanilide, both popular as analgesics and antipyretics at that time. However, unlike phenacetin, acetanilide and their combinations, paracetamol is not considered carcinogenic at therapeutic doses.

Paracetamol was first marketed in the United States in 1950 under the name Triagesic, a combination of paracetamol, aspirin, and caffeine. (177) However, it was quickly removed from the market in 1951 due to three cases of agranulocytosis. It took several years to prove that the disease was not related with paracetamol. In 1953, paracetamol was marketed by the Sterling-Winthrop Company. It was promoted as preferable to aspirin since it was safer in children and people with ulcers. (178) In 1955, McNeil introduced TYLENOL Elixir for Children. (179) In 1956, 500 mg tablets of paracetamol went on sale in the United Kingdom under the trade name Panadol. In 1963, paracetamol was added to the British Pharmacopoeia, and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents. (177) In the 1980s, paracetamol sales exceeded those of aspirin in many countries, including the United Kingdom. This was accompanied by the commercial demise of phenacetin, blamed as the cause of analgesic nephropathy and hematological toxicity. (176)(180)

Paracetamol has been available without a prescription since 1959, and has become a common household drug. Generic versions of the drug are available worldwide.

1.2. Mechanism of action

Paracetamol is one of the most widely used over-the-counter analgesic drugs worldwide.

Despite its extensive use, its mode of action is still unclear. For more than three decades it was commonly stated that paracetamol acts centrally and is a weak inhibitor of prostaglandin synthesis by COX-1 and COX-2, (181) based on the early work of Flower and Vane in 1972.

(182) Attempts to explain the pharmacological action of paracetamol as inhibition of a central COX isoform, referred to as COX-3, (183) (184) have meanwhile been rejected. (185)

Two recent studies have suggested a preferential COX-2 inhibitory action of paracetamol under different clinically relevant conditions.

In the first of these studies, Hinz *et al.* (186) evaluated the ex-vivo COX inhibition and pharmacokinetics of paracetamol in 5 volunteers receiving single 1000 mg doses orally. They found that acetaminophen elicited a 4.4-fold selectivity toward COX-2 inhibition in vitro (IC₅₀ 113.7 µmol/L for COX-1; IC₅₀ 25.8 µmol/L for COX-2). Following oral administration of the drug, maximal ex-vivo inhibitions were 56% (COX-1) and 83% (COX-2). Paracetamol plasma concentrations remained above the in vitro IC₅₀ for COX-2 for at least 5 h post-administration. Ex-vivo IC₅₀ values (COX-1: 105.2 µmol/L; COX-2: 26.3 µmol/L) of paracetamol compared favourably with its in vitro IC₅₀ values. In contrast to previous concepts, paracetamol inhibited COX-2 by more than 80%, i.e., to a degree comparable to NSAIDs and selective COX-2 inhibitors. However, a >95% COX-1 blockade relevant for suppression of platelet function was not achieved.

A second study evaluated acetaminophen's effect on PG release and the expression patterns of genes related to PG production in a clinical model of tissue injury and acute inflammation. (187) Subjects received either 1000 mg acetaminophen, or placebo before the surgical removal of two impacted mandibular third molars. PGE₂ release was suppressed by acetaminophen compared to placebo at 3 h coincident with increased COX-2 gene expression in biopsies collected from the surgical site. COX-2 gene expression remained elevated at 24 h with continued acetaminophen treatment. COX-1 gene expression was significantly down-regulated

at 24h by acetaminophen. Acetaminophen suppression of PGE₂ without inhibiting TXB₂ release, when COX-2 gene expression is up-regulated, suggests that acetaminophen is a selective COX-2 inhibitor in vivo. The up-regulation of COX-2 gene and down-regulation of COX-1 gene expression suggests that acetaminophen may result in changes in COX-derived prostanoids with repeated doses.

Regarding to the mode of its cyclooxygenase inhibition, whereas traditional NSAID and selective COX-2 inhibitors inhibit cyclooxygenase by competing with arachidonic acid for entering the cyclooxygenase reaction, paracetamol has been suggested to act as a reducer of the active form of COX, rendering it catalytically deficient. (188)(189) Distinction between mechanism of action of NSAIDs and paracetamol is described in Figure 1. (190)

COX inhibition by paracetamol only occurs in areas where peroxide levels are very low, as in the brain. (188) This peroxide-mediated inhibition of COX activity can also explain why paracetamol is not active in peripheral sites of inflammation, where the concentration of peroxide is greater than that encountered in brain. Similarly, low doses of paracetamol has been suggested to reduce the oxidative stress (191)(192), that has been implicated in prostaglandin release and fever. (193)(194)

In conclusion, the pharmacological effects of paracetamol are highly selective. It has antipyretic (195)(196) and moderate analgesic (197)(198) properties, with little antiinflammatory effect (199). In most humans, its effect on platelets is slight and reversible at doses that are antipyretic (200).

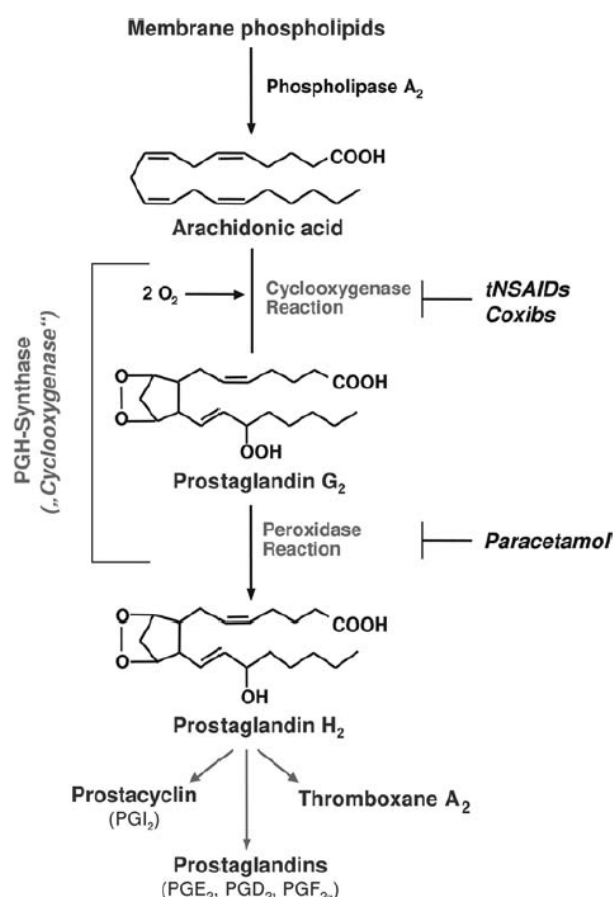


Figure 1. Biochemical function of the cyclooxygenase enzyme and pharmacological targets within its two activity sites.

(Source: Hinz, B. & Brune, K. Paracetamol and cyclooxygenase inhibition: is there a cause for concern? *Ann. Rheum. Dis.* 71, 20–25 (2012). (190))

Analgesic Effects

The precise analgesic actions of paracetamol remain uncertain. It is becoming clear that the predominant mechanisms largely responsible for paracetamol's analgesic activity are located in the CNS. (182) However, which central effects are largely responsible for paracetamol's effects on pain continue to be uncertain. (201) The most accepted theory might be paracetamol's positive effects on the serotonergic descending inhibitory pathways. However, interactions with opioidergic systems, eicosanoid systems, and/or nitric oxide containing pathways may be involved as well. (201) Furthermore, endocannabinoid signaling may play a role in paracetamol's activation of the serotonergic descending inhibitory pathways. (201) Smith proposed multiple mechanisms which may contribute to paracetamol's analgesic activity. (201)

Antipyretic Effect

Paracetamol is believed to be centrally active, producing analgesia and antipyretic effect by inhibiting COX2 in the hypothalamus. (182) Paracetamol penetrates the blood-brain barrier, achieving CFS levels comparable to those in serum. (202) CNS levels of PGE2 rise during fever and fall to normal levels upon administration of the drug. (203) Paracetamol lowers the thermoregulatory set point primarily by blocking cyclooxygenase production of prostaglandin E2 (PGE2). (204) Additional effects may stem from provoking the release of endogenous antipyretic compounds such as arginine vasopressin. (204) Another hypothesis is that paracetamol reduces the oxidative stress (191)·(192) that has been implicated in prostaglandin release and fever.(193)·(194) Acetaminophen differs from other antipyretic agents by its lack of effect on endogenous antipyretics. (205)

Antiinflammatory Effect

Paracetamol does not suppress serious inflammation associated with rheumatoid arthritis.(199) This lack of effect can be explained by the high extracellular concentrations of arachidonic acid and peroxide in the inflamed tissue, both of which diminish the effect of paracetamol on prostaglandin synthesis. (206)·(188)·(189) In addition, paracetamol does not decrease the concentration of diverse prostanoids in the synovial fluid of patients with rheumatoid arthritis, which explains its lack of anti-inflammatory effect. (207) However, paracetamol decreases tissue swelling following oral surgery in humans, (208,208,209) and reduces local inflammatory temperature increase, (208) suggesting that paracetamol has some anti-inflammatory action. Several experimental studies have found a peripheral anti-inflammatory action of paracetamol.(210)·(211)

1.3. Pharmacokinetics properties

Absorption

Paracetamol can be administered via the oral, intravenous or rectal routes. Following oral administration paracetamol is rapidly absorbed from the gastrointestinal tract, its systemic bioavailability being dose-dependent and ranging from 70 to 90%. (212)·(213) However, there is no direct correlation between serum concentrations of paracetamol and its analgesic or antipyretic effect. (214) Its rate of oral absorption is predominantly dependent on the rate of

gastric emptying, being delayed by food, propantheline, pethidine and diamorphine and enhanced by metoclopramide. (212) (213) Paracetamol is also well absorbed from the rectum. (212)

Distribution

Paracetamol distributes rapidly and evenly throughout most tissues and fluids and has a volume of distribution of approximately 0.9L/kg. 10 to 20% of the drug is bound to red blood cells. (212) Since the antipyretic and probably the analgesic effects of paracetamol are centrally mediated, its plasma and CSF concentrations might reflect its efficacy. Bannwarth *et al.* measured plasma and CSF concentrations of paracetamol after a single intravenous dose of propacetamol and found a maximum CSF concentrations at 4th hour, the subsequent concentrations exceeding those in plasma (215) The CSF concentration lagged behind those of plasma. (202) (215) An open-label prospective study investigated the cerebrospinal fluid penetration of paracetamol in 32 healthy children, who were undergoing surgery in the lower body using spinal anesthesia. (216) Paracetamol was detected in CSF from the earliest sample at 5 minutes after a single intravenous injection of paracetamol (15 mg/kg). CSF/plasma ratios ranged between 0.06 and 2.0 from 5 minutes to 5 hours. The highest CSF paracetamol concentration was detected at 57 minutes. (216)

Elimination and metabolism

Paracetamol is extensively metabolized and the plasma half-life is 1.5-2.5 hours. The elimination half-life of paracetamol was shorter in plasma (2.4 h) than in CSF (3.2 h). (215) The time-course of paracetamol in CSF may parallel that of the analgesic effect. About 55% and 30% of a therapeutic dose is excreted in the urine as glucuronide and sulphate conjugates, respectively, whereas mercapturic acid and cysteine conjugates (representing conversion to a potentially toxic intermediate metabolite) each account for some 4% of the dose. (213)

Large doses of paracetamol (overdoses) cause acute hepatic necrosis as a result of depletion of glutathione and of binding of the excess reactive metabolite to vital cell constituents. This damage can be prevented by the early administration of sulfhydryl compounds such as methionine and N-acetylcysteine. In healthy subjects 85 to 95% of a therapeutic dose is excreted in the urine within 24 hours with about 4, 55, 30, 4 and 4% appearing as unchanged

paracetamol and its glucuronide, sulphate, mercapturic acid and cysteine conjugates, respectively. The total body clearance from 4.5 to 5.5 ml/kg/min. (212)

Age has little effect on the plasma half-life, (212) (213) which is shortened in patients taking anticonvulsants. The plasma half-life is usually normal in patients with mild chronic liver disease, but it is prolonged in those with decompensated liver disease. (212)

1.4. Indications and efficacy profiles

Painful conditions

Paracetamol is suitable for the treatment of mild to moderate pain (from headaches, menstrual periods, toothaches, backaches, osteoarthritis, or cold/flu aches and pains).

Migraine headaches, dysmenorrhea and joint pain can also be influenced advantageously. In cancer patients, paracetamol is used for mild pain or it can be administered in combination with opioids (e.g. codeine).

In acute postoperative pain treatment, a Cochrane review found that a single dose of paracetamol provides effective analgesia for about half of patients, for a period of about four hours (compared with about 20% treated with placebo). (217) There was no dose response. NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were as follows: 500 mg NNT 3.5 [2.7–4.8]; 600–650 mg NNT 4.6 [3.9–5.5]; 975 to 1000 mg NNT 3.6 [3.4–4.0]. (217) Compared to NSAIDs, overall, NSAIDs seem to be superior to paracetamol in postoperative pain management, but the magnitude of the difference may depend on the type of surgery performed. (218) In major surgery, the efficacies of NSAIDs and paracetamol seem to be comparable, whereas in minor surgery NSAIDs seem to be superior. (218)

Among all kind of acute pain treatments, paracetamol has equivalent efficacy to aspirin but inferior to NSAIDs (especially ibuprofen). (113)

Paracetamol is less efficacious than salicylates and other antirheumatic agents for problems that require anti-inflammatory treatment. In spite of the inferior efficacy of paracetamol compared to NSAIDs, paracetamol is still the first-line reference standard for relieving the symptoms of knee and hip OA according to recent guidelines (EULAR, OARSI, ACR, UK National

Institute for Health and Clinical Excellence) because of its good safety profile. (78) (219–223) However, a recent meta-analysis found no role for single-agent paracetamol for the treatment of patients with osteoarthritis irrespective of dose, whereas diclofenac 150 mg/day is the most effective NSAID available at present, in terms of improving both pain and function. (75) The safety of paracetamol is also questioned, (224) not just in overdose. (225) Therefore, its recommendation as the universal first-line analgesic in OA should be reconsidered. (226)

Efficacy of paracetamol combinations

The two common formulations of paracetamol combination are with codeine and with ibuprofen. A systematic review reported codeine added to paracetamol provided a 5% increase in analgesia on the sum pain intensity difference. (227) This effect was comparable to the difference in analgesic effect between codeine and placebo. (227) Another literature review reported a non-inferior efficacy of paracetamol/codeine combination compared to NSAIDs. (228)

As we mentioned in section 1.4, paracetamol combinations with ibuprofen showed high efficacy in pain relief. (113) Efficacy of the two available combinations, Paracetamol 1000mg plus Ibuprofen 400mg, and 500/200 were not different and better than ibuprofen alone. (113)

Fever

A randomized, double-blind, placebo-controlled trial compared the antipyretic efficacy of aspirin and paracetamol and found a superior antipyretic drug in endotoxemia compared with aspirin. (195) Treatment with acetaminophen ameliorates subjective symptoms induced by endotoxemia without compromising the humoral response of a subject to endotoxin. (195)

A meta-analysis comparing efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever found that single doses of ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. (110) Ibuprofen (5-10 mg/kg) was a more effective antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours posttreatment. (110)

Two randomized, double-blind, double-dummy, parallel-group, phase III studies in children found that ketoprofen 0.5 mg/kg appeared to be equivalent to the standard antipyretic doses of the reference products ibuprofen 5 mg/kg and paracetamol 15 mg/kg. (117)

1.5. Safety profiles

Hepatotoxicity

Hepatotoxicity and liver failure by paracetamol intoxication were not recognized until the first cases of fatal paracetamol poisoning were reported in the mid-1980s, three decades after its approval for clinical use. Paracetamol intoxication is now the most common cause of acute liver failure (ALF) in the United States, Great Britain and several countries in Europe. (229) In the multi-country Study of Acute Liver Transplantation (SALT), overdose represented 20% of all-cause ALF transplantation (in six hundred cases of ALF transplantation, 114 were overdoses). 111 (97%) of the overdoses involved paracetamol.(230) In the same study, non-overdose paracetamol-exposed liver failure was found to be twice more common than NSAID-exposed liver failure. (225)

Cases of paracetamol liver toxicity can be classified as intentional and unintentional. Intentional paracetamol overdosing involving single ingestion is a common form of suicide attempt due to its low cost and accessibility. Unintentional overdoses, which are common in adults and children, account for more than 50% of all cases and is primarily due to therapeutic misuse and excessive dosing over a period of time; usually more than 3 days. (231) Moreover, the use of non-prescription combined formulations containing paracetamol also contributes to the risk of overdose. Under certain conditions, paracetamol hepatotoxicity can occur even at therapeutic doses. There are a number of well documented risk factors that lower the dose threshold for paracetamol toxicity such as chronic alcohol use, co-administration of other drugs that induce the activity of cytochrome P450 (CYP 450) enzymes, and malnutrition which reduces the stores of protective thiols in liver. (231)

The mechanisms of paracetamol's hepatotoxicity involve its hepatic metabolism which comprises of two phases: non-toxic phase under therapeutic dose and toxic phase under overdose condition (Figure 2). (231)

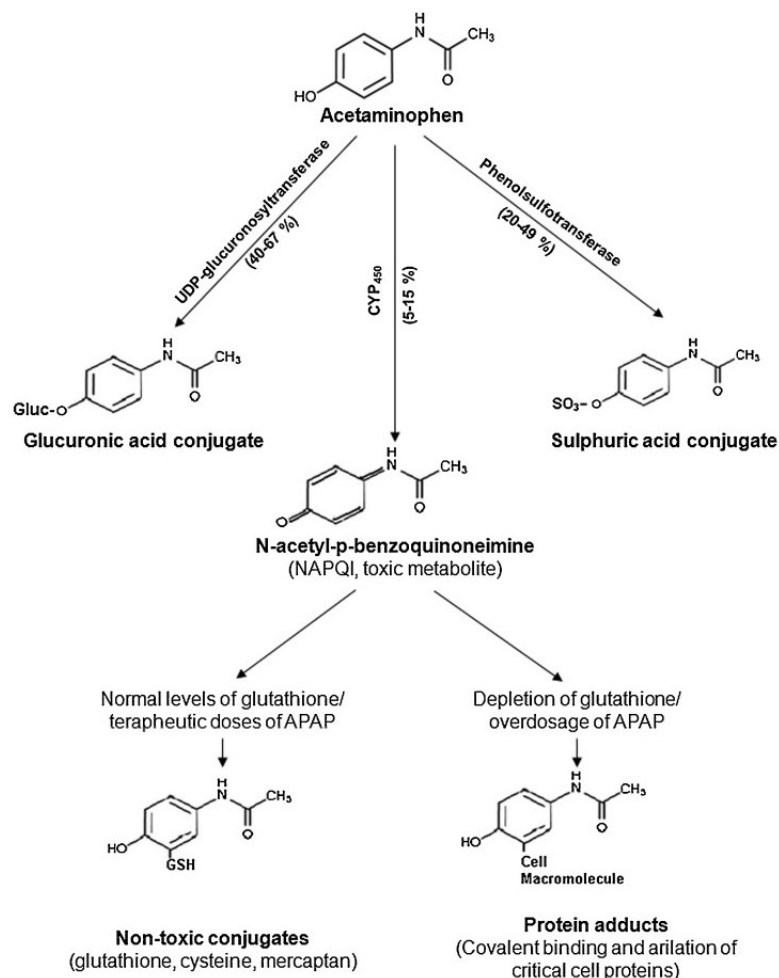


Figure 2. Main metabolic pathways of paracetamol in liver after administration of therapeutic or toxic doses.

(Source: Ghanem, C. I., Pérez, M. J., Manautou, J. E. & Mottino, A. D. Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacol. Res.* (2016).**(231)**)

Gastro-intestinal toxicity

Paracetamol has been traditionally considered a safer than NSAIDs regarding to gastrointestinal complications. However, some data showed a similar risk of GI bleeding and perforation to that seen with NSAIDs.

In a recent randomized double-blind controlled trial comparing acetaminophen, ibuprofen, or their combinations, in patients with knee OA. (232) After 13 weeks, 20.3% of patients taking 3 g/d acetaminophen and 19.6% of those taking 1200 mg/d ibuprofen exhibited occult GI bleeding, defined as a hemoglobin level decrease of at least 1 g/dl. (232) Both drugs in

combination induced occult gastrointestinal bleeding in 38.4% of patients without significantly improving the analgesic effect as compared with ibuprofen alone. (232)

A meta-analysis of observational studies about upper gastrointestinal complications among users of paracetamol reported an overall summary RRs of 1.3 [95% CI: 1.2–1.5] (fixed effect) and 1.4 [1.1–1.6] (random-effects). (233) Among twelve case-control studies (7,894 cases) included, 3 studies explored the association of daily dose of paracetamol and gastrointestinal complications. A gradient dose-effect was detected with higher doses. In one study, the adjusted RR was 1.0 [95% CI: 0.8–1.2] for users of at most 1,000 mg/day (n=752), 0.8 [95% CI: 0.6–1.1] for users of 1,001 to 1,999 mg/day (n=301), 1.9 [1.4–2.6] for users of 2,000 mg/day (n=211), 3.4 [2.4–4.8] for users of 2,001 to 3,999 mg/day (n=78), and 6.5 [2.4–17.6] for users of at least 4,000 mg/day (n=20). (233) In the other 2 studies, users of more than 20 tablets in the past week had an RR of 2.4 compared with non-users and users of >1000 mg/day had an adjusted RR of 2.6. (233)

Another study found that paracetamol might potentiate the GI toxicity of NSAIDs or add its own effects to that of NSAIDs. In this retrospective cohort, the risk of hospitalization due to GI events (ulceration, perforation, bleeding from the upper or lower digestive tract) was twofold higher for patients taking acetaminophen combined with traditional NSAIDs than NSAIDs alone. (234)

Cardiovascular toxicity

As we mentioned in section 1.5.2, the two plausible mechanisms underlying the CV risk of NSAIDs is the predominant inhibition of COX-2, resulting in a net pro-thrombotic and vasoconstrictive effect, and the long-term consequence of the renal effects of COX-2 inhibition resulting in increases in blood pressure. Since two studies have suggested a preferential COX-2 inhibitory action of paracetamol, a comparable effect in the endothelium is expected to confer a cardiovascular risk.

Blockade of COX-1 is the basis of the anti-aggregatory action of traditional NSAID and aspirin on platelets. (235)(137)(139) Paracetamol is a weak inhibitor of platelet COX-1. (186) Oral administration of 1 g paracetamol caused maximal plasma concentrations of 104.8 µmol/l results in an approximately 50% inhibition of COX-1. (186) Early investigations with this assay,

which uses endogenous thrombin generated during a 1 h blood clotting as COX-1 stimulus, implied a greater than 95% COX-1 inhibition as necessary for the suppression or the inhibition of platelet function. (236) In line with this notion, paracetamol does not interfere with platelet function when given at single oral doses of 1 g (237) or up to 1.95 g (139). Apart from that, paracetamol has been shown to exert a reversible anti-aggregatory effect in healthy volunteers when used at higher parenteral doses.(238)·(239) Paracetamol dose-dependently inhibited platelet aggregation stimulated with arachidonic acid, adenosine diphosphate or epinephrine. (239) As expected, increasing the concentration of arachidonic acid counteracted this inhibition. (239) The authors concluded that an anti-aggregatory action of paracetamol may become clinically significant in patients with intrinsic or drug-induced impairment of haemostasis. (239)

A long-term increase in blood pressure has been proposed to underlie CV side-effects occurring after the prolonged use of NSAIDs. In contrast to the inflamed tissue, endothelial cells possess low levels of peroxide making an undisturbed COX-2 inhibition by paracetamol possible.(188)

Two studies examined the interference of common NSAIDs with the anti-platelet activity of aspirin on the human platelet and found that some NSAIDs (e.g. ibuprofen, flufenamic acid, naproxen, nimesulide, oxaprozin, piroxicam, and celecoxib) may preclude aspirin's antiplatelet effect by interfering with aspirin on platelet COX-1. (240)·(168) One of those studies examined paracetamol and did not find a significant interference with the anti-platelet activity of aspirin. (168) However, since this study only used paracetamol 1 g and did not test for a dose-dependent effect, significant interactions at higher doses has not been dismissed. Also, in this study, arachidonic acid 1,000 μM was used to stimulate platelet rich plasma aggregation. However, antiaggregatory effect of paracetamol was found to be dependent on the concentration of arachidonic acid: with an increase from 500 μM to 1,000 μM the antiaggregatory effect paracetamol is attenuated. (239)

In conclusion, the mechanisms explaining cardiotoxicity of paracetamol is still vague. However, since paracetamol was revealed as a selective inhibitor of COX-2-dependent prostaglandin E₂ (PGE₂) formation, a comparable effect in the endothelium is expected to confer a CV risk. A review of epidemiological data will be presented in Chapter II.

CHAPTER II– Review of published studies about the cardiovascular risks of OTC NSAIDs and paracetamol

The risks of prescription (higher) dose NSAIDs has been extensively explored, over the past 40 years or more, concentrating first on the gastro-intestinal bleeding which was the aim of most of the early safety trials and observational studies, at high and low doses, for short and long-term indications. The understanding of that risk led to the development of the COX-2 selective inhibitors to prevent or avoid this COX-1 dependent GI toxicity. However the development of these so-called "coxibs" in turn led to the discovery of a cardiovascular risk in long-term studies at high doses (essentially VIGOR, APPRoVE and APS). Since then, many observational studies have been performed, and a few clinical trials, all mostly concerned by the prescription use of NSAIDs, essentially in indications such as Osteoarthritis or rheumatoid arthritis. Meta-analyses have confirmed the risk associated with certain COX-2 inhibitors, as well as high-dose diclofenac, probably in relation with their COX-2 inhibitory potency more than their COX-1/COX-2 selectivity. One might be tempted to simply scale the relative risks found at high doses long term to the short-term low-dose use of these drugs, and apply these relative risks to the absolute background risk of cardiovascular events in mostly young patients, to deduce the risk associated with these low-dose NSAIDs. However, in pharmacology, the dose-response relationship is not linear beyond the 20-80% of maximal effect in sigmoid dose-response curves, so that relative effects observed for high doses may be very different from those at lower doses. In addition, in the absence of knowledge on the exact mechanism of action for cardiotoxicity of NSAIDs, it is difficult to predict the time course of risk. For instance, statins take up to a year to establish their effect, and shorter studies show different results than longer studies. The same is true for risk. A risk that develops through tissue accumulation will not appear if the use of the drug stops before it has time to accumulate.

The results of high-dose long-term studies will be indicative of what may be sought for, but will unless proven otherwise probably be poor predictors of actual risks of drugs used differently. This is why the objective of this review was not to repeat the several excellent reviews and meta-analyses of the risks of prescription dose NSAIDs, but to attempt to identify these studies that

might give information or insight on the risks associated with short-term low dose use of NSAIDs or paracetamol.

1. OTC NSAIDs

1.1. Methods

There are many high quality meta-analyses and literature reviews done on the cardiovascular risk associated with NSAIDs. In this review we will not try to repeat these studies. The purpose is to review clinical trials and observational studies, which focused on the dose and duration relationship, in order to assess the risk in OTC-like conditions.

The inclusion criteria for literature review of cardiovascular risk associated with the use of NSAIDs in OTC-like conditions are described in Table 2.

Table 2. Inclusion criteria for literature review of cardiovascular risk associated with NSAIDs in OTC-like conditions

Characteristics	Inclusion criteria
Context	NSAIDs are widely used over-the-counter for treatment of common painful conditions, without medical supervision. Their CV risk in real life conditions need to be assessed.
Objective	Review studies reporting on the CV risk associated with the use of NSAIDs in OTC-like conditions (low-dose, short term); in an effort to approximate the risk of OTC NSAIDs
Database	Medline
Period	1 st January, 1990 to 12 May, 2016
Languages	English
Designs	Interventional studies: Clinical trial Non interventional (observational) studies: Case control, Cohort, Nested case-control, Case-crossover, Self-controlled cohort, Self-controlled case series, Case-time-control, Case cohort
Population	General population, all countries and regions
Exposures	NSAIDs with dose effect or duration of exposure assessments

Characteristics	Inclusion criteria
	Study definitions of low-dose : <ul style="list-style-type: none"> ○ Low-dose ibuprofen: 1200 mg daily (or 1600 mg in sensitivity analysis) ○ Low-dose diclofenac: 75 mg daily (or 100 mg in sensitivity analysis) ○ Low-dose naproxen: 500 or mg daily (or 750 or 1000 mg in sensitivity analysis) ○ Low-dose ketoprofen: 75 mg daily or (or 100 mg in sensitivity analysis)
Reference groups	Nonuse or remote use of NSAID, use of comparative drug (NSAID, aspirin or paracetamol)
Outcomes	Main outcomes: Acute myocardial infarction (or myocardial infarction), acute coronary syndrome (ACS) and stroke Secondary outcomes: cerebrovascular disease, coronary heart disease, heart failure, sudden cardiac death, cardiovascular mortality, cardiac failure, cardiorenal syndrome, transient ischemic attack (TIA)

Literature search strategy

We conducted a PubMed search with restriction to English-language publications and human subjects. The medical subject headings (MeSH) and free-text terms were used to identified outcomes and exposure of interest. Appendix 3 provides details of the search strategy.

1.2. Results

Description of studies

Clinical trials

One randomised controlled trial was identified. (241) This trial assessed gastrointestinal and cardiovascular safety of the COX-2 inhibitor lumiracoxib 400 mg once daily compared with naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily. In the naproxen substudy, rates of MI (clinical and silent) did not differ significantly with lumiracoxib compared to naproxen with in the population not taking low-dose aspirin (hazard ratio 2.37 [95% CI 0.74–7.55]), in patients taking aspirin (1.36 [0.47–3.93]), and overall (1.77 [0.82–3.84]). (241) However, the power of this study was too weak to make firm conclusions. Similarly, there was no significant difference regarding incidence of composite of non-fatal and silent myocardial

infarction, stroke, or cardiovascular death in the population not taking low-dose aspirin (1.49 [0.76–2.92]), in patients taking aspirin (1.42 [0.70–2.90]), and overall (1.46 [0.89–2.37]). (241)

An ongoing Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) (242) aims to evaluate cardiovascular safety of celecoxib 100 mg twice daily, ibuprofen 600 mg three times daily, and naproxen 375 mg twice daily in patients with osteoarthritis or rheumatoid arthritis. Results are not available yet, but the doses used and the durations are way beyond those of the usual OTC usage of these drugs, so the results may be of doubtful relevance for our purpose.

Observational studies

After reviewing all articles found by PubMed search, we identified 18 studies that fulfilled our criteria (Table 3), in of which seven were nested case-control studies, 10 cohort studies and 1 case-crossover study. In the next part, we will review studies according to dose- and duration approaches.

Table 3. Observational studies identified by PubMed search about cardiovascular risks associated with the use of NSAIDs in OTC-like conditions (low-dose or short term)

No.	Study First Author	Year*	Design	Journal
1	García-Poza (243)	2015	Nested case-control	Journal of thrombosis and haemostasis
2	Chuang (244)	2015	Case-crossover	Stroke; a Journal of Cerebral Circulation
3	de Abajo (245)	2014	Nested case-control	Pharmacoepidemiology and Drug Safety
4	Schjerning Olsen (246)	2013	Cohort	PLoS ONE
5	Schjerning Olsen (149)	2011	Cohort	Circulation
6	Fosbøl (247) [¶]	2010	Cohort	Circulation: Cardiovascular Quality and Outcomes
7	Ray (248)	2009	Cohort	Circulation: Cardiovascular Quality and Outcomes
8	Van der Linden (249)	2009	Nested case-control	Annals of the Rheumatic Diseases
9	Varas-Lorenzo (250)	2009	Nested case-control	Pharmacoepidemiology and Drug Safety
10	Gislason (251)	2008	Cohort	Archives of Internal Medicine

No.	Study First Author	Year*	Design	Journal
11	García Rodríguez (133)	2008	Nested case-control	Journal of the American College of Cardiology
12	Van Staa (252)	2008	Cohort	Journal of Internal Medicine
13	Fosbøl (253) [¶]	2008	Cohort	Clinical Pharmacology & Therapeutics
14	Andersohn (254)	2006	Nested case-control	Circulation
15	Velentgas (255)	2006	Cohort	Pharmacoepidemiology and Drug Safety
16	García Rodríguez (256)	2005	Nested case-control	BMC medicine
17	Gislason (257)	2006	Cohort	Circulation
18	Ray (258)	2002	Cohort	Lancet

*Year of publication

Studies that report dose effect

After reviewing all eligible articles, we found 15 eligible studies that reported dose relationships of ibuprofen, diclofenac, and naproxen. We found no study which reported the dose effect of ketoprofen. The definitions of low-dose were not similar in all studies as presented in Table 4. Three studies chose the cut-off doses for ibuprofen higher than the recommended maximum OTC daily dose (1,200 mg). All studies chose the cut-off doses for diclofenac higher than the recommended maximum daily OTC dose (75 mg). Only four chose the cut-offs doses for naproxen lower than the maximum recommended daily OTC dose (600mg). The study of Schjerning Olsen *et al.* (246) did not report the adjusted hazard ratio (HR) for individual NSAIDs at low-dose and therefore is excluded in the summarised findings in Table 6.

Table 4. Study definitions of low and high dose for individual NSAIDs

Study First Author, Year	Naproxen		Ibuprofen		Diclofenac	
	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose
García-Poza, 2015 (243)	–	–	≤ 1200	> 1200	≤ 100	> 100
de Abajo, 2014 (245)	–	–	≤ 1200	> 1200	≤ 100	> 100
Schjerning Olsen, 2013 (246)	≤ 500	> 500	≤ 1200	> 1200	≤ 100	> 100
Fosbøl, 2010 (247) [¶]	≤ 500	> 500	≤ 1200	> 1200	< 100	≥ 100

Study First Author, Year	Naproxen		Ibuprofen		Diclofenac	
	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose
Ray, 2009 (248)	< 1000	≥ 1000	≤ 1600	> 1600	< 150	≥ 150
Van der Linden, 2009 (249)	–	–	≤ 1200	> 1200	≤ 100	> 100
Varas-Lorenzo 2009 (250)	≤ 1000	> 1000	≤ 1800	> 1800	≤ 100	> 100
Gislason, 2009 (251)	≤ 500	> 500	≤ 1200	> 1200	≤ 100	> 100
García Rodríguez, 2008 (133) *	≤ 750	> 750	≤ 1200	> 1200	≤ 100	> 100
Van Staa, 2008 (252)	< 1000	≥ 1000	< 1200	≥ 1200	< 150	≥ 150
Fosbøl, 2008 (253) ¶	≤ 500	> 500	≤ 1200	> 1200	< 100	≥ 100
Andersohn, 2006 (254)	≤ 750	> 750	≤ 1200	> 1200	≤ 100	> 100
Velentgas, 2006 (255)	< 1000	≥ 1000	Reference group			
Gislason, 2006 (257)	–	–	≤ 1200	> 1200	< 100	≥ 100
Ray, 2002 (258)	< 1000	≥ 1000	< 1800	≥ 1800	–	–

All dosages are in mg per day

*Dose range from 50 to 150 mg of diclofenac were also evaluated; ¶ Studies conducted in the same population

Characteristics of selected studies are described in Table 5. Fosbøl *et al.* conducted two studies in the same population in 2010 and 2008 (247) (253) with similar outcomes. We therefore reported only the more recent study in 2010. Fosbøl *et al.* (2010) (247) and Gislason *et al.* (2009) (251) used two different study designs in their studies: cohort and case-crossover. We reported only results of corresponding to cohort design due to its higher level of evidence according to PCCRP Guidelines. (259) Van Staa *et al.* (2008) (252) used two analyses, one compared current use with a control cohort, another compared current use with past use. We reported only results corresponding to analysis using a control cohort because of its higher level of evidence.

Table 5. Main characteristics of published studies about cardiovascular risk of NSAIDs with dose relationship assessment

Author, Year	Source Population Study Period	Study Population N, Age (Years)	Study Design	Outcomes	Case Validation	Exposure Assessment	Exposure Definition	Reference Category
García-Poza, 2015 (243)	BIFAP database, Spain 2001-2007	2,888 cases 20,000 controls Age 40-90	Nested case-control	Nonfatal ischemic stroke/unspecific stroke	Cases with supporting evidence Free text clinical note	Claimed prescriptions, with dose regimens	Current: EOS +30 days	Nonuse of NSAIDs
de Abajo, 2014 (245)	BIFAP database, Spain 2001-2007	3,833 cases 20,000 controls Age 40-90	Nested case-control	Nonfatal AMI	Cases with supporting evidence GPs validation 38%	Claimed prescriptions, with dose regimens	Current: EOS +30 days	Nonuse of NSAIDs
Schjerning Olsen, 2013 (246)	DNPR, Denmark 1997-2009	97,698 patients with prior MI No age limits	Cohort	CV death; Nonfatal MI/coronary death; Fatal/nonfatal stroke	PPV 93% for MI, 74-97% for fatal and nonfatal stroke	Claimed prescriptions, without dose regimens	Current: EOS Sensitive analysis + 14, 30, 90 days	Nonuse of NSAIDs
Fosbøl, 2010 (247) [¶]	DNPR, Denmark 1997-2005	1,028,427 Age ≥ 10	Cohort and case-crossover	CV death; Nonfatal MI/coronary death; Fatal/nonfatal stroke	PPV 91% for fatal and nonfatal MI, 74-97% for fatal and nonfatal stroke	Claimed prescriptions, without dose regimens	Current: EOS Any use: all current use irrespective of dose	Nonuse of NSAIDs
Ray, 2009 (248)	Tennessee Medicaid - US, Saskatchewan-Canada, GPRD- UK 1999-2004	48,566 patients with serious CHD Age 40-89	Cohort	MI/CHD death; Nonfatal MI/stroke/death	PPV 92%-96% for MI, 76%-100% for stroke	Prescriptions filled in or out-of-hospital, with dose regimens (except in Saskatchewan)	Current: EOS Indeterminate: EOS – EOS + 90 days	Nonuse of NSAIDs or current use of naproxen
Van der Linden, 2009 (249)	PHARMO Record Linkage System, Netherland	485,059 NSAIDs users No age limits	Nested case-control	AMI	Not mentioned	Outpatient prescriptions, with dose regimens	Current: EOS Recent: EOS – EOS + 60 days	Current/recent use vs. Remote use

Author, Year	Source Population Study Period	Study Population N, Age (Years)	Study Design	Outcomes	Case Validation	Exposure Assessment	Exposure Definition	Reference Category
	2001-2004						Remote: From EOS + 60 days	
Varas-Lorenzo 2009 (250)	Saskatchewan, Canada 1999-2001	364,658 Age 40-84	Nested case-control	AMI	Internal, PPV AMI 95% for code 410 and 9% for code 411	Outpatient prescriptions, without dose regimens	Current: EOS + 7 days Recent: EOS + 7 – EOS + 60 days Past: EOS + 60 – EOS + 365 days	Nonuse of NSAIDs
Gislason, 2009 (251)	DNPR, Denmark 1995-2004	107,092 patients with heart failure Age ≥ 30	Cohort Case-crossover	MI; Heart Failure; Death	High specificity but low sensitivity to identify Heart Failure	Outpatient prescriptions, without dose regimens	Current: EOS	Nonuse of NSAIDs
García Rodríguez, 2008 (133)	THIN, UK 2000-2005	716,395 Age 50-84	Nested case-control	Nonfatal AMI	90% confirmation by primary care physicians in a random sample of 500 cases	Outpatient prescriptions, with dose regimens Human whole blood assays	Current: EOS + 7 days Recent: EOS + 7 – EOS + 90 days Past: EOS + 90 – EOS + 365 days	Nonuse of NSAIDs
Van Staa, 2008 (252)	GPRD, UK 1987-2006	729,294 NSAIDs cohort and 443,047 control cohort Age ≥ 40	Cohort	MI	Not mentioned	Prescription details of GPs, with dose regimens	Current: EOS + 3 months Past: EOS + 3 months – next prescription	Control cohort of non-users Past use of NSAIDs
Fosbøl, 2008 (253) [¶]	DNPR, Denmark 1997-2005	1,028,437 Age ≥ 10	Cohort Case-crossover	Death/MI; Death alone	Not mentioned	Dispensed drug prescriptions, without dose regimens	Any use	Nonuse of NSAIDs

Author, Year	Source Population Study Period	Study Population N, Age (Years)	Study Design	Outcomes	Case Validation	Exposure Assessment	Exposure Definition	Reference Category
		Subpopulation 153,465 healthy individuals						
Andersohn, 2006 (254)	GPRD, UK 2000-2004	486,378 NSAIDs users Age ≥40	Nested case-control	AMI	Additional codes indicating the acuteness, hospital stay ≥3 days; Exclusion of multi-causes deaths	Prescription details of GPs, with dose regimens	Current: EOS + 14 days Recent: EOS + 14 - EOS + 183 days Past: EOS + 183 - EOS + 365 days	Nonuse of NSAIDs
Velentgas, 2006 (255)	UnitedHealthcare, US 1999-2001	424,584 non-aspirin NSAIDs user Age 40-64	Cohort	Nonfatal MI/ACS/sudden cardiac death; Fatal MI/CHD death	Review of patients' hospital medical records for MI and ACS National Death Index confirmation	Pharmacies claims data, with dose regimens	Current: EOS Recent: EOS - EOS + 60 days No-use: From EOS + 60	Current use of ibuprofen/d i-clofenac (all doses)
Gislason, 2006 (257)	DNPR, Denmark 1995-2002	58,432 patients with first-time MI Age ≥ 30	Cohort Case-crossover	Death/ Re-MI	Specificity for acute MI >90%	Claim prescription without dose regimens	Any use	Nonuse of NSAIDs
Ray, 2002 (258)	Tennessee Medicaid, US 1987-1998	181,441 periods of non-aspirin NSAIDs use	Cohort	MI/CHD death	PPV 92%-95% for MI, sensitivity 94%; Death certificate with no evidence of other causes	Pharmacy records with dose regimens	Current use: EOS Former: From EOS	Control cohort : Non NSAIDs users

BIFAP, Base de datos Informatizada para la Investigación Epidemiológica en Atención Primaria ; GPRD, General Practice Research Database ; DNPR, Danish National Patient Registry; THIN, The Health Improvement Network; EOS, End of supply ; AMI, Acute Myocardial Infarction ; Re-MI, Recurrent Myocardial Infarction ; CHD, Coronary Heart Disease ; CV, Cardiovascular; GP, General Practitioner ; UK, United Kingdom; US, United States.

¶ Studies conducted in the same population

Table 6. Results summary of published studies about cardiovascular risk of NSAIDs with dose relationship assessment

Author, Year	Design	Outcomes	Drug	Dose	Events/ exposure	Relative risk	95% CI
García-Poza, 2015 (243)	Nested case-control	Nonfatal ischemic stroke	Ibuprofen	≤ 1200	42	0.97	0.69 – 1.37
			Ibuprofen	> 1200	37	0.92	0.64 – 1.32
			Diclofenac	≤ 100	32	1.37	0.92 – 2.03
			Diclofenac	> 100	30	1.62	1.06 – 2.46
de Abajo, 2014 (245)	Nested case-control	Nonfatal AMI	Ibuprofen	≤ 1200	38	0.90	0.62 – 1.30
			Ibuprofen	> 1200	44	0.77	0.55 – 1.07
			Diclofenac	≤ 100	36	0.91	0.69 – 1.19
			Diclofenac	> 100	28	1.00	0.62 – 1.65
Fosbøl, 2010 (247) ¶	Cohort	CV death	Ibuprofen	≤ 1200	362	0.79	0.71 – 0.87
			Ibuprofen	> 1200	91	1.63	1.32 – 2.00
			Diclofenac	≤ 100	56	0.80	0.62 – 1.05
			Diclofenac	> 100	162	1.46	1.25 – 1.70
			Naproxen	≤ 500	50	0.84	0.64 – 1.11
			Naproxen	> 500	12	0.92	0.52 – 1.62
Fosbøl, 2010 (247) ¶	Cohort	Nonfatal MI or coronary death	Ibuprofen	≤ 1200	394	1.24	1.12 – 1.37
			Ibuprofen	> 1200	71	1.94	1.54 – 2.45
			Diclofenac	≤ 100	66	1.39	1.09 – 1.77
			Diclofenac	> 100	163	2.10	1.81 – 2.45
			Naproxen	≤ 500	61	0.69	0.51 – 0.93
			Naproxen	> 500	9	1.22	0.75 – 2.00
Fosbøl, 2010 (247) ¶	Cohort	Fatal or nonfatal stroke	Ibuprofen	≤ 1200	348	1.39	1.24 – 1.54
			Ibuprofen	> 1200	64	2.22	1.74 – 2.84
			Diclofenac	≤ 100	51	1.33	1.00 – 1.75
			Diclofenac	> 100	144	2.41	2.04 – 2.84
			Naproxen	≤ 500	49	1.55	1.17 – 2.05

Author, Year	Design	Outcomes	Drug	Dose	Events/ exposur e	Relativ e risk	95% CI
Ray, 2009 (248)	Cohort (vs. nonuse)	MI or CHD death	Naproxen	> 500	10	1.48	0.80 – 2.76
			Ibuprofen	≤ 1600	23	0.99	0.66 – 1.50
			Ibuprofen	> 1600	37	1.35	0.97 – 1.87
			Diclofenac	≤ 150	27	1.65	1.13 – 2.42
			Diclofenac	> 150	20	0.97	0.62 – 1.50
			Naproxen	≤ 1000	16	1.22	0.74 – 1.99
			Naproxen	> 1000	33	0.78	0.55 – 1.10
Ray, 2009 (248)	Cohort (vs. naproxen ≥1000 mg)	MI or CHD death	Ibuprofen	≤ 1600	23	1.27	0.75 – 2.17
			Ibuprofen	> 1600	37	1.73	1.08 – 2.76
			Diclofenac	≤ 150	27	2.12	1.27 – 3.53
			Diclofenac	> 150	20	1.24	0.71 – 2.17
Ray, 2009 (248)	Cohort (vs. nonuse)	MI or stroke or death from any cause	Ibuprofen	≤ 1600	102	1.13	0.92 – 1.37
			Ibuprofen	> 1600	112	1.14	0.95 – 1.38
			Diclofenac	≤ 150	81	1.43	1.14 – 1.78
			Diclofenac	> 150	89	1.34	1.09 – 1.65
			Naproxen	≤ 1000	49	1.06	0.80 – 1.40
			Naproxen	> 1000	114	0.85	0.71 – 1.03
Ray, 2009 (248)	Cohort (vs. naproxen ≥1000 mg)	MI or stroke or death from any cause	Ibuprofen	≤ 1600	102	1.32	1.01 – 1.72
			Ibuprofen	> 1600	112	1.34	1.03 – 1.74
			Diclofenac	≤ 150	81	1.67	1.25 – 2.23
			Diclofenac	> 150	89	1.57	1.19 – 2.07
Van der Linden, 2009 (249)	Nested case- control	AMI	Ibuprofen	≤ 1200	-	1.51	1.06 – 2.14
			Ibuprofen	> 1200	-	1.66	0.92 – 3.00
			Diclofenac	≤ 100	-	1.13	0.79 – 1.61

Author, Year	Design	Outcomes	Drug	Dose	Events/ exposur e	Relativ e risk	95% CI
Varas- Lorenzo 2009 (250)	Nested case- control	AMI	Diclofenac	> 100	-	1.75	1.29 – 2.38
			Ibuprofen	≤ 1800	5	0.63	0.21 – 1.80
			Ibuprofen	> 1800	3	3.69	0.84 – 16.31
			Diclofenac	≤ 100	27	1.29	0.78 – 2.13
			Diclofenac	> 100	20	0.63	0.37 – 1.08
			Naproxen	≤ 1000	6	0.62	0.24 – 1.59
			Naproxen	> 1000	8	2.10	0.79 – 5.36
Gislason, 2009 (251)	Cohort	Death	Ibuprofen	≤ 1200	–	0.99	0.94 – 1.04
			Ibuprofen	> 1200	–	2.83	2.64 – 3.02
			Diclofenac	≤ 100	–	1.31	1.20 – 1.42
			Diclofenac	> 100	–	5.54	5.08 – 6.03
			Naproxen	≤ 500	–	0.88	0.73 – 1.05
			Naproxen	> 500	–	1.97	1.64 – 2.36
Gislason, 2009 (251)	Cohort	AMI	Ibuprofen	≤ 1200	–	1.31	1.15 – 1.48
			Ibuprofen	> 1200	–	1.47	1.02 – 2.10
			Diclofenac	≤ 100	–	1.14	0.91 – 1.43
			Diclofenac	> 100	–	2.43	1.74 – 3.40
			Naproxen	≤ 500	–	1.47	1.02 – 2.10
			Naproxen	> 500	–	1.62	0.97 – 2.72
García Rodríguez, 2008 (133)	Nested case- control	Nonfatal AMI	Ibuprofen	≤ 1200	120	1.00	0.80 – 1.25
			Ibuprofen	> 1200	23	1.56	0.90 – 2.71
			Diclofenac	≤ 100	141	1.51	1.20 – 1.89
			Diclofenac	> 100	212	1.80	1.49 – 2.18
			Diclofenac	50	–	1.12	0.57 – 2.19
			Diclofenac	75	–	1.31	0.80 – 2.16
			Diclofenac	100	–	1.65	1.26 – 2.18
			Diclofenac	150	–	1.80	1.49 – 2.18
			Naproxen	≤ 750	17	0.90	0.50 – 1.60

Author, Year	Design	Outcomes	Drug	Dose	Events/ exposur e	Relativ e risk	95% CI
Van Staa, 2008 (252)	Cohort	MI	Naproxen	> 750	37	1.12	0.74 – 1.69
			Ibuprofen	< 1200	176	1.05	0.91 – 1.22
			Ibuprofen	1200	600	1.02	0.94 – 1.11
			Ibuprofen	1200- 2400	146	1.22	1.03 – 1.44
			Ibuprofen	≥ 2400	10	1.96	1.05 – 3.65
			Diclofenac	< 150	675	1.13	1.04 – 1.22
			Diclofenac	150	650	1.28	1.18 – 1.39
			Diclofenac	150-300	35	1.18	0.85 – 1.65
			Diclofenac	≥ 300	10	2.03	1.09 – 3.77
			Naproxen	< 1000	155	0.99	0.85 – 1.17
			Naproxen	1000	250	1.12	0.98 – 1.27
			Naproxen	> 1000	10	0.92	0.49 – 1.71
Fosbøl, 2008 (253) ¶	Cohort	Death or MI	Ibuprofen	≤ 1200	1059	0.92	0.86 – 0.97
			Ibuprofen	> 1200	244	1.84	1.62 – 2.08
			Diclofenac	≤ 100	174	1.05	0.90 – 1.21
			Diclofenac	> 100	541	1.99	1.83 – 2.17
			Naproxen	≤ 500	137	0.90	0.76 – 1.06
			Naproxen	> 500	41	1.28	0.95 – 1.74
Andersohn , 2006 (254)	Nested case- control	AMI or CHD death	Ibuprofen	≤ 1200	173	0.99	0.81 – 1.21
			Ibuprofen	> 1200	28	1.14	0.74 – 1.77
			Diclofenac	≤ 100	148	1.31	1.06 – 1.62
			Diclofenac	> 100	245	1.35	1.13 – 1.61
			Naproxen	≤ 750	33	1.19	0.79 – 1.80
			Naproxen	> 750	26	1.05	0.66 – 1.66
Velentgas, 2006 (255)	Cohort	Confirmed MI/ACS	Naproxen	< 1000	14	0.75	0.44 – 1.30
			Naproxen	1000	113	0.99	0.78 – 1.27

Author, Year	Design	Outcomes	Drug	Dose	Events/ exposur e	Relativ e risk	95% CI
Gislason, 2006 (257)	Cohort	Death	Naproxen	> 1000	20	0.67	0.42 – 1.07
			Ibuprofen	≤ 1200	47	0.75	0.61 – 0.92
			Ibuprofen	> 1200	219	2.20	1.95 – 2.48
			Diclofenac	≤ 100	28	0.89	0.66 – 1.20
			Diclofenac	> 100	132	4.44	3.79 – 5.19
Gislason, 2006 (257)	Cohort	Re-MI	Ibuprofen	≤ 1200	77	1.28	1.03 – 1.60
			Ibuprofen	> 1200	59	1.22	0.99 – 1.51
			Diclofenac	≤ 100	40	1.27	0.92 – 1.76
			Diclofenac	> 100	21	1.89	1.40 – 2.55
Ray, 2002 (258)	Cohort	MI or CHD death	Ibuprofen	< 1800	108	0.95	0.78 – 1.15
			Ibuprofen	≥ 1800	231	1.27	1.11 – 1.45
			Naproxen	< 1000	57	0.83	0.64 – 1.09
			Naproxen	≥ 1000	144	1.00	0.84 – 1.18

AMI, Acute Myocardial Infarction; Re-MI, Recurrent Myocardial Infarction; CHD, Coronary Heart Disease; CV, Cardiovascular

Studies that report duration effect

After reviewing all obtained articles, we found 9 studies that reported duration relationships of ibuprofen, diclofenac, and naproxen. All of these studies were conducted in databases. The main characteristics of identified studies are summarized in Table 7, and their results are in Table 8.

Table 7. Main characteristics of published studies about cardiovascular risk of NSAIDs with duration of exposure assessment

Study First Author, Year	Source Population Study Period	Population, N, Age (Years)	Design	Outcome	NSAIDs studied	Exposure definition	Duration of exposure	Reference Category
García-Poza, 2015 (243)	BIFAP database, Spain 2001-2007	2,888 cases Age 40-90	Nested case-control	Nonfatal ischemic stroke	Diclofenac, ibuprofen	Current: EOS +30 days	<31, 31 - 365, >365 days	Nonuse of NSAIDs
Chuang, 2015 (244)	NHIRD, Taiwan 2005 and 2010	1,653 cases with hypertension	Case-crossover	Stroke, ischemic stroke, hemorrhagic stroke	Diclofenac, ibuprofen, Naproxen	Exposure within 30 days before events	30 days	Control period: 91-120 days before event
de Abajo, 2014 (245)	BIFAP database, Spain 2001-2007	3,833 cases 20,000 controls Age 40-90	Nested case-control	Nonfatal AMI	Diclofenac, ibuprofen	Current: EOS +30 days	<31, 31 - 365, >365 days	Nonuse of NSAIDs
Schjerning Olsen, 2011 (149)	DNPR, Denmark 1997-2006	83,677 patients with prior MI Age ≥ 30	Cohort	Death; Death/re-MI	Diclofenac, ibuprofen, Naproxen	Current: EOS	0-7, 7-14, 14-30, 30-90, >90 days	Nonuse of NSAIDs
Ray, 2009 (248)	Tennessee Medicaid - US, Saskatchewan-Canada, GPRD- UK 1999-2004	48,566 patients with serious CHD Age 40-89	Cohort	MI , CHD death	Diclofenac, ibuprofen, Naproxen	Current: EOS Indeterminate: EOS to EOS + 90 days	< 90, 90-364, ≥365 days	Nonuse of NSAIDs or current use of naproxen
Varas-Lorenzo, 2009 (250)	Saskatchewan, Canada 1999-2001	364,658 Age 40-84	Nested case-control	AMI	Diclofenac, ibuprofen, Naproxen	Current: EOS + 7 days Recent: EOS + 7 to EOS + 60 days;	0-30, >30 days	Nonuse of NSAIDs

Study First Author, Year	Source Population Study Period	Population, N, Age (Years)	Design	Outcome	NSAIDs studied	Exposure definition	Duration of exposure	Reference Category
						Past: EOS + 60 to EOS + 365 days		
Andersohn, 2006 (254)	GPRD, UK 2000-2004	486,378 NSAIDs users Age ≥40	Nested case-control	AMI	Diclofenac, ibuprofen, Naproxen	Current: EOS + 14 days Recent: EOS + 14 to EOS + 183 days Past: EOS + 183 to EOS + 365 days	< 3, 3-12, > 12 months	Nonuse of NSAIDs
Velentgas, 2006 (255)	UnitedHealthcare, US 1999-2001	424,584 non-aspirin NSAIDs user Age 40-64	Cohort	Nonfatal MI, ACS, sudden or cardiac death; Fatal MI or CHD death	Diclofenac, ibuprofen, Naproxen	Current: EOS Recent: EOS to EOS + 60 days	0-30, 31-60, 61-90, >90 days	Current use of Ibuprofen/diclofenac (all doses)
García Rodríguez, 2005 (256)	GPRD, UK 1997-2000	4,975 cases 20,000 controls Age	Nested case-control	AMI	Diclofenac, ibuprofen, Naproxen	Current: EOS + 30 days Recent: EOS + 30 to EOS + 180 days Past: EOS + 180 days to EOS + 2 years	0-30, 31-365, >365 days	Nonuse of NSAIDs

BIFAP, Base de datos Informatizada para la Investigación Epidemiológica en Atención Primaria ; GPRD, General Practice Research Database ; DNPR, Danish National Patient Registry; THIN, The Health Improvement Network; NHIRD, National Health Institute Research Database ; EOS, End of supply ; AMI, Acute Myocardial Infarction ; Re-MI, Recurrent Myocardial Infarction ; CHD, Coronary Heart Disease ; CV, Cardiovascular; GP, General Practitioner ; UK, United Kingdom; US, United States.

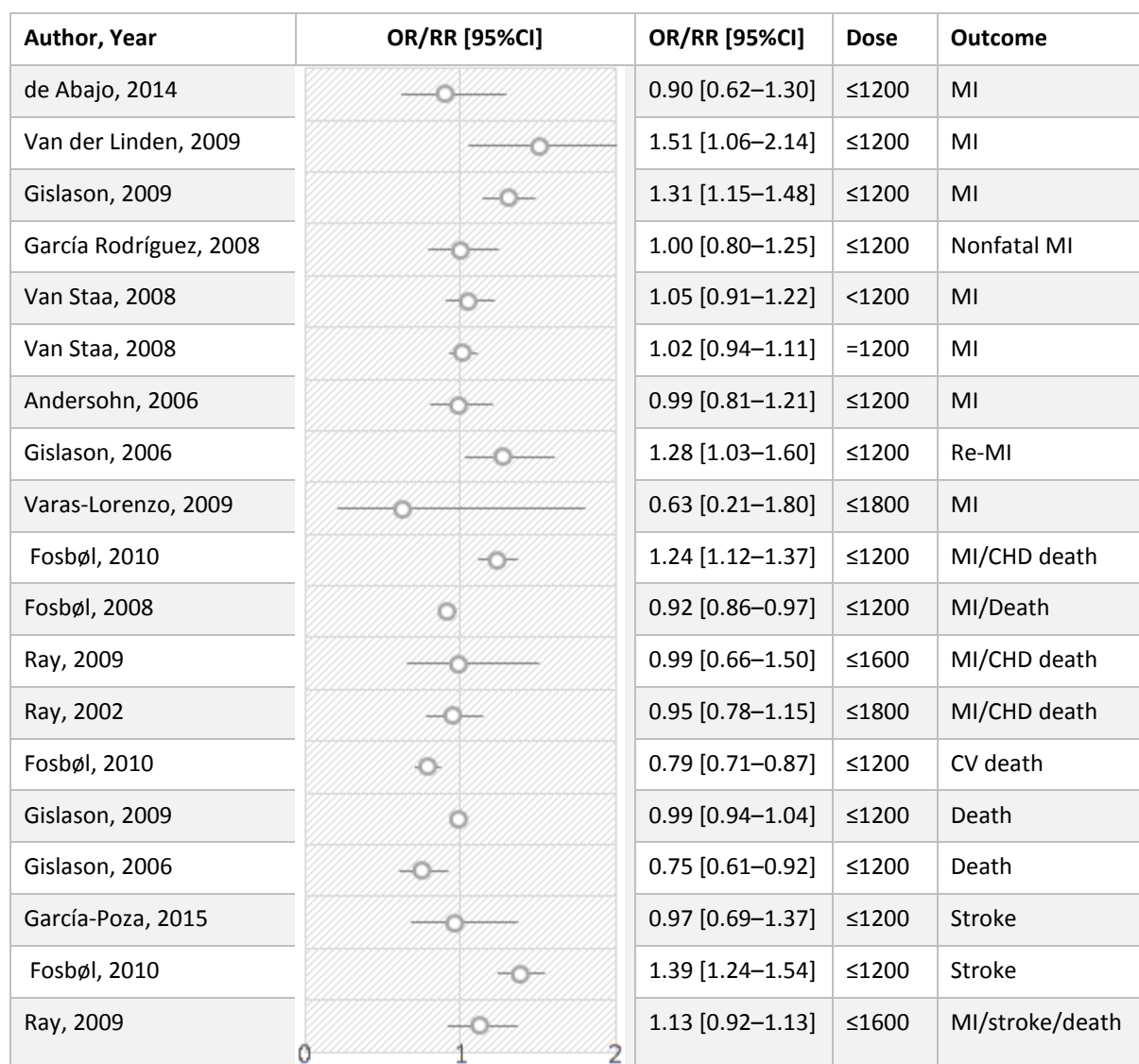
Table 8. Results summary of studies about cardiovascular risk of NSAIDs with duration of exposure assessment

Author, Year	Design	Outcomes	Drug	Duration (days)	Events/ exposure	Adjusted RR/OR/HR	95% CI
García-Poza, 2015 (243)	Nested case-control	Nonfatal ischemic stroke	Ibuprofen	< 31	53	0.89	0.65 – 1.20
			Ibuprofen	31–365	38	0.90	0.63 – 1.29
			Diclofenac	< 31	39	1.60	1.11 – 2.32
			Diclofenac	31–365	24	1.02	0.65 – 1.61
Chuang, 2015 (244)	Case-crossover	Stroke	Ibuprofen	≤ 30	69	0.91	0.61 – 1.37
			Diclofenac	≤ 30	217	1.43	1.10 – 1.87
			Naproxen	≤ 30	19	1.55	0.61 – 3.96
Chuang, 2015 (244)	Case-crossover	Ischemic stroke	Ibuprofen	≤ 30	59	0.99	0.63 – 1.54
			Diclofenac	≤ 30	181	1.48	1.10 – 1.98
			Naproxen	≤ 30	16	1.54	0.56 – 4.26
Chuang, 2015 (244)	Case-crossover	Hemorrhagic stroke	Ibuprofen	≤ 30	10	0.73	0.25 – 2.19
			Diclofenac	≤ 30	36	1.33	0.67 – 2.62
			Naproxen	≤ 30	3	1.76	0.14 – 21.49
de Abajo, 2014 (245)	Nested case-control	Nonfatal AMI	Ibuprofen	0-30	70	0.91	0.69 – 1.19
			Ibuprofen	31–365	48	1.00	0.72 – 1.39
			Diclofenac	0-30	34	1.02	0.69 – 1.51
			Diclofenac	31–365	23	0.93	0.58 – 1.49
Schjerning Olsen, 2011 (149)	Cohort	Death/Re-MI	Ibuprofen	0–7	–	1.04	0.83 – 1.30
			Ibuprofen	7–14	–	1.50	1.24 – 1.82
			Ibuprofen	14–30	–	1.33	1.15 – 1.53
			Ibuprofen	30–90	–	1.70	1.55 – 1.87
			Ibuprofen	> 90	–	1.53	1.40 – 1.69
			Diclofenac	0–7	–	3.26	2.75 – 3.86
			Diclofenac	7–14	–	2.12	1.69 – 2.67
			Diclofenac	14–30	–	1.67	1.38 – 2.02
			Diclofenac	30–90	–	2.15	1.86 – 2.48
			Diclofenac	> 90	–	1.92	1.66 – 2.22
			Naproxen	0–7	–	1.76	1.04 – 2.98
			Naproxen	7–14	–	1.21	0.63 – 2.32
			Naproxen	14–30	–	1.20	0.74 – 1.93
			Naproxen	30–90	–	1.15	0.80 – 1.65
			Naproxen	> 90	–	1.50	0.10 – 2.05

Author, Year	Design	Outcomes	Drug	Duration (days)	Events/ exposure	Adjusted RR/OR/HR	95% CI
Ray, 2009 (248)	Cohort	MI, CHD death	Ibuprofen	< 90	21	1.67	1.1 – 2.6
			Ibuprofen	90–364	17	0.96	0.6 – 1.5
			Diclofenac	< 90	19	1.86	1.2 – 2.9
			Diclofenac	90–364	15	1.21	0.7 – 2.0
			Naproxen	< 90	12	0.88	0.5 – 1.5
			Naproxen	90–364	15	0.76	0.5 – 1.3
Varas- Lorenzo, 2009 (250)	Nested case- control	AMI	Ibuprofen	0–30	12	2.49	1.12 – 5.53
			Ibuprofen	>30	8	1.00	0.41 – 2.42
			Diclofenac	0–30	24	1.38	0.80 – 2.34
			Diclofenac	>30	47	0.90	0.62 – 1.30
			Naproxen	0–30	13	2.84	1.43 – 5.63
			Naproxen	>30	14	1.04	0.54 – 1.99
Andersohn, 2006 (254)	Nested case- control	AMI, CHD death	Ibuprofen	< 90	131	0.97	0.62 – 1.52
			Ibuprofen	91–365	44	0.87	0.61 – 1.22
			Diclofenac	< 90	196	1.27	1.04 – 1.55
			Diclofenac	91–365	113	1.20	0.95 – 1.53
			Naproxen	< 90	25	0.97	0.61 – 1.53
			Naproxen	91–365	19	1.37	0.79 – 2.38
Velentgas, 2006 (255)	Cohort	Confirmed ACS/MI	Ibuprofen/ Diclofenac	31–60	35	0.78	0.51 – 1.17
			Ibuprofen/ Diclofenac	61–90	15	0.74	0.42 – 1.29
			Ibuprofen/ Diclofenac	>90	36	0.89	0.59 – 1.34
			Naproxen	0–30	69	1.01	0.72 – 1.42
			Naproxen	31–60	32	0.62	0.40 – 0.94
			Naproxen	61–90	14	0.62	0.35 – 1.11
			Naproxen	>90	34	0.83	0.54 – 1.26
García Rodríguez, 2005 (256)	Nested case- control	AMI	Ibuprofen	0–30	–	1.04	0.78 – 1.40
			Ibuprofen	31–365	–	1.04	0.78 – 1.39
			Diclofenac	0–30	–	0.99	0.73 – 1.35
			Diclofenac	31–365	–	1.19	0.92 – 1.53
			Naproxen	0–30	–	0.95	0.52 – 1.75
			Naproxen	31–365	–	0.85	0.52 – 1.40

RR, Relative risk; OR, Odd ratio, HR, hazard ratio

AMI, Acute Myocardial Infarction; Re-MI, Recurrent Myocardial Infarction; CHD, Coronary Heart Disease; CV, Cardiovascular



AMI, Acute Myocardial Infarction; Re-MI, Recurrent Myocardial Infarction; CHD, Coronary Heart Disease; CV, Cardiovascular

Figure 3. Summary of results of observational studies about cardiovascular risk associated with low-dose ibuprofen relative to NSAIDs nonuse

Cardiovascular risk associated with ibuprofen in OTC-like conditions

Low-dose

For myocardial infarction outcome alone, the RR/OR ranged from 0.63 to 1.51. Three studies found significant increase of MI risk related with low-dose ibuprofen: 1.51 [1.06–2.14] (249), 1.31 [1.15–1.48] (251) and 1.28 [1.03–1.60] (257). No study found significant protective effect against MI (Figure 3).

For the composite of outcomes MI and CHD death, one study found a significant increase of risk: RR 1.24 [1.12–1.37]. (247) Also, no study found significant protective effect (Figure 3).

For the death outcomes (death, CHD death and CV death), studies found a slight protective effect of low-dose ibuprofen : 0.79 [0.71–0.87] (247), 0.75 [0.61–0.92] (257), 0.99 [0.94–1.04] (251) (Figure 3).

For stroke outcome, two studies found different results: RR 1.39 [1.24–1.54] (247) and OR 0.97 [0.69–1.37] (243) (Figure 3).

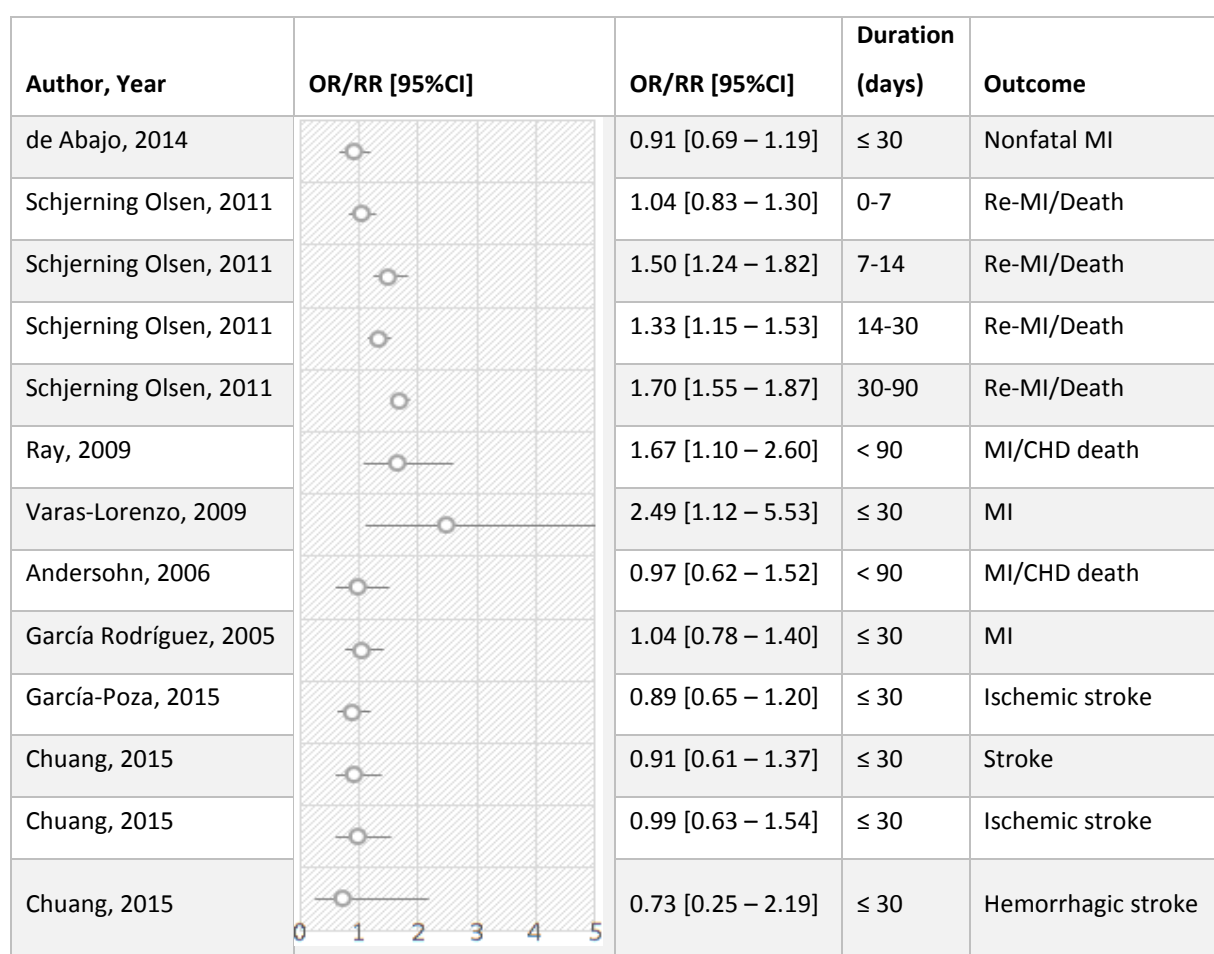


Figure 4. Summary of results of observational studies about cardiovascular risk associated with short term use of ibuprofen relative to NSAIDs nonuse

Short term

For MI/Re-MI or the composite of MI and death/CHD death outcome, findings were not consistent, RRs/ORs ranged from 0.91 to 2.49. Schjerning Olsen *et al.* (149) found increase of risk from the second week. Varas-Lorenzo *et al.* (250) found OR 2.49 [1.12 – 5.53] for 0-30 days of use. Risk of stroke did not increase in any study (Figure 4).

Cardiovascular risk associated with diclofenac in OTC-like conditions

Low-dose

The risk of MI alone associated with low-dose diclofenac ranged from 0.91 to 1.80. García Rodríguez (2008) (133) demonstrated a clear dose-dependent effect: MI risk increased from 1.12 to 1.80 with dose 50 to 150 mg. Andersohn *et al.* (254) also found a significant increase with dose ≤ 100 mg (1.31 [1.06–1.62]) (Figure 7). Ray *et al.* (248) found significant risk of MI/CHD death with dose ≤ 150 mg (1.43 [1.14–1.78]). Using the same cut off dose, Fosbøl *et al.* (247) found an increase of MI/CHD death risk of 1.39 [1.09–1.77]. Risk of stroke were found to be around 1.3 in two studies: 1.33 [1.00 – 1.75] (247) and 1.37 [0.92 – 2.03] (243) (Figure 5).

Author, Year	OR/RR [95%CI]	OR/RR [95%CI]	Dose	Outcome
Van der Linden, 2009		1.13 [0.79 – 1.61]	≤ 100	MI
Gislason, 2009		1.14 [0.91 – 1.43]	≤ 100	MI
Van Staa, 2008		1.13 [1.04 – 1.22]	< 150	MI
Varas-Lorenzo 2009		1.29 [0.78 – 2.13]	≤ 100	MI
de Abajo, 2014		0.91 [0.69 – 1.19]	≤ 100	Nonfatal MI
García Rodríguez, 2008		1.51 [1.20 – 1.89]	≤ 100	Nonfatal MI
García Rodríguez, 2008		1.12 [0.57 – 2.19]	50	Nonfatal MI
García Rodríguez, 2008		1.31 [0.80 – 2.16]	75	Nonfatal MI
García Rodríguez, 2008		1.65 [1.26 – 2.18]	100	Nonfatal MI
García Rodríguez, 2008		1.80 [1.49 – 2.18]	150	Nonfatal MI
Gislason, 2006		1.27 [0.92 – 1.76]	≤ 100	Re-MI
Fosbøl, 2008		1.05 [0.90 – 1.21]	≤ 100	MI/Death
Andersohn, 2006		1.31 [1.06 – 1.62]	≤ 100	MI
Ray, 2009		1.43 [1.14 – 1.78]	≤ 150	MI/stroke/death
Fosbøl, 2010		1.39 [1.09 – 1.77]	≤ 150	MI/CHD death
Fosbøl, 2010		0.80 [0.62 – 1.05]	≤ 100	CV death
Gislason, 2009		1.31 [1.20 – 1.42]	≤ 100	Death
Gislason, 2006		0.89 [0.66 – 1.20]	≤ 100	Death
Fosbøl, 2010		1.33 [1.00 – 1.75]	≤ 100	Fatal/nonfatal stroke
García-Poza, 2015		1.37 [0.92 – 2.03]	≤ 100	Nonfatal ischemic stroke

Figure 5. Summary of results of observational studies about cardiovascular risk associated with low-dose diclofenac relative to NSAIDs nonuse

Short term

Most studies reported early increase of cardiovascular risk (both MI and stroke) associated with the use of diclofenac. In particular, Schjerning Olsen *et al.* (149) found increases of Re-MI/Death risk in the first week and during all time of use (Figure 6).

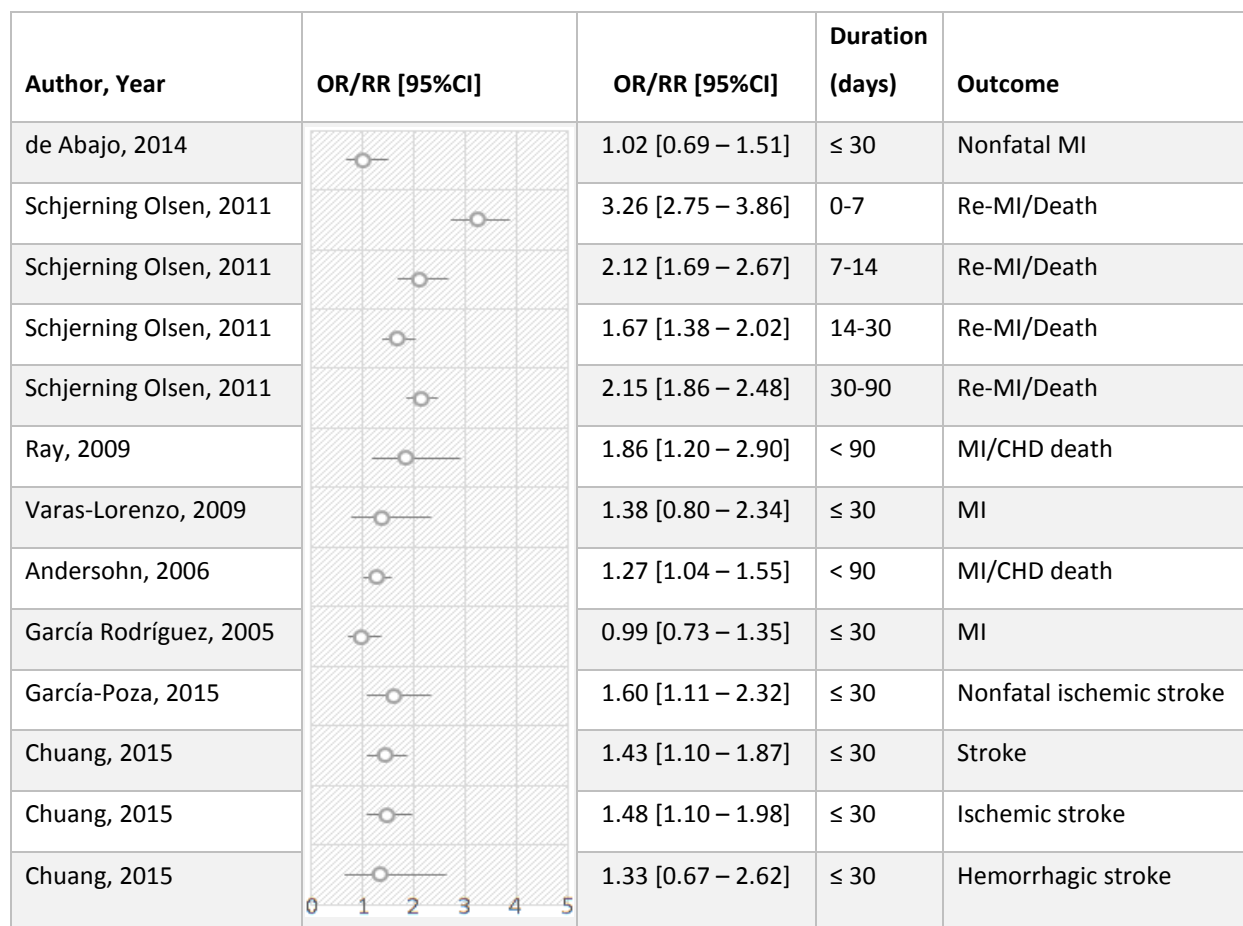
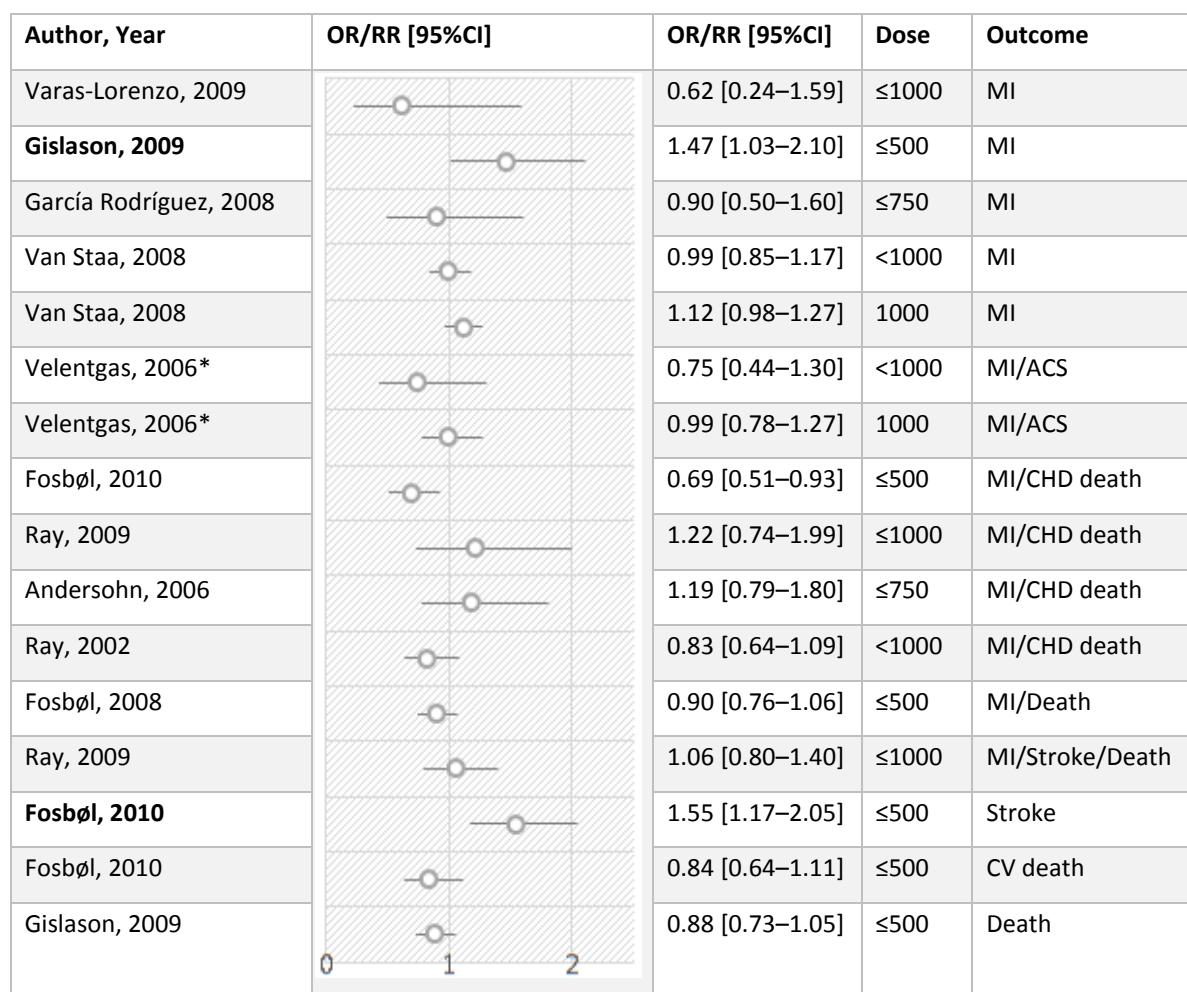


Figure 6. Summary of results of observational studies about cardiovascular risk associated with short term use of diclofenac relative to NSAIDs nonuse

Cardiovascular risk associated with naproxen in OTC-like conditions

Low-dose



* Reference: current use of ibuprofen/diclofenac (all doses)

Figure 7. Summary of results of observational studies about cardiovascular risk associated with low-dose naproxen

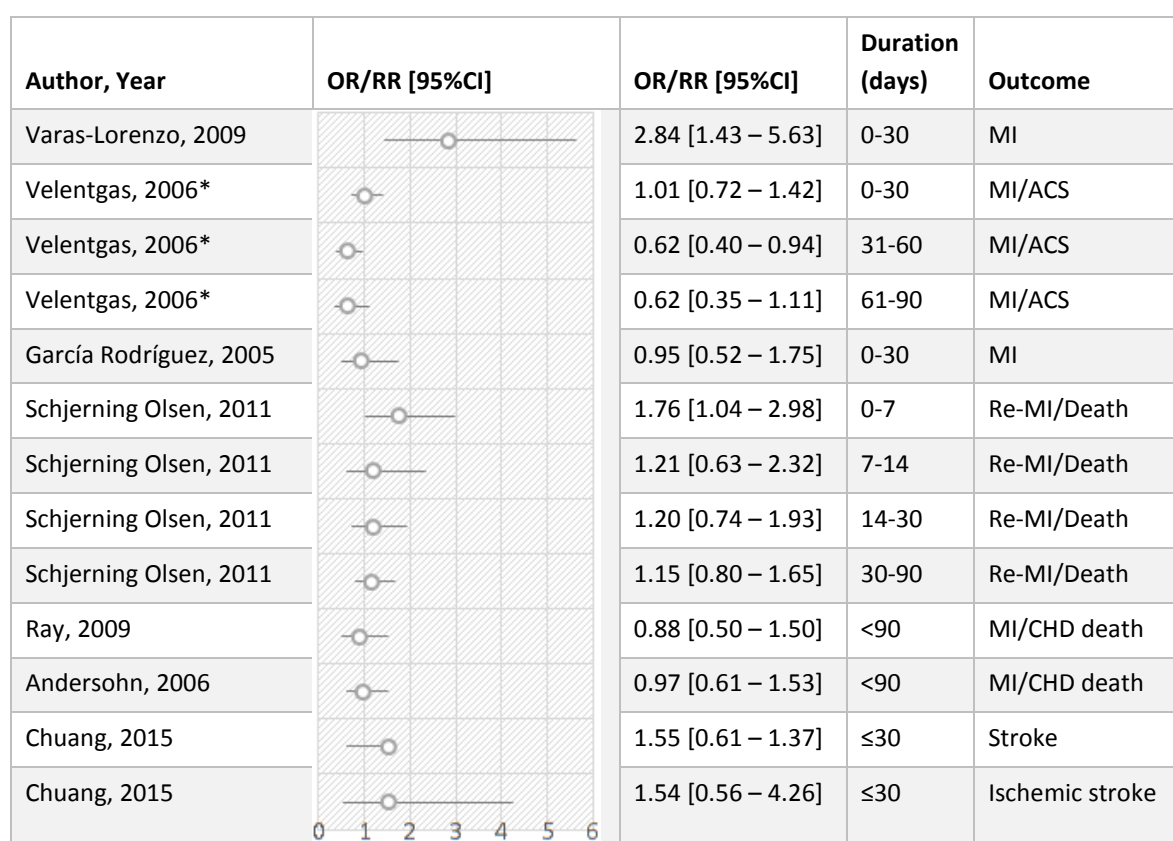
Low-dose naproxen was not associated with increase of MI risk in most of studies, except for the study of Gislason *et al.* (251) who, in their cohort study of patients with chronic heart failure (RR 1.47[1.03–2.10]), showed a protective effect of low-dose naproxen on risk of death/CHD death (Figure 7).

Only one study that of Fosbøl *et al.* (247) reported the risk of stroke associated to low-dose naproxen, but their results were inconsistent between the two different analyses they used. We present only the results of the sex-, age- and time-matched analysis of initiators and non-NSAID initiators which found an increase of risk of stroke risk (HR 1.55 [1.17–2.05]). The other analysis

with sex-, age- and calendar year showed a protective effect of low-dose naproxen: 0.89 [0.67 – 1.18] (247) (Figure 7).

Short term

Varas-Lorenzo *et al.* (250) reported an early increase of MI risk in the first month of use (OR 2.84[1.43 – 5.63]) and Schjerning Olsen *et al.* (149) also found an increased Re-MI/Death risk in the first week (HR 1.76 [1.04 – 2.98]). Uses beyond 30 days were not related with an increase of cardiovascular risk. Only one case-crossover study (244) reported stroke risk associated with short term naproxen use, which found an increase of stroke and ischemic stroke risk, although not significant (Figure 8).



* Reference: current use of ibuprofen/diclofenac (all doses)

Figure 8. Summary of results of observational studies about cardiovascular risk associated with short term use of naproxen

Effect of concomitant aspirin use

Among studies identified, there was no study that presented analysis results in patients using aspirin concomitantly with low-dose/short term diclofenac/ibuprofen/naproxen. We therefore carried out an additional search without the restriction on dose and duration analysis and found

five studies that reported the effect of aspirin concomitant use with ibuprofen, diclofenac or naproxen; the results are shown in Table 9.

Table 9. Effect of concomitant aspirin use on the cardiovascular risk associated with ibuprofen, diclofenac and naproxen

Author, Year	Design	Outcomes	Drug	Reference group	Events/ exposure	RR/OR/HR	95% CI
García-Poza, 2015 (243)	Nested case-control	Nonfatal ischemic stroke	Ibuprofen + LDA	Nonuse	30	1.39	0.86 – 2.22
			Ibuprofen alone		76	0.83	0.64 – 1.08
			Diclofenac+ LDA		22	2.07	1.18 – 3.62
			Diclofenac alone		63	1.43	1.07 – 1.93
de Abajo, 2014 (245)	Nested case-control	Nonfatal MI	Ibuprofen + LDA	Nonuse	21	0.70	0.40 – 1.22
			Ibuprofen alone		108	0.94	0.75 – 1.18
			Diclofenac+ LDA		17	1.55	0.82 – 2.95
			Diclofenac alone		62	1.12	0.83 – 1.51
García Rodríguez, 2008 (133)	Nested case-control	MI	Aspirin alone	Nonuse	–	1.04	0.96 – 1.12
			Ibuprofen + aspirin		–	1.22	0.83 – 1.78
			Ibuprofen alone		–	1.02	0.80 – 1.32
			Diclofenac + aspirin		–	1.41	1.03 – 1.93
			Diclofenac alone		–	1.79	1.52 – 2.12
			Naproxen + aspirin		–	1.26	0.60 – 2.62
			Naproxen alone		–	1.00	0.68 – 1.47
García Rodríguez, 2004 (172)	Nested case-control	MI	Ibuprofen + aspirin	Aspirin alone	46	1.08	0.74 – 1.58
			Diclofenac+ aspirin		57	1.16	0.82 – 1.65
			Naproxen + aspirin		14	0.96	0.49 – 1.86
MacDonald, 2003 (171)	Cohort	CV mortality	Ibuprofen + LDA	Aspirin alone	39	1.73	1.05 – 2.84
			Diclofenac + LDA		44	0.80	0.49 – 1.31
		All-cause mortality	Ibuprofen + LDA	Aspirin alone	62	1.93	1.30 – 2.87
			Diclofenac + LDA		60	0.82	0.54 – 1.25

LDA, low-dose aspirin

García Rodríguez *et al.* (133) found a slight increase of MI risk associated with ibuprofen-aspirin and naproxen-aspirin concomitant use compared to NSAID alone or aspirin alone. However, the increases of risk were not significant. On the contrary, the concomitant use of diclofenac and

aspirin did not increase the risk compared to diclofenac alone Table 9. This finding is not consistent with that of de Abajo *et al.* (245)

There were two studies that compared the concomitant use of ibuprofen and low-dose aspirin with the use of low-dose aspirin alone. MacDonald *et al.* (171) found an increase of both cardiovascular mortality and all-cause mortality in patients taking ibuprofen plus low-dose aspirin (HR 1.73, 1.05– 2.84 and 1.93, 1.30– 2.87 respectively). García Rodríguez *et al.*, (172) however, did not find significant interaction of those two drugs. Both studies (171,172) also evaluate the interaction of diclofenac and low-dose aspirin; no significant increase of MI risk (172) or CV mortality/ all-cause mortality was found.(171)

García-Poza *et al.* (243) found an increase of stroke risk in patients using ibuprofen with low-dose aspirin (OR 1.39, 0.86–2.22) compared with ibuprofen alone (OR 0.83, 0.64–1.08).

Quality assessment

We use the Newcastle-Ottawa scale to evaluate quality of cohort and case-control studies. We exclude the case crossover studied in the quality assessment because the Newcastle-Ottawa scale is not designed to evaluate the quality of crossover designs.

Table 10. Quality assessment of cohort and case-control studies about cardiovascular risk of NSAIDs in OTC-like conditions

Study First Author	Year	Design	Exposure/			
			Selection (max. 4)	Comparability (max. 2)	Outcome (max. 3)	Total (max. 9)
García-Poza (243)	2015	Nested case-control	* * *	* *	* *	7
de Abajo (245)	2014	Nested case-control	* * *	* *	* *	7
Van der Linden (249)	2009	Nested case-control	*	* *	* *	5
Varas-Lorenzo (250)	2009	Nested case-control	* * *	*	*	5
García Rodríguez (133)	2008	Nested case-control	* * *	* *	* *	7
Andersohn (254)	2006	Nested case-control	* * *	* *	* *	7
García Rodríguez (256)	2005	Nested case-control	* * *	* *	* *	7
Schjerning Olsen (149)	2011	Cohort	* * *	* *	* *	7
Fosbøl (247) [¶]	2010	Cohort	* * * *	* *	* * *	9

Study First Author	Year	Design	Exposure/			
			Selection (max. 4)	Comparability (max. 2)	Outcome (max. 3)	Total (max. 9)
Ray (248)	2009	Cohort	* * *	* *	* * *	8
Gislason (251)	2008	Cohort	* * *	* *	* *	7
Van Staa (252)	2008	Cohort	* * *	* *	* * *	8
Fosbøl (253) [¶]	2008	Cohort	* * * *	* *	* * *	9
Velentgas (255)	2006	Cohort	* * * *	* *	* *	9
Gislason (257)	2006	Cohort	* * *	* *	* *	7
Ray (258)	2002	Cohort	* * * *	* *	* * *	9

The quality of selected studies was relatively even according to our review. Cohort studies seem to have higher quality than case-control studies (Table 10).

1.3. Discussion

Dose and duration relationship of ibuprofen use and cardiovascular risk

According to our literature review, The MI risk related with to low-dose ibuprofen was not consistent among studies. Some found significant increase of risk while some did not. The study studies of van der Linden *et al.*(249) and Gislason *et al.* (251) found significant increases of risk associated with the use of ibuprofen ≤ 1200 mg. The former study was a nested case-control study and the latter was a cohort study in patients with chronic heart failure. The populations of the two studies were both at high cardiovascular risk (mean age 66 and 75 year-old respectively), which could contribute to the increase of MI risk.

The duration relationship was not clear through our literature review. The risk seems increased in short term according Schjerning Olsen *et al.* (149) but not clearly duration-dependent in the study studies of Varas-Lorenzo *et al.* (250) and Ray *et al.* (248) as well as other studies (Table 8).

A recent meta-analysis of observational studies (260) on the risk of acute myocardial infarction (AMI) associated with the use of NSAIDs found random-effects RRs (95%CI) of 0.97 (0.76–1.22] for low-dose ibuprofen versus 1.20 (0.99-1.46) for high-dose; 1.20 (0.96–1.49) for low-dose & high risk patients; 1.43 (1.20 – 1.71) for high risk & short duration versus 1.28 (0.87–1.90) for high risk & long duration. This suggests that the risk of myocardial infarction might be dose-

dependent and depend on baseline cardiovascular risk, but might not depend on duration, perhaps related to a depletion of susceptibles effect.

Risk of death did not increase relative with the use of low-dose ibuprofen. There is little and insufficient data on the risk of stroke.

Dose and duration relationship of diclofenac use and cardiovascular risk

Most studies found a dose-dependent relationship with diclofenac use and risk of MI and stroke, except for two studies: Ray et al (2009) (248) and Varas-Lorenzo *et al.* (2009) (250). Early increases of cardiovascular risk associated with diclofenac were found in some studies, for MI (149)·(248)·(250)·(254) and stroke (243)·(244).

In the meta-analysis of Varas-Lorenzo *et al.* (260), the random-effects RRs (95%CI) were 1.26 (1.03–1.53] for low-dose diclofenac versus 1.32 (1.07-1.63) for high-dose; 1.42 (1.10–1.83) for low-dose & high risk patients; 2.13 (1.68 – 2.69) for high risk & short duration versus 1.48 (0.84–2.61) for high risk & long duration.

Dose- and duration- relationship of naproxen use and cardiovascular risk

According to our review of observational studies, low-dose naproxen seems to be quite safe for CV risk at low-dose. However, the risk might depend on the baseline risk of the population. Gislason *et al.*(251) found a significant increase of MI risk associated with naproxen ≤ 500 mg in patients with chronic heart failure. Duration of treatment longer than 1 month was found to be safe. In the meta-analysis of Varas-Lorenzo *et al.* in 2013 (260) , they reported the random-effects RR (95%CI) for MI risk associated with naproxen use in 0-3 months in high risk population of 1.15 [0.84 – 1.58]. This meta-analysis also included the study of Schjerning Olsen *et al.* (246) but did not specify the effect of less than 1 month duration. Schjerning Olsen *et al.* (246) found an increase of death/MI risk in the first week of treatment with naproxen (HR 1.76 [1.04-2.98]).

In conclusion, we found some common points of the three NSAIDs ibuprofen, diclofenac and naproxen regarding their cardiovascular risk through our literature review. First, the risk of the three substances seems to depend on the dose, and also on other conditions of use like the duration, or the characteristic of population. When they were used in high risk population, even low-dose could be harmful. (113,249,251) The explanation for the increase of CV risk associated with diclofenac in short term use (≤ 30 days or maybe less than 2 weeks) found in some studies

(149,243,248,250,254) could be related to the predominant inhibition of COX-2 resulting in a pro-aggregant and vasoconstrictive effect.

Generalizability to the population of real OTC NSAIDs users

These results come from studies with various designs and in various settings, from 'healthy' subjects and from patients with a previous MI, using different endpoints (all death, cardiovascular deaths, coronary deaths, MI, fatal MI, etc.), and without always specifying the number of patients in the source or in the exposed populations. This would make a proper meta-analysis extremely tentative. Moreover, the adjustment factors varied among the studies, making their pooling, compilation or meta-analysis even more difficult.

None of these studies looked at real OTC use, only at the lower end of prescription dose range, or in short duration (less than 30 days). OTC ibuprofen is indicated for a maximum daily dose of 1200 mg taken for a maximum of 7–10 days, for the treatment of self-limiting conditions such as headache, fever, backache, dental pain and dysmenorrhoea. Experience shows that the mean use will be 20 tablets (200 mg each) over 5 days. (127) Similarly, a maximum OTC treatment duration of 5 days for pain and 3 days for fever is recommended for OTC diclofenac. (106,261)

In addition, the usual cut-off for 'low dose' is 1200 mg for ibuprofen, which indeed is the maximum approved daily dose for OTC use, and half the usual prescription dose used in clinical trials such as CLASS. (16) The usual cut-off dose in these studies was 100 mg for diclofenac, which is clearly above the upper limit of the maximum approved dose for OTC use of diclofenac, 75 mg/day. The study of Garcia Rodriguez *et al.* (133) was the only one that evaluated the risk associated with diclofenac 50 and 75 mg. Moore *et al.* applied the dose-response curve of Garcia Rodriguez (133) to the pooled RR in the meta-analysis McGettigan *et al.* (134) and found a RR of 0.90 for diclofenac 50 mg and 1.04 for diclofenac 75 mg. (262) If one constrains the minimal RR to 1.00 (no effect) along a sigmoid dose-response curve, the RR associated with 50 and 75 mg diclofenac should be 1.05 and 1.13, respectively. (262) Whether the confidence intervals include or not 1.0 will depend on the size of the populations studied. (262)

The effect of duration of treatment remains very confused, in line with the hypotheses concerning cardiovascular risk: one hypothesis suggests the increased risk from prolonged use through increased blood pressure, whilst another suggests immediate risk in susceptible subjects related to platelet-endothelial TXA₂/PGI₂ imbalance.

Most studies consider the risk by using non-use or distant past use as reference which gives absolute risk, whereas the reason for the use of an NSAID might not be irrelevant to the risk of MI or death. This comparison may be the subject of indication and prothopathic bias. One study used diclofenac/ibuprofen as reference to study the risk associated with naproxen (255). It might be more appropriate to consider another analgesic such as paracetamol as reference, which in some studies does not seem to be associated with a risk of MI [107,108], even though in others there may be some indications of a moderately increased risk [109,110].

Finally, because real OTC and prescription NSAIDs may be used differently in different risk patients, even at the same nominal dose, it is not certain how these results apply to actual OTC use.

2. Paracetamol

2.1. Methods

The inclusion criteria for literature review of cardiovascular risk associated with paracetamol is described in Table 11.

Table 11. Inclusion criteria for literature review of cardiovascular risk associated with paracetamol

Characteristics	Inclusion criteria
Context	The hypothesis of a preferential COX-2 inhibitory action of paracetamol raised concerns with respect to cardiovascular safety. Very little is known of its real-life safety.
Objective	Review studies reporting on the CV risk associated with the use of paracetamol
Database	Medline
Period	1 st January, 1990 to 12 May, 2016
Languages	English
Designs	Interventional studies: Clinical trials Non interventional (observational) studies: Case control, Cohort, Nested case-control, Case-crossover, Self-controlled cohort, Self-controlled case series, Case-time-control, Case cohort
Population	General population, all countries and regions
Exposures	Paracetamol (single-ingredient or in combination)
Reference groups	Nonuse of paracetamol
Outcomes	Main outcomes: MI, ACS and stroke Secondary outcomes: cerebrovascular disease, coronary heart disease, heart failure, sudden cardiac death, cardiovascular mortality, cardiac failure, cardiorenal syndrome, TIA

Literature search strategy

We carried out a PubMed search with restriction to English-language publications and human subjects. The medical subject headings (MeSH) and free-text terms were used to identify outcomes and exposures of interest. The Appendix 4 provides details of the search strategy.

2.2. Results

Description of studies

Clinical trials

No clinical trial was found. However, we found a study that used VISTA (The Virtual International Stroke Trials Archive), a collaborative venture that collates data from completed clinical trials and provides access to anonymised data for novel exploratory analyses to inform clinical trial design and to investigate the safety and benefit of paracetamol treatment in the acute phase of ischemic stroke. (263) Of 6015 patients with ischemic stroke, 2435 (40.5%) had been treated with paracetamol. No association of paracetamol use with overall stroke outcome were detected among patients who experienced pain or fever (OR 1.03, 95%CI 0.86-1.20). However, in patients without recorded pain and/or fever, paracetamol was associated with an increase of recurrent stroke in 7 days (OR 3.57, 95%CI 1.37-9.32).

Observational studies

After reviewing all obtained articles, we found 7 eligible studies. Their main characteristics and findings are described in Table 12 and Table 13 respectively. There were two field studies conducted in the US (264)·(265) and five conducted in database in Spain, (243)· (245) the UK, (266)·(267) and Italy. (268)

Table 12. Main characteristics of published studies about cardiovascular risk of paracetamol

Study First Author, Year	Source Population Study Period	Population, N, Age (Years)	Design	Outcome	Case validation	Exposure assessment	Exposure definition	Reference Category
Fulton, 2015 (266)	CPRD, UK 1996 -2006	224,496 patients with hypertension Age ≥ 65	Cohort	Fatal and nonfatal MI; Fatal/nonfatal stroke; Any CV event	Presence of at least one compatible and prespecified diagnostic code	Prescription records	≥ 3 prescriptions of paracetamol High, medium and low frequency	Nonuse of paracetamol
García-Poza, 2015 (243)	BIFAP database, Spain 2001-2007	2,888 cases Age 40-90	Nested case-control	Nonfatal ischemic stroke	Cases with supporting evidence Free text clinical note	Prescriptions records of GPs	Current: EOS +30 days	Nonuse of paracetamol
Roberto, 2015 (268)	IMS Health LPD, Italy 2002-1012	36,754 patients with OA and incident use of NSAIDs Age ≥ 18	Nested case-control	AMI , angina pectoris, TIA, hemorrhagic stroke	“Definite” case: ICD-9-CM confirmed by patients’ medical chart, free text “Probable”: ICD-9-CM only	Prescription records of GPs	Current: 0-90 days from the last recorded prescription; Recent: 91-180; Past: 181-365	Nonuse of paracetamol
de Abajo, 2014 (245)	BIFAP database, Spain 2001-2007	3,833 cases 20,000 controls Age 40-90	Nested case-control	Nonfatal AMI	Cases with supporting evidence GPs validation 38%	Claimed prescriptions	Current: EOS +30 days	Nonuse of paracetamol
de Vries, 2010 (267)	GPRD, UK 1987-2007	382,404 paracetamol alone, 13,079 paracetamol + ibuprofen Age ≥ 18	Cohort	MI Stroke Congestive heart failure	OXMIS and Read codes medical terms, review of all free text entries, death certificates	Prescription records	Current: EOS + 3 months Recent: EOS + 3 – EOS + 6 months Past: From EOS + 6 months	Past exposure of paracetamol
Chan, 2006 (264)	US female registered nurses, 1990-2002	70,971 women Age 30-55 in 1976	Cohort	MI , stroke, CHD death	MI: WHO criteria; Stroke: National Survey of stroke CHD death: medical record and death certificate	Questionnaires, 91% response	Current: intake at least 1 day per month Frequency: 1-4, 5-14, 15-21, ≥ 21 days per months	Nonuse of paracetamol
Rosenberg, 2003 (265)	Hospitals in US 1980-1983	2035 men cases, 2656 men controls Age ≤ 55	Case-control	First MI	WHO criteria	Questionnaires (participation rate 87% and 93% for cases and controls)	≥ 1 days/week for ≥ 3 months; ≥ 4 days/week for ≥ 3 months; Daily for ≥ 3 months; Use on the day before admission	Nonuse of paracetamol

BIFAP, Base de datos Informatizada para la Investigación Epidemiológica en Atención Primaria ; GPRD, General Practice Research Database ; CPRD, Clinical Practice Research Datalink; DNPR, Danish National Patient Registry; THIN, The Health Improvement Network; NHIRD, National Health Institute Research Database ; OXMIS, Oxford Medical Information Systems; EOS, End of supply ; AMI, Acute Myocardial Infarction ; Re-MI, Recurrent Myocardial Infarction ; CHD, Coronary Heart Disease ; CV, Cardiovascular; ICD-9-CM, The International Classification of Diseases, Ninth Revision, Clinical Modification; GP, General Practitioner ; UK, United Kingdom; US, United States.

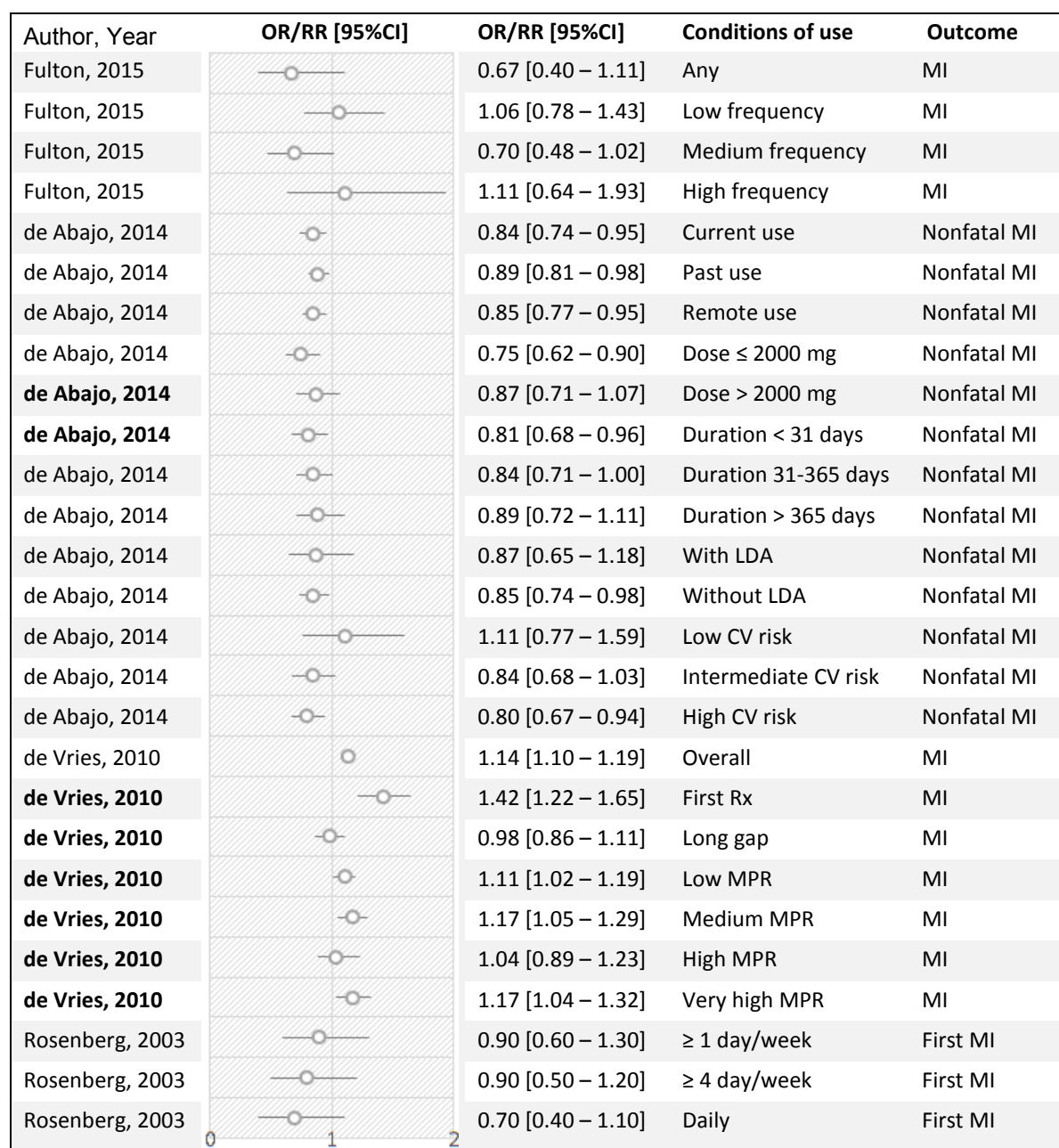
Table 13. Results summary of studies about cardiovascular risk of NSAIDs paracetamol with duration of exposure assessment

Author, Year	Design	Outcomes	Condition of use	Events/ exposure	RR/OR/HR	95% CI
Fulton, 2015 (266)	Cohort	MI	Any	–	0.67	0.40 – 1.11
			Low frequency	–	1.06	0.78 – 1.43
			Medium frequency	–	0.70	0.48 – 1.02
			High frequency	–	1.11	0.64 – 1.93
Fulton, 2015 (266)	Cohort	Stroke	Any	–	1.31	0.92 – 1.87
			Low frequency	–	1.11	0.84 – 1.47
			Medium frequency	–	0.73	0.50 – 1.06
			High frequency	–	0.87	0.49 – 1.55
Fulton, 2015 (266)	Cohort	Any CV event	Any	–	1.16	0.90 – 1.50
			Low frequency	–	1.10	0.91 – 1.23
			Medium frequency	–	0.75	0.59 – 0.95
			High frequency	–	1.41	0.98 – 2.02
García-Poza, 2015 (243)	Nested case- control	Nonfatal ischemic stroke	Dose < 2000 mg	172	0.93	0.78 – 1.12
			Dose > 2000 mg	143	0.99	0.81 – 1.21
			Current use	513	0.97	0.85 – 1.10
			Recent use	889	1.06	0.95 – 1.18
			Past use	554	1.05	0.94 – 1.19
			Duration < 31 days	186	1.06	0.89 – 1.27
			Duration 31-365 days	208	0.94	0.75 – 1.15
			Duration > 365 days	119	0.89	0.71 – 1.10
			With LDA	114	0.93	0.69 – 1.25
			Without LDA	357	0.97	0.83 – 1.13
			Low CV risk	62	1.23	0.87 – 1.73
			Intermediate CV risk	185	0.93	0.75 – 1.15
			High CV risk	266	0.94	0.78 – 1.14
Roberto, 2015 (268)	Nested case- control	ACCES	Current use P	27	1.27	0.81 – 1.99
			Current use P codeine	70	1.22	0.92 – 1.63
			Recent use	49	1.12	0.80 – 1.55
			Past use	77	1.13	0.86 – 1.48
de Abajo, 2014 (245)	Nested case- control	Nonfatal AMI	Current use	552	0.84	0.74 – 0.95
			Past use	1060	0.89	0.81 – 0.98
			Remote use	689	0.85	0.77 – 0.95
			Dose ≤ 2000 mg	183	0.75	0.62 – 0.90
			Dose > 2000 mg	142	0.87	0.71 – 1.07

Author, Year	Design	Outcomes	Condition of use	Events/ exposure	RR/OR/HR	95% CI
			Duration < 31 days	198	0.81	0.68 – 0.96
			Duration 31-365 days	218	0.84	0.71 – 1.00
			Duration > 365 days	138	0.89	0.72 – 1.11
			With LD aspirin	124	0.87	0.65 – 1.18
			Without LD aspirin	382	0.85	0.74 – 0.98
			Low CV risk	51	1.11	0.77 – 1.59
			Intermediate CV risk	165	0.84	0.68 – 1.03
			High CV risk	336	0.80	0.67 – 0.94
de Vries, 2010 (267)	Cohort	MI	Overall	2,761	1.14	1.10 – 1.19
			First Rx	177	1.42	1.22 – 1.65
			Long gap	254	0.98	0.86 – 1.11
			Low MPR	860	1.11	1.02 – 1.19
			Medium MPR	407	1.17	1.05 – 1.29
			High MPR	157	1.04	0.89 – 1.23
			Very high MPR	313	1.17	1.04 – 1.32
de Vries, 2010 (267)	Cohort	Stroke	Overall	4,285	1.14	1.10 – 1.18
			First Rx	214	1.17	1.02 – 1.35
			Long gap	453	1.14	1.03 – 1.25
			Low MPR	1,248	1.03	0.97 – 1.10
			Medium MPR	655	1.17	1.08 – 1.27
			High MPR	249	1.02	0.89 – 1.15
			Very high MPR	600	1.30	1.19 – 1.41
de Vries, 2010 (267)	Cohort	Heart failure	Overall	5,673	1.19	1.16 – 1.23
			First Rx	355	1.52	1.36 – 1.69
			Long gap	579	1.23	1.13 – 1.34
			Low MPR	1566	1.06	1.00 – 1.12
			Medium MPR	810	1.21	1.12 – 1.30
			High MPR	398	1.37	1.24 – 1.52
			Very high MPR	733	1.38	1.28 – 1.50
de Vries, 2010 (267)	Cohort	Mortality	Overall	28,813	1.28	1.26 – 1.30
			First Rx	2,176	1.95	1.87 – 2.04
			Long gap	2,771	1.18	1.14 – 1.23
			Low MPR	6,784	0.95	0.92 – 0.97
			Medium MPR	3,821	1.08	1.05 – 1.12
			High MPR	2,012	1.27	1.21 – 1.33
			Very high MPR	5,201	1.63	1.58 – 1.68

Author, Year	Design	Outcomes	Condition of use	Events/ exposure	RR/OR/HR	95% CI
Chan, 2006 (264)	Cohort	MI , stroke, CHD death	1-4 days per month	221	0.98	0.84 – 1.14
			5-14 days per month	143	1.09	0.91 – 1.30
			15 -21 days per month	68	1.22	0.95 – 1.56
			≥ 22 days per month	168	1.35	1.14 – 1.59
			1 day per week	24	0.94	0.62 – 1.44
			2-3 days per week	48	1.28	0.94 – 1.75
			4-5 days per week	26	1.49	0.99 – 2.24
			≥ 6 days per week	50	1.50*	1.10 – 2.04
			1-2 tablets per week	30	1.19	0.81 – 1.76
			3-5 tablets per week	27	1.16	0.76 – 1.76
			6-14 tablets per week	45	1.47	1.06 – 2.03
			≥ 15 tablets per week	25	1.68	1.10 – 2.58
Rosenberg, 2003 (265)	Case- control	First MI	≥ 1 day/week	65	0.9	0.6 – 1.3
			≥ 1 day/week in < 1 year	9	0.4	0.2 – 1.0
			≥ 1 day/week in 1-2 years	20	0.9	0.5 – 1.8
			≥ 1 day/week in 3-4 years	9	1.0	0.4 – 2.6
			≥ 1 day/week in ≥ 5 years	27	1.1	0.6 – 2.0
			≥ 4 day/week	37	0.8	0.5 – 1.2
			≥ 4 day/week in < 1 year	8	0.5	0.2 – 1.2
			≥ 4 day/week in 1-2 years	16	1.1	0.5 – 2.4
			≥ 4 day/week in 3-4 years	6	1.3	0.4 – 4.6
			≥ 4 day/week in ≥ 5 years	7	0.6	0.2 – 1.5
			Daily	31	0.7	0.4 – 1.1
			Daily in < 1 year	7	0.4	0.1 – 1.0
			Daily in 1-2 years	13	1.0	0.4 – 2.2
			Daily in 3-4 years	6	1.3	0.4 – 4.6
			Daily in ≥ 5 years	5	0.5	0.2 – 1.6

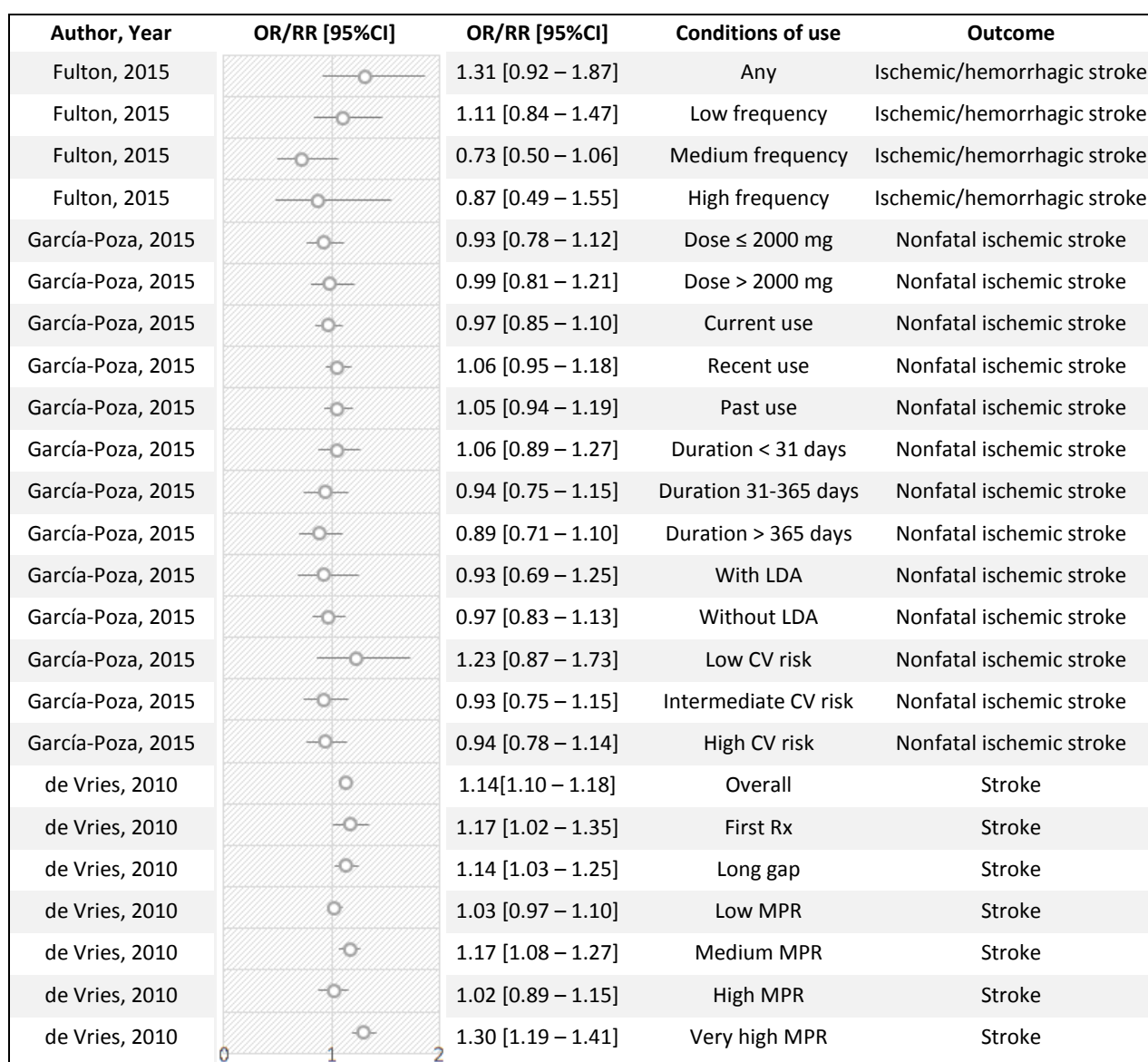
ACCes, Acute Cerebrovascular and Cardiovascular Events (including AMI, angina pectoris, TIA, hemorrhagic stroke); MI, myocardial infarction; CHD, Coronary Heart Diseases; LDA, low-dose aspirin; MPR, Medication Possession Ratio; P, paracetamol



MPR, Medication Possession Ratio; CV, cardiovascular; LDA, low-dose aspirin; MI, myocardial infarction

Figure 9. Summary of observational studies about risk of myocardial infarction associated with paracetamol relative to nonuse

Overall, paracetamol did not appear to be associated with increased of MI risk. The risk seems to not clearly depend on dose, duration or frequency of use. There was a small protective effect in patients with high CV risk patients, but not in patients with low CV risk (study of de Abajo *et al.*) (Figure 19).



MPR, Medication Possession Ratio; CV, cardiovascular; LDA, low-dose aspirin.

Figure 10. Summary of observational studies about risk of stroke associated with paracetamol relative to nonuse

Overall, there was no increase of stroke risk associated with paracetamol. The only increase of stroke risk was patients with very high medication possession ratio (according to de Vries *et al.*). The risk of stroke did not clearly depend on dose, frequency or duration. Patients with low CV risk were associated with higher increase of risk, but not significant (according to García-Poza *et al.*) (Figure 10).



CHD, Coronary Heart Diseases; MI, myocardial Infarction; MPR, Medication Possession Ratio; P, Paracetamol; ACCEs, Acute Cerebrovascular and Cardiovascular Events (including AMI, angina pectoris, TIA, hemorrhagic stroke)

[¶] Any CV event: MI, stroke, transient ischemic attack, coronary artery bypass grafting, carotid endarterectomy, major limb amputation, surgical embolectomy.

Figure 11. Summary of observational studies' results on risk a composite of cardiovascular outcomes and/or death associated with paracetamol relative to nonuse

Both Chan *et al.* (264) and de Vries *et al.* (267) reported a frequency dependent effect of paracetamol use and risk of MI/stroke/CHD death and death. Chan *et al.* found no increase of risk of MI/stroke/CHD death risk associated with low/medium frequency of use (less than 15 -21 days per month, or less than 4 days per week, or 5 tablets per week) but did find an increase of risk at high/very high frequency (≥ 22 days per month, or more than 4 days per week, or more than 6 tablets per week). de Vries *et al.* (267) found increases of risk of mortality and heart failure in patients with high and very high MPR (Figure 11). Fulton *et al.* (266) found increase of risk of any CV event associated with only high frequency use. Roberto *et al.* (268) did not find a significant difference between paracetamol and paracetamol codeine with regard to the risk of acute cerebrovascular and cardiovascular events.

Quality assessment

We used the Newcastle-Ottawa (269) scale to assess cohort and case-control studies. Results are shown in Table 14.

Table 14. Quality assessment of cohort and case-control studies about cardiovascular risk of NSAIDs in OTC-like conditions

Study First Author	Design	Selection (max. 4)	Comparability (max. 2)	Exposure/ Outcome (max. 3)	Total (max. 9)
Fulton, 2015 (266)	Cohort	* * *	* *	* * *	8
de Vries, 2010 (267)	Cohort	* * *	* *	*	7
Chan, 2006 (264)	Cohort	* * *	* *	* * *	8
García-Poza, 2015 (243)	Nested case-control	* * * *	* *	* *	8
Roberto, 2015 (268)	Nested case-control	* * * *	* *	* *	8
de Abajo, 2014 (245)	Nested case-control	* * * *	*	* *	8
Rosenberg, 2003 (265)	Case-control	* *	* *	* *	6

2.3. Discussion

According to our literature review, there was not much evidence on cardiovascular safety of paracetamol and it is not consistent. Interestingly, studies that found increase of CV risk or death

were two cohort studies, either in the general population (de Vries *et al.* (267)) or in a low-risk population (Chan *et al.* (264)). Studies that did not find an increase of CV risk were case-control or nested case-control studies, which included more patients at high risk. Only one cohort study did not report an increase of risk (266), this study actually included only hypertensive patients aged ≥ 65 years. Study of de Abajo (245) and García-Poza (243) both showed that the effect of paracetamol use in low and high CV risk patients seems in the opposite directions, that is an increase of risk in low CV risk patients, and a decrease of risk in high CV risk patients. This might be due to the interaction with other concomitant drugs like aspirin or antiplatelet agents, which was not clearly demonstrated.

Studies that analysed MI or stroke outcome alone reported a smaller increase of risk or even a protective effect associated with paracetamol compared to studies that included other outcomes such as death, CHD death or heart failure. More pronounced increases of risk were found with high frequency of use. This might be due to the mechanism of paracetamol increasing blood pressure, (147,270) which is a risk factor for any CV diseases, not only MI or stroke. The hypertensive effect of acetaminophen could be mediated by the COX-2 inhibition by acetaminophen (186,190) or by an indirect activation of cannabinoid receptors. (176) Data showed that the renal effects of COX-2 inhibition might result in small but significant increases in blood pressure. (144–147) Consequently, increased blood pressure over time would alter the arterial wall structure and increase the risk of atherosclerotic plaques resulting in increased risk of coronary thrombosis. If that is the mechanism, the CV risk could increase with the long term and frequent use of paracetamol.

All studies identified compared use of paracetamol to non-use. The indication and protopathic bias were not addressed. One important limit of these studies is that non-users of paracetamol might be a user of NSAIDs. This is not a misclassification bias, however, because the use of NSAIDs is an effect modification factor when studying the cardiovascular risk. NSAIDs exposure should be excluded or stratified in the analysis. Inclusion of NSAIDs in the non-paracetamol use period might underestimate the risk associated with paracetamol.

On the other hand, the apprehension of cardiovascular risks of NSAIDs might channel patients at higher risk to paracetamol rather than NSAIDs, which might result in an apparently higher risk with paracetamol.

CHAPTER III- Methodological approaches to the cardiovascular safety of paracetamol and low-dose NSAIDs

Introduction

From the analysis of the literature reported above, there is quite a large amount of information concerning the cardiovascular risks of prescription strength NSAIDs as used in chronic diseases such as OA and RA, usually in older persons with concomitant risk factors and medication, from clinical trials and from observational studies. However these data do not help on low-dose NSAIDs as used OTC, i.e., at low doses, for short periods of time in younger, mostly risk-free patients. When lower doses of NSAIDs are mentioned, there is no indication if the lower prescription doses were used because of potential risks.

There are very few large clinical trials of low-dose NSAIDs in the indications of common acute pain that are those of the OTC usage, even though these represent the vast majority of users. The presumably low risk of cardiovascular events in these mostly healthy subjects make the numbers of subjects needed very high, rendering clinical trials essentially unfeasible. Pharmacoepidemiological studies, especially using population databases appear to be the only information resource that could contribute to answer these very simple questions:

What is the background risk of cardiovascular events in the users of paracetamol or ibuprofen?

Is there an excess cardiovascular risk associated with the dispensing of OTC-strength (and usage) NSAIDs?

Is there a risk associated with the dispensing (use) of paracetamol in the same conditions?

How do the risks associated with low-dose NSAIDs and paracetamol compare, both in terms of relative and absolute risks

Are these risks modified by other cardiovascular risks or medication, including low-dose aspirin?

The answers to these questions might help patients, prescribers, regulators and scientific societies make decisions as to the most appropriate drug to recommend in these conditions of common acute pain. This of course should include therapeutic efficacy or effectiveness, and we presume equipotency between paracetamol and OTC-strength ibuprofen.

These answers must take into account the presumably very low incidence rate of events in the user population, as well as the usual biases, especially in this context protopathic bias (the drug being given for early symptoms of the outcome of interest), indication bias (where the indication (pain and fever) increases the risk of the event), and channelling (where because of real or perceived risk, one drug is given to patients who are more at risk of the event, or with a higher baseline risk of having had an event).

1. Consideration of data sources

1.1. Sample size estimation

OTC drugs are difficult to study for the following reasons:

- i. They usually do not appear in physician notes or electronic health records
- ii. Claims databases normally only include prescription only medicines (POM)

Thrombotic cardiovascular events like myocardial infarction and stroke have very low event rates in the general population. In France, the total number of MI hospitalisation in 2008 was 56 102 cases (incidence 0.88 per thousand person-year). (271) In our previous study, we found 44 484 OTC-Strength NSAID only users in the Echantillon Généraliste de Bénéficiaires (EGB) database over 2 years, represented 19% of the total ≥ 15 year-old EGB population), (272) or about 8% in the one year. Based on these data, we estimated the sample size for cohort and case-control studies using the predefined confidence level 0.95, power 0.8 and a duration of follow-up one year (Table 15).

Table 15. Sample size estimation for cohort and case-control studies to estimate the risk of myocardial infarction associated with OTC-Strength NSAID

OR/RR	No. Exposed in cohort study	No. Case in case-control study
1.1	1 829 671	22 567
1.2	479 175	5 952
1.3	222 635	2 783
1.4	130 670	1 643
1.5	87 108	1 102
1.6	62 908	800
1.7	47 993	613
1.8	38 103	489
1.9	31 179	402
2.0	26 124	338

To identify an increase of 40% of MI risk associated with OTC-Strength NSAIDs, we would need 130 670 OTC-Strength NSAIDs users for a cohort study, or about 1 600 cases for a case-control study. This number is difficult to acquire with randomized comparative trials. The only way is to conduct observational studies in a big healthcare database.

In France some drugs available OTC are also reimbursed and recorded if prescribed, such as low-dose aspirin for cardiovascular prevention, ibuprofen at OTC strengths and paracetamol. Reimbursed low-dose ibuprofen in France represents about 70% of all sales, (273) so that there is a sizable amount of data on OTC-strength ibuprofen usage. The same is true for paracetamol, where about 84% of all paracetamol sales are prescription, (225,273) and can be found in the national claims database. This gives us an opportunity to evaluate the cardiovascular risk associated with the use of OTC-strength NSAIDs and paracetamol. In the next parts we will describe all available French databases and the ability to use them for our study's objectives.

1.2. Description of the French databases

SNIIRAM

SNIIRAM (*Système national d'informations inter-régimes de l'Assurance Maladie*) is the main healthcare claims database, which now covers over 98% of the French population. (274,275) It

includes information from the three main claims systems, and an increasing number of the smaller systems. It contains:

- Demographic data such as date of birth, gender, address (area or region). There is also information on the mutual complementary insurance systems, or the presence of CMUc (Couverture médicale universelle complémentaire), which indicates joblessness.
- Presence of chronic disease, and date of first registration. There is a list of 30 long term diseases (*Affection de longue durée* - ALD) along with ICD-10 codes, for a total of 3448 available ICD-10 codes in these ALD. Patients registered for these diseases benefit from full coverage for all medical expenses related to the disease. Registration with a ALD is obtained at the request of a patient's general practitioner and must be validated by the health insurance system physician. Not all patients always register for chronic disease status, because they are already registered for a related disease (e.g. coronary heart disease or diabetes), or because the treatment is cheap (e.g. Atrial fibrillation treated with vitamin K antagonist (VKA) and amiodarone), or because it might carry a social onus (e.g. epilepsy). ALD diagnoses are rather specific, but often not very sensitive.
- Occupational accidents and diseases
- Outpatient medical expenses
- Medication, recorded as dispensed preparations packs, including unique registration code (CIP), ATC and The Anatomical Classification of Pharmaceutical Products (EPhMRA) codes. This includes the description of packs in content: number of tablets, strength, and the number of packs dispensed. It also includes the date of prescription and nature of prescriber, date of dispensing, and the dispensing pharmacy (anonymized).
- Date and nature of physician interactions, with procedures if any (e.g., endoscopy).
- Date and nature of paramedical (nurses, physiotherapists, etc.) interventions.
- Date and nature of all lab tests, but without the results.
- Date and nature of medical transports.
- Certain lifestyle interventions or aids such as wheelchairs or crutches.
- Days of paid sick leave.

There is no information about in-hospital prescriptions (except for very expensive drugs) and expenses. This concerns essentially public hospitals. Private clinics may provide more information, especially concerning physician interventions or procedures.

All these items are accompanied by costing information including total cost, amount reimbursed by the main healthcare insurance and by possible complementary mutual funds or private insurances, though this information is often complex to decrypt and understand without expertise.

PMSI

PMSI is the national hospital discharge database, concerning both public and private hospitals. In addition to admission and stay duration, it includes main, related and associate diagnoses, coded in ICD-10, as well as procedures (medical acts, biology) and especially costly drugs. Validation studies show a high validity of main diagnostic codes. (276) It includes hospital admissions in medical, surgical and obstetrical wards. Psychiatric hospitalisations are being included, as well as rehabilitation centres. Information also includes the source of the admission, and the destination of discharge, which may be another department of the same hospital, or another hospital, in addition to discharge for home.

Death registry

The national death registry includes causes of deaths, and is maintained by the national institute for statistics and economic studies (*Institut national de la statistique et des études économiques* - INSEE). At this time, only date of death is linked to the other data.

These three databases are linked by the unique personal identification number NIR, de-identified using a two successive hash scrambling operations. (6-9). This one-way scrambling algorithm allows the linkage of the different databases, but does not permit to go back to the original NIR.

The whole data array represents over a hundred tables, with an extremely complex architecture: the main source data was developed to ensure the reimbursement of individual medical expenses and claims, not for medical research. Using it to follow individual patients over time and across different types of information, and linking to two other databases can be challenging.

Other databases exist including socioeconomic information for instance, but are not linked to the main healthcare claims databases yet.

Though formally there are three separate but linked databases, the full database including all three bases (claims, hospital admissions and deaths) is usually referred to as SNIIRAM. Access to only four years of database is routinely allowed but more years may be authorized with special permission.

Echantillon généraliste de bénéficiaires (EGB)

EGB is a 1/97th random permanent sample of SNIIRAM that will in time have 20 years' follow-up. It was started in 2004 from The National Fund of health insurance for employees (*La Caisse nationale de l'assurance maladie des travailleurs salariés* – CNAMTS), and has been progressively enriched over time, including the Regime for independents (*Régime des indépendants* - RSI) and the Regime for farmers (*Régime des agriculteurs* - MSA) since 2011. The dataset is the same as SNIIRAM, the main difference being the size of the dataset, 62 millions in the full database, vs. 720 000 for EGB. Because the data are mostly the same, and access to EGB is easy, studies will often start with feasibility and algorithm testing in EGB before going to the full SNIIRAM.

Both datasets SNIIRAM and EGB contain in principle mostly the same data, but whereas initially going from one to the other was very simple using the same queries and query structures, the evolution of EGB to a more researcher friendly structure has made it a little more complex to scale up studies from EGB to SNIIRAM.

1.3. Feasibility of using the French database for study objectives

Sample size

As we mention in section 4.1.1, to identify an increase of 40% of MI risk associated with OTC-Strength NSAIDs, we need 130 670 OTC-Strength NSAIDs users for a cohort study, and about 1 600 cases for a case-control study. Ideally, the SNIIRAM database will fit the best for this objective. Calculating based on data from our previous study, (27) we expect to have 4.4 million OTC-Strength NSAIDs users in SNIIRAM over two years, which makes it possible to detect a relative risk of 1.1. However, SNIIRAM access authorizations are granted under strict criteria and after long procedure. Based on our experience, the time from first submission to the provision of data is currently about 15 months, ranging from 13 months to up to 2 years or more. Accredited persons can access the

EGB database with a simple request to the *Institut des données de Santé* (IDS). Accredited researchers affiliated to INSERM and other public research institutes have direct access, though they must submit a protocol or a detailed synopsis and the funding source one month before starting (one week for publicly funded studies). We therefore started with EGB database in the first step. If a SNIIRAM approach is necessary, we will submit the written protocol to acquire the authorization to access SNIIRAM database.

With a quick check of the EGB database over six years from 2009 to 2014, we found about 168 000 ibuprofen users, 2930 MI and 5542 acute coronary syndrome (ACS) and 3 463 stroke hospitalizations. Using those data, we can identify RRs ≥ 1.4 or ORs ≥ 1.3 . The percentage of paracetamol users was 51% in the previous year, in comparison to 19% for OTC NSAIDs over two years. (27) So, EGB is absolutely feasible to study the CV risk of paracetamol.

Stratification on individual NSAIDs may need more data. In previous studies ibuprofen at OTC strengths represented over 90% of all OTC NSAIDs use. Therefore, it would be difficult to study the risk of other OTC-Strength NSAIDs in EGB.

Outcomes validation

Outcomes in databases are standardized and have already been used in some studies. (277–282) From field studies, we know that in France all ACS are hospitalized. (281) The validation of ICD-10 codes for ACS and MI has also been confirmed. (276) Of the individual codes, I20.0, I21 and I24 had the highest the positive predictive value (PPV); 100.0% for I24 (95%CI [15.8-100.0]); 90.0% for I21 (95%CI [76.3-97.2]); and 66.7% for I20.0 (95%CI [38.4-88.2]). The combination of I20.0 or I24 codes was able to identify 12 of the 56 validated ACS cases with a PPV of 70.6% (95%CI [44.0-89.7]), the combination of I21 or I24 identified 38 cases with a PPV of 90.5% (95%CI [77.4-97.3]), the combination of I20.0 or I21 identified 46 cases with a PPV of 83.6% (95%CI [71.2-92.2]), and the combination of I20.0, I21 or I24 identified 48 cases with a PPV of 84.2% (95%CI [72.1-92.5]). The combination of I20.0, I21 or I24 codes had the best performance to identify occurrence of ACS in the French hospitalization database. Of course it might be preferable to demonstrate sensitivity rather than PPV, but this would involve examining large numbers of hospital reports to identify uncoded events. Not coding such an important event if diagnosed is unlikely, especially since it has important financial consequences for the hospital. Of course nothing much can be done about

unrecognized events. In this context, a good positive predictive value is conservative: there may be more events than recorded, but not fewer.

The SNIIRAM and EGB database includes date but not cause of death. Therefore, it might be difficult to study death of cardiovascular causes.

Exposure validation

Non-prescribed self-medication with OTC drugs is not registered, but in a previous study, we found that 84% of all paracetamol and 70% of OTC-Strength ibuprofen sold in France had been prescribed, reimbursed by the healthcare systems and could be identified in this database. (225,273) This has allowed us to describe the usage patterns of prescription and OTC-strength NSAIDs (27) and of paracetamol. (272) In the same way, low-dose aspirin for cardiovascular prevention and is usually prescribed and can be retrieved from the database.

To compare with other countries' claim databases, no OTC drugs could be found in the US claim database. In the UK, use of OTC medications is rarely recorded by GPs and therefore only a small proportion of the total use is recorded in the UK Clinical Practice Research Datalink (CPRD), formally General Practice Research Database (GPRD). (267)·(266) To limit the misclassification or confounding of exposure, some studies included only patients ≥ 65 years old because from that age, they do not pay the prescription charges. (266) In Spain, the *Base de datos Informatizada para la Investigación Epidemiológica en Atención Primaria* (BIFAP) database also includes some OTC drugs such as paracetamol (15.71 DDD per 1000 inhabitants/day). (245)·(243)

Dispensing data include the number of tablets per pack, their strength, and the number of packs dispensed per dispensing. There is no information about dose regimen or the prescribed dose. So, the estimation of exposure time might be not exact, especially if there was only one dispensing. In chronic use, the dispensing history and patterns quite clear indicate the dosing regimen. However, even knowing the prescribed dose, we cannot say with certainty that patients will comply in real life, especially with analgesics treatment, or rather exactly when the product is taken relative to the prescription or dispensing.

2. Consideration of methods

2.1. Study design

The two main traditional designs of observational studies are cohort and case-control. Besides these, there are other variants such as nested case-control, case cohort, case-crossover, self-controlled cohort, self-controlled case series, and self-controlled risk interval. Each study design has typical advantages and disadvantages. We summarize characteristics of cohort and case-control study designs in Table 16, and characteristics of other designs in Table 17.

Table 16. Summary of characteristics, strength and weakness of cohort and case-control studies

Study design	Population	Comparison group	Measure-ment	Statistical Analysis	Strength	Weakness	Recommendation
Cohort	Exposed and non-exposed (or exposed to competitive drugs)	- Internal or external unexposed subjects - Active controls	- RRs - IRs - HR	- Linear or logistic regression - Cox regression - Poisson regression	- Potentially more strong for causal investigation - Easily implemented in claim database - Good for rare exposure - Good for multiple outcomes - Less potential for recall bias - Possibly generalizable - Allows describing time course of risk - Protopathic bias and confounding by indication can be addressed by using an active control - No risk of misclassification of exposure if active controls are used	- Require large sample size →Expensive for field study - Require long-term follow-up in case late outcomes onset - More potential for loss to follow-up - Sometimes non-exposed group is limited (e.g. unvaccinated) - Selection bias of exposed and non-exposed subjects - Time-varying confounders - Misclassification bias on outcomes occurrence - Immortal time bias	- Exposure is rare - Long-term exposure - Multiple outcomes - Direct comparison of safety or effectiveness of two competitive drugs
Case-control	Cases and controls (often matched on potential confounders)	Internal or external controls	ORs	Logistic regression	- Less expensive - Save time, suitable both field and database studies - Can be powerful with small sample of cases - Efficient for rare diseases - Good for multiple exposures - Less potential for loss-to-follow up - Time-varying confounders and seasonal trend of disease may be controlled by matching on time	- Potentially weaker causal investigation - More potential for recall bias - Probably not generalizable - Does not allow examination of time course of risk - Confounding by indication, protopathic bias - Impossible to use active controls or compare directly two drugs	- Outcome is rare - Multiple exposure - Good for acute onset of the outcome - When budget and time is limited

Table 17. Summary of characteristics, strength and weakness of other variants of cohort and case-control design

Study design	Population	Comparison group	Measurement	Statistical Analysis	Strength	Weakness	Recommendation
Case cohort	Cases and controls chosen from the same cohort	A random sub-cohort chosen from the full cohort (regardless of whether they have the disease of interest or not)	<ul style="list-style-type: none"> - HRs - RRs - Kaplan-Meier plots 	<ul style="list-style-type: none"> - Logistic regression - Cox regression (weighted or unweighted) 	<ul style="list-style-type: none"> - Diagnostic testing are not required for all cohort participants - Reduces selection bias (cases and non-cases sampled from same population) - Sub-cohort can be used to study multiple outcomes - Possible to examine the time course of risk 	<ul style="list-style-type: none"> - Potential for loss to follow-up, cases occurring late will not have assigned controls - Exposure information collected at different times - Loss of efficiency relative to a full cohort analysis 	<ul style="list-style-type: none"> - Short follow-up time - Multiple outcomes - Not suitable when exposure changes over time or multiple exposures
Nested case control	Cases and controls chosen from the same cohort	Controls are cohort members who do not meet the case definition (matched, not matched or counter-matched)	ORs	<ul style="list-style-type: none"> - Conditional or unconditional logistic regression 	<ul style="list-style-type: none"> - Diagnostic testing are not required for all cohort participants - Over-sampling from controls with longer follow-ups - Possible to evaluate multiple exposures - Time-varying confounders, seasonal trend of disease can be addressed because controls are matched on study time 	<ul style="list-style-type: none"> - Only estimate OR - Loss in efficiency relative to a full-cohort analysis - Controls cannot be reused across studies of different endpoints 	<ul style="list-style-type: none"> - Long or short follow-up time - Multiple exposures - In situations where a careful matching on confounders is needed to avoid bias
Case-crossover	Only cases	Control windows only before outcome's occurrence (unidirectional design)	ORs: odd of exposure during case window vs. odd of exposure during control window	<ul style="list-style-type: none"> - Conditional logistic regression - Conditional Poisson regression 	<ul style="list-style-type: none"> - Self-controlled, adjusts for time-invariant confounders and unmeasured confounders - Only data of cases are needed → Save time and money - No reverse causality 	<ul style="list-style-type: none"> - Time varying confounding if control window is too far - Confounding by indication - Exposure trend bias (especial for new products) - Recall bias 	Intermittent exposure and acute onset of the outcome
Case-time-control	Cases and external controls	Self-controlled within cases + external controls chosen at the same time as the cases	ORs: case-crossover odds ratio (from the cases) divided by the time trend odds ratio	<ul style="list-style-type: none"> - Conditional logistic regression - Conditional Poisson regression 	<ul style="list-style-type: none"> - Self-controlled - Correct time trend bias in case-crossover design - Reduce recall bias between cases and controls but not within person recall 	<ul style="list-style-type: none"> - Require assumption: the absence of unmeasured confounders - The trend of exposure is equal among cases and controls - Confounding by indication 	<ul style="list-style-type: none"> - Intermittent exposure and acute onset of the outcome - Strong exposure trend (e.g. new

Study design	Population	Comparison group	Measurement	Statistical Analysis	Strength	Weakness	Recommendation
			(from the controls)			- Recall bias	drug or seasonal trend)
Self-controlled risk interval	Only Cases exposed	Internal control: non-exposed periods (pre- or post-exposure)	IRRs: IR during exposed periods vs. IR during self-matched non-exposed periods	Conditional Poisson regression	<ul style="list-style-type: none"> - Self-controlled, adjust for time invariant confounders - Only data of exposed patients are needed 	<ul style="list-style-type: none"> - Require assumption: subsequent exposure is not affected by the previous of event - Time-varying confounding - Reverse causality bias - Indication and protopathic bias - Immortal time bias 	<ul style="list-style-type: none"> - Intermittent exposure and acute onset of the outcome - Rare outcomes
Self-controlled cohort	Only exposed (cases or noncases)	Only pre-exposure windows as control	IRRs: IR during post-exposure period vs. IR during pre-exposure period	Conditional Poisson regression	<ol style="list-style-type: none"> 1. Self-controlled, adjust for time invariant confounders 2. Only data of exposed subjects are needed 3. Produced estimates for the entire exposed cohort population, not only cases 	<ul style="list-style-type: none"> - Require assumption like the risk interval design - Indication and protopathic bias - Time-varying confounding - Reverse causality bias - Immortal time bias 	<ul style="list-style-type: none"> - Intermittent exposure and acute onset of the outcome - Rare exposure
Self-controlled case series	Only cases (exposed or nonexposed)	Internal control: nonexposed periods pre- or post-exposure)	IRRs: IR during exposed periods vs. IR during non-exposed periods	Conditional Poisson regression	<ul style="list-style-type: none"> - Only data of cases are needed - Self-controlled, adjust for time invariant confounders 	<ul style="list-style-type: none"> - Require assumption like the risk interval design - Produced estimates for only cases - Time-varying confounding - Indication and protopathic bias - Reverse causality bias 	<ul style="list-style-type: none"> - Intermittent exposure and acute onset of the outcome - Rare outcomes

OR, odds ratio; RR, relative risk; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio

2.2. Methods to control bias

Bias is a systematic error in the design, recruitment, data collection, analysis or interpretation of a study that results in a mistaken estimation of the true effect of the exposure and the outcome. Bias can occur in randomized controlled trials but tends to be a much greater problem in observational studies.

There are three main types of bias: selection, information, and confounding bias.

Selection bias arises when the study population is not a random selection from the target population for which a statement is to be made. Individuals are then recruited in such a way that they are not representative of the target population. (283)

Information bias results from wrong or inexact recording of individual factors, either risk factors or the disease being studied. With continuous variables (such as blood pressure), this is referred to as measurement error; with categorical variables (such as tumor stage), this is known as misclassification. Measurement error or misclassification may result from lack of care by the investigator or from poor quality of measuring or survey instruments (283)

Confounding is present when the association between an exposure and an outcome is distorted by an extraneous third variable (referred to a confounding variable).

Biases can be controlled at different steps of study conduct, from design, recruitment, and data collection to analysis. Our study is conducted in the National French healthcare systems database, thus the data collection step is independent. Information bias is limited. If there were, it would be at the same level in two groups of comparisons. Selection bias is also not a big worry, because the EGB database is a representative sample of the national database, and we are going to include all users in the general population. The bias that concerns most, is the confounding.

Potential confounding factors always have to be considered in the design and analysis of epidemiological studies. A number of methods can be applied to control for potential confounding factors, either at the design stage or in the analysis. The aim is to make the two groups of comparison (exposed and nonexposed in cohort study, cases and controls in case-control study) as similar as possible with respect to the confounders.

At the design stage

The best way to control confounding factors is randomisation, as in clinical trials. Because of the random allocation of individuals to the two group of treatment, the distribution of known and unknown confounding variables will be similar in the two groups. However, it is impossible to randomize actual patients in two groups of treatment in observational studies, because treatment decisions have already been made by physicians. Restriction is a method that limits participation in the study to individuals who are similar in relation to the confounders. For example, a study restricted to non-smokers only will eliminate any confounding effect of smoking. However, a disadvantage of restriction is that it may be difficult to generalize to the rest of the population based on a homogeneous study group and the smaller study population.

Matching is a useful technique of restriction that has been used frequently in case control studies and in cohorts. Its principle is to select controls so that the distribution of potential confounders among them will be similar to those of the cases. For example, controls may be chosen in the same population where cases were identified, with same age, sex, region of residence.

Disease risk score (DRS) matching is a new method of matching cases and controls that might increase the statistical efficiency of case-control studies, particularly when the outcome is rare. (284) DRS is a predicted score which can summarize multiple confounding variables. The applications of DRS might be at the step of design, but also in analysis. In the design step, DRS can be used for the selection of controls with similar DRS to the cases. In the analysis step, DRS can be used for the stratification, or be included in the multivariable analysis. Despite the efficiency in controlling for confounding factors, the use of DRS methods remains low. (285) More research is needed to support the application of DRS methods, particularly in case-control studies. (285)

Propensity score (PS) matching is a method based on the same principle as DRS. The PS is the probability of treatment assignment conditional on observed baseline characteristics. The propensity score is a balancing score: conditional on the propensity score, the distribution of measured baseline covariates is similar between treated and untreated subjects. (286) Thus, in a set of subjects all of whom have the same propensity score, the distribution of observed baseline covariates will be the same between the treated and untreated subjects. (286) There

are different propensity score methods: matching on the PS, stratification on the PS, inverse probability of treatment weighting using the PS, and covariate adjustment using the PS. (286) Depending on the study, some methods of PS matching may have superior performance to others. A simulation study found that matching using calipers of width of 0.2 of the standard deviation of the logit of the propensity score and the use of calipers of width 0.02 and 0.03 tended to have superior performance for estimating treatment effects. (287) The three other methods (matching on the PS, stratification on the PS, inverse probability of treatment weighting) are applied directly in the analysis step, in the total study population.

At the analysis stage

There are two main methods to control for confounders at the analysis steps: stratified analysis and multivariable regression. Stratification allows the association between exposure and outcome to be examined within different strata of the confounding variable, for example by age or sex. Stratification also allows distinguishing a confounder from an effect modifier. With a confounder, the crude estimator (e.g. RR, OR) is outside the range of the two stratum-specific estimators, while with an effect modifier, the crude estimator is closer to a weighted average of the stratum-specific estimators. The problem with simply creating strata is that in general, strata with more individuals will tend to have a more precise estimate of the association (with a smaller standard error) than strata with fewer individuals. Therefore we calculate a weighted average where greater weight is given to the strata with more data. The most common weighting scheme used is the Mantel-Haenszel method. (288) Stratified analysis works best when there are few strata (i.e. if only 1 or 2 confounders have to be controlled). It adjusts for covariates and all interactions among those covariates. However, if the number of potential confounders is large, multivariate analyses will be a better solution. Multivariate analyses are based on statistical regression models such as logistic regression, linear regression or survival regression. In both stratifications and multivariate analyses, PS and DRS can be applied.

2.3. Choice of methods

In this part we will explain our choice of study design and other method to adjust for confounding factors and bias.

The self-controlled cohort design

Taking advantage of the large database, we consider cohort designs to estimate the relationship of OTC-Strength NSAIDs and paracetamol use and cardiovascular outcomes. In addition, because OTC-Strength NSAIDs and paracetamol use are intermittent (27,272) and the onset of the thrombotic cardiovascular outcomes may be acute after short term use, the self-controlled designs are good choices. Between self-controlled case series (SCSS) and self-controlled cohort design (SCC), we prefer SCC design because in EGB we have data of all exposed subjects (both cases and non-cases). The SCC design allows us to generalize results to the overall population, as well as assessing the time course of risk.

The advantage of SCC designs is the automatic adjustment for time invariant confounders and unmeasured confounders such as genetic factors. However, there are some other biases which cannot be addressed such as concomitant drugs use, (289) time-varying confounders, indication and protopathic bias.

To limit the time-varying confounders in the SCC design, we will use the period immediately preceding dispensing as the control period. To limit the effect of concomitant use with aspirin and prescription only NSAIDs, we will either restrict or stratify the study population. For other concomitant drugs, adjustments will be done in the analysis step.

The propensity score-matched cohort design

The protopathic bias is the prescription of an analgesic to treat symptoms of coronary heart disease or myocardial infarction (e.g. referred neck, jaw, or shoulders pains).²⁸⁷⁻²⁸⁹ In the same way analgesics may be prescribed for headache as an early sign of stroke, especially hemorrhagic. Confounding by indication is the use of drugs for indications that may of themselves be a cause of myocardial ischemia, such as acute pain or fever: these increase blood pressure and heart rate, the main components of myocardial oxygen consumption, and may precipitate myocardial ischemia, especially in patients with underlying coronary disease. Because of these biases, the comparison of cardiac events in users of analgesics compared to non-users is not relevant. The comparison of paracetamol to OTC-Strength NSAIDs, which share the same indications, may neutralize these biases. We therefore will compare the risk of OTC-Strength NSAIDs to paracetamol in a traditional cohort study.

The traditional cohort design does not cancel the time invariant confounders like SCC design. We consider using the **propensity score method** to adjust for confounders. There are many different ways to apply PS, and some maybe better than others in some circumstances but worse in others. (286,287,293–297) We thus have to choose the most suitable methods for our study.

Since the number of paracetamol users (control group) are much more numerous compared with OTC-Strength NSAIDs users (51% in the last year vs. 19% over two years (27,272)), the matching method would be more suitable than adjustment on PS or stratification on PS. (287) There are two types of matching algorithms for pair matching: greedy matching and optimal matching. (287) With greedy matching, a random treated subject is selected. The nearest untreated subject is then selected for matching to this treated subject. This untreated subject is selected even if it would better serve as a match for a subsequent treated subject. The alternative to greedy matching is optimal matching. (298) With optimal matching, pairs of treated and untreated subjects are formed so as to minimize the total within-pair differences in the propensity score. For computational reasons, optimal matching can be difficult to implement in medium to large datasets. For this reason it is not considered in the current study. (287) We will thus using the greedy matching technique.

Several propensity-score matching methods are currently employed in the medical literature: matching on the logit of the propensity score using calipers of width either 0.2 or 0.6 of the standard deviation of the logit of the propensity score; matching on the propensity score using calipers of 0.005, 0.01, 0.02, 0.03, and 0.1; and 1 digit matching on the propensity score. One study using Monte Carlo simulations found that matching using calipers of width of 0.2 of the standard deviation of the logit of the propensity score and the use of calipers of width 0.02 and 0.03 tended to have superior performance for estimating treatment effects. (287) This suggests to us to use the calipers of width of 0.2 of the standard deviation of the logit of the propensity score to match the two groups of treatment.

In conclusion, we decided to use the following designs and methods to study the cardiovascular risk of paracetamol and OTC-Strength NSAIDs

- i. Self-controlled cohort study for OTC-Strength NSAIDs and paracetamol.
- ii. Cohort study OTC-Strength NSAIDs vs. paracetamol, applying propensity score

Moreover, we also applied an additional method, **the case-control study applying disease risk score**, to verify the robustness of study results and to understand the effect of multi-exposure of OTC NSAIDs, POM NSAIDs, paracetamol as well as interactions with low-dose aspirin.

CHAPTER IV – Descriptive studies - Usage patterns of OTC NSAIDs and paracetamol in France

Introduction

Paracetamol and OTC NSAIDs such as ibuprofen are widely used to treat common pain and fever in many countries. However, because OTC drugs are usually not recorded in most healthcare databases, there are very few usage studies of these drugs, their usage patterns, quantities bought and concomitant risk factors, all of which could impact their risk profile. Before quantifying the cardiovascular risk, it is essential understanding how these drugs are used in real-life.

In France, some drugs that are available OTC can be reimbursed if prescribed, including paracetamol and NSAIDs. It is estimated that about 85% of all paracetamol sales 70% of all ibuprofen sales can be found in the national claims databases. (273) Taking advantage of this large number of users, we conducted two studies in the EGB database to describe usage patterns of paracetamol and OTC NSAIDs in France.

These two studies have been published on the British Journal of Clinical Pharmacology (BJCP). (27,272)

1. Usage patterns of 'over-the-counter' vs. prescription-strength NSAIDs

Usage patterns of 'over-the-counter' vs. prescription-strength nonsteroidal anti-inflammatory drugs in France

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Most nonsteroidal anti-inflammatory drug (NSAID)-related risks are pharmacological, dose and duration dependent.
- Although low-dose 'over-the-counter (OTC)' NSAIDs generate much speculation about their putative risks, little is known of their usage patterns, which could impact risks.
- The same is mostly true also of prescription NSAIDs.

WHAT THIS STUDY ADDS

- Only a small number (<20%) of prescription NSAIDs users buy enough drug to cover the use described in the clinical trials from which risks have been derived or modelled.
- For OTC NSAIDs, the numbers are even lower, and only a few per cent buy more than a few days' worth over a 2 year span.
- Risk models derived from clinical trials or from observational studies not including OTC-type usage may not be applicable to the real-life use of these drugs.

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AIMS

Most risks of nonsteroidal anti-inflammatory drugs (NSAIDs) are pharmacological, dose and duration dependent. Usage patterns of prescription-only (POM) or 'over-the-counter (OTC)' NSAIDs may influence risks, but are not commonly described.

METHODS

The Echantillon Généraliste de Bénéficiaires database, the permanent 1/97 representative sample from the French national healthcare insurance systems, was queried over 2009–2010 to identify usage patterns, concomitant chronic diseases and cardiovascular medication in OTC and POM NSAID users.

RESULTS

Over 2 years, 229 477 of 526 108 patients had at least one NSAID dispensation; 44 484 patients (19%) were dispensed only OTC NSAIDs (93% ibuprofen) and 121 208 (53%) only POM NSAIDs. The OTC users were younger (39.9 vs. 47.4 years old) and more often female (57 vs. 53%); 69% of OTC users and 49% of POM users had only one dispensation. A mean of 14.6 defined daily doses (DDD) were dispensed over 2 years for OTC vs. 53 for POM; 93% OTC vs. 60% POM patients bought ≤ 30 DDD over 2 years, and 1.5 vs. 12% bought ≥ 90 DDD. Chronic comorbidities were found in 19% of OTC users vs. 28% of POM users; 24 vs. 37% had at least one dispensation of a cardiovascular drug over the 2 years.

CONCLUSIONS

Most of the use of NSAIDs appears to be short term, especially for OTC-type NSAIDs, such as ibuprofen. The validity of risk estimates for NSAIDs extrapolated from clinical trials or from observational studies not including OTC-type usage may need to be revised.

1.1. Background and objective

NSAIDs, as inhibitors of COX are called, which also includes the so-called 'coxibs', are used over a very wide range of indications and patterns, from very short-term, intermittent use of low doses in common painful conditions, such as cold and influenza, headache or menstrual pain, to long-term continuous use of high doses in chronic inflammatory diseases, such as rheumatoid arthritis. Although the range of therapeutic and adverse effects of NSAIDs is very wide, in line with the ubiquitous distribution of prostaglandins, the adverse reactions of greatest concern for NSAIDs in recent years have been gastrointestinal and cardiovascular; for both of these, the dose and duration dependence of the risk has been demonstrated, in addition to other parameters such as drug half-life and selectivity for the COX isoforms. (134,172,299–306) The NSAIDs exist as prescription-only medicines (POM) and as OTC preparations, sometimes at the same dosage but with different names and pack sizes, promoted for different indications. Although NSAIDs are very common drugs, little is known of how they are really used.

The real-life use of POM NSAIDs is probably more intermittent and shorter term, even for chronic diseases, (307) than in the randomized clinical trials from which event rates or risks are often computed. (15,16,308) This would explain the lower than expected real-life event rates. (281,309) Over-the-counter NSAIDs are probably used in younger people, at lower doses, for shorter times and for different indications than POM NSAIDs. (127,310)

Given that OTC NSAIDs are usually not recorded in most healthcare databases, there are very few usage studies of these drugs, their usage patterns, quantities bought and concomitant risk factors, all of which could impact their risk profile. (127,261,311–315) In France, OTC NSAIDs may be reimbursed and recorded in the healthcare system databases if prescribed. This may represent up to 70% of all ibuprofen sales. (273) Many patients with recurrent or expected pain, such as osteoarthritis, migraine or dysmenorrhoea, will ask their physician for a prescription for these painkillers, for present or future use. In the same way, those who consult for influenza or trauma will also receive prescribed low-dose NSAIDs. Using a representative sample of the French healthcare system database, (316,317) our objective was to describe the characteristics of patients prescribed OTC and POM NSAIDs.

1.2. Methods

Data were extracted from the EGB database. Characteristic of EGB database were described in Chapter III, Section 1.2. Non prescribed self-medication OTC NSAIDs are not registered. In a previous study, we found that 84% of paracetamol sales and 70% of ibuprofen sales were reimbursed by the healthcare systems and could be identified in this database. (273)

The study cohort included all patients in EGB aged ≥ 15 years with at least one dispensation of any oral NSAID between 1 January 2009 and 31 December 2010. OTC and POM NSAIDs were identified by their ATC doses and European Pharmaceutical Market Research Association (EphMRA) codes, both of which are included in the EGB database. The ATC code M01A includes all NSAIDs. In EphRMA, low-dose NSAIDs that are used for the treatment of painful conditions and mostly approved for OTC use are identified with code N02B (analgesics), which also includes paracetamol and other analgesics (also coded N02B in ATC). The POM NSAIDs with indications for chronic inflammatory diseases have the EphRMA code M01A (anti-inflammatory drugs). The combination of ATC code M01A and EphRMA code N02B therefore identifies low-dose 'OTC' NSAIDs used for analgesia, whereas those with both ATC and EphMRA codes M01A (anti-inflammatory drugs) are the POM NSAIDs. Drugs with ATC and EphMRA codes M01A that are not NSAIDs, such as diacerein, chondroitin sulfate or glucosamine, were excluded from the study. The NSAIDs users were divided into exclusive OTC users, exclusive POM users, and mixed OTC and POM users. Exclusive OTC users were dispensed only OTC NSAIDs during the study period, whereas exclusive POM users were dispensed only POM NSAIDs. Patients who were dispensed both POM and OTC NSAIDs were not studied beyond basic demographics.

Demographic characteristics included age at the first NSAID dispensation, sex, and registration for long-term illnesses (ALD). The ALD are diagnoses that result in full coverage of all medical expenses concerning the disease. The ALD were categorized into prevalent, when patients had been registered with an ALD before inclusion, or incident, when patients had a new ALD registered after inclusion. All-type ALD was registered, and any of the five following cardiovascular ALD: stroke; chronic lower-limb arterial disease with ischaemic events; severe heart failure, severe arrhythmias, severe heart valve disease or severe congenital heart defects; severe arterial hypertension; and coronary heart disease. Cardiovascular drugs dispensed after inclusion were identified from ATC first-level code C, stratified on second-level code.

Exposure to NSAIDs was described by the name and number of NSAIDs dispensed, number and frequency of dispensations, number of DDD per dispensation, and total number of DDD dispensed over the 2 year study period. The DDD was obtained from the WHO Collaborating Centre for drug statistics methodology (http://www.whocc.no/atc_ddd_index/). If the DDD was not available, the recommended daily dose in the 2012 French national drug formulary (VIDAL® dictionary, Paris) was used. For individual drugs, DDD, strength and numbers of DDD dispensed per pack are indicated in Tables S1 and S2. The statistical analyses were conducted with SAS® 9.2 (SAS Institute, Cary, NC, USA), and were limited to descriptive analyses. There was no prior hypothesis to test, and no formal statistical comparisons were made. Considering the number of subjects in the samples, any descriptive difference >0.1% would be statistically significant, and 95% CI would be <1% of the point estimates.

1.3. Results

In the EGB, 229 477 patients aged ≥15 years had at least one dispensation of any NSAID in 2009–2010 (43.6% of the total database population of 526 108). Of these, 44 484 (19.4%) patients used only OTC NSAIDs, 121 208 (52.8%) used only POM NSAIDs, and 63 785 patients (27.8%) were dispensed both OTC and POM NSAIDs.

There were six OTC NSAIDs, namely ibuprofen, diclofenac, ketoprofen, naproxen, fenoprofen and mefenamic acid, and 20 POM NSAIDs (Appendix 5 and Appendix 6). Four NSAIDs (ibuprofen, ketoprofen, diclofenac and naproxen) were available as both OTC and POM preparations. Other NSAIDs had either only OTC preparations (1924 patients, 4.3% of exclusive OTC NSAIDs users) or only POM preparations (78 423 patients, 64.7% of exclusive POM NSAIDs users).

Table 18 shows the demographic characteristics of exclusive OTC and POM NSAID users, for all drugs combined, including those with no POM or OTC counterpart, respectively. The OTC users were younger than POM users (39.9 vs. 47.4 years old) and more often female (56.7 vs. 53.0%). Those who used both OTC and POM NSAIDs were on average 41 years old and 62.7% female. The OTC users had fewer prevalent ALD than POM users (18.9 vs. 27.6%) and fewer cardiovascular ALD. Severe arterial hypertension was the most common of the cardiovascular ALD present at inclusion, reported in 1.4% OTC vs. 2.5% POM users. New ALD reported during follow-up were more common in POM users (4.3 vs. 2.5%). There were <1% of any individual

incident cardiovascular ALD over the 2 years of observation. During follow-up, 23.7% of OTC users had at least one dispensation of a cardiovascular drug, vs. 36.7% of POM users; these were mostly β -blockers, agents acting on the renin–angiotensin system and lipid-lowering agents.

Table 18. Demographic characteristics of exclusive OTC or prescription only (POM) NSAID users

	OTC n = 44 484	POM n = 121 208
Age at the first dispensation		
Mean (years)	39.9	47.4
Median (years)	37.0	47.0
15-30	32.9	18.7
31-45	31.8	26.6
46-60	20.3	28.4
61-75	10.7	18.1
>75	4.3	8.1
Female, n (%)	56.7	53.0
Any prevalent ALD	8 407 (18.9)	33 393 (27.6)
Stroke	162 (0.4)	583 (0.5)
Lower-limb arterial disease with ischemia, n (%)	189 (0.4)	957 (0.8)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects, n (%)	302 (0.7)	1 099 (0.9)
Severe arterial hypertension, n (%)	636 (1.4)	3 066 (2.5)
Coronary artery diseases, n (%)	454 (1.0)	2 069 (1.7)
Any incident ALD	1 121 (2.4)	5 256 (4.3)
Stroke	38 (0.1)	153 (0.1)
Lower-limb arterial disease with ischemia, n (%)	28 (0.1)	201 (0.2)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects, n (%)	67 (0.2)	327 (0.3)
Severe arterial hypertension, n (%)	113 (0.3)	588 (0.5)
Coronary artery diseases, n (%)	76 (0.2)	2127 (3.5)
Users with at least one dispensation of cardiovascular drugs during follow-up (ATC code)	23.7%	36.7%
C01-Cardiac therapies	4.9%	8.0%
C02-Antihypertensive agents	1.2%	2.0%
C03-Diuretics	4.3%	7.3%
C04-Peripheral vasodilators	1.3%	2.3%
C05-Vasoprotectors	4.4%	5.9%

	OTC n = 44 484	POM n = 121 208
C07-β-Blockers	7.2%	11.3%
C08-Calcium channel inhibitors	4.2%	7.4%
C09-Agents acting on the renin–angiotensin system	10.1%	17.4%
C10-Serum lipid-reducing agents	10.4%	18.3%

ALD: long-term chronic disease resulting in full healthcare coverage

Over 2 years, OTC users bought 14.6 DDD on average, POM users 53.0 DDD (

Table 19) and the users of both OTC and POM NSAIDs bought 68 DDD (not shown). Two-thirds of OTC users had only one NSAID dispensation over 2 years, compared with half of POM users. Among patients having at least two dispensations, the average interval between dispensations was about 5 months. Half the OTC users bought fewer than seven DDD (e.g. a total of 21 400 mg or 42 200 mg ibuprofen tablets) over 2 years, and >90% of OTC users bought fewer than 30 DDD. Only 1.5% bought 90 days or more. Among POM users, 60% bought fewer than 30 DDD, 34% bought 30–180 DDD, and ~2% of users were dispensed more than 180 DDD over 2 years.

Table 19. Dispensing pattern for all exclusive OTC and POM NSAIDs

	OTC n = 44 484	POM n = 121 208
Number of different NSAIDs used within the study period		
Mean	1.0	1.5
1	97.6%	65.6%
2-3	2.4%	31.4%
≥4	0.0%	2.9%
Total number of dispensations		
Mean	1.7	2.6
1	68.7%	49.4%
2	18.5%	21.6%
3	6.2%	10.6%
≥4	6.6%	18.4%
Users with at least two dispensations of NSAIDs [n,%]		
Time interval between two dispensation (months)		
Mean	5.8	5.0
>1	11.4%	11.9%
1-2	13.1%	16.1%
2-3	11.4%	13.9%

	OTC n = 44 484	POM n = 121 208
3-4	26.9%	28.5%
6-12	25.5%	21.4%
≥12	11.6%	8.2%
Total number of DDD dispensed		
Mean	14.6	53.0
Median	6.7	22.5
Number of DDD per dispensation		
Mean	7.7	17.3
Number of DDD dispensed over 2 years (%)		
1-7	51.2	6.3
7-14	27.0	12.4
14-21	10.3	27.5
21-28	3.5	8.0
1-30	93.3	60.2
30-60	4.3	20.9
60-90	1.0	7.3
90-120	0.4	3.6
120-150	0.3	2.0
150-180	0.2	1.3
180-210	0.1	0.8
210-240	0.1	0.6
240-270	0.1	0.5
270-300	0.1	0.4
300-330	0.1	0.3
330-360	0	0.3
360-390	0	0.2
>390	0.1	1.7

DDD, defined daily dose; NSAID, nonsteroidal antiinflammatory drug; OTC, over-the-counter preparations; and POM, prescription only preparations. Any difference of >0.1% can be considered significant (P <0.05).

Among the drugs with both OTC and POM formulations (Table 20), ibuprofen users had the same OTC-type pattern for both OTC and POM NSAIDs, with >90% of users buying fewer than 30 DDD, and little or no long-term use. Ketoprofen showed distinct patterns for OTC and POM prescription, with frequent long-term use for the POM but not for the OTC forms. Diclofenac followed the OTC–POM divide, in that 87% of OTC diclofenac users bought fewer than 14 DDD over 2 years and only 3% of users bought more than 90 DDD, whereas POM users more often bought 14–35 DDD, and 10% bought more than 90 DDD. Naproxen users usually bought small amounts (mostly 14–21 DDD), but in contrast with other OTC NSAIDs, there seemed to be a more sizable long-term use for the OTC preparations. While the other drugs have only one strength available for OTC usage, ibuprofen has two main preparations, i.e. 200 and 400 mg tablets. Other strengths, such as 300 mg slow-release tablets, have marginal usage. Considering all exclusive users of ibuprofen, about 69% used exclusively 400 mg preparations (OTC or POM), and 24% used exclusively 200 mg preparations. The latter were dispensed a mean of 9.0 (SD 20.3) DDD over 2 years (median 5, interquartile range 5–8.3), and exclusive users of 400 mg preparations bought a mean of 14.7 (SD 27.2) DDD over 2 years (median 10, interquartile range 6.7–13.3). The 1 year use of individual drugs, including those with only POM preparations, which were not the main focus of the present study, is shown in Appendix 7, from the SALT study.

Table 20. Data for exclusive users of OTC or POM formulations of individual NSAIDs

	Ibuprofen		Ketoprofen		Diclofenac		Naproxen	
	OTC	POM	OTC	POM	OTC	POM	OTC	POM
n (% of all OTC or POM)	41 178 (93.0%)	3 096 (7.0%)	805 (1.8%)	19 581 (16.2%)	244 (0.5%)	15 056 (12.4%)	333 (0.7%)	5052 (4.2%)
Age at first dispensation (years)	39.8	40.6	44.7	45.2	49.8	52.6	45.6	46.
Gender female (%)	55.8	52.3	53.3%	44.5	62.7%	50.6%	62.8%	49.6%
Prevalent ALD	18.8%	18.0%	25.5%	27.2%	23.4%	30.4%	19.5%	25.3%
Incident ALD	2.5%	1.9%	2.4%	3.3%	2.0%	4.0%	3.3%	3.2%
Cardiovascular drugs	23.5%	23.3%	32.3%	30.0%	37.7%	48.2%	33.0%	32.6%
Number of dispensations	1.66	1.26	1.69	1.79	1.97	2.16	1.92	1.77
One dispensation (%)	70	87	79.3	73.5	79.5	70.3	78.4	77.9
Two or three dispensations (%)	23.9	10.9	13.8	19.7	11.2	19.1	12.3	16.4
Four or more dispensations (%)	6.1	2.1	7.0	6.8	8.6	10.7	9.3	6.7
Total number of DDD dispensed								
Mean	14.3	14.9	9.24	43.72	11.9	47.5	31.8	46.3
Median	6.67	10.0	3.33	20	3.75	22.5	8.8	17.6
Number of DDD dispensed over 2 years (%)								
1-7	52.1	0	81.9	0	67.6	0	0	0.5
7-14	26.9	79.9	8.3	9.8	19.7	2.7	66.1	0.2
14-21	10.0	13.4	3	58.6	4.1	36.1	17.4	63.8
21-28	3.3	0	1.2	1.3	2	28	3.9	3.4
1-30	93.6	96.4	94.9	69.8	93.9	74.3	87.4	69.1

	Ibuprofen		Ketoprofen		Diclofenac		Naproxen	
	OTC	POM	OTC	POM	OTC	POM	OTC	POM
30-60	4.1	2.2	2.7	20.9	2.5	12.6	4.5	20.2
60-90	0.9	0.5	1.1	2.7	1.6	4.7	2.1	4
90-120	0.4	0.4	0.4	2.2	0	1.7	0.6	1
120-150	0.3	0.1	0.1	0.6	0.8	1.2	0.6	1.3
150-180	0.2	0.1	0.1	0.8	0	1	1.5	0.8
180-210	0.1	0.1	0.4	0.4	0.4	0.6	0	0.4
210-240	0.1	0	0.2	0.4	0.4	0.5	0.9	0.2
240-270	0.1	0.1	0	0.2	0	0.5	0.3	0.4
270-300	0.1	0	0	0.2	0.4	0.3	0	0.2
300-330	0.1	0	0	0.2	0	0.2	0.3	0.1
330-360	0	0.1	0	0.2	0	0.3	0.3	0.1
360-390	0	0	0	0.1	0	0.3	0	0.2
>390	0.1	0.1	0	1.4	0	1.8	1.5	2

Abbreviations are as follows: ALD, chronic disease resulting in 100% coverage of medical expenses; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter preparations; and POM, prescription-only preparat

1.4. Discussion

About 40% of a representative sample of persons registered in the French national healthcare insurance system had at least one reimbursed dispensation of an OTC or prescription NSAID over 2 years, i.e. ~20% per year, as in Denmark. (148) About half of these were exclusive users of POM NSAIDs, and 20% exclusive users of OTC NSAIDs. Whether POM or OTC, each patient received only a very small number of dispensations, and only a few days' worth of the drugs; for the OTC NSAIDs, the average number of DDD dispensed was 14 DDD over 2 years, and 50% of users had fewer than 7 DDD, enough for two treatment episodes (3.3 DDD per episode) over 2 years. (127,261) Users of prescription NSAIDs bought an average of 53 DDD over 2 years, and half bought 23 or fewer DDD. Almost half had only one dispensation, and only 18% had four or more dispensations. These numbers are similar to a nationwide study of prescription NSAIDs in Denmark. (148)

Similar results had been found in previous studies in France, whether from regional reimbursement databases (318) or from field or combination studies.(307,310,319,320) In a randomized clinical trial of paracetamol, aspirin and ibuprofen for common pain, on average patients used 20 tablets (3.3 DDD) over 5 days of any of the three analgesics, even though they were provided with 7 DDD. (127) Similar results were found in an observational pharmacy-based study of OTC diclofenac. (261) Among 14 000 initial users of celecoxib,(321) 30% had four or more dispensations, and only 7% had six dispensations or more, similar to the CLASS study. (16) The distribution of 60–70% short-term users of POM NSAIDs (<30 days' worth over 2 years), with 30% of users using between 30 and 120 DDD, and a few per cent using 180 DDD or more, is also consistent with the usage and indications distribution found in field studies, with ~60–70% of patients using NSAIDs for common pain, 30% for osteoarthritis, and 3% for rheumatoid arthritis. (310,318–320)

Users of NSAIDs, whether OTC or POM, were rather young, slightly <40 years old for the OTC users and ~47 years old for POM users, as found in previous studies.

(127,148,261,307,310,312,313) Both OTC and prescription users had low rates of concomitant chronic diseases, as expected from their age. The younger OTC users had fewer concomitant diseases than the older POM users. Among the drugs used to treat or prevent cardiovascular

disease, the most commonly dispensed were β -blockers, agents acting on the renin–angiotensin system and lipid-lowering agents. New-onset chronic disease during the study period was rare, between 0.3 and 0.5% for hypertension and 0.2–0.3% for ischaemic heart disease. Considering the very short exposure to NSAIDs for the vast majority of these low-risk patients, the probability of a significant impact on cardiovascular risk or interaction with cardiovascular drugs appears remote. (146,161–164,322–326)

Most OTC users were dispensed fewer than 30 DDD over 2 years, whereas 40% of prescription NSAIDs users received more than 30 DDD, 12% more than 90 DDD, and ~2% more than 360 DDD. In the VIGOR study, patients received 1000 mg of naproxen daily (2 DDD), with a median follow-up of 9 months (i.e. a total of 540 DDD). In the CLASS study, patients were given 2400 mg ibuprofen (2 DDD) or 150 mg diclofenac (1.5 DDD), daily for 6 months, i.e. 360 and 270 DDD, respectively.(16) Tramer et al., (308) reviewing the gastrointestinal risks associated with NSAIDs, included only clinical trials of at least 3 months (90 DDD), which in our study represents at most 12% of POM and 1.5% of OTC users. Longer usage patterns are found only in a very small number of patients. This probably explains, at least in part, why gastrointestinal risks predicted from clinical trials(308,327) are not found at the same level in real life. (281,309) The cardiovascular risks of NSAIDs were initially demonstrated in clinical trials of selective COX-2 inhibitors. (328–330) They seem mostly to be of concern beyond 30 days of treatment,(133) which in our study is only 19% of POM users and 2.4% of OTC users. Although NSAIDs are very commonly used, only a small minority of users may be at increased risk. This is also true when the same drug exists as both OTC and POM preparations. Although OTC usage is overwhelmingly ibuprofen, other drugs, such as ketoprofen or diclofenac, also show distinct usage patterns for OTC vs. POM preparations, with less use in somewhat younger patients.

These considerations apply mostly to the pharmacologically induced adverse reactions, such as gastrointestinal bleeding and cardiovascular risk, which in both cases when this could be measured have shown a dose dependence in observational studies. (134,260,300,301,301) For nondose-dependent reactions, such as acute liver failure, we found no difference between individual NSAIDs.(225,273)

One limit of this study may be that the OTC drugs we studied had to have been prescribed to be included in the database. The use of nonprescribed OTC NSAIDs may differ from that of those prescribed OTC. However, prescribed ibuprofen represents >70% of the overall sales of ibuprofen in the country (273) (IMS, http://www.afipa.org/fichiers/20110310133130_Presentation_IMS.pdf). In a country with essentially free healthcare, including medical consultations, ibuprofen can be prescribed because of an acute pain (127) or to anticipate an expected need in patients with repeated painful episodes, such as osteoarthritis, intermittent musculoskeletal pain, migraine or period pain, so that nonprescribed OTC NSAIDs would be used only for an unanticipated or first pain episode, before a visit to a physician. Nonprescribed OTC usage in France might concern patients who would not routinely consult a physician, maybe a different population from the one studied here, but probably with even fewer concomitant medications and illnesses. Another strong incentive for using prescribed OTC medication if possible is the cost; for nonreimbursed OTC medication, the pharmacist can charge freely. The cost of prescribed OTC ibuprofen is 2.46€ (3.28\$) for 30 200 mg tablets [0.5€ (0.66\$) per DDD], mostly paid by the healthcare insurance system, compared with 2.90€ (3.87\$) for 20 200 mg tablets for the nonprescription OTC [0.9€ (1.20\$) per DDD], paid out of pocket. This may seem trivial, but could represent a significant incentive to have analgesic NSAIDs prescribed. In a study of OTC diclofenac from Norwegian pharmacies, (261) the reasons for the use and the usage pattern of individual OTC episodes were mostly the same as for prescribed OTC in the PAIN study in France. (127) However, these short-term, single-episode studies do not provide longitudinal information on possible repeated usage. In Scotland, about 30% of responders in a population survey had already used OTC analgesics (much the same as our repeat OTC dispensations), but the usage patterns were not described. (312,313)

Chronic concomitant diseases, which mainly concern the more severe chronic forms of these diseases, were rare. Severe hypertension concerned only 1.7–2.3% of the patients, and all cardiovascular ALD together concerned 4.8% of OTC and 7.8% of POM NSAIDs users; 23.7% of OTC and 36.7% of POM users had at least one cardiovascular drug (ATC class C) prescribed at any time during the study period. Of course, actual concomitance is uncertain; for OTC drugs, the average dispensation covered 2.0% of the 2 year study period, and 7.3% for prescription

NSAIDs. Most NSAIDs are not taken regularly, and an NSAID used on a given day might have been bought long before, (331) so it is difficult to say when any of the NSAIDs dispensed might have been taken, and whether that was within the period during which other drugs were used.

Other limitations are common to most healthcare databases, i.e. the dearth of data concerning comorbidities, except long-term illnesses, the lack of information on drug indications and dose prescribed. This may be a major issue in countries where the amount dispensed depends on the prescription. In France, products are dispensed as boxes with a constant number of defined-strength tablets. The total quantity of drug dispensed is perfectly determined, and so the number of DDD. As a result of this, the general indications can be deduced; it is highly unlikely that the dispensation of only a few days' worth of treatment over 2 years would be for rheumatoid arthritis or osteoarthritis, but more probably for episodes of acute pain. However, because NSAIDs are symptom-relieving drugs, the time of use in relationship to the time of dispensation may be uncertain, (331) whereas for chronically used drugs, such as antiepileptic, antihypertensive or lipid-lowering drugs, utilization will usually be consistent with dispensation.(331,332)

1.5. Conclusion

The usage patterns of OTC NSAIDs are consistent with the usual OTC or common pain indications. (127,261) Users in this study bought much less NSAID, whether OTC or prescription, than participants are usually given in clinical trials. Very few patients bought the amount of drug dispensed in most clinical trials, from which many of the risks of NSAIDs are derived. Applying the results of clinical trials to real-life usage and risks of NSAIDs should take these usage patterns into account. Any extrapolation of risk from clinical trials to real use may be only at best extremely tentative. Clearly, further real-life studies are needed to specify better the real risks of prescription or low-dose OTC NSAIDs in practice.

2. Usage patterns of paracetamol



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Usage patterns of paracetamol in France

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Keywords adults, drug utilization, paracetamol, risk factors

AIMS

The aim of the present study was to describe the real-life usage patterns of paracetamol.

METHODS

The *Echantillon Généraliste de Bénéficiaires* (EGB) database, the permanent 1/97 representative sample from the French national healthcare insurance system, was searched in 2011 to identify usage patterns, concomitant chronic diseases and use of cardiovascular medication in users prescribed single-ingredient (SP) and combination (CP) paracetamol, representing 85% of all sales.

RESULTS

Of 5 261 088 subjects aged ≥ 15 years in the EGB, 268 725 (51%) had paracetamol dispensed on ≥ 1 occasion; of these, 207 707 (77%) were dispensed only SP and 61 018 (23%) received CP with or without SP. SP users were younger (48.3 years vs. 50.5 years), and 57% of SP users vs. 58% of CP users were female. Chronic comorbidities were more common in CP than SP users. SP users had, on average, 3.4 dispensings per year vs. 5.0 for CP users, for 36 defined daily doses (DDD, 3 g) of SP vs. 53 DDD per year for CP; 49% SP users bought 1–4 DDD or fewer; 15% bought > 60 DDD. Use of paracetamol increased with age from about 16 DDD per year in 15–30-year-olds to over 90 DDD per year in patients above the age of 75; 53% of patients ≤ 60 years bought fewer than 14 DDD per year, whereas 55% of those > 60 bought more than 30 DDD per year. More than half the dispensings exceeded the legal per-box limit of 8 g.

CONCLUSIONS

Over 50% of the French adult population were dispensed paracetamol at least once over the course of a year, generally for short-term use. Considering recent misgivings on the real efficacy and safety of paracetamol, such widespread use might have important public health consequences.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Although paracetamol is used mostly in mild-to-moderate pain conditions and in chronic arthritis, and its usage pattern might be derived from these indications, there are few or no studies of actual usage patterns and drug exposure or burden.

WHAT THIS STUDY ADDS

- Over 50% of all adults in the database were dispensed paracetamol at least once in 2011.
- The median amount of paracetamol dispensed over 1 year was seven defined daily doses (or 21 g), and this increased with age.
- Only 15% of subjects received more than 60 days' worth of paracetamol in a year.

2.1. Background and objective

Paracetamol (acetaminophen in the USA) is a widely used, relatively weak analgesic with a mostly unknown mechanism of action, although it has been suggested that it may act as a weak cyclooxygenase 2 inhibitor. (333) As it has been marketed for over 70 years, it has a reputation of being safe, except in overdose. (230,334) However, there have been recent reports that paracetamol might not be as safe (224,225) or as effective (75,335–339) as commonly believed.

Paracetamol is available OTC without prescription in most countries, and therefore its use is not captured in population databases, be they electronic health records or claims reimbursement databases. In France, even though it is also available OTC, paracetamol will be reimbursed if prescribed. It will then be found in the national claims databases. In fact, paracetamol is the most widely prescribed drug in France, with 2.4 billion defined daily doses (DDD, 3 g), equivalent to >7.5 kilotons paracetamol reimbursed over 3 years. (225,230,273) Comparing overall sales data to reimbursed quantities, it is estimated that about 85% of all paracetamol sales can be found in the national claims databases. (273) As prescribed drugs are mostly free of charge within the national healthcare system, this may explain why France has the highest per capita sales of paracetamol among the seven countries (France, UK, Italy, Netherlands, Ireland, Portugal, Greece) in the SALT study (51.5 g per inhabitant per year, vs., for example, 34.9 g in the UK and 24.1 g in Ireland). (230)

In spite of its widespread use, little is known of the usage patterns of paracetamol. (340) Taking advantage of its presence in the French claims databases, the aim of the present study was to describe the usage pattern of single-ingredient paracetamol (SP) and paracetamol in combination with other agents (CP) in France, much as we had studied OTC and prescription NSAIDs. (27)

2.2. Methods

Data source

Data were extracted EGB database. Characteristic of database we described in Chapter III, Section 1.2.

Study population

The study cohort included all patients in the EGB aged ≥ 15 years with at least one dispensing of any oral paracetamol preparation between 1 January 2011 and 31 December 2011. Patients in the study cohort were followed for 365 days after the first dispensing in 2011. Demographic characteristics included age at the first paracetamol dispensing, gender and registration for chronic diseases (*Affections de Longue Durée* - ALDs). ALDs are diagnoses that result in full coverage of all medical expenses related to the disease. (277,282,341) Prevalent ALDs were those that were present at the time of inclusion. All-type ALD was considered, as well as any of the five cardiovascular ALDs: stroke; chronic lower-limb arterial disease with ischaemic events; severe heart failure, severe arrhythmias, severe heart valve disease or severe congenital heart defects; severe arterial hypertension; coronary heart disease. Use of other drugs, including NSAIDs, amoxicillin, aspirin, cardiovascular drugs antithrombotic agents and antidiabetic agents, during follow-up was also identified by their ATC codes.

Exposure definition

SC and CP preparations were identified by their ATC codes. The ATC code for SP is N02BE01; CP preparations were identified by the following codes: N02BE51 (combinations of paracetamol excluding psycholeptic agents), N02BE71 (combinations of paracetamol and psycholeptic agents) and N02AA59 (combinations of paracetamol and codeine). Paracetamol users were classified into exclusive SP users and CP users. Exclusive SP users were dispensed only SP during the study period, whereas CP users had at least one dispensing of CP, but could also receive SP. Paracetamol exposure was described by the number of dispensings, number of DDD per dispensing and total number of DDD dispensed over the study period. The DDD for SP was 3 g, as described by the World Health Organization Collaborating Centre for drug statistics methodology (http://www.whocc.no/atc_ddd_index/). If the DDD was not available, the recommended daily dose in the 2012 French national drug formulary (VIDAL® dictionary, Paris) was used.

Statistical analysis

The statistical analyses were carried out using SAS® (SAS Institute, Cary, NC, USA) 9.2, and were limited to descriptive analyses. There was no prior hypothesis to test and no formal statistical comparisons were made. Considering the number of subjects in the samples, any descriptive difference greater than 0.1% was considered statistically significant, and 95% confidence intervals (CIs) would be less than 1% of the point estimates. (27)

2.3. Results

In 2011, the EGB database included a total population of 526 108 patients aged ≥ 15 years. Among them, 268 725 patients (51%) had at least one dispensing of paracetamol in 2011. Of these, 207 707 (77%) were SP users and 61 018 (23%) were CP users. Table 21 shows the demographic characteristics of the two populations of paracetamol users. Gender distribution was similar between the two groups (57% of SP users were female vs. 58% for CP). Exclusive SP users were younger (mean age \pm standard deviation: 48.3 ± 20.2 years) than CP users (50.5 ± 18.7 years); CP users had more ALD, including diabetes, coronary heart disease and hypertension. During the 1-year follow-up, SP users also bought NSAIDs (53%), amoxicillin (36%), aspirin (3.4%), antithrombotic agents (including low-dose aspirin), cardiovascular drugs (17%) and antidiabetics (7%). CP users bought more NSAIDs, amoxicillin, aspirin, antithrombotic agents, other cardiovascular drugs and antidiabetics than SP users.

Table 21. Demographic characteristics of paracetamol users

	Single component Paracetamol only users N = 207707	Combined Paracetamol users N = 61018
Age		
Mean (\pm sd)	48.3 (20.2)	50.5 (18.7)
Median (IQR)	47.0 (31.0)	50.0 (28.0)
15-30	47709 (23.0)	9969 (16.3)
31-45	52194 (25.1)	15670 (25.7)
46-60	47129 (22.7)	16996 (27.9)

	Single component Paracetamol only users N = 207707	Combined Paracetamol users N = 61018
61-75	35355 (17.0)	11172 (18.3)
>75	25320 (12.2)	7211 (11.8)
Female, n (%)	118367 (57.0)	35625 (58.4)
Any prevalent ALD, n (%)	44756 (21.5)	16069 (26.3)
Stroke, n (%)	1506 (0.7)	451 (0.7)
Lower-limb arterial disease with ischemia, n (%)	2067 (1.0)	804 (1.3)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects, n (%)	3512 (1.7)	1156 (1.9)
Diabetes type I, II, n (%)	9355 (4.5)	3298 (5.4)
Severe arterial hypertension, n (%)	6137 (3.0)	2127 (3.5)
Coronary artery diseases, n (%)	4469 (2.2)	1402 (2.3)

ALD: long-term chronic disease resulting in full healthcare coverage.

SP users had an average of three dispensings over the year, compared with five for CP, with an average of 8.3DDDper SP dispensing vs. 8.4 for CP (Table 22). Over the course of the year, SP users bought a mean of 36DDD, with a median of 16DDDper year. CP bought a mean of 53DDD, with a median of 25DDD. Forty-nine percent of SP users bought 14 DDD or fewer over the year, and 25% of CP users bought more than 60 DDD over the year.

Table 22. Dispensation pattern of paracetamol users

	Single component Paracetamol only users N = 197888	Combined Paracetamol users N = 59739
Number of dispensations		
Mean (\pm sd)	3.4 (3.1)	5.0 (4.0)
Median (IQR)	2.0 (3.0)	4.0 (5.0)
1	63186 (30.4)	7075 (11.6)
2-3	79050 (38.1)	20668 (33.9)
4-6	37760 (18.2)	17617 (28.9)
7-12	22506 (10.8)	12011 (19.7)

	Single component Paracetamol only users N = 197888	Combined Paracetamol users N = 59739
>12	5205 (2.5)	3647 (6.0)
Average DDD per dispensation:		
Mean (\pm sd)	8.3 (6.0)	8.4 (5.8)
Median (IQR)	7.0 (5.0)	7.0 (5.0)
Total number of DDD dispensed in one year		
Mean (\pm sd)	35.9 (58.8)	53.1 (80.8)
Median (IQR)	16.0 (27.0)	25.0 (47.0)
1-7	45738 (22.0)	8749 (14.3)
8-14	55372 (26.7)	10379 (17.0)
15-21	32010 (15.4)	8516 (14.0)
22-28	12563 (6.0)	5346 (8.8)
>28	62024 (29.9)	28028 (45.9)
1-30	150060 (72.2)	34465 (56.5)
31-60	26972 (13.0)	11530 (18.9)
>60	30675 (14.8)	15023 (24.6)
Dispensations of other drugs during follow-up		
NSAIDs, n (%)	109985 (53.0)	43463 (71.2)
Amoxicillin, n (%)	73874 (35.6)	24651 (40.4)
Aspirin, n (%)	7104 (3.4)	2211 (3.6)
Antithrombotic agents, n (%)	34920 (16.8)	12684 (20.8)
Other cardiovascular drugs, n (%)	76871 (37.0)	25903 (42.5)
Antidiabetic drugs, n (%)	14832 (7.1)	5050 (8.3)

Use of paracetamol increased with age, from about 16 DDD in patients aged 15–30 years, to over 90 DDD in patients above the age of 75 years (Figure 12). The distribution of usage in DDD per year was clearly different between those who were ≤ 60 years and >60 years: 53% of patients aged ≤ 60 years bought fewer than 14 DDD and only 9% of them bought more than 60 DDD, whereas 37% of users aged ≥ 60 years bought more than 60 DDD of paracetamol (Figure 13). Women bought slightly more paracetamol than men, with 35% buying more than 30 DDD

vs. 28% in men. The proportion of SP and CP users were not different among age groups (around 80% and 20%, respectively, in all age groups) (Figure 14).

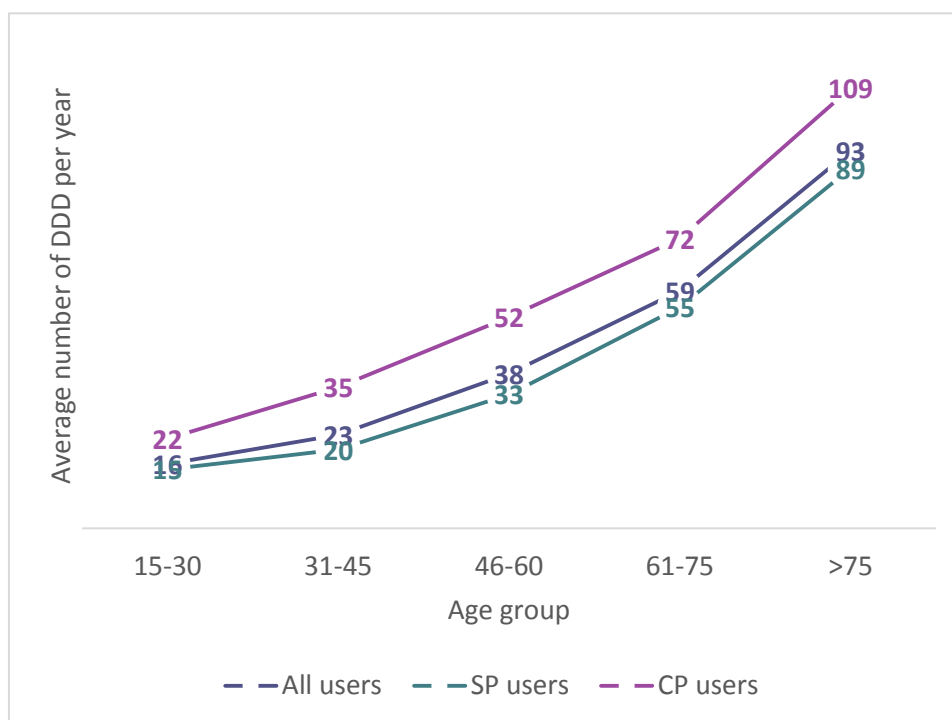


Figure 12. Average number of DDD dispensed per year in paracetamol users

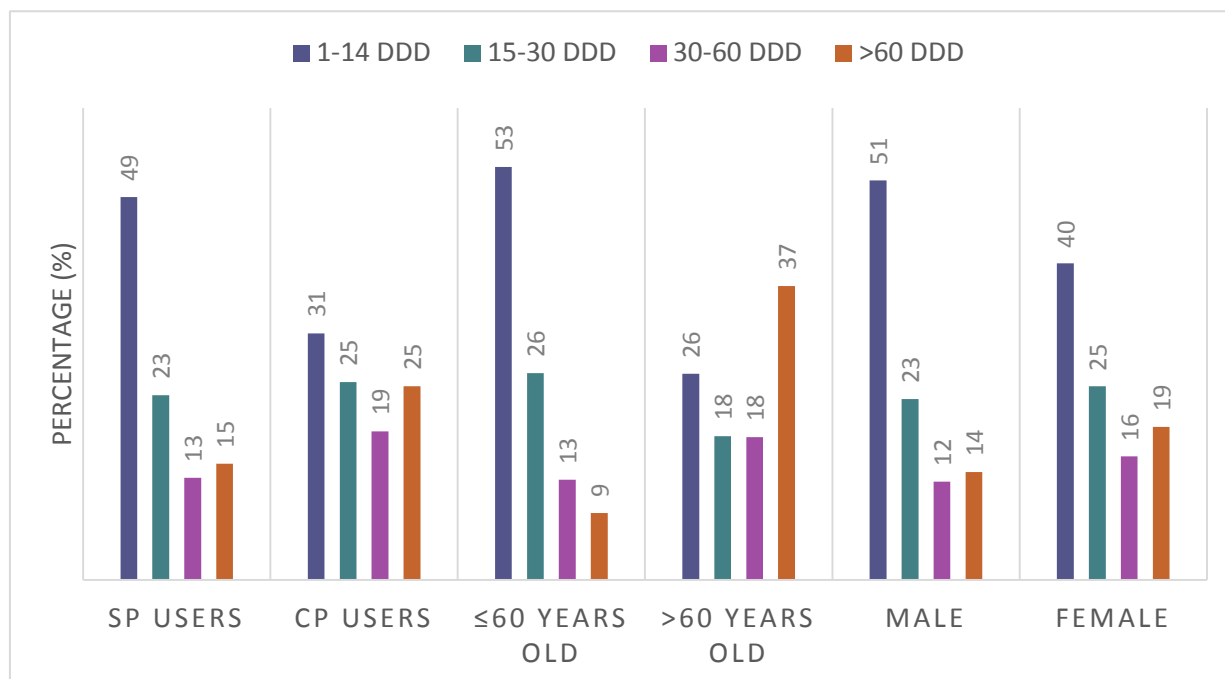


Figure 13. Number of DDD by types of paracetamol users, age groups and gender

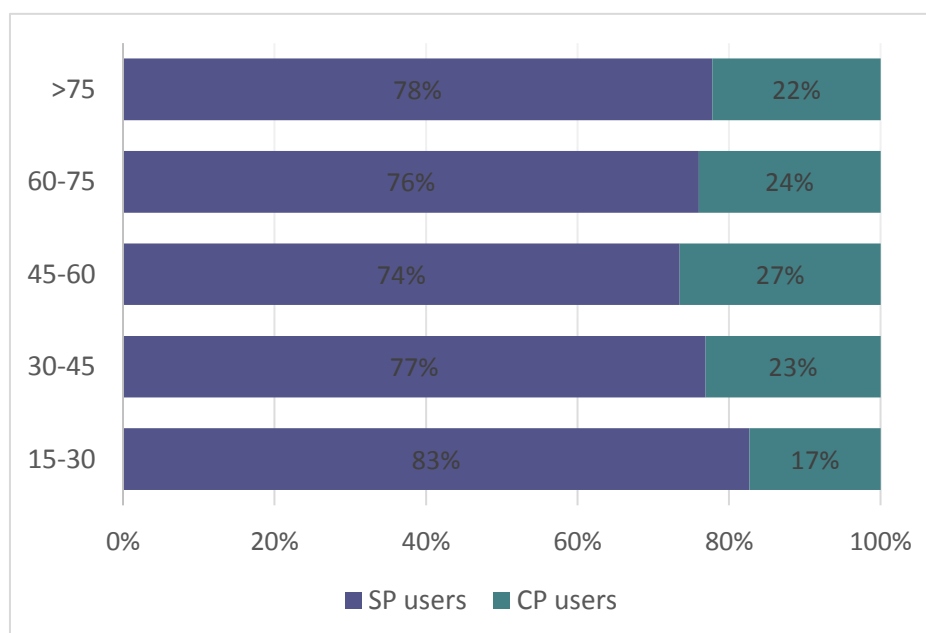


Figure 14. Type of Paracetamol users by age groups

2.4. Discussion

Little is known about the usage patterns of paracetamol, either in the form of SP (available OTC) or as CP, mostly in combination with opiates such as codeine, available only by prescription. In this representative sample of the French population, 51% of the population aged ≥ 15 years were prescribed and dispensed paracetamol at least once in a year. This was mostly SP, with 23% being prescribed CP at least once. The usage patterns in SP and CP users are likely to correspond to different indications, the former for acute pain episodes, with short term intermittent use, and the latter for more chronic indications such as osteoarthritis and rheumatoid arthritis, in the same way as for NSAIDs. (310,319,320) The average SP user was around 48 years of age, which is similar to the findings in other studies of common pain. (127) Users of CP received an average of 53 DDD over the year, which is similar to the findings for prescription-only NSAIDs. (27) Forty-four per cent of CP users received more than 30 DDD (compared with 40% for prescription-only NSAIDs). SP users bought an average of 36 DDD over

a year but 49% received fewer than 14 DDD per year, compared with 78% for OTC-strength NSAIDs. (27) Forty percent were also dispensed antibiotics, predominantly amoxicillin, which suggests the use of paracetamol for acute infectious episodes.(342) This certainly could contribute to the high rate of prescribed paracetamol; patients seeing their physician for painful febrile episodes would be prescribed paracetamol along with antibiotics and other medicines. The added risk of this combination on hepatotoxicity is unknown.

2.5 Conclusion

Over 50% of the French population buy prescribed paracetamol at least once in a year, mostly in quantities consistent with short-term use. The increased use with increasing patient age is consistent with concomitant chronic disease and a reluctance to use NSAIDs in this population, in spite of evidence of poor efficacy of paracetamol. Considering the increasing concerns about the potential risks of paracetamol, even in non-overdose quantities, (225) the recommendations on the use of paracetamol should be revisited.

3. General conclusion of the utilisation studies

These two studies, presented as they were published, confirm the widespread use of NSAIDs at OTC and POM doses, and of paracetamol. The descriptions of low-dose ibuprofen and paracetamol is original: though there has been some data on the usage patterns of OTC Strength NSAIDs, from the PAIN and the Hasford studies among others, which the present study confirms, there was no indication of the actual size of the user population in France. The same is even more true for paracetamol. This is the first countrywide survey of paracetamol usage, showing that in France at least, about 50% of the population is prescribed and dispensed paracetamol at least once in a year. They also confirmed that the users are predominantly young, especially for NSAIDs, and female, predicting lower event rates in this population.

Short term exposure is predicated by the small number of yearly tablets bought, the equivalent of 14 days worth of treatment. Fewer than a small percent of users, even for prescription strength preparations, buy enough medicine to have exposures similar to those incurred in the trials demonstrating the cardiovascular toxicity of Cox-2 preferential NSAIDs.

Paracetamol users tend to be older than NSAIDs users, and to receive more drug each year.

These patterns are described in the National calims database, which cover 85% of all paracetamol sold in France, and about 70 of all ibuprofen at OTC or prescription strength, where OTC strength represents over 80% of all prescriptions. There is no information on the remainder, which might be bought wholesale by hospitals or clinics for inpatient use, or bought in pharmacies by patients. However, the likelihood that patients with chronic use and regular visits to their physician for concomitant diseases would not ask for a prescription is more than remote. Spontaneous OTC use of the drugs without a prescription would most probably be for unexpected acute pain such as toothache or trauma, not leading to medical consultation and prescription. These patterns would probably not alter the risks we describe in the prescribed population.

CHAPTER V - Analytical studies – Cardiovascular risk associated with OTC-Strength NSAIDs and paracetamol

Introduction

In the descriptive studies, we have found that 'OTC' NSAIDs users in real-life bought much less than prescription NSAIDs users. In two years, only 2.4% OTC users bought more than 30 DDD, which is the shortest treatment duration in clinical trials. Thus, applying the results of clinical trials or observational studies of prescription NSAIDs to real-life OTC NSAIDs usage may be inappropriate.

Over 50% of the French population buy prescribed paracetamol at least once in a year. Any risk associated with paracetamol might be a major public health issue. The increased use with increasing patient age is consistent with concomitant chronic disease and a reluctance to use NSAIDs in this population. In spite of evidence of poor efficacy of paracetamol, the increasing use of paracetamol in the elderly might be a concern, particularly when its cardiovascular safety has not been confirmed.

To help patients, prescribers, and regulators make decisions as to the most appropriate drug to recommend in conditions of common acute pain, this Chapter aims to answer the questions that we posed earlier:

1. Is there an excess cardiovascular risk associated with OTC-strength NSAIDs?
2. Is there a cardiovascular risk associated with the use of paracetamol?
3. How do the risks associated with low-dose NSAIDs and paracetamol compare?
4. Are these risks modified by other cardiovascular risks or medication, including low-dose aspirin?

To answer the first questions, the risks associated with OTC-strength NSAIDs were compared to non-users in a self-controlled cohort study (Section 1.1). According to the descriptive study,

Ibuprofen represents over 90% OTC-strength NSAIDs use in France, (27) we therefore restricted the analyses to OTC-strength ibuprofen only. Similarly, a self-controlled cohort study was used to evaluate the risks associated with paracetamol (Section 1.2). To answer the third question, we conducted a propensity matched cohort study (Section 2). For the last question, we conducted stratified analyses by low-dose aspirin concomitant use.

In addition, to ensure the robustness of results, and to understand the effect of multi-exposure of OTC NSAIDs, prescription NSAIDs, paracetamol and low-dose aspirin, we we carried out a nested case-control study (Section 3).

The manuscript about the cardiovascular safety of paracetamol in the self-controlled cohort study has been submitted to the British Medical Journal and in the peer review process. Two other papers about the cardiovascular risk of OTC-Strength ibuprofen, corresponding to the self-controlled cohort and the PS-matched cohort study, are going to be submitted very soon.

1. Self-controlled cohort studies

1.1. OTC-Strength ibuprofen

1.1.1. Background and objective

NSAIDs are among the most frequently prescribed drugs worldwide with a very wide range of indications and usage patterns, from very short-term, intermittent use of low doses in common painful conditions such as headache or menstrual pain, to long-term continuous use of high doses in chronic inflammatory diseases such as RA or OA. (272,319,320) About 70% of NSAIDs users take it for common pain, 30% for OA and RA. (310,319)

Our previous study showed that the usage pattern of OTC-Strength and Prescription-Strength NSAIDs in France were much different. OTC-strength NSAIDs was used for much shorter periods of time, only 14.6 defined daily doses (DDD) over two year in average, than prescription-strength (53 DDD over 2 years). (27) OTC users were also younger with less concomitant diseases.(27) Most of the published data on cardiovascular safety of NSAIDs refers to

prescription rather than OTC strength and use. OTC drugs are notoriously difficult to study because they usually do not appear in physician notes or electronic health records, and thus are not included in claims databases. Because of the low event rates, randomized comparative trials would require inordinate patient populations, of several hundred thousand patients to acquire the required number of events. (127,343) In France, some drugs available OTC are also reimbursed and recorded if prescribed, such as low-dose aspirin for cardiovascular prevention, ibuprofen at OTC strengths and paracetamol. (27,272) Reimbursed low-dose ibuprofen in France represents about 70% of all sales (273) so that there is a sizable amount of data on OTC-strength ibuprofen in France. Ibuprofen is available by prescription and OTC and OTC-Strength ibuprofen (OSI) represented over 90% of OTC NSAIDs in France. (272) Taking advantage of the large number of OSI available in the claim database, this study aimed to evaluate the risk of acute coronary syndromes (ACS), myocardial infarction (MI) and stroke associated with the use of OSI in the general population.

1.1.2. Methods

Study design

This was a population-based self-controlled cohort study of OTC-strength ibuprofen (OSI) in the EGB database. The analysis unit was treatment episode with exclusive use of OSI. Outcomes were hospital discharge diagnoses of acute coronary syndrome (ACS), myocardial infarction (MI) and stroke.

Data source

Data were retrieved from the EGB database. Characteristics of EGB database was described in Chapter III - Section 1.2.

Study population

All persons with at least one dispensing of OTC-strength ibuprofen between May 1st, 2009 and September 1st, 2014 in EGB, aged ≥ 18 year-old were included in this study.

Ibuprofen preparations were identified by the ATC code M01AE01. We used the EphMRA classifications to identify OSI and prescription-strength ibuprofen (PSI). EphMRA classifies products according to their indications and use. Ibuprofen preparations with EphMRA code

M01A (anti-inflammatory and anti-rheumatic products, non-steroidals) were classified as PSI, whereas ibuprofen preparations with EphMRA code N02B (analgesic) were classified as OSI. Paracetamol was identified by ATC code N02BE01, N02BE51, N02BE71, N02AA59 (single-ingredient and in combinations). Low-dose aspirin was identified by ATC code B01AC06.

Exposure

The number of DDD per dispensing was calculated as the total dose dispensed divided by the DDD of the substance, 1200 mg for ibuprofen. We created episodes of use by linking consecutive dispensings of the same substance when the time elapsed between the end of supply of one dispensing and the next dispensing was 30 days or less. The index date (t0) was defined as the first day of the treatment episode. The last day of the episode was defined as the 30th day after the end of drug supply. We excluded OSI episodes with current exposure to other NSAIDs or PSI at t0. Episodes with no history of exposure to OSI in the six previous months were defined as new users; otherwise, they were defined as past/recent users.

Outcomes and follow-up

Outcomes of interest were ACS, MI and stroke. ACS was identified by primary discharge diagnosis ICD-10 codes I21 (MI - myocardial infarction) and I20.0 (unstable angina). This combination of ICD-10 codes could identify 83.6% of ACS. (276) In cases of multiple admissions of a patient for MI or unstable angina, only the first stay was included in our final analysis. Stroke was identified by ICD-10 code I63 (ischemic or unspecified stroke).

The risk period started at t0, ended at any of the following: 3 months from t0, the next treatment episode of OSI or a dispensing of other NSAIDs, the end of study period (December 31st, 2014), or death of patient.

For ACS and MI outcome, the control period started at the 105th day (3.5 months) before t0 or the beginning of study period (January 1st, 2009); ended at the day of any NSAIDs dispensing or 15 days before t0 (

Figure 15). For stroke, the control period started at the 120th day (4 months) before t0 or the beginning of study period (January 1st, 2009); ended at the day of any NSAIDs dispensing or 30 days before t0. Thus, all patients have about 3 months of follow-up before and after t0. The 15

and 30 days of wash-out period are to limit the immortal time bias due to the duration of hospitalization before t0 (because our database does not include drugs use in hospital). Patients were followed-up during their risk and control period until the day of hospital admission of any outcome of interest.

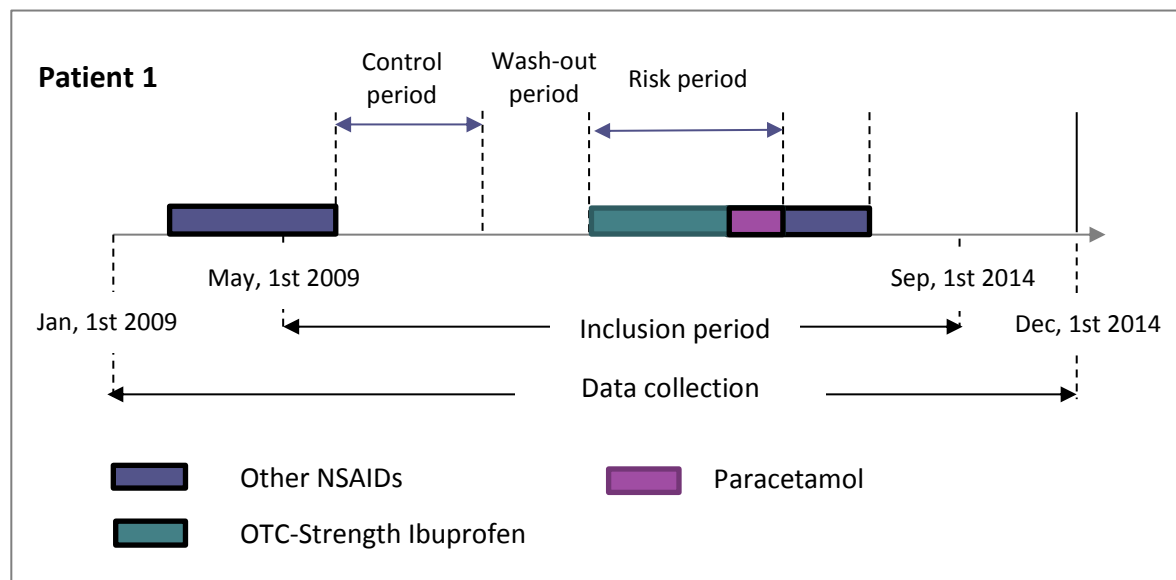


Figure 15. OTC-Strength Ibuprofen self-controlled cohort study design

Potential confounders

All time-invariant confounders (age, sex, comorbidities) are self-adjusted with a self-controlled cohort design. (289) However, concomitant drugs cannot be addressed. Thus, we excluded OSI episodes with co-exposure to other NSAIDs or PSI. Episodes with concomitant paracetamol and low-dose aspirin (LDA) were kept for the interaction analysis.

Demographic variables (age, sex) and other baselines variables (prevalent long-term diagnosis of stroke, lower-limb arterial disease with ischemia, severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects, diabetes type 1 or 2, severe arterial hypertension and coronary artery diseases), concomitant drugs (high dose aspirin, low-dose aspirin, other thrombotic agents, antidiabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, vasoprotectors, β -blockers, calcium channel

inhibitors, agents acting on the renin-angiotensin system, serum lipid reducing agents) were used to described the study population.

Statistical analysis

In addition to usual descriptive analysis of the population included in the study, the crude events rates (ERs) during risk and control periods were described. ERs were estimated as the number of outcomes observed divided by the number of episode-months followed-up during risk and control periods. Event rate ratio (ERR) was then calculated as the event rate during risk period, divided by the event rate during control period. Conditional Poisson regression was used estimate ERRs and their 95% confidence interval (CI). Because of the potential interaction of low- LDA and ibuprofen (139,168,171,344), we stratified OSI in two separate groups, with LDA (at least one LDA dispensing in the four months preceding and/or 3 months following t0) and without LDA (no LDA dispensing during the total 7-month follow-up before and after t0).

Analyses were also done in different strata according to different condition of use, including age, concomitant use of paracetamol, previous exposure (new episodes or episodes of recent/past use). To study the time course of ACS risk, we divided the follow-up times to months and fortnight interval and estimated the event rates and HRs in interval time.

All statistical analyses and data management were performed with the SAS statistical software package, version 9.4 (SAS Institute Inc, Cary, NC).

1.1.3. Results

The study cohort included 316 265 OSI episodes in 168 407 subjects (

Figure 16).

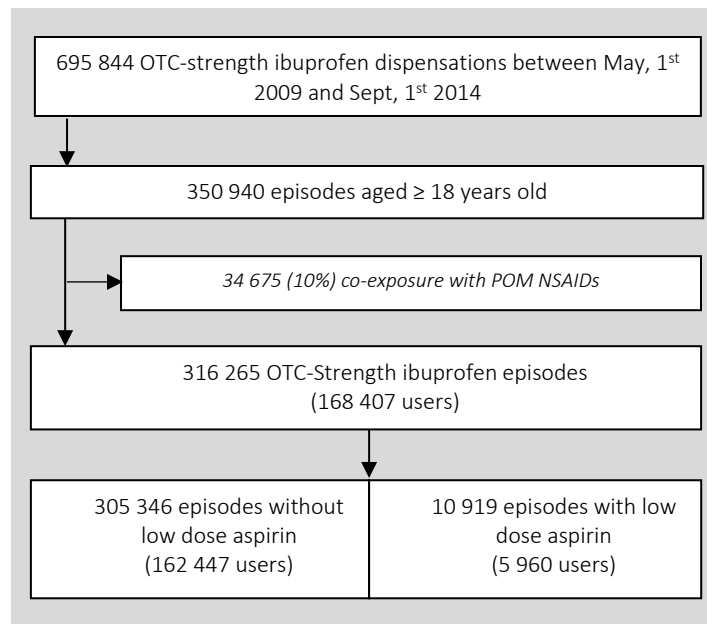


Figure 16. Patient flow-chart of OTC-Strength ibuprofen self-controlled cohort study

Baseline characteristics of OSI users at the time of their first episodes of use and over all episodes are described in Table 23. Mean age of users at the time their first treatment episode was 43.0 years; 58.2% were female. Prevalence of long-term illnesses was low in the study cohort; the most frequent was diabetes type 1 or 2. Paracetamol was co-dispensed in 32.6% of all OSI episodes. Episodes with low-dose aspirin represented only 3.5% of the whole cohort.

In 824 606 person-months (PM) followed-up before t0 and 843 570 PM followed-up after t0, respectively 67 and 100 ACS events were identified (ER 0.81 vs. 1.18 per 10 000 PM (10 KPM), equivalent to 1.0 vs. 1.4 per thousand person-years); 30 and 54 MI events (ER 0.36 vs. 0.64 per 10 KPM, equivalent to 0.4 vs. 0.8 per thousand person-years) (Table 24). For stroke outcome, we identified respectively 22 and 50 event in 824 140 PM followed-up before t0 and 843 570 PM followed-up after t0 (ER 0.27 vs. 0.59 per 10 000 PM, equivalent to 0.32 vs. 0.71 per thousand person-years).

Overall, there were significant increases of all cardiovascular risks after OSI dispensing compared to the period before dispensing (ACS ERR 1.46 [95%CI 1.07-1.99]; MI 1.76 [1.13-2.75]; Stroke 2.22 [1.34-3.67]) (Table 24, **Erreur ! Source du renvoi introuvable.**).

Table 23. Characteristics of patient in all episodes and at their first episodes of OTC-Strength Ibuprofen use

	All episodes n = 316 265	First episodes n = 168 407
Mean age, years (\pm SD)	43.5 (16.0)	43.0 (16.5)
<60 year-old	262385 (83.0)	139455 (82.8)
\geq 60 year-old	53880 (17.0)	28952 (17.2)
Female, n (%)	198238 (62.7)	98047 (58.2)
Prevalent long-term illnesses, n (%)		
Stroke	1129 (0.4)	612 (0.4)
Lower-limb arterial disease with ischemia	1331 (0.4)	765 (0.5)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	2024 (0.6)	1169 (0.7)
Diabetes type I, II	10640 (3.4)	5366 (3.2)
Severe arterial hypertension	4314 (1.4)	2362 (1.4)
Coronary artery diseases	2994 (0.9)	1751 (1.0)
Low-dose aspirin dispensed in 3 preceding and following months, n (%)	11132 (3.5)	5960 (3.5)
Other concomitant drugs		
Paracetamol	103047 (32.6)	56096 (33.3)
High dose aspirin	958 (0.3)	464 (0.3)
Thrombotic agents	6042 (1.9)	2849 (1.7)
Antidiabetic agents	5651 (1.8)	2356 (1.4)
Cardiac therapies	2462 (0.8)	1169 (0.7)
Antihypertensive agents	1281 (0.4)	529 (0.3)
Diuretics	4114 (1.3)	1725 (1.0)
Peripheral vasodilators	553 (0.2)	300 (0.2)
Vasoprotectors	1007 (0.3)	614 (0.4)
β -blockers	10256 (3.2)	3868 (2.3)
Calcium channel inhibitors	4144 (1.3)	1756 (1.0)
Agents acting on the renin-angiotensin system	14516 (4.6)	5925 (3.5)
Serum lipid reducing agents	13218 (4.2)	5513 (3.3)
Number of DDD in episode		
Mean (days)	10.3 (27.2)	9.2 (27.5)
Median (days)	7.0	7.0
New users	181416 (57.4)	129448 (76.9)
Past/recent users	134849 (42.6)	38959 (23.1)

Table 24. Risk of myocardial infarction, acute coronary syndrome and stroke associated with OTC-strength ibuprofen use

	No. Episodes		Control period			Risk period			ERR (95%CI)
			Person- months	Event	rate [¶]	Person- months	Event	rate [¶]	
ACS									
All episodes	316265	(100.0)	824606	67	0.81	843570	100	1.18	1.46 (1.07 – 1.99)
With LDA [§]	10919	(3.5)	29009	51	17.6	29883	80	26.8	1.52 (1.07 – 2.16)
Age <60	3377	(1.1)	9215	18	19.5	9561	35	36.6	1.87 (1.06 – 3.31)
Age ≥60	7542	(2.4)	19793	33	16.6	20322	45	22.1	1.33 (0.85 – 2.08)
Without LDA	305346	(96.5)	795597	16	0.20	813687	20	0.24	1.22 (0.63 – 2.36)
Age <60	259008	(81.3)	675596	6	0.09	689638	11	0.16	1.80 (0.66 – 4.85)
Age ≥60	46338	(15.2)	120001	10	0.83	124049	9	0.72	0.87 (0.35 – 2.14)
Age <60	262385	(83.0)	684812	24	0.35	699199	46	0.66	1.88 (1.15 – 3.07)
Age ≥60	53880	(17.0)	139794	43	3.07	144371	54	3.74	1.22 (0.81 – 1.82)
With P [¥]	56096	(17.7)	272474	12	0.44	277511	24	0.86	1.96 (0.98 – 3.93)
Without P	260169	(82.3)	552132	55	0.10	566058	76	1.34	1.35 (0.95 – 1.91)
New users	181416	(57.4)	544248	48	0.88	497510	58	1.16	1.32 (0.90 – 1.94)
Recent/Past user	134849	(42.6)	280358	19	0.68	346060	42	1.21	1.79 (1.04 – 3.08)
MI									
All episodes	316265	(100.0)	824606	30	0.36	843570	54	0.64	1.76 (1.13 – 2.75)
With LDA	10919	(3.5)	29009	22	7.58	29883	45	15.0	1.98 (1.19 – 3.31)
Age <60	3377	(1.1)	9215	7	7.60	9561	19	19.9	2.62 (1.10 – 6.22)
Age ≥60	7542	(2.4)	19793	15	7.57	20322	26	12.8	1.67 (0.89 – 3.19)
Without LDA	305346	(96.5)	795597	8	0.10	813687	9	0.11	1.10 (0.42 – 2.85)
Age <60	259008	(81.3)	675596	4	0.06	689638	5	0.07	1.22 (0.33 – 4.56)
Age ≥60	46338	(15.2)	120001	4	0.33	124049	4	0.32	0.97 (0.24 – 3.87)
Age <60	262385	(83.0)	684812	11	0.16	699199	24	0.34	2.14 (1.05 – 4.36)
Age ≥60	53880	(17.0)	139794	19	1.36	144371	30	2.08	1.53 (0.86 – 2.71)
With P [¥]	56096	(17.7)	272474	5	0.18	277511	11	0.39	2.16 (0.75 – 6.22)
Without P	260169	(82.3)	552132	25	0.45	566058	43	0.76	1.68 (1.02 – 2.75)
New users	181416	(57.4)	544248	23	0.42	497510	30	0.60	1.43 (0.83 – 2.46)
Recent/Past user	134849	(42.6)	280358	7	0.25	346060	24	0.69	2.78 (1.20 – 6.45)

	No. Episodes		Control period			Risk period			ERR (95%CI)
			Person-	Event		Person-	Event		
	(%)	months	Event	rate [¶]	months	Event	rate [¶]		
Stroke									
All episodes	316265	(100.0)	824140	22	0.27	843570	50	0.59	2.22 (1.34 – 3.67)
With LDA	10919	(3.5)	29008	17	5.86	29883	30	10.0	1.71 (0.94 – 3.10)
Without LDA	305346	(96.5)	795132	5	0.06	813687	20	0.24	3.91 (1.47 – 10.4)
Age <60	262385	(83.0)	684345	11	0.12	699199	11	0.16	0.98 (0.42 – 2.26)
Age ≥60	53880	(17.0)	139795	11	0.79	144371	39	2.70	3.43 (1.76 – 6.70)

LDA, Low-dose aspirin; P, paracetamol; [¶] Episodes with at least one dispensing of low-dose aspirin in ±3 months from the index date; ^{*} Episodes with paracetamol dispensed on the index date; [¶] Event rate per 10,000 episodes-month

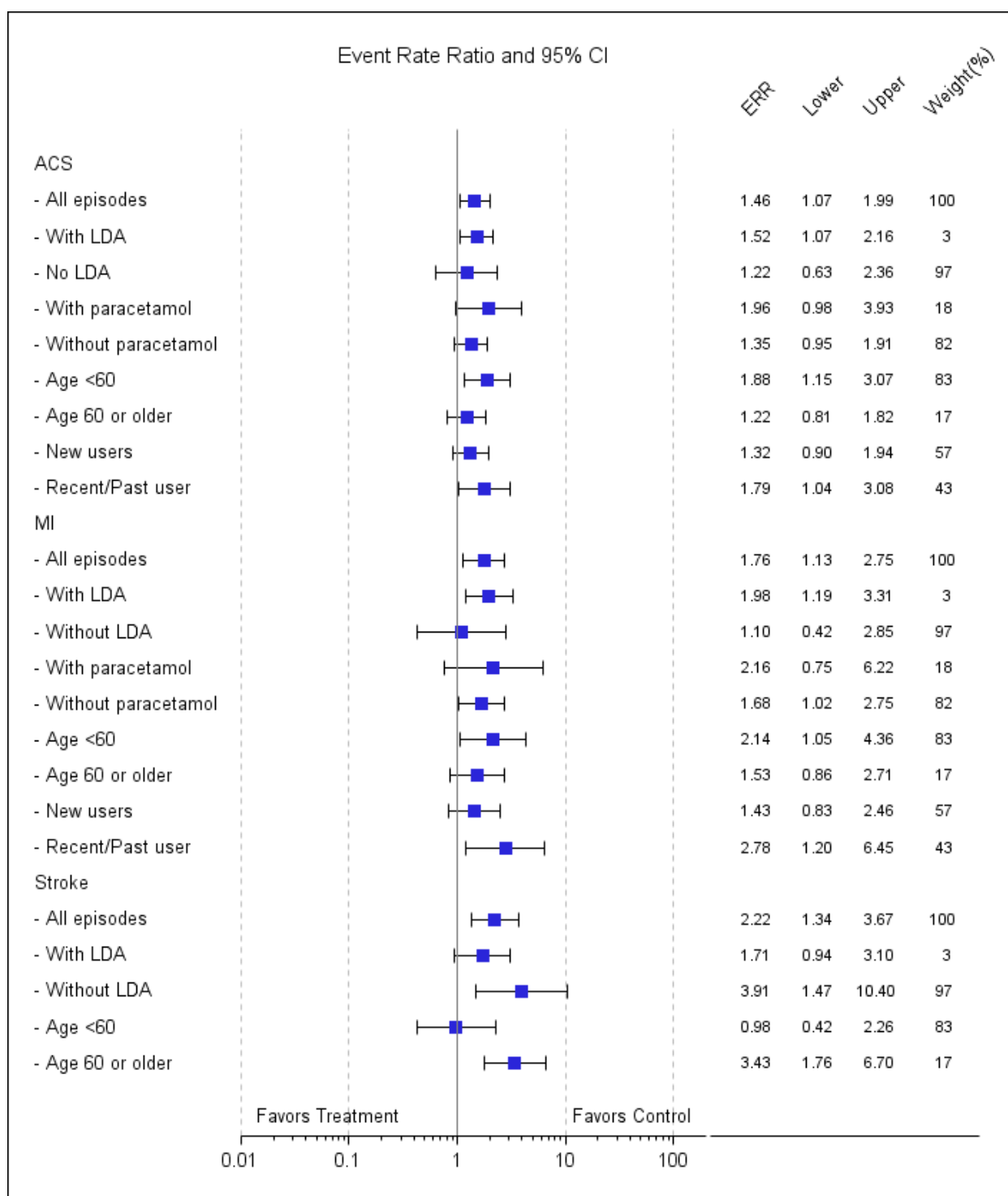


Figure 17. Risk of acute coronary syndrome, myocardial infarction and stroke associated with OTC-strength ibuprofen in different sub-groups

ACS and MI:

Event rates were different between LDA users and non-users. In LDA users, ACS and MI control period event rates were about 20 times higher than LDA non-users (Table 24, **Erreur ! Source du renvoi introuvable.**) and there was an increased risk after OSI dispensing (ACS ERR 1.52 [1.07-2.16]; MI 2.38 [1.38-4.11]). Absolute increases in event rates in LDA users after OSI dispensing were about 11 ACS, 9 MI per thousand person-years. In episodes without LDA use, there was no increase of ACS or MI with OSI overall (ACS ERR 1.22 [0.63-2.36]; MI 1.10 [0.42-2.85]).

The increase of ACS and MI risk after OSI dispensing were significant in patients younger than 60 year-old (ACS ERR 1.88 [1.15 – 3.07]; MI 2.14 [1.05-4.36]) but not in patients aged 60 and older. The increase of risk was significant in recent/past user (ACS ERR 1.79 [1.04-3.08]; MI 2.78 [1.20-6.45]) but not in new users (ACS ERR 1.32 [0.90 – 1.94] and MI 1.43 [0.83 – 2.46]).

The risk of ACS was highest in the first two week after initiation of OSI, (ERR 3.52 [2.28-5.44] in LDA users and 1.98 [0.78-5.08] in non-LDA users), then decreased in the second fortnight (ERR 0.53 [0.21-1.34] LDA and 1.02 [0.30 – 3.52] non-LDA). ACS risk was back to baseline in the 2nd and 3rd month in both LDA and non-LDA users (Table 28, Figure 18).

Concomitant use of paracetamol insignificantly increased the risk of ACS and MI (ACS ERR 1.96 [0.98-3.93]; MI 2.16 [0.75-6.22]) (Table 24)

Stroke:

Stroke risk increased in non-LDA users after OSI dispensing (ERR 3.91 [1.47 – 10.4]) and in patients aged 60 year-old and older (ERR 3.43 [1.76-6.70]). In patients younger than 60 year-old, OSI was not related with an increase of stroke risk (ERR 0.98 [0.42 – 2.26]) (Table 27, Figure 21).

Table 25. Time course of acute coronary syndrome risk in low-dose aspirin users after OTC-strength ibuprofen dispensing (PS-matched study)

	Control period			Risk period			ERR (95%CI)
	Person-months	Event	Event rate [¶]	Person-months	Event	Event rate [¶]	
Non-LDA users							
Day 1-14	795597	16	0.20	150199	6	0.40	1.98 (0.78 – 5.08)
Day 15-30	795597	16	0.20	145332	3	0.20	1.02 (0.30 – 3.52)
Month 1	795597	16	0.20	295532	9	0.30	1.51 (0.70 – 3.43)
Month 2	795597	16	0.20	273563	6	0.22	1.09 (0.43 – 2.79)
Month 3	795597	16	0.20	244593	5	0.20	1.02 (0.37 – 2.77)
LDA users							
Day 1-14	29009	51	17.6	5485	34	62.0	3.52 (2.28 – 5.44)
Day 15-30	29009	51	17.6	5324	5	9.39	0.53 (0.21 – 1.34)
Month 1	29009	51	17.6	10809	40	37.0	2.10 (1.39 – 3.18)
Month 2	29009	51	17.6	10062	22	21.9	1.24 (0.75 – 2.05)
Month 3	29009	51	17.6	9012	18	20.0	1.14 (0.66 – 1.94)

LDA, Low-dose aspirin; [¶] Event rate per 10,000 episodes-months

The period of 3 months before the index date were used as reference to estimate ERR in each time intervals

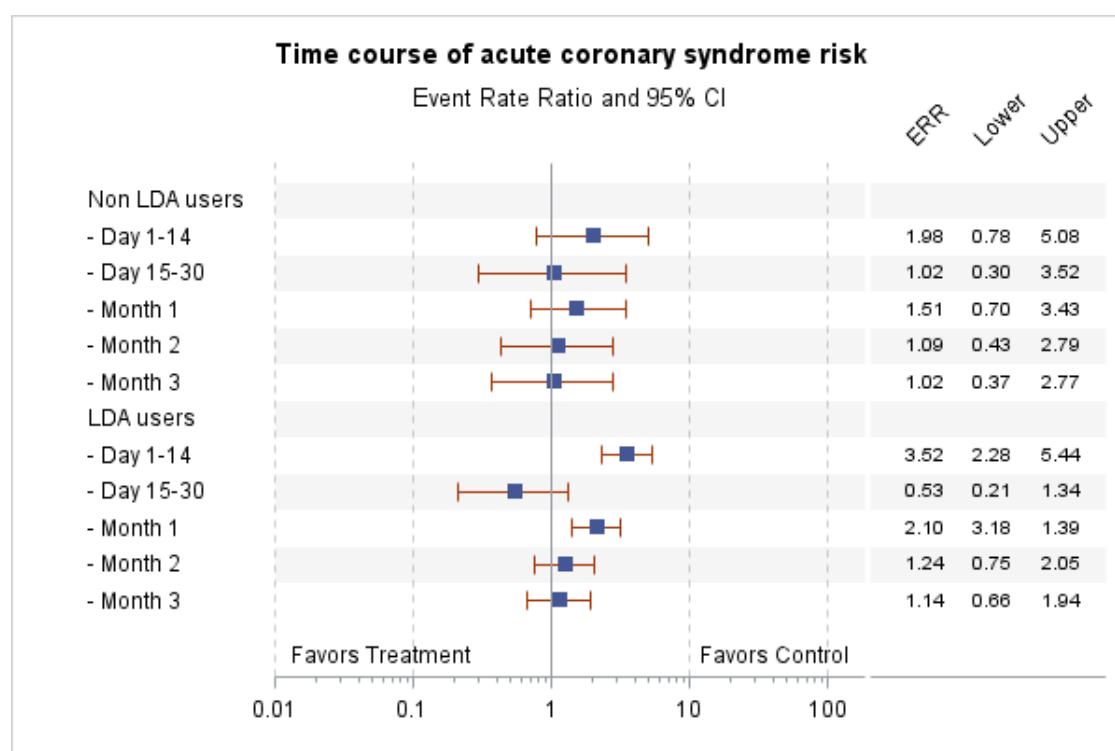


Figure 18. Time course of acute coronary syndrome risk after OTC-strength ibuprofen dispensing

1.1.4. Discussion

A meta-analysis of randomized trials on vascular effects of NSAIDs found that Ibuprofen significantly increased major coronary events (non-fatal MI or coronary death) (RR 2.22, 1.10 to 4.48). (345) However, ibuprofen daily dose in those clinical trials was 2400 mg daily, while the maximal dose for OTC strength ibuprofen is only 1200 mg. There is no information about the association between daily dosage of ibuprofen and thrombotic risk in individual clinical trials. Observational studies showed a dose-dependent association of ibuprofen and CV risk. (133,247,249,254) Among those studies, some found significant increase of MI or recurrent MI risk related with low-dose ibuprofen: Van der Linden *et al.* (249) (MI OR: 1.51 [1.06–2.14]), Gislason *et al.* (2009) (251) (MI HR: 1.31 [1.15–1.48]) and Gislason *et al.* (257) (Re-MI HR: 1.28 [1.03–1.60]).

A recent meta-analysis of observational study reported a random effect RR of MI associated with low-dose ibuprofen of 0.97 (0.76-1.22). (260) However, the random effect RR in the high risk population of low-dose ibuprofen was 1.20 (0.96-1.49), and 1.43 (1.20-1.71) in short duration-high risk population. (260)

Cardiovascular risk in low-dose aspirin users

In this study, we found that use of OSI in LDA users increased ACS and MI risk (ACS ERR 1.52 [1.07–2.16], MI 1.98 [1.19–3.31]). MacDonald and Wei also found an increase of cardiovascular mortality associated with concomitant use of ibuprofen and LDA in patients with cardiovascular disease, compared with LDA alone (HR 1.73, 1.05–2.84). (171) Some case-control studies analysed effect of concomitant aspirin use but did not find significant increase of either nonfatal MI risk, (133,172,245) or nonfatal ischemic stroke risk. (243) Interestingly, our data show that the increase of ACS and MI risk were more pronounced in LDA users less than 60 year-old (ERR 1.88 [1.15-3.07] and 2.14 [1.05-4.36]). In non LDA users, OSI did not increase either MI or ACS risk, in whichever age groups. This is consistent with results of de Abajo *et al.* (245)

Effect of concomitant use with paracetamol

We found that concomitant use with paracetamol increased MI risk (ERR 1.96 [0.98–3.93]) compared to OSI alone (ERR 1.35 [0.95–1.91]). This is consistent with finding of de Vries *et al.* (HR 1.12 [0.86–1.46] concomitant use vs. 1.09 [1.04–1.14] ibuprofen alone). (267)

Time course of risk (duration effect)

The time course of risk were demonstrated in a cohort study of Schjerning Olsen *et al.* (149) who found an increase of risk of death/re-MI in the second week (HR 1.50 [1.24-1.82]), in days 14 to 30 (HR 1.33 [1.15-1.53], and in days 30 to 90 (HR 1.70 [1.55-1.87]), but no increase in the first week (HR 1.04 [0.83-1.30]). Their study population included patients with prior MI, which had some characteristics in common with our population of LDA users. However, they found no increase in the first week and the risk remained high in the following months. In our study, ACS risk decreased from the third weeks back to baseline in the 2nd month. The difference could be because of the difference of usage pattern and/or study population. Schjerning-Olsen *et al.* included high-risk patients with prior MI and mostly prescription ibuprofen use, while we included only OTC-strength ibuprofen in a young general population. Also, the duration of use in our study was likely to be shorter (median 7 days) and more certain in the first week (to treat acute pain). Ray *et al.* (248) found increase of MI/CHD death associated with ibuprofen use within 90 days (incidence rate ratio 1.67, 95% CI 1.10-2.60).

The risk of MI associated with ibuprofen use seems not clearly depend on the duration according to our literature review (149)(250)(248), especially the study of Varas-Lorenzo *et al.* (149) found an OR of 2.49 (1.12–5.53) for the duration less than 30 days. There is no information on the actual daily doses used in our claims database, only the amounts dispensed. These are small (median 7 DDD), consistent with a clinical trial of the use of these drugs for common pain indications that found that for both ibuprofen and paracetamol the average use was 20 tablets (3.3 DDD of either) over 5 days.(127) With these small amounts dispensed, the use of OSI is predicted to be short. Dosage might depend on the intensity of pain. Although there is a small chance of use above the maximum recommended dose 1200 mg, the early increase of ACS risk in such a young population with mainly short term use like our study population is still a concern.

In a population with a very low baseline risk like our study population, a small absolute increase of event rate can lead to a significant relative risk. A meta-analysis of observational studies (260) reported a random effect RR of 1.43 (1.20–1.71) associated with short duration of ibuprofen use in high risk population, which seems similar to our findings in LDA users.

Stroke risk

We found global increase of stroke risk associated with OTC-strength ibuprofen use (ERR 2.22, 1.34 to 3.67). A systematic review of observational studies of stroke risk and NSAIDs found no significant increase of stroke risk associated with ibuprofen (pooled RR 1.10, 0.89–1.36). (345) García-Poza *et al.* (243) in a recent population-based case-control study did not found increase of stroke risk related with ibuprofen use in any specific conditions of use (low- or high-dose, duration < or ≥ 31 days, low or high CV risk, with or without concomitant aspirin). However, Fosbøl *et al.* (247) found increase of stroke risk associated with either low- or high-dose ibuprofen (HR 1.39 [1.24–1.54] and 2.22 [1.74–2.84], low- and high-dose respectively).

Strengths and weaknesses of the study

Data completeness and selection bias

Our study was done in a representative sample of the French population. The data collection in this claims database is independent from the study and its objectives, and is not subject to selection bias. There are essentially no missing data, because the information is initially used for healthcare reimbursement. Patients are followed lifelong, and there are fewer persons who leave the database.

Exposure misclassification

The National French healthcare systems database includes 70% of all sales of ibuprofen.(272) The risk of unrecorded exposure during the control period is low, and would have a conservative effect, reducing the apparent risk of paracetamol if the unrecorded use of paracetamol were associated with increased risk of outcomes. Though low-dose aspirin is also available OTC, the existence of a reimbursed preparation specifically marketed for cardiovascular prevention, and the long-term use of low-dose aspirin for cardiovascular prevention makes the chronic use of non-reimbursed aspirin for cardiovascular prevention unlikely.

We cannot exclude the risk of non-exposure in patients with a dispensing of a drug, but this is common to all studies of medicines, including randomized trials. Actual exposure is more likely when there is a repeat dispensing. In the same way, non-exposure during the control period

cannot be guaranteed, in that, even without the issue of OTC availability, there may be self-medication from previous dispensing. First-time dispensings are less likely to have exposure misclassification during the control period.

Outcomes misclassification

Outcomes are standardized and have already been used in other studies in the same database.(277,278,282) The validity of ACS diagnoses has been confirmed.(276) The outcomes were recorded independent from the study, and there is no reason for there to be any outcome misclassification bias. Non-selective misclassification might weaken the link by inducing noise, but this would probably not affect the final result.

Study Design

The use of a self-controlled design avoids all extrinsic biases related to differential patient characteristics in parallel cohort or case-control studies. However, this design cannot control for time-dependent variables such as concomitant medication, which we took into account by stratification and restriction. Our choice of control periods immediately preceding the index date may limit the impact of time-dependent variables. Another limit is that the self-controlled cohort design cannot study death, since patients would be censored at the time of the event and only patients with exposure are used in the analysis, only events post-exposure could be identified meaning that the pre-exposure time would be subject to immortal time bias.(289) Therefore, we could not study the risk of coronary heart disease death.

Another aspect of the immortal time bias is that if a patient used OSI during the time of hospitalisation, he/she would not present in the study population due to the lack of data of drug use in hospitals. In other words, the hospitalisation decreases the probability of being exposed to the study drug afterward. To limit that bias, the period of 15 days before t0 for MI and 30 days for stroke were not taken into the control period.

Confounders

We cannot exclude the possibility of confounding by indication, if the reason for prescribing OSI were associated with the occurrence of ACS, stroke. This might be the case for ACS if one can hypothesize that pain and/or fever; the usual indications for OTC NSAIDs are associated with an

increased risk of ACS. A link with stroke might be related to headache. Moreover, referred pain might be a prodromal symptom of myocardial ischemia, and headache might be a symptom of impending stroke or cerebral hemorrhage. Both would also be indications for the use of NSAIDs (protopathic bias). The indication and protopathic bias might overestimate the risk in these circumstances.

Events during the control period might lower the probability of ulterior prescription of ibuprofen. This would of course increase the risk of random events occurring after exposure. However, the impact is expected to be minor for ibuprofen, especially OTC formulations, than other NSAIDs such as selective COX-2 inhibitors.

1.1.5. Conclusion

Overall, OTC-strength Ibuprofen use was associated with increased CV risk compared to the non-use period before dispensing. However, this increase of CV risk was only observed in users of low-dose aspirin. In patients not using aspirin, ibuprofen was not associated with an increased risk of myocardial infarction or acute coronary syndrome.

Our findings might be subject of indication and/or protopathic biases suggesting further studies comparing OTC-strength ibuprofen with an active comparator such as paracetamol, which would share the same confounders.

1.2. Paracetamol

1.2.1. Background and objective

Paracetamol, widely used worldwide for its analgesic and antipyretic effect since the mid-20th century, (346–348) is a weaker analgesic than NSAIDs. (75,217,335,337,338,349,350) It is often recommended as a first-line analgesic because of its reputation of better gastrointestinal (GI) and cardiovascular (CV) tolerance, especially in the elderly. However, there is little reliable information on its actual safety. (224,351) Its mechanism of action remains uncertain, possibly related to a preferential COX-2 inhibitory action, found under different conditions. (186,187,352,353) It has some effect on platelet function, (238,239) though this is disputed (139,237) and it does not seem to inhibit the platelet effects of aspirin. (139,168) The hypothesis of a preferential COX-2 inhibitory action raised concerns with respect to cardiovascular safety, justified by some epidemiological data. (264,267) However, there are inconsistencies. (266)

The favorable gastrointestinal (GI) tolerability of paracetamol compared with NSAIDs was found in endoscopic studies in healthy volunteers. (354,355) Observational studies have shown that higher doses of paracetamol taken for a longer period of time might result in a GI risk profile similar to that of similarly used NSAIDs. (232,234,356–358)

Rare events such as myocardial infarction (MI), acute coronary syndrome (ACS) or upper GI bleeding (UGIB) in these mostly young patients can only be studied in large clinical trials, (127) in *ad hoc* cohorts (264), or in large population databases. However, in most countries, paracetamol is not captured in electronic health records or claims databases. (267) In France, paracetamol is reimbursed if prescribed, and will be recorded in the national claims database. (27,225,230,273–275) This allowed us to describe the usage patterns of paracetamol and OTC-strength NSAIDs. (27,127,272) The objective of the present study was therefore to assess the risk of hospital admission for MI, ACS, stroke or UGIB associated with the dispensing of paracetamol in the general French population, using a subset of the national claims database.

1.2.2. Methods

Data source

The database used in this study is the EGB, has been described in Chapter III, Section 1.2.

Study design

This was a self-controlled cohort, in which the cohort serves as its own control (Figure 19). The period of non-exposure immediately preceding the exposure period was chosen as control. Event rates during exposure (at-risk) periods were compared to event rates during control periods.

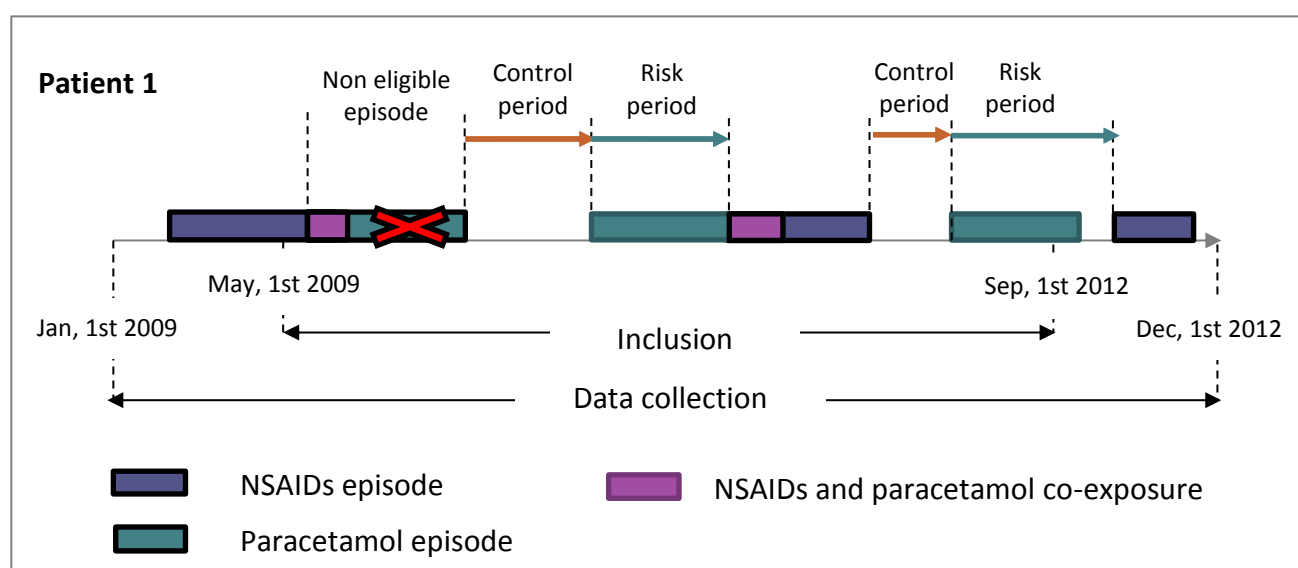


Figure 19. Self-controlled cohort design for paracetamol

Exposure

Paracetamol (single ingredient or combined preparations) was identified by its ATC codes²⁵³: N02BE01, N02BE51, N02BE71 and N02AA59. Number of defined daily doses (DDD) per dispensing was estimated as the total dose dispensed divided by a defined daily dose (DDD) of 3 g/day (http://www.whooc.no/atc_ddd_index/). Episodes of use were created by linking consecutive dispensings when the time elapsed between the end of one dispensing's supply and the next dispensing was 30 days or less. The index date (t0) was the first day of a treatment episode. The end of treatment episode was defined as 30 days after the end of drug supply (Figure 15). As NSAIDs are an important potential effect modifier, we created similar episodes of exposure to NSAIDs and then excluded all paracetamol episodes with co-exposure to NSAIDs.

The number of DDD dispensed per treatment episodes was stratified into ≤ 7 , 8-14 and >14 DDD.

Outcomes and follow-up

Data elements included age, sex, existing long-term illnesses (*affection de long durée*, ALD), as well as all outpatient dispensed drugs, and other medical encounters (visits, lab tests (not results), X-rays, outpatient procedures), or sick leave.

ALD are diagnoses that result in full coverage of all medical expenses concerning the disease, especially those that might associated to patients' baseline cardiovascular risk, including: stroke; lower-limb arterial disease with ischemia; severe heart failure, arrhythmias, valve diseases, or congenital heart defects; diabetes type 1 and 2; severe arterial hypertension; and coronary artery disease.

Drugs dispensed in the 3 preceding months were also extracted, including high-dose aspirin, antithrombotic agents including low-dose aspirin, anti-diabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, beta-blockers, calcium channel blockers, agents acting on the renin-angiotensin system, or lipid lowering agents.

Episodes were classified as high CV risk if at least one ATC-class C (cardiovascular system) drug was co-dispensed with paracetamol.

Outcomes of interest were MI, ACS, stroke and upper gastrointestinal bleeding (UGIB). Hospital admission for MI was identified as a primary discharge diagnosis ICD 10 code I21 (MI - myocardial infarction). For ACS, hospital discharge code I20.0 (unstable angina) was added to MI. This combination of ICD-10 codes identifies 83.6% of ACS. (276) In cases of multiple admissions of a patient for MI or unstable angina, only the first stay was included. Hospital admissions for stroke were identified by ICD 10 code I63. A set of ICD 10 codes K250, K254, K260, K270, K290, K920, K921, and K922 was used to identify GI bleeding events.

Death was not an outcome of this study, as death could not occur in the control period.

The at-risk period was defined as the period from t_0 to the first occurrence of the following events: 3 months after t_0 , the next episode of paracetamol or NSAIDs use, death, or the end of the study period (December 31st, 2011).

The control period was the symmetrical period, started from the most recent of the following events: 3 months after t0, the end of the previous episode of paracetamol or NSAIDs use, the beginning of study period (January 1st, 2009); ended at the day before t0.

Patients were studied during their at-risk and control period. Other durations of follow-up (one and two months before and after t0) were tested in sensitivity analyses (Appendix 8).

Statistical analysis

Event rates were the number of outcomes divided by the number of person-months (PM) of follow-up in each study period. Monthly events rates were estimated using the Kaplan–Meier life-table method. Fully adjusted Cox regression was used to assess associations between paracetamol use and outcomes. Hazard ratios (HRs) and their 95% CIs were estimated from the COX proportional hazard models as hazard rate during risk periods divided by hazard rate during control periods. Analysis was done on the whole population, stratified on low-dose aspirin (LDA) use (yes/no) and on age (< and ≥ 60 years). In LDA non-users, stratifications were made on the amount of paracetamol dispensed per episode (≤ 7 DDD, 8-14 DDD, >14 DDD) and on cardiovascular risk.

Analysis was adjusted on concomitant cardiovascular medications.

Sensitivity analyses used follow-up times of 1 and 2 months, and stratifications by any co-dispensed platelet aggregation inhibitors (ATC code B01AC) and co-dispensed aspirin (low- or high-dose). Results are shown in Appendix 9. In addition to the Cox regression, we also used the Poisson regression (Appendix 10). All statistical analyses and data management were performed with the SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, NC).

1.2.3. Results

The study population included 1 025 877 non-fatal paracetamol treatment episodes in 342 494 subjects (Figure 20).

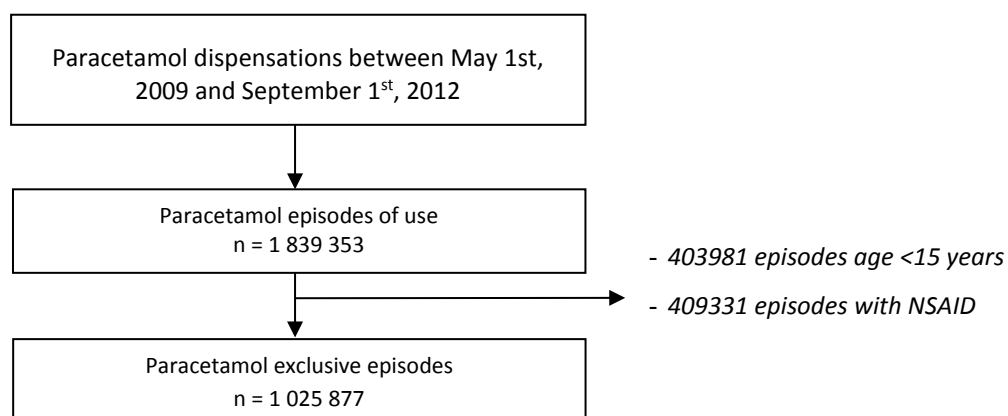


Figure 20. Patients flow-chart of paracetamol self-control cohort study

Baseline characteristics of users at the time of their first episode of use and over all episodes are described in Table 26. There was no missing data, and no loss to follow-up. Mean age of users was 47.2 years; 55.8% were female. The most common long-term illness was diabetes. Agents acting on the renin-angiotensin system, serum lipid lowering agents and antithrombotic agents were the most frequently dispensed drugs (18.5, 17.5 and 14.0%); 5.4% of episodes had co-dispensed low-dose aspirin. A median 8 DDD paracetamol were dispensed during treatment episodes. About 45% of the episodes received fewer than 7 DDD.

Table 26. Characteristics of all and first episodes of paracetamol use

	All episodes n = 1 025 877	First episode n = 342 494
Mean age, years (\pm SD)	51.0 (20.3)	47.2 (20.1)
<60 year-old	656160 (64.0)	244085 (71.3)
\geq 60 year-old	369717 (36.0)	98409 (28.7)
Female, n (%)	628570 (61.3)	190981 (55.8)
Prevalent long-term illnesses, n (%)		
Stroke	9670 (0.9)	2280 (0.7)
Lower-limb arterial disease with ischemia	14712 (1.4)	3456 (1.0)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	24940 (2.4)	5363 (1.6)
Diabetes type 1 or 2	62354 (6.1)	14348 (4.2)
Severe arterial hypertension	40344 (3.9)	9150 (2.7)
Coronary artery diseases	29681 (2.9)	7158 (2.1)
Drugs co-dispensed		

	All episodes n = 1 025 877	First episode n = 342 494
Low-dose aspirin	54878 (5.3)	11860 (3.5)
High-dose aspirin	13070 (1.3)	5028 (1.5)
Other anti-thrombotic agents	51985 (5.1)	13897 (4.1)
Antidiabetic agents	54620 (5.3)	11898 (3.5)
Cardiac therapies	43897 (4.3)	10708 (3.1)
Antihypertensive agents	14000 (1.4)	3238 (0.9)
Diuretics	52512 (5.1)	12149 (3.5)
Peripheral vasodilators	8844 (0.9)	2538 (0.7)
Vasoprotectors	6584 (0.6)	2101 (0.6)
beta-blockers	84571 (8.2)	18853 (5.5)
Calcium Channel Blockers	51627 (5.0)	11554 (3.4)
Agents acting on the renin-angiotensin system	138778 (13.5)	30839 (9.0)
Serum lipid reducing agents	125780 (12.3)	28344 (8.3)
High CV risk episodes	269470 (26.3)	62347 (18.2)
Number of DDD in episode		
≤7	464036 (45.2)	184354 (53.8)
8-14	303341 (29.6)	96453 (28.2)
>14	258500 (25.2)	61687 (18.0)
Type of episodes		
Recent exposure	372572 (36.3)	43014 (12.6)
Past exposure	254275 (24.8)	51448 (15.0)
New episodes	399030 (38.9)	248032 (72.4)

DDD: Defined Daily Dose; CV: cardiovascular

The 1 025 877 treatment episodes accrued 2 108 765 control person-months (PM), and 2 575 088 at-risk PM. (Table 27) The 54 878 episodes with LDA accrued 90 266 control PM and 138 997 at-risk PM; the 970 999 episodes without LDA accrued 2 108 497 control PM and 2 436 091 at-risk person-months.

Table 27. Risk of myocardial infarction, acute coronary syndrome, stroke and upper gastrointestinal bleeding associated with paracetamol use

	%‡	Control period			At-risk period			Crude HR (95%CI)	aHR* (95%CI)
		Person- months	Event	Event rate¶	Person- months	Event	Event rate¶		
ACS									
All episodes	100	2108765	684	3.2	2575088	825	3.2	1.00 (0.90 – 1.10)	0.91 (0.82 – 1.01)
With LDA	5.3	90268	287	31.8	138997	171	12.3	0.39 (0.32 – 0.47)	0.39 (0.32 – 0.47)
<60 years old	0.8	14885	86	57.8	21344	43	20.1	0.35 (0.24 – 0.51)	0.35 (0.24 – 0.51)
≥60 years old	4.5	75348	201	26.7	117652	128	10.9	0.41 (0.33 – 0.51)	0.41 (0.33 – 0.51)
Without LDA	94.7	2018497	397	2.0	2436091	654	2.7	1.38 (1.22 – 1.56)	1.32 (1.16 – 1.49)
<60 years old	63.2	1420964	139	1.1	1636583	175	1.0	1.10 (0.88 – 1.37)	1.05 (0.84 – 1.32)
≥60 years old	31.5	597533	258	4.3	799508	479	6.0	1.41 (1.21 – 1.64)	1.38 (1.19 – 1.61)
<60 years old	64.0	1435850	225	1.6	1657928	218	1.3	0.84 (0.70 – 1.01)	0.77 (0.64 – 0.93)
≥60 years old	36.0	672915	459	6.8	917160	607	6.6	0.97 (0.86 – 1.09)	0.94 (0.84 – 1.07)
MI									
All episodes	100	2108765	215	1.0	2575088	285	1.1	1.10 (0.92 – 1.31)	1.01 (0.85 – 1.21)
With LDA	5.3	90268	89	9.9	138997	39	2.8	0.29 (0.20 – 0.42)	0.29 (0.20 – 0.42)
<60 years old	0.8	14885	31	20.8	21344	8	3.7	0.18 (0.08 – 0.39)	0.18 (0.08 – 0.39)
≥60 years old	4.5	75382	58	7.7	117652	31	2.6	0.34 (0.22 – 0.53)	0.35 (0.23 – 0.55)
Without LDA	94.7	2018497	126	0.6	2436091	246	1.0	1.63 (1.32 – 2.03)	1.56 (1.26 – 1.93)
<60 years old	63.2	1420964	60	0.4	1636583	77	0.5	1.11 (0.79 – 1.56)	1.08 (0.77 – 1.51)
≥60 years old	31.5	597533	66	1.1	799508	169	2.1	1.96 (1.47 – 2.60)	1.91 (1.43 – 2.54)
Stroke									
All episodes	100	2108765	340	1.6	2575088	374	1.5	0.91 (0.78 – 1.05)	0.85 (0.73 – 0.98)
With LDA	5.3	90268	118	13.1	138997	63	4.5	0.35 (0.26 – 0.48)	0.35 (0.26 – 0.48)
<60 years old	0.8	14885	33	22.2	21344	6	2.8	0.13 (0.05 – 0.30)	0.13 (0.06 – 0.32)
≥60 years old	4.5	75382	58	7.7	117652	31	2.6	0.34 (0.22 – 0.53)	0.43 (0.31 – 0.60)
Without LDA	94.7	2018497	222	1.1	2436091	311	1.3	1.17 (0.98 – 1.39)	1.11 (0.94 – 1.32)
<60 years old	63.2	1420964	51	0.4	1636583	48	0.3	0.83 (0.56 – 1.23)	0.80 (0.54 – 1.19)
≥60 years old	31.5	597533	171	2.9	799508	263	3.3	1.15 (0.95 – 1.40)	1.13 (0.93 – 1.37)
UGIB									
All episodes	100	2108765	132	0.6	2575088	220	0.9	1.38 (1.11 – 1.71)	1.34 (1.08 – 1.66)
With LDA	5.3	90268	15	1.7	138997	22	1.6	0.97 (0.50 – 1.88)	0.97 (0.50 – 1.88)
<60 years old	0.8	14885	5	3.3	21344	5	2.3	0.70 (0.20 – 2.40)	0.73 (0.21 – 2.52)
≥60 years old	4.5	75382	10	1.3	117652	17	1.4	1.09 (0.50 – 2.38)	1.10 (0.50 – 2.41)
Without LDA	94.7	2018497	117	0.6	2436091	198	0.8	1.42 (1.13 – 1.78)	1.38 (1.10 – 1.73)
<60 years old	63.2	1420964	51	0.3	1636583	66	0.4	1.15 (0.80 – 1.66)	1.13 (0.78 – 1.63)
≥60 years old	31.5	597533	66	1.1	799508	132	1.7	1.49 (1.11 – 2.00)	1.45 (1.08 – 1.95)

¶ Event rate per 10000 patient-months; ‡ % episodes in the total number of episodes; MI, Myocardial Infarction; ACS, Acute Coronary Syndrome; UGIB, Upper Gastrointestinal Bleeding; LDA: low-dose aspirin; * HR adjusted for concomitant use of cardiovascular drugs

Acute coronary syndromes and MI risk

There were 685 ACS (3.2 per 10,000 PM) in the control period, and 843 ACS (3.2 per 10,000 PM) in the at-risk period (Table 27). In LDA users, control ACS risk was >10 times higher than in non-users (32 vs. 2 per 10000 PM). Paracetamol was associated with a lower risk of ACS (adjusted Hazard Ratio (aHR) (0.39, 95%CI [0.38-0.46])). The ACS risk decreased in both LDA users younger than 60 year-old and 60 year-old or older (0.35 [0.24 – 0.51] and 0.41 [0.33 – 0.51] respectively).

In subjects without LDA (95% of the total population), the risk of ACS was significantly higher after paracetamol dispensing (aHR 1.32 [1.16-1.49]) (Table 27). However, ACS risk increased only in subjects aged 60 or older (aHR 1.38 [1.19-1.61]) but did not in subjects younger than 60 year-old (aHR 1.05 [0.84-1.32]).

For MI alone, aHR was 1.01 [0.85 - 1.21] overall, 0.29 [0.20-0.43] with LDA, and 1.56 [1.26-1.93] without LDA.

Table 28 shows the ACS and MI risk in episodes without co-dispensed low-dose aspirin in different conditions. The risk of ACS and MI was increased after dispensing in subjects with recent exposure (ACS 1.60 (1.18 – 2.19), MI 2.04 (1.14 – 3.64), and when dispensing was less than 14 days (Table 28, Figure 21).

Stroke

There were 340 and 378 strokes during control and risk periods (event rates 1.6 and 1.4 per 10,000 PM respectively, aHR 0.85 [0.73 – 0.88]) (Table 27). The risk of stroke was lower with LDA (aHR 0.35 [0.26-0.48]), higher in patients without LDA at low cardiovascular risk (HR 1.45 [1.09 – 1.92]). Other strata did not have increased risk of stroke after paracetamol (

Table 29, Figure 21).

UGIB

There were 132 and 227 UGIB in control and risk periods (event rates 0.6 and 0.9 per 10,000 PM, aHR 1.39 [1.12 – 1.73]) (Table 27). Risk of bleeding was about double with LDA vs. non-LDA (1.7 vs. 0.6 episodes per 10 000 person-months). Paracetamol did not change the already

increased risk in LDA, but clearly increased the risk of bleeding in non-LDA (aHR 1.38 [1.10-1.88]). In non-LDA, the risk of bleeding was also increased with short-term use of paracetamol (≤ 7 DDD, 1.66 [1.11 – 2.49]), and with age above 60 (1.45 [1.08 – 1.95] (

Table **29**, Figure 21).

When the observation time was limited to the month before and after dispensing of paracetamol, the results were essentially unchanged (Appendix 8). Stratification by platelet aggregation inhibitors and co-dispensed aspirin shows similar trend as stratification by low-dose aspirin only (Appendix 9). Results of analyses using Poisson regression were similar to Cox regression (Appendix 10).

Table 28. Event rate and hazard ratio of acute coronary syndrome and myocardial infarction in paracetamol episodes without co-dispensed low-dose aspirin

	Control period			At-risk period			HR (95%CI)	Adjusted HR* (95%CI)
	Person- months	Event	Event rate¶	Person- months	Event	Event rate¶		
ACS								
Number of DDD in episodes								
≤7 DDD	1034654	145	1.4	1156654	215	1.9	1.33 (1.08 – 1.65)	1.31 (1.06 – 1.62)
8-14 DDD	609894	117	1.9	714875	191	2.7	1.40 (1.11 – 1.76)	1.36 (1.08 – 1.71)
>14 DDD	373949	135	3.6	564561	248	4.4	1.24 (1.00 – 1.53)	1.19 (0.96 – 1.47)
Type of episodes								
New episodes	1105143	218	2.0	1008737	237	2.3	1.18 (0.98 – 1.42)	1.18 (0.99 – 1.42)
Past exposure	638255	124	1.9	605230	156	2.6	1.32 (1.04 – 1.67)	1.31 (1.04 – 1.66)
Recent exposure	275099	55	2.0	822124	261	3.2	1.64 (1.20 – 2.23)	1.60 (1.18 – 2.19)
CV baseline risk								
Low CV risk	1643087	259	1.6	1888872	367	1.9	1.24 (1.06 – 1.45)	1.24 (1.06 – 1.45)
High CV risk	375411	138	3.7	547219	287	5.2	1.46 (1.19 – 1.79)	1.43 (1.17 – 1.75)
MI								
Number of DDD in episodes								
≤7 DDD	1034654	49	0.5	1156654	81	0.7	1.50 (1.05 – 2.13)	1.48 (1.04 – 2.11)
8-14 DDD	609894	34	0.6	714875	74	1.0	1.86 (1.24 – 2.80)	1.81 (1.20 – 2.71)
>14 DDD	373949	43	1.1	564561	91	1.6	1.41 (0.98 – 2.03)	1.35 (0.93 – 1.94)
Type of episodes								
New episodes	1105143	67	0.6	1008737	90	0.9	1.46 (1.06 – 2.00)	1.46 (1.06 – 2.00)
Past exposure	638255	44	0.7	605230	55	0.9	1.31 (0.88 – 1.94)	1.30 (0.88 – 1.94)
Recent exposure	275099	15	0.5	822124	101	1.2	2.08 (1.17 – 3.71)	2.04 (1.14 – 3.64)
CV baseline risk								
Low CV risk	1643087	78	0.5	1888872	143	0.8	1.61 (1.22 – 2.12)	1.60 (1.22 – 2.11)
High CV risk	375411	48	1.3	547219	103	1.9	1.49 (1.06 – 2.10)	1.45 (1.03 – 2.05)

[¶] Event rate per 10,000 episodes-months; ACS, Acute coronary syndrome; MI, myocardial infarction; CV, cardiovascular.

* HR adjusted for medications co-dispensed: high dose aspirin, other thrombotic agents, antidiabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, vasoprotectors, β -blockers, calcium channel inhibitors, agents acting on the renin-angiotensin system, serum lipid reducing agents.

Table 29. Event rate and hazard ratio of stroke and upper gastrointestinal bleeding in paracetamol episodes without co-dispensed low-dose aspirin

	Control period			At-risk period			HR (95%CI)	Adjusted HR* (95%CI)
	Person-	Event	Event rate¶	Person-	Event	Event rate¶		
	months			months				
Stroke								
<60 years old	1420964	51	0.4	1636583	48	0.3	0.83 (0.56 – 1.23)	0.80 (0.54 – 1.19)
≥60 years old	597533	171	2.9	799508	263	3.3	1.15 (0.95 – 1.40)	1.13 (0.93 – 1.37)
Number of DDD in episodes								
≤7 DDD	1034654	54	0.5	1156654	84	0.7	1.39 (0.99 – 1.96)	1.37 (0.97 – 1.92)
8-14 DDD	609894	52	0.9	714875	104	1.5	1.72 (1.24 – 2.40)	1.68 (1.20 – 2.34)
>14 DDD	373949	116	3.1	564561	123	2.2	0.70 (0.55 – 0.91)	0.67 (0.52 – 0.87)
Type of episodes								
New episodes	1105143	132	1.2	1008737	112	1.1	0.92 (0.72 – 1.19)	0.93 (0.72 – 1.19)
Past exposure	638255	59	0.9	605230	67	1.1	1.20 (0.85 – 1.70)	1.20 (0.84 – 1.70)
Recent exposure	275099	31	1.1	822124	132	1.6	1.40 (0.92 – 2.12)	1.38 (0.90 – 2.08)
CV baseline risk								
Low CV risk	1643087	104	0.6	1888872	167	0.9	1.40 (1.10 – 1.79)	1.40 (1.10 – 1.79)
High CV risk	375410	118	3.1	547219	144	2.6	0.84 (0.66 – 1.07)	0.83 (0.65 – 1.06)
UGIB								
<60 years old	1420964	51	0.3	1636583	66	0.4	1.15 (0.80 – 1.66)	1.13 (0.78 – 1.63)
≥60 years old	597533	66	1.1	799508	132	1.7	1.49 (1.11 – 2.00)	1.45 (1.08 – 1.95)
Number of DDD in episodes								
≤7 DDD	1034654	36	0.3	1156655	65	0.5	1.63 (1.09 – 2.45)	1.62 (1.08 – 2.43)
8-14 DDD	609894	33	0.5	714875	44	0.6	1.15 (0.73 – 1.80)	1.12 (0.72 – 1.77)
>14 DDD	373949	48	1.3	564562	89	1.6	1.22 (0.86 – 1.74)	1.18 (0.83 – 1.68)
Type of episodes								
New episodes	1105143	66	0.6	1008737	76	0.7	1.25 (0.90 – 1.74)	1.25 (0.90 – 1.74)
Past exposure	638255	31	0.5	605230	43	0.7	1.47 (0.93 – 2.34)	1.47 (0.93 – 2.33)
Recent exposure	275099	20	0.7	822124	79	1.0	1.31 (0.77 – 2.23)	1.28 (0.75 – 2.18)

[¶] Event rate per 10,000 episodes-months

* HR adjusted for medications co-dispensed: high dose aspirin, other thrombotic agents, antidiabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, vasoprotectors, β-blockers, calcium channel inhibitors, agents acting on the renin-angiotensin system, serum lipid reducing agents.

UGIB, upper gastrointestinal bleeding

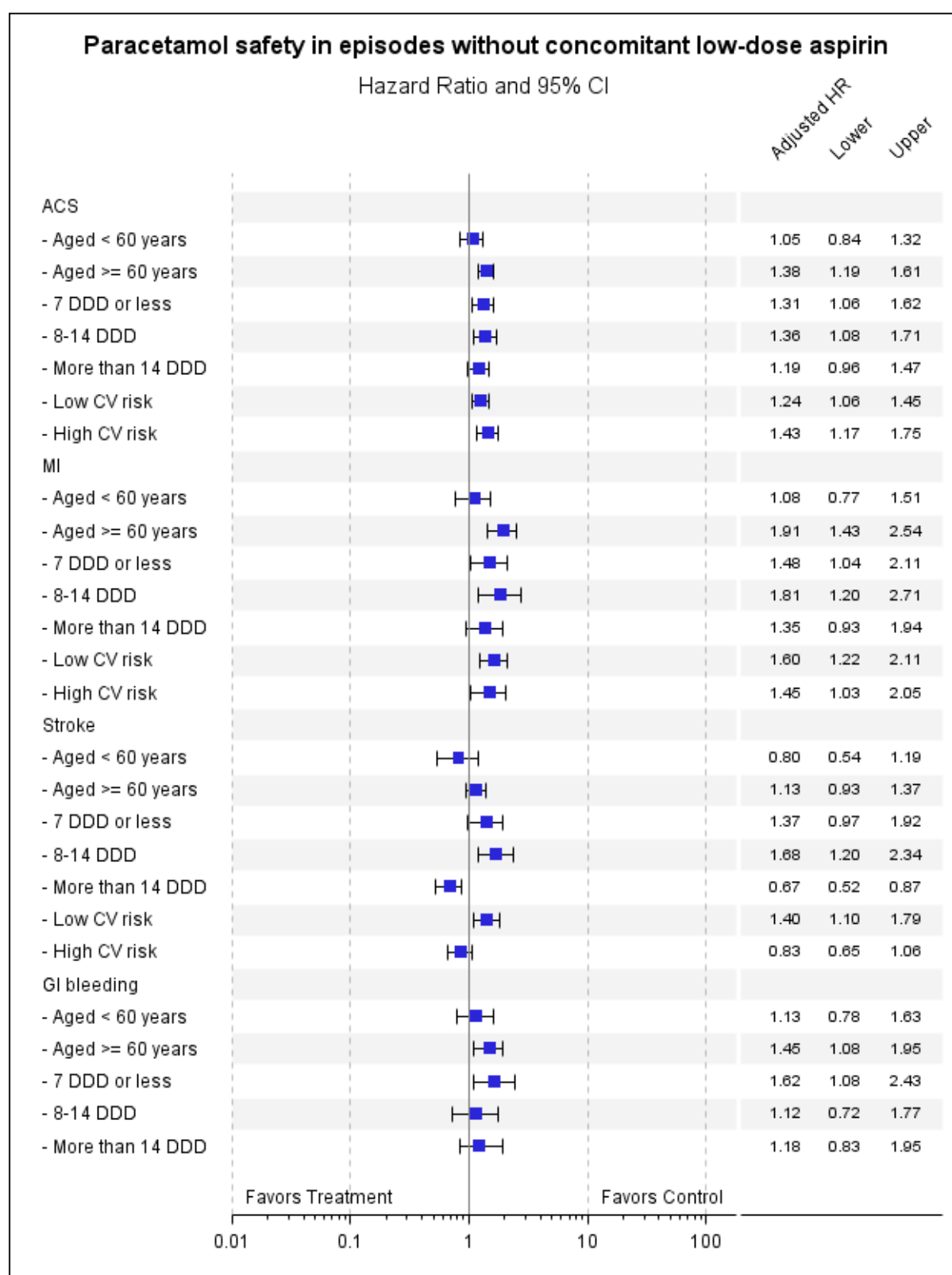


Figure 21. Risk of acute coronary syndrome, myocardial infarction, stroke and upper gastrointestinal bleeding associated with paracetamol in episodes without low-dose aspirin

1.2.4. Discussion

In this self-controlled cohort study in a database representative of the French population, with over one million paracetamol treatment episodes, we found overall an increased risk of GI bleeding, and no increase in the risk of cardiovascular events after the dispensing of paracetamol. However this was not homogeneous over population strata: In patients taking LDA (about 5% of the population), the baseline risk of MI, ACS, stroke and UGIB was much higher than in those not dispensed LDA. In these paracetamol reduced the rates of MI, ACS and stroke. However, this protective effect could be the effect of interaction or the result of the channelling bias. A cardio-protective effect of paracetamol against ischemic injury has been described before. (359)

When no LDA was co-dispensed (95% of the episodes), paracetamol was associated with higher risks of MI, ACS and bleeding, especially in patients above the age of 60. Similarly, the channeling bias should be taken into account.

Strengths and weaknesses of the study

- **Data completeness and selection bias**

EGB is a representative sample of the French population. (274) Data collection was independent from the study and its objectives, and not subject to selection bias. There is essentially no missing data. Patients are followed lifelong, whatever their socioeconomic or working status. Entry in the database is at birth or immigration, exit at death or emigration.

- **Exposure misclassification**

Non-prescribed self-medication with OTC drugs is not registered, so that our dataset might not represent all paracetamol users. However, in a previous study, we found that 84% of all paracetamol and 70% of OTC strength ibuprofen sold in France had been prescribed, covered by the healthcare systems and identified in this database. (272,273) This provides a positive identification of the dispensing of paracetamol, and of an association between this dispensing of paracetamol and the ulterior occurrence of outcomes, compared to the pre-exposure period. Low-dose aspirin (LDA) for cardiovascular prevention is also prescribed; one brand has over 95% market share, and can also be readily identified.

Unrecorded exposure would reduce the apparent risk of paracetamol if it were associated with an increased risk of outcomes. The same is true for low-dose aspirin. The risk of non-

compliance and non-exposure in patients with a dispensing of a drug is common to all studies of drugs, including randomized trials. Dispensing is one step closer to actual use than prescriptions. Exposure may be more likely close to the actual dispensing. In the same way, non-exposure during the control period cannot be excluded, since there may be self-medication from previous dispensing.

- **Outcomes misclassification**

Outcomes are standardized and have already been used in other studies in the same database. (277–282) From field studies, all ACS are hospitalized in France. (281) The validity of ACS diagnoses has been confirmed. (282) The outcomes were recorded independently from the study thus avoiding selective misclassification bias. Non-selective misclassification might induce noise, but would not affect the result.

- **Study design**

The self-controlled cohort design has strong predictive accuracy for risks associated with acute myocardial infarction and UGIB. (289) It explicitly addresses time-invariant confounding factors such as gender, age, genetic attributes, and chronic diseases, but not time-varying confounders such as concomitant medication. These were taken into account by stratification, and the choice of the control period immediately preceding dispensing. This was feasible because of the large number of treatment episodes (over 1 million) and patients (over 300 000), compared to a small number of events (around 1/10000 PM).

- **Confounders**

There could be confounding by indication, if the reason for prescribing paracetamol were associated with the occurrence of MI, ACS, stroke, or UGIB. This might be the case for MI or ACS since pain and/or fever, the usual indications for paracetamol, may be associated with a risk of myocardial ischemia. For stroke or UGIB, the risk of confounding by indication would be small.

Protopathic bias, use of the drug for early symptoms of an event, might exist for MI if the drug is prescribed for deferred pain, or stroke if paracetamol were prescribed for headache that could precede intracerebral hemorrhage. For UGIB, it is less likely, unless paracetamol were prescribed for abdominal pain, which would be unusual. Protopathic bias could explain an association of the dispensing of paracetamol with some outcomes, but would not explain why

this would be more pronounced in some categories of users such as patients above the age of 60.

The before- after- comparison could be the subject of the channeling bias. Paracetamol is more preferable than NSAIDs in patients with high CV risk or prior thrombotic events. Because thrombotic events are less likely to reappear in few months, one might expect more events before dispensing than after. This can lead to an underestimation of the cardiovascular risk associated with paracetamol in the total population. In LDA users, the effect of this channeling bias could be more important because the use of aspirin strongly indicates a prior thrombotic event. The non-LDA users are less likely to be affected by the channeling bias, because the use of LDA can be a proxy for thrombotic events, but the non-use of LDA does not indicate that subjects are less likely to have thrombotic events before than after dispensing.

Study results

- **CV outcomes**

A study in hypertensive patients aged ≥ 65 years in the UK General Practice Research Database found no increased risk of MI or stroke. (266) However they did not exclude the concomitant use of NSAIDs, nor did they include the use of low-dose aspirin in their analysis. In our study there was also no overall effect of paracetamol, because the decreased risk in LDA users masked the increased risk in LDA non-users. In their propensity-score matched populations, about 61% used NSAIDs, so any effect of paracetamol could have been diluted by co-exposure to NSAIDs. The same bias existed in the study of *et al.*, (264) in which there was a mixed use of NSAIDs, aspirin and paracetamol during follow-up. In the paracetamol group, the more patients used paracetamol, the more they used NSAIDs and the less they used aspirin. The non-paracetamol-exposed group was actually a mostly aspirin-exposed group. That could explain why they found high and similar relative risks for NSAIDs and paracetamol.

De Vries *et al.* (267), in their study of concomitant use of ibuprofen and paracetamol, found overall MI and stroke relative risks associated with paracetamol and ibuprofen of 1.14 (1.10 to 1.19) and 1.14 (1.10 to 1.18). They compared current exposure (less than 3 months after end of prescription) with past exposure (more than 6 months), which could be biased by time-dependent variables. There was no mention of concomitant use of low-dose aspirin.

A systematic literature review of observational studies on adverse events of paracetamol (224) also reported a frequency–response association of paracetamol and CV events in four studies, one showing an increased risk ratio of all CV AEs from 1.19 (0.81 – 1.75) for 1-2 tablets per week to 1.68 (1.10 to 2.57) for ≥ 15 tablets per week, that was consistent with our results.

García-Poza *et al.* (243) found no overall increased risk of stroke associated to paracetamol (RR 0.97, 0.85 to 1.10). They also found a trend for a higher increase of stroke risk in patients with low CV risk (HR 1.23, 0.87 – 1.73). However, this study did not explore the interaction of paracetamol with concomitant use of low-dose aspirin or NSAIDs.

- **UGIB**

A meta-analysis of observational studies (224) found a small increase in risk of gastrointestinal complications in users of paracetamol (RR 1.3 (95% CI: 1.2, 1.5), consistent with our findings. The lack of increased risk with long-term use could result from depletion of susceptible. (360)

In LDA users the background risk of bleeding was higher than in non-LDA users, consistent with many studies of low-dose aspirin. (361,362) There was no increased risk with paracetamol, in the same way that in the CLASS study there was no benefit from the use of celecoxib compared to ibuprofen or diclofenac in aspirin users. (16) If there is a channeling bias like in the case of CV outcome, one might expect more UGIB events before dispensing than after in the high risk population like the elderly. The fact that we found an increased of UGIB risk after paracetamol dispensing in subjects aged 60 years or older (RR 1.45 [1.08–1.95]) suggests that it should be taken with caution in the elderly.

The first main finding was that of an interaction between paracetamol and LDA: the addition of paracetamol in low-dose aspirin users resulted in a decreased risk of MI or stroke. There is no clear explanation for this. It could be related to platelet inhibition by paracetamol (239,363), though this was not found by others. (139,186,237) However, these authors looked for an inhibition of aspirin effects, not an increase. The reduced risk of MI in a very small but high-risk population masked a moderately increased risk of MI in non LDA- users, especially in persons above the age of 60. These are the ones in whom the use of NSAIDs is discouraged because of cardiovascular risk. The increased risk of MI in these patients (hazard ratio 1.6) is of the same order of magnitude as that reported with NSAIDs. (345) Observational studies in users of paracetamol that do not take LDA into account might be viewed with a degree of wariness.

The added risk of MI in non-users of LDA was about one per 10000 PM during the paracetamol risk period. This may seem small but In France about 6 million persons above the age of 60 use paracetamol each year. (272) This might translate into as many as 1800 to 2000 paracetamol-related extra cases of myocardial infarction in low-risk older patients yearly in France.

1.2.5. Conclusion

Although overall there was non increase of cardiovascular risk associated with paracetamol dispensing, the risk of acute coronary syndrome and MI increased in patients above the age of 60 not using low-dose aspirin. Since in parallel there are arguments for a the lack of benefit of paracetamol in acute of chronic painful conditions, (75,335,337,364) it may be time to reassess the real place of paracetamol and the recommendations for its use in the elderly.

1.3. Common discussion of SCC studies of paracetamol and OTC-Strength ibuprofen

	LDA ⁻	LDA ⁺
Age < 60	OSI (81%): 1.80 (0.66–4.85) P (63%): 1.05 (0.84–1.32)	OSI (1%): 1.87 (1.06–3.31) P (0.8%): 0.35 (0.24–0.51)
Age ≥ 60	OSI (15%): 0.87 (0.35–2.14) P (32%): 1.38 (1.19–1.61)	OSI (2.5%): 1.33 (0.85–2.08) P (4.5%): 0.41 (0.33–0.51)
<u>Total</u>	<u>OSI (96%): 1.22 (0.63–2.36)</u> <u>P (95%): 1.32 (1.16–1.49)</u>	<u>OSI (3.5%): 1.52 (1.07–2.16)</u> <u>P (5.3%): 0.39 (0.32–0.47)</u>

Figure 22. Summary of results of the ACS risk associated with OTC-Strength Ibuprofen and paracetamol in the self-controlled cohort studies

Figure 22 summarises results of the two self-controlled cohort studies. In subjects without LDA and younger than 60 year-old, there OSI was associated and increase of ACS risk (but not significant) whereas paracetamol was not. On the contrary, in subjects without LDA and aged 60 years or older, paracetamol was associated with an increase of ACS after dispensing and OSI was not. In subjects with LDA, OSI but not paracetamol was associated with increase of risk after dispensing. However this should take into account potential biases.

These independent studies compared event rates before and after the dispensing of paracetamol or ibuprofen. They control for all patient-specific confounders, but not for external confounders,

such as protopathic, indication or channelling biases (Figure 23). In our self-controlled cohort studies, the pre-dispensing period was taken as control period to the post-dispensing. Due to the knowledge about the cardiovascular risk associated with NSAIDs, one might prefer paracetamol to OTC-Strength Ibuprofen if they had previous MI. A recurrent MI is less likely to happen in a few following months, the event rate therefore seems higher before paracetamol dispensing and lower after dispensing. The reversed situation is expected for OTC-Strength Ibuprofen because subjects with recent MI would not choose NSAIDs but paracetamol. The MI rate is therefore lower before OTC-Strength Ibuprofen dispensing than after. In this case, including the period before dispensing in the analysis could underestimate the MI risk associated with paracetamol, and overestimate the risk associated with OTC-Strength Ibuprofen. Although we have excluded the one month period before exposure in the SCC study of OTC-Strength Ibuprofen, this channelling bias can only be addressed in a cohort study that does not take into account the period before dispensing.

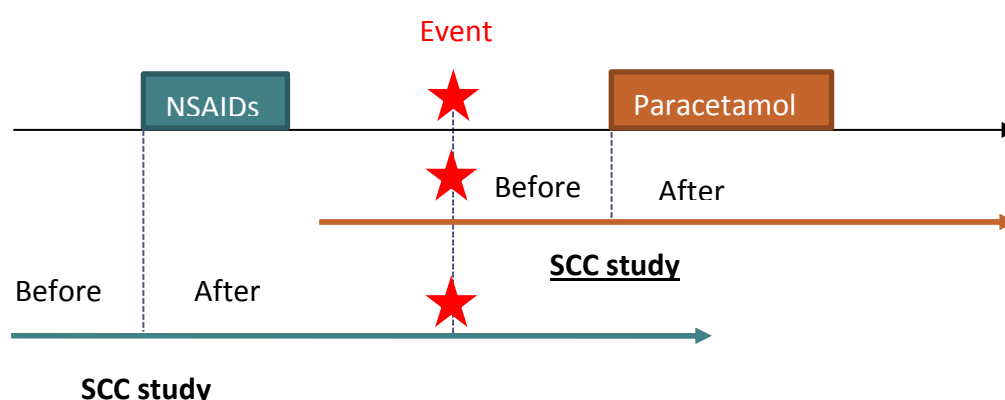


Figure 23. Channelling bias in self-controlled cohort studies

One might presume that since the indications of the drugs are essentially the same, as seen by the distribution of propensity scores in Appendix 11, the risk of a differential protopathic bias or indication bias between paracetamol and ibuprofen would be low. If there were major effects of confounding by indication, it would apply equally to both cohorts. However this is not true for channelling, and there are some indications of this when the event rates are considered. Of course the patient population ages are different, older by about 6 years for paracetamol, but this could hardly explain the rates differences: Among patients using low-dose aspirin, the control period

event rates for ACS were 3.19 per 1000 patient months before paracetamol (Table 27), and 1.76 before ibuprofen (Table 24). This would indicate more use of paracetamol in patients with a recent ACS. After dispensing of paracetamol or ibuprofen, the event rates were respectively 1.23 and 2.66 per thousand patient-months, respectively. How much of these results of a decrease in risk with paracetamol and an increase in risk with ibuprofen might be attributed to regression to the mean.

Channelling also appears in the non-aspirin users where one would expect similar control period event rates: in paracetamol users below 60 the control event rate for ACS was 0.11 per thousand patient-months (Table 27) and 0.009 in ibuprofen users (Table 24), a 10-fold difference. The same was found for patients above the age of 60. Channelling may explain the decrease in risk in patients with initially high risk, or an increase in patients at lower risk. Can it explain an increased risk in patients at already high risk as seen in our elderly paracetamol users?

The clear baseline risk differences between paracetamol and ibuprofen and the existing biases in the self-controlled cohort design (confounding by indication, protopathic bias and channeling bias) are the reason why we decided to continue with a propensity score matched parallel-arms cohort study to compare users of ibuprofen or paracetamol that would be as similar as possible.

2. Propensity score matched cohort study to compare OTC-Strength NSAIDs and paracetamol

1.1. Background and objective

Events associated with NSAIDs used for acute pain and/or fever are highly confounded: pain and fever, by increasing heart rate and blood pressure, increase myocardial oxygen demand and therefore increase the risk of myocardial ischemia (indication bias). Referred pain might be a prodromal symptom of myocardial ischemia, and headache might be a symptom of impending stroke or cerebral hemorrhage. Both would also be indications for the use of NSAIDs (protopathic bias). Comparing the risks associated with the use of NSAIDs to non-use is therefore irrelevant and potentially misleading. (253,365) It would be preferable to compare the event rates in users of low-dose NSAIDs or paracetamol, which have the same indications for pain and fever, to take these biases into account.

OTC drugs are notoriously difficult to study: they usually do not appear in physician notes or electronic health records, and they are generally not included in claims databases, so that they are not included in most population-based studies. Because of the low event rates, randomized comparative trials would require inordinate patient populations, of several hundred thousand patients to acquire the required number of events. (127,343)

We took advantage of the fact that in France some drugs available OTC are also reimbursed and recorded if prescribed, such as low-dose aspirin for cardiovascular prevention, ibuprofen at OTC strengths and paracetamol. (272,272) Reimbursed low-dose ibuprofen in France represents about 70% of all sales (273) so that there is a sizable amount of data on OTC-strength ibuprofen and risks in France. (27) The same is true for paracetamol, where about 84% of all paracetamol sales are prescription (230,272,273) and can be found in the national claims database.

The country-wide National French healthcare systems database, SNIIRAM, combines medical claims and hospital diagnoses (274,275) and has already served to study cardiovascular risks in other settings. (277,278,282) We therefore used it to evaluate the risk of acute coronary syndromes (ACS), myocardial infarction (MI), stroke and all-cause death associated with the use of OTC-strength NSAIDs compared to paracetamol in real-life use in the general population,

using a propensity score-matched cohort design. Because over 90% of OTC strength NSAIDs is ibuprofen, we restricted the study to episodes of ibuprofen use.

1.2. Methods

Data source

The database used in this study is the EGB, has been described in Chapter III, Section 1.2.

Study design

This was a population-based propensity score-matched comparative cohort study of OTC-strength ibuprofen (OSI) vs. paracetamol (P) in the EGB database.

The analysis unit was treatment episode with exclusive use of either P or OSI. Treatment episodes were matched on a propensity score. Outcomes were hospital discharge diagnoses of acute coronary syndrome (ACS), myocardial infarction (MI), stroke, or all-cause death (in and out of hospital).

Study population

All persons with at least one dispensing of oral paracetamol or OTC-strength ibuprofen between May 1st, 2009 and September 1st, 2014 in EGB, aged ≥ 18 year-old were included in this study.

Ibuprofen preparations were identified by the ATC code M01AE01. We used the European Pharmaceutical Market Research Association (EphMRA) classifications to identify OSI and prescription-strength ibuprofen (PSI). EphMRA classifies products according to their indications and use. Ibuprofen preparations with EphMRA code M01A (anti-inflammatory and anti-rheumatic products, non-steroidals) were classified as PSI, whereas ibuprofen preparations with EphMRA code N02B (analgesic) were classified as OSI. Single ingredient paracetamol was identified by ATC code N02BE01.

Exposure

The number of DDD per dispensing was calculated as the total dose dispensed divided by the defined daily dose (DDD) of the substance, 1200 mg for ibuprofen and 3g for paracetamol. We created episodes of use by linking consecutive dispensings of the same substance when the time elapsed between the end of supply of one dispensing and the next dispensing was 30 days

or less. The index date (t0) was defined as the first day of the treatment episode. The last day of the episode was defined as the 30th day after the end of drug supply. We excluded all paracetamol episodes with current exposure to NSAIDs or with co-dispensed aspirin (either high- or low-dose) at t0. Likewise, we excluded OSI episodes with current exposure to other NSAIDs, PSI, paracetamol or aspirin at t0 (Figure 24). The exclusion of co-dispensed aspirin was due to a potential interaction between aspirin and ibuprofen (139,168,171,344) and to an observed interaction between paracetamol and low-dose aspirin that we found in the paracetamol self-controlled cohort study in Chapter II – Part I – Section 1.1. To limit protopathic bias, we excluded all episodes with hospital admissions for ACS or stroke in the 3 preceding months.

Outcomes and follow-up

Outcomes of interest were ACS, MI, stroke and all-cause death. ACS was identified by primary discharge diagnosis ICD-10 codes I21 (MI - myocardial infarction) and I20.0 (unstable angina). This combination of ICD-10 codes could identify 83.6% of ACS. (29) In cases of multiple admissions of a patient for MI or unstable angina, only the first stay was included in our final analysis. Stroke was identified by ICD-10 code I63.

Patients were followed-up from the index date (t0) to the first occurrence of any of the following: three months after t0, the next treatment episode identified by a dispensing of P, OSI or another NSAIDs, an aspirin dispensing, a hospital admission for any outcome of interest, the end of study period (December 31st, 2014), or patient death.

Potential confounders

Control variables included demographics (age, sex, year of dispensation) and other baseline variables: prevalent long-term diagnosis of stroke, lower-limb arterial disease with ischemia, severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects, diabetes type 1 or 2, severe arterial hypertension and coronary artery diseases.

Dispensation of other drugs in the three preceding months and at the index date were also extracted including high-dose aspirin, antithrombotic agents (including low-dose aspirin), antidiabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, vasoprotectors, β -blockers, calcium channel inhibitors, agents acting on the renin-angiotensin system and serum lipid lowering agents.

Statistical analysis

To control for the differences in patient characteristics in the two treatment groups, propensity scores (PS) were used to predict the propensity to be dispensed OSI relative to paracetamol. To estimate PS, all aforementioned variables were included in a logistic model and selected if their alpha-value were less than 0.3. (296) PS was used to match OSI and P cohorts, using a PS greedy matching method with a 1:2 ratio and calipers set at 0.2 standard deviations of the logit of the propensity score in the OSI group. This method was suggested by Austin *et al.* (293) as minimizing the mean squared error of the estimated treatment effect in several scenarios. The balance in baseline covariates between treatment groups after matching was tested by using the standardized difference; a standardized difference less than 10% has been taken to indicate a negligible difference in the mean or prevalence of a covariate. (297,366) The event rates in the matched cohorts was estimated by using the Kaplan–Meier time table method. Hazard ratios (HRs) and their 95% CI were estimated in the matched cohorts by the Cox proportional hazard models using paracetamol as reference.

All statistical analyses and data management used the SAS statistical software package, version 9.4 (SAS Institute Inc, Cary, NC).

Sensitivity analysis

Censoring in survival analysis should be “non-informative,” i.e. participants who drop out of the study should do so due to reasons unrelated to the study. (367) In our study design, patients could be dropt out due to reasons that might related to outcomes, i.e the use of low-dose aspirin or hospitalizations for other causes. We therefore conducted a sensitivity analysis in the PS-matched sample, in which we continued to follow patients after their dispensings of LDA, or their hospital admissions for other reasons (beyond the outcomes of interest). In addition, because the inclusion of LDA use after t0 afer may have impact on the occurence of outcomes, we included the exposure to LDA after t0 as a time-independent variable in the COX model to estimate HRs. The period of exposure to LDA was defined as the number of tablets dispensed plus 7 days.

1.3. Results

The study cohort included 1 368 664 exclusive P episodes and 209 566 exclusive OSI episodes, in respectively 372 089 and 125 964 subjects (Figure 24).

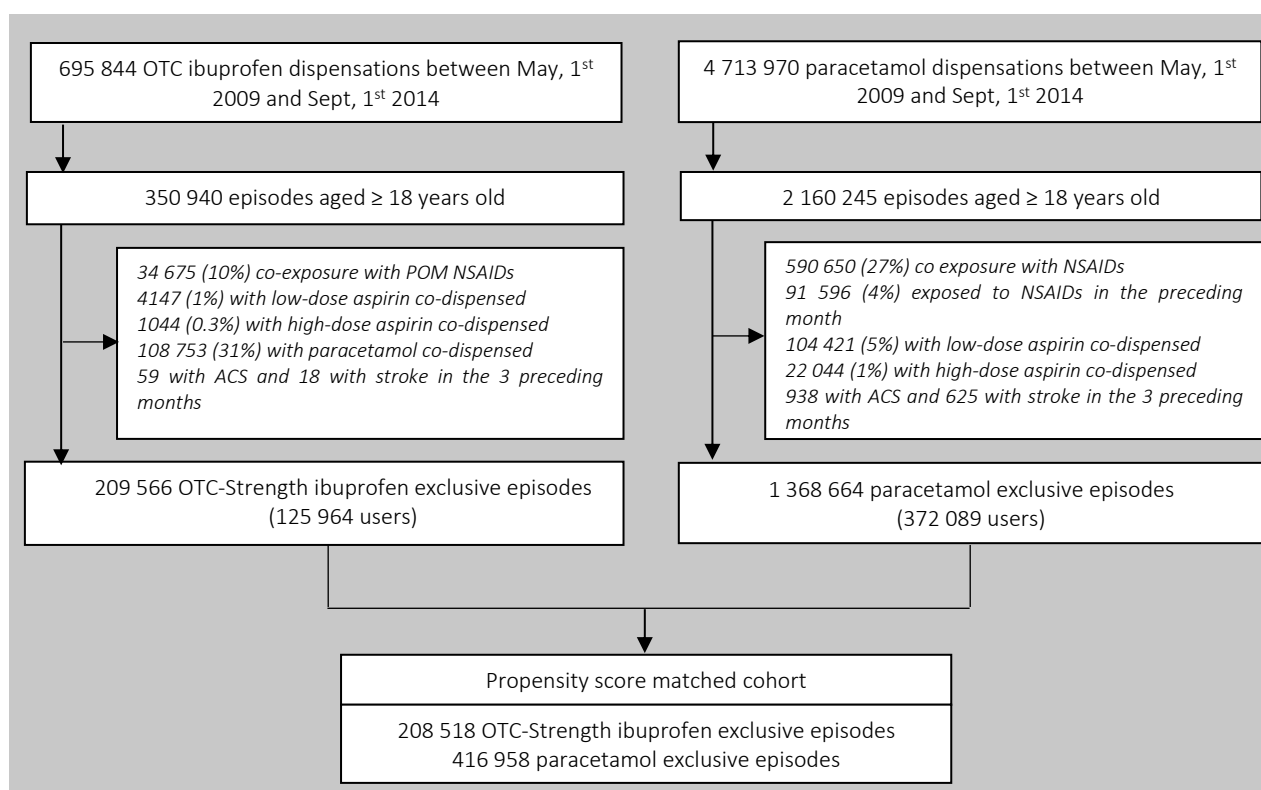


Figure 24. Patients flow-chart of propensity score matched cohort study

The PS matched cohorts included 208 518 OSI and 416 958 P episodes. Baseline characteristics of OSI and P episodes before and after matching are described in **Table 30**. Baseline characteristics of OSI and paracetamol users (at the first episode) before and after matching are described in

Table 31. Paracetamol users were older than OSI users, with more cardiovascular history and use of drugs, as expected from the age difference. After matching, the standardized differences of all covariates were within 2%. Logit of propensity score distribution before and after matching of the two treatment groups are shown in Appendix 11. Matched OSI episodes represent 99.5% of the OSI episodes in the original population, with identical characteristics.

Table 30. Characteristics of OTC-Strength Ibuprofen and paracetamol episodes in the PS-matched cohort study before and after matching

	Before matching		After matching		Standardized difference (%)
	Paracetamol n = 1368664	OSI n = 209566	Paracetamol n = 416958	OSI n = 208518	
Mean age, years (\pm SD)	51.8 (19.4)	44.5 (16.1)	44.5 (16.1)	44.5 (16.1)	0.00
<60 year-old	869485 (63.5)	170221 (81.2)	338592 (81.2)	169326 (81.2)	0.00
\geq 60 year-old	499179 (36.5)	39345 (18.8)	78366 (18.8)	39192 (18.8)	0.00
Female, n (%)	848168 (62.0)	133819 (63.9)	266383 (63.9)	133211 (63.9)	0.00
Prevalent long-term illnesses, n (%)					
Stroke	13476 (1.0)	723 (0.3)	1404 (0.3)	708 (0.3)	0.00
Lower-limb arterial disease with ischemia	19200 (1.4)	922 (0.4)	1800 (0.4)	916 (0.4)	0.15
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	41740 (3.0)	1399 (0.7)	2833 (0.7)	1392 (0.7)	-0.12
Diabetes type I, II	86397 (6.3)	7407 (3.5)	15298 (3.7)	7272 (3.5)	-0.97
Severe arterial hypertension	49470 (3.6)	2988 (1.4)	5741 (1.4)	2970 (1.4)	0.34
Coronary artery diseases	32743 (2.4)	1786 (0.9)	3329 (0.8)	1785 (0.9)	0.66
Drug use in the 3 preceding months, n (%)					
High-dose aspirin	11050 (0.8)	2145 (1.0)	3669 (0.9)	1914 (0.9)	0.42
Antithrombotic agents	148013 (10.8)	9069 (4.3)	17434 (4.2)	8950 (4.3)	0.55
Anti-diabetes	98781 (7.2)	8884 (4.2)	17950 (4.3)	8658 (4.2)	-0.75
Cardiac therapies	71494 (5.2)	4395 (2.1)	7934 (1.9)	4360 (2.1)	1.36
Antihypertensive agents	23592 (1.7)	1891 (0.9)	3405 (0.8)	1851 (0.9)	0.76
Diuretics	94051 (6.9)	6209 (3.0)	11329 (2.7)	6150 (2.9)	1.39
Peripheral vasodilators	11956 (0.9)	1007 (0.5)	1773 (0.4)	960 (0.5)	0.45
Vasoprotectors	10433 (0.8)	1641 (0.8)	3194 (0.8)	1560 (0.7)	-0.23
β -blockers	151567 (11.1)	14146 (6.8)	27771 (6.7)	13879 (6.7)	0.00
Calcium channel inhibitors	91122 (6.7)	6615 (3.2)	12773 (3.1)	6519 (3.1)	0.40
Agents acting on the renin- angiotensin system	242253 (17.7)	21116 (10.1)	41006 (9.8)	20764 (10.0)	0.44
Serum lipid reducing agents	217305 (15.9)	20319 (9.7)	39392 (9.4)	19985 (9.6)	0.44
Hospitalisation in 3 preceding months	126985 (9.3)	8874 (4.2)	17330 (4.2)	8810 (4.2)	0.35
Number of DDD dispensed					
Mean (\pm SD)	19.2 (60.9)	10.7 (30.5)	13.7 (42.6)	10.7 (30.5)	-
Median	8.0	7.0	8.0	7.0	-

	Before matching		After matching		
	Paracetamol n = 1368664	OSI n = 209566	Paracetamol n = 416958	OSI n = 208518	Standardized difference (%)
Mean total followed-up time, days (\pm SD)	74.2 (25.3)	69.4 (28.8)	74.5 (25.2)	69.4 (28.8)	

Table 31. Characteristics of OTC-Strength Ibuprofen and paracetamol users before and after matching

	Before matching		After matching	
	Paracetamol n = 372089	OSI n = 125964	Paracetamol n = 224784	OTC-Strength Ibuprofen n = 125594
Mean age, years (\pm SD)	47.9 (19.3)	43.8 (16.5)	44.8 (17.2)	43.8 (16.5)
Female, n (%)	205090 (55.1)	75421 (59.9)	132581 (59.0)	75246 (59.9)
Prevalent long-term illnesses, n (%)				
Stroke	2821 (0.8)	463 (0.4)	912 (0.4)	453 (0.4)
Lower-limb arterial disease with ischemia	4116 (1.1)	591 (0.5)	1309 (0.6)	590 (0.5)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	7346 (2.0)	895 (0.7)	2065 (0.9)	893 (0.7)
Diabetes type I, II	17074 (4.6)	4217 (3.3)	8443 (3.8)	4169 (3.3)
Severe arterial hypertension	10357 (2.8)	1836 (1.5)	3753 (1.7)	1830 (1.5)
Coronary artery diseases	8397 (2.3)	1247 (1.0)	2469 (1.1)	1247 (1.0)
Drug use in the 3 preceding months, n (%)				
High-dose aspirin	3564 (1.0)	1305 (1.0)	2010 (0.9)	1164 (0.9)
Antithrombotic agents	33657 (9.0)	6048 (4.8)	11762 (5.2)	5994 (4.8)
Anti-diabetes	20073 (5.4)	5117 (4.1)	10103 (4.5)	5019 (4.0)
Cardiac therapies	17120 (4.6)	2767 (2.2)	5611 (2.5)	2750 (2.2)
Antihypertensive agents	4887 (1.3)	1071 (0.9)	2035 (0.9)	1051 (0.8)
Diuretics	18851 (5.1)	3602 (2.9)	7191 (3.2)	3583 (2.9)
Peripheral vasodilators	3564 (1.0)	682 (0.5)	1228 (0.5)	648 (0.5)
Vasoprotectors	3311 (0.9)	1086 (0.9)	1886 (0.8)	1038 (0.8)
β -blockers	31735 (8.5)	7621 (6.1)	15586 (6.9)	7526 (6.0)
Calcium channel inhibitors	18803 (5.1)	3974 (3.2)	7786 (3.5)	3934 (3.1)
Agents acting on the renin- angiotensin system	49552 (13.3)	12116 (9.6)	23978 (10.7)	11970 (9.5)

	Before matching		After matching	
	Paracetamol n = 372089	OSI n = 125964	Paracetamol n = 224784	OTC-Strength Ibuprofen n = 125594
Serum lipid reducing agents	47005 (12.6)	11844 (9.4)	23149 (10.3)	11704 (9.3)
Hospitalisation in 3 preceding months	41642 (11.2)	5851 (4.6)	10460 (4.7)	5826 (4.6)
Number of DDD dispensed				
Mean (\pm SD)	17.8 (78.9)	9.5 (28.6)	13.7 (50.3)	9.5 (29.0)
Median	5.0	7.0	5.0	7.0

The total person-months (PM) followed-up in the matched cohorts were 482 192 for OSI and 1 035 668 for P (Table 32). We identified in OSI and P matched group respectively 57 and 125 ACS events (event rates 1.18 vs. 1.21 per 10 000 PM (10KPM), about 0.14 per hundred person-years); 34 and 70 MI events (event rates 0.70 vs. 0.67 per 10KPM, 0.08 per hundred patient years); 26 and 74 stroke events (event rates 0.54 vs. 0.71 per 10KPM, 0.07 per hundred patient years); 65 and 166 all-cause deaths (event rates 1.35 vs. 1.60 per 10 000 PM (0.17 per hundred patient-years)). Overall, there was no difference in the event rates for ACS, MI, stroke, or all-cause death associated with OSI (ACS HR 0.97 [95%CI 0.71-1.32]; MI 1.04 [0.69-1.57]; Stroke 0.75 [0.48-1.17]; or all cause-death 0.84 [0.63-1.12]) (Table 32, Figure 25).

Table 32. Event rates and risk of acute coronary syndrome, myocardial infarction, stroke, or all-cause death associated with OTC-Strength Ibuprofen compared with paracetamol use

	Paracetamol (ref.)			OSI			Hazard ratio (95%CI)
	Person- months	Events	Event rate	Person- months	Events	Event rate	
ACS							
Day 1-15	202856	36	1.77	99918	31	3.10	1.75 (1.08 – 2.82)
Day 16-30	193098	22	1.14	91883	4	0.44	0.38 (0.13 – 1.11)
Month 1	395954	58	1.46	191802	35	1.82	1.24 (0.81 – 1.88)
Month 2	350642	31	0.88	160422	14	0.87	0.99 (0.53 – 1.86)
Month 3	289072	36	1.24	129968	8	0.61	0.49 (0.23 – 1.06)
All follow-up	1035668	125	1.21	482192	57	1.18	0.97 (0.71 – 1.32)
MI							
Day 1-15	202856	17	0.84	99918	16	1.60	1.91 (0.96 – 3.78)
Day 16-30	193098	14	0.72	91883	4	0.44	0.60 (0.20 – 1.83)
Month 1	395954	31	0.78	191802	20	1.04	1.33 (0.76 – 2.32)
Month 2	350642	16	0.46	160422	11	0.68	1.50 (0.70 – 3.24)
Month 3	289072	23	0.79	129968	3	0.23	0.29 (0.09 – 0.97)
All follow-up	1035668	70	0.67	482192	34	0.70	1.04 (0.69 – 1.57)
Stroke							
Month 1	395954	34	0.86	191802	16	0.83	0.97 (0.53 – 1.75)
Month 2	350642	24	0.68	160422	4	0.25	0.36 (0.13 – 1.05)
Month 3	289072	16	0.55	129968	6	0.46	0.84 (0.33 – 2.13)
All follow-up	1035668	74	0.71	482192	26	0.54	0.75 (0.48 – 1.17)
All-cause death							
Day 1-15	202856	37	1.82	99918	20	2.00	1.10 (0.64 – 1.89)
Day 16-30	193098	32	1.66	91883	11	1.20	0.72 (0.36 – 1.43)
Month 1	395954	69	1.74	191802	31	1.62	0.93 (0.61 – 1.41)
Month 2	350642	56	1.60	160422	20	1.25	0.78 (0.47 – 1.30)
Month 3	289072	41	1.41	129968	14	1.08	0.76 (0.41 – 1.39)
All follow-up	1035668	166	1.60	482192	65	1.35	0.84 (0.63 – 1.12)

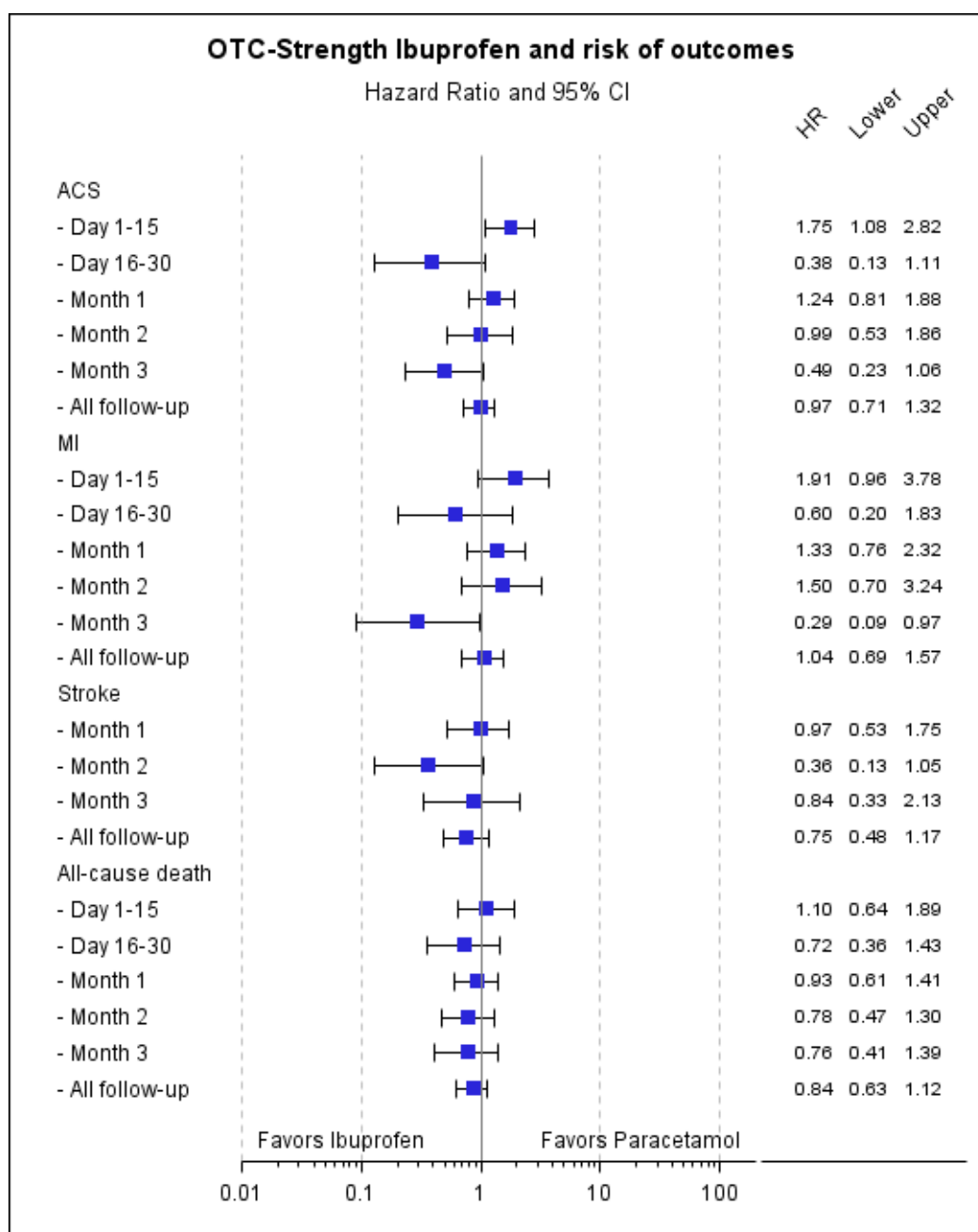


Figure 25. Risk of acute coronary syndrome, myocardial infarction, stroke, or all-cause death associated with OTC-Strength Ibuprofen compared with paracetamol

In the whole cohort, event rates were relatively stable over time for P (Figure 27), whereas they were initially higher with OSI, then rapidly decreased (Figure 26). During the first two weeks after t0, the risk of MI associated with OSI was almost double that with matched paracetamol (1.91 [0.96-3.78]). The difference then reversed in the next fortnight (0.60 [0.20-1.83]) to reach equality at the end of the first month and over the study period. Similar trends were observed for ACS (first fortnight: 1.75 [1.08-2.82] and second fortnight: 0.38 [0.13-1.11]). For coronary outcomes, the risks in the first month were slightly higher than in the 2nd and 3rd month (first month ACS: 1.24 [0.81-1.88]; MI: 1.33 [0.76-2.32]) but not for Stroke: 0.97 [0.53-1.75]; or All-cause death 0.93 [0.61-1.41].

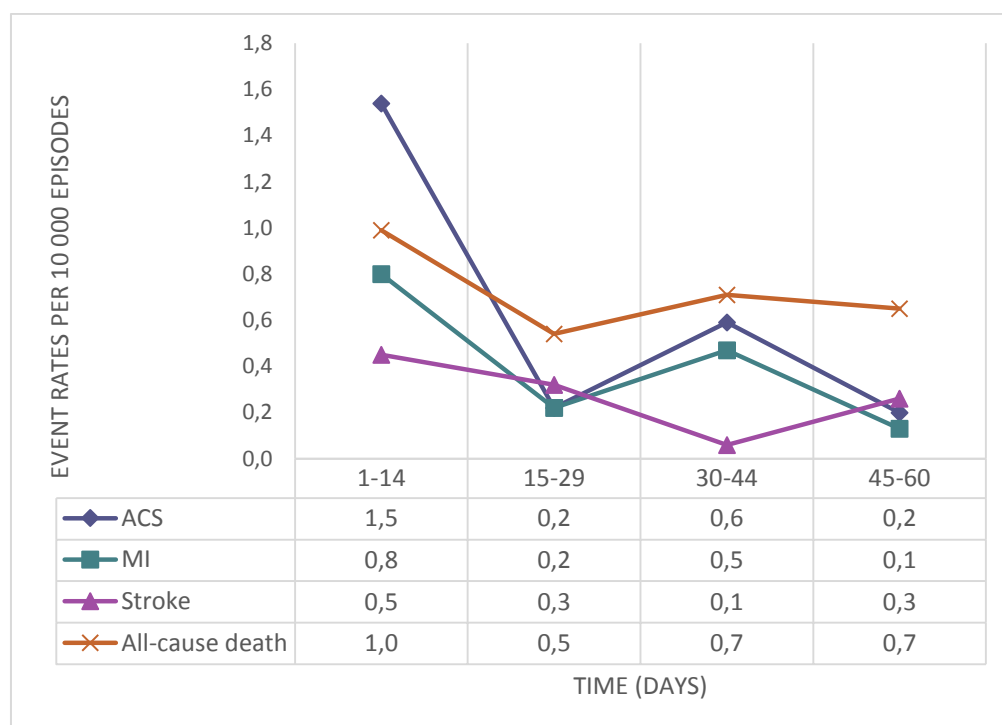


Figure 26. Outcomes rates during follow-up time in OTC-Strength Ibuprofen exclusive episodes

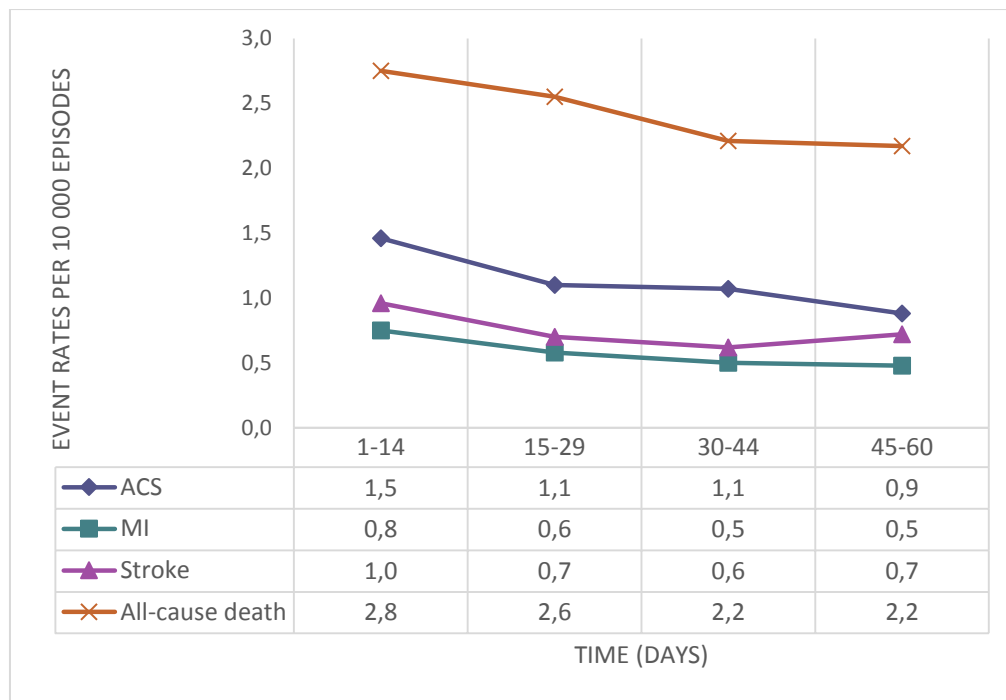


Figure 27. Outcomes rates during follow-up time in paracetamol exclusive episodes

In the sensitivity analysis, HRs of ACS and MI did not change much compared to results of the main analysis, however there were more events identified during follow-up (Table 33). Particularly, All cause-death rate increased significantly in both groups (paracetamol: 466 deaths identified, ER 4.28 per 10KPM and OSI: 159 deaths, ER 3.18 per 10KPM) compared with results of the main analysis (paracetamol: 166 deaths, ER 1.60 per 10KPM and OSI: 65 deaths, ER 1.35 per 10KPM). There was a decrease of all-cause death risk associated with OSI compared with paracetamol (overall HR 0.74 [0.62 – 0.89]).

Table 33. Sensitivity analysis - Risk of acute coronary syndrome, myocardial infarction, stroke, or all-cause death associated with OTC-Strength Ibuprofen compared with paracetamol use

	Paracetamol (ref.)			OSI			Hazard ratio (95%CI)
	Person- months	Events	Event rate	Person- months	Events	Event rate	
ACS							
Day 1-15	218852	38	1.74	107519	31	2.88	1.66 (1.03 – 2.67)
Day 16-30	198105	24	1.21	93302	4	0.43	0.37 (0.13 – 1.06)
Month 1	416957	62	1.49	200821	35	1.74	1.17 (0.77 – 1.77)
All follow-up	1089340	135	1.24	499750	59	1.18	0.95 (0.70 – 1.29)
MI							
Day 1-15	218852	17	0.78	107519	16	1.49	1.91 (0.97 – 3.79)
Day 16-30	198105	14	0.71	93302	4	0.43	0.63 (0.21 – 1.91)
Month 1	416957	31	0.74	200821	20	1.00	1.34 (0.76 – 2.35)
All follow-up	1089340	73	0.67	499750	34	0.68	1.01 (0.67 – 1.52)
Stroke							
Month 1	416957	38	0.91	200835	17	0.85	0.93 (0.52 – 1.64)
All follow-up	1089340	79	0.72	499750	30	0.60	0.83 (0.54 – 1.26)
All-cause death							
Day 1-15	218852	70	3.20	107519	23	2.14	0.67 (0.42 – 1.07)
Day 16-30	198105	83	4.19	93302	29	3.11	0.76 (0.49 – 1.17)
Month 1	416957	153	3.67	200821	52	2.59	0.71 (0.51 – 0.97)
All follow-up	1075214	466	4.28	492691	159	3.18	0.74 (0.62 – 0.89)

1.4. Discussion

Results

In this PS-matched cohort study of exclusive episodes of paracetamol or OTC-Strength ibuprofen use, we found an increased risk of ACS and MI associated with OTC-Strength ibuprofen in the first fortnight after dispensation, which evened out over the study period, so that over the study period there was no difference between OSI or paracetamol in any of the outcomes. Absolute event rates in OSI users were low (about 14 ACS, 8 MI, 6 stroke, 16 all-cause death per ten thousand patient-year), consistent with population characteristics.

High-dose and long-term use of prescription strength NSAIDs has been associated with a dose and duration dependent increase in the risk of cardiac ischemic events (330,368) that seems related to the COX2 inhibitory potency of the drugs. (133) The association of analgesics, such as paracetamol or low dose ibuprofen, with coronary heart disease remains uncertain, not the least because of the difficulty in observing these drugs, and because of the potential biases related to their use. (262) Because of the very low event rates, around 0.1% patient years, any field study desiring to study these would need to include very large numbers of patients. Even here with over 200 000 ibuprofen treatment episodes, only 34 MI were observed over 3 months. To obtain the 100 events needed to establish risk equivalence, one would therefore need at least 600 000 treatment episodes (343) for an upper limit of the risk equivalence band of 1.43, 1.4 million treatment episodes for a 1.25 risk equivalence limit. These numbers are beyond the possibilities of clinical trials or field studies, and can only be obtained in large population databases, and then only if these drugs can be identified. These studies are open to biases, of course.

Protopathic bias is the prescription of an analgesic to treat symptoms of coronary heart disease or myocardial infarction (MI) (e.g. referred neck, jaw, or shoulders pains). (290–292) In the same way analgesics may be prescribed for headache as an early sign of stroke, especially hemorrhagic. Confounding by indication is the use of the drugs for indications that may of themselves be a cause of myocardial ischemia, such as acute pain or fever: these increase blood pressure and heart rate, the main components of myocardial oxygen consumption, and may precipitate myocardial ischemia, especially in patients with underlying coronary disease. Because of these biases, the comparison of cardiac events in users of analgesics compared to non-users is not relevant. The comparison of paracetamol to low-dose NSAIDs, which share the same indications, in propensity score matched cohorts may neutralize these biases. This allows us to compare the relative effect of the drugs, but cannot explore an additional effect of the indication itself. The absence of difference between the drugs cannot exclude similar risks related to the drugs or their indications.

Our study compared specifically the cardiovascular risk of OTC strength ibuprofen to paracetamol, drugs used in similar patients for the same indications. There was no significant increase of ACS or MI risk associated with ibuprofen in these propensity-score matched cohorts. Our finding is consistent with previous studies of MI risk associated with the use of

low-dose ibuprofen: Garcia Rodriguez *et al.* (133) found an OR of 1.00 [0.80-1.25]), Andersohn *et al.* 0.99 [0.81-1.21,(254) Gislason *et al.* 1.28 [1.03-1.60)). (251)

However, we did find excess MI in the first fortnight after ibuprofen (HR 1.91 [0.96-3.78]), decreasing in the second fortnight (HR 0.60 [0.20-1.83]). Schjerning Olsen *et al.* (149) also found a significant increase of death/reinfarction associated with ibuprofen during the second week of exposure (HR 1.50 [1.24 – 1.82]) decreasing in the second fortnight, to HR 1.33 [1.15 – 1.53], compared to non-users.

A meta-analysis of randomized trials on vascular effects of NSAIDs found that Ibuprofen significantly increased major coronary events (non-fatal MI or coronary death) (RR 2.22, 1.10 – 4.48). (345) However, ibuprofen daily dose in those clinical trials was 2400mg daily, while the maximal dose for OTC strength ibuprofen is only 1200mg. There is no information about the association between daily dosage of ibuprofen and CV thrombotic risk in individual clinical trials. Observational studies showed a dose-dependent association of ibuprofen and CV risk. (247,249,254) Ray *et al.* (248), in a large cohort of patients recently discharged from the hospital with coronary heart disease, found serious coronary heart disease risk increased with short term (<90 days) use for ibuprofen (incidence rate ratio 1.67, 1.09 to 2.57). There is no information on the actual daily doses used in our claims database, only the amounts dispensed. These are small, consistent with a clinical trial of the use of these drugs for common pain indications that found that for both ibuprofen and paracetamol the average use was 20 tablets (3.3 DDD of either) over 5 days. (127) This is consistent with the average dispensation in this study, as we previously reported. (27,272) The average age at dispensing of ibuprofen in the matched cohorts was 44, similar to what was found in other studies of low-dose NSAIDs. (127,261,272) In these young patients with a very low baseline risk, even a small increase in event rates can lead to a large increase of relative risk.

We found no global increase of stroke risk associated with OTC-strength ibuprofen use compared to paracetamol (HR 0.75 [0.48 – 1.17]). A meta-analysis of randomized trials also found no increase of stroke risk associated with ibuprofen vs. placebo (RR 0.97, 0.42 – 2.24). (345) A systematic review of observational studies of stroke risk and NSAIDs found no significant increase of stroke risk associated with ibuprofen (pooled RR 1.10, 0.89 – 1.36). (369) All these studies compared current use of NSAIDs with no use. F. de Vries *et al.* (267) found similar results (RR 1.11, 1.06 – 1.16 and 1.30, 1.01 – 1.66 for ibuprofen alone and concomitant

ibuprofen and paracetamol respectively). The relationship of stroke risk and ibuprofen dose was not clear in previous studies (247)(243). The stroke risk also depends on background CV risk of patients and duration of exposure. Garcia-Poza *et al.* (243) found no increase of non-fatal stroke risk associated to ibuprofen use in low CV risk patients (OR 1.06, 0.63 – 1.78) and for less than 30 days of exposure (OR 0.89, 0.65 – 1.20). OTC NSAIDs users are generally young with little concomitant diseases, and our findings are consistent with results of Garcia-Poza *et al.* They also found that stroke risk associated with paracetamol was relatively higher in low background CV risk patients (OR 1.23, 0.87 – 1.73). Paracetamol use itself in a low CV risk population like ours may be associated with a slight increase of stroke risk, and therefore underestimate a stroke risk related to OTC-strength Ibuprofen.

Causes of death are not recorded in the national health claim database. (275)(274) We therefore could not separate cardiovascular deaths from other-cause deaths. We found a slightly lower risk of all-cause death associated with OSI compared to P (HR 0.84 [0.63 – 1.12]). This is consistent with the findings of Fosbol *et al.* (247) (CV death associated with ibuprofen ≤ 1200 mg daily dose : HR 0.79 [0.71 – 0.87]) and Gislason *et al.* (257) (death related with ibuprofen ≤ 1200 mg daily dose: HR 0.75 [0.61 – 0.92]).

In the sensitivity analysis, we identified more deaths in paracetamol group and a significant lower risk of death of OSI compared with paracetamol. In the main analysis, the follow-up time stopped at the day of LDA dispensing or patient's hospitalization for any causes. This may limit the chance to identify patients who died after hospital admission or after LDA dispensings. The results of the sensitivity analysis might be more exact for death outcome.

In fact, previous observational studies have confirmed the increased risk of death in paracetamol users. Study of de Vries *et al.* (267) found an increase of risk of death associated to paracetamol alone (RR 1.28 [1.26 – 1.30]) while the risk associated with ibuprofen was only 1.12 (1.10 to 1.15). They also found that the higher medication possession ratio (MPR), the higher increase of death risk (RR 1.63 [1.58 – 1.68] in very high MPR users of paracetamol. Almost studies found no increase of stroke or MI risk associated with paracetamol, (243,245,266,267) but when death in included as one of the cardiovascular outcomes, the risk increased e.g the study of Chan *et al.* (264) found an increase of risk of MI/Stroke/CDH death in high frequency paracetamol users (≥ 22 days/month: 1.35 [1.14 – 1.59]; ≥ 6 days/week: 1.50 [1.10 – 2.04]; 6-14 tablets/week: 1.47 [1.06 – 2.03]; ≥ 15 tablets/week: 1.68 [1.10 – 2.58]). In

our study, we found a significant lower risk of all-causes death in OSI users compared with paracetamol. This might due to the protective effect of ibuprofen, or the adverse effect of of paracetamol.

Strengths and weaknesses of study

Our study is the first to assess the CV risk associated with OTC-strength Ibuprofen separately from prescription-strength ibuprofen, compared to paracetamol. The main strengths of our studies are:

- i. We could identify and study large numbers of treatment episodes with OTC strength Ibuprofen or paracetamol. Since actual OTC use of these drugs represents only 15% (P) to 30% (OSI) of all drug use, the probability that our results could be influenced by significant unrecorded OTC use of the drugs is low.
- ii. Using paracetamol as an active comparator help to address confounding by indication and protopathic bias, which could be present in both arms. Though we cannot yet eliminate that there might be an increased risk of cardiovascular events associated with the use of OSI or P, the risk appears to be similar, so that there is no reason to choose one drug over the other because of concerns about cardiovascular safety. Of course this does not alter previous findings of potentially increased risk of cardiovascular events with higher dose ibuprofen or other prescription-strength NSAIDs.
- iii. OTC-strength ibuprofen and paracetamol were analyzed in exclusive episodes of use, to avoid the impact of other NSAIDs and the potential drug-drug interaction between ibuprofen and aspirin, which will be explored in further studies.
- iv. The database is representative of the French population, and there are little or no missing values for the variables of interest, or events such as death, hospital admissions, or drug dispensings.
- v. The sensitivity analysis enhances the robustness of results for ACS, MI and stroke outcome and provides more information for all-cause death outcome.

Our study also has some limitations.

Firstly, even though the database is exhaustive, misclassification of exposure time due to self-medication is possible. We presumed that the exposure started at drug dispensing, and ended

when the supply dispensed was exhausted, assuming continuous use. This may not be the case, and exposure may have continued at lower doses, or might have stopped and restarted at a later date using residual drugs. We chose to use a standard exposure period of 3 months to cover drug use, even if dispensing was of a smaller amount. Sensitivity analyses using shorter exposure times did not change the results except for the first 2 weeks, showing a greater early risk of MI associated with Ibuprofen. However this fully canceled out when surveillance was one month or more. Because of small event numbers, this might be a fluke, or it might be a real difference between ibuprofen and paracetamol, one associated with short-term increased risk, the other with longer-term risk.

Events and hospital admissions are readily identified and coded with reasonable quality. (276) Coronary events are systematically hospitalized, (288) but immediately fatal events may not be hospitalized, and therefore not recognized. However, all deaths in or out of hospital are recorded, and any disproportion would appear in the all-cause death numbers.

Finally, although we included many potential confounding factors in the propensity score estimation, a residual confounding for unmeasured factors (BMI, smoking, diet, and blood pressure) cannot be ruled out. However for such residual confounding to affect our results it would need to affect the choice of analgesic. There are no guidelines that recommend the use of one or the other depending on the presence of these confounders, so that residual confounding by an unmeasured known confounder is unlikely, even more so in propensity score matched cohorts that have very similar characteristics.

1.5. Conclusion

Overall, OTC-strength Ibuprofen was not associated with increased CV risk or all-cause death compared to paracetamol, though some questions remain unanswered, mostly because of insufficient power despite the population sizes. One might also wonder about the real public health impact of risks that require populations of millions of users to be measured.

3. Nested case-control study

We saw from the drug utilisation and the SCC studies that most ibuprofen users were younger, and paracetamol users older. The PS-Matched study selected mostly younger patients (mean age 45) and had consequently a low number of events. Most ACS and MI occur in older patients who might have different risk factors and where the drugs might have different effects. We therefore chose to complete this study by a nested case-controls study, studying the older, at-risk population.

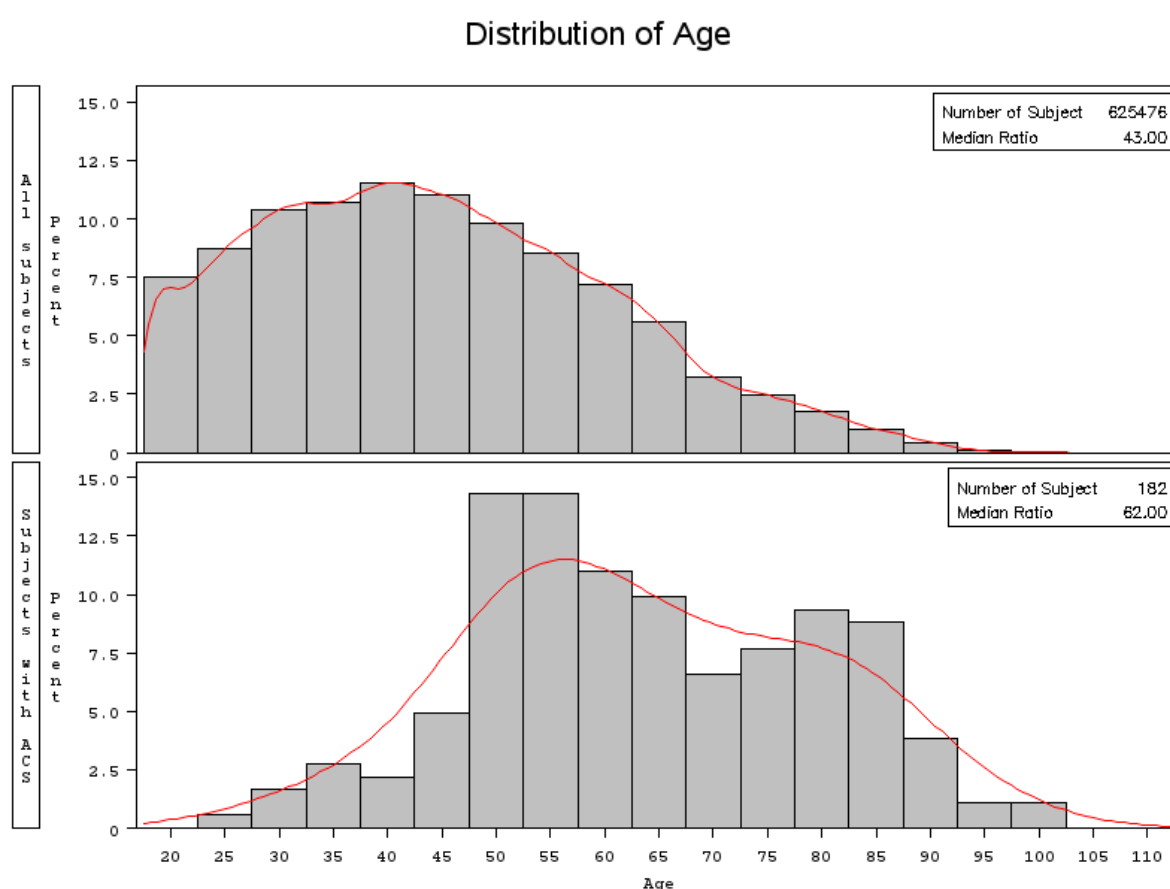


Figure 28. Distribution of age of patients and events in the PS-matched population

3.1. Background and objective

The Cohort design is appropriate to analyse multiple outcomes, but more complicated in case of multi-exposures. On the contrary, case-control design is simpler to study multi-exposure issues but not appropriate for multiple outcomes. We therefore used a nested case-control design to test CV risk of prescription-strength ibuprofen (PSI), of OTC-strength ibuprofen and of paracetamol, and again to test the effect of concomitant low-dose aspirin use.

As the original study population were NSAIDs and paracetamol users, this study was nested in that population.

Because of the small number of MI and strokes, we tested the nested case-control design for ACS outcome only. The objective of the study is to evaluate the risk of acute coronary syndrome associated with the use of paracetamol, OTC-strength ibuprofen, prescription-strength ibuprofen, co-exposure between those drugs of interest, and/or with low-dose aspirin.

3.2. Methods

Data source

This study was conducted in EGB. Characteristics of this this database have been described earlier.

Study design

This is a nested case control study in a primary cohort comprised of beneficiaries in EGB in the period 2005 – 2012, who fulfilled the following criteria: had at least one dispensation of oral paracetamol or NSAIDs at prescription or OTC- strength, age ≥ 18 years old at the first dispensation, had no hospital admissions for ACS in the period 2005-2008 (Figure 29).

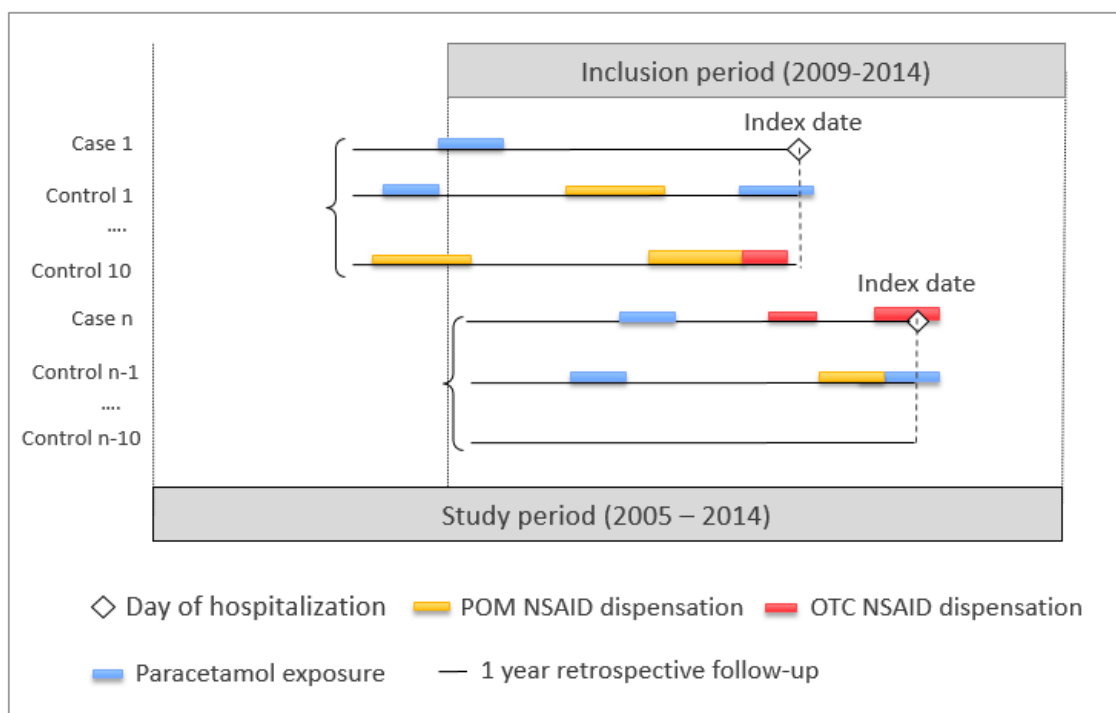


Figure 29. Nested case-control study design

Case definition

ACS was identified by primary discharge diagnosis ICD-10 codes I21 (MI - myocardial infarction) and I20.0 (unstable angina) during period 2009-2012. This combination of ICD-10 codes could identify 83.6% of ACS. (276) For each patient, **only the first ACS hospitalisation** was included. The first day of the first hospitalization was defined as the index date (t_0). Cases with less than one year follow-up were also excluded.

Controls

We used two different groups of controls. The first group of controls includes non-cases that were matched with cases on the year of birth and gender (matching ratio 1:10). The second group of controls were created from the first group of controls by matching on age, gender and disease risk score (DRS). The same index date as the cases was assigned to their controls. Controls with less than one year follow-up (time from the database entry to t_0 was less than 1 year), or not alive at the index date were excluded.

Exposure definition

Dispensing of study drugs during one year preceding t0 was retrieved. OTC-Strenth NSAIDs, prescription- strength NSAIDs and paracetamol were identified in the same ways as described in the self-controlled cohort studies and PS-matched cohort study.

We defined exposure time as the total dose dispensed divided by the defined daily dose (DDD) plus 30 days for paracetamol, prescription-Strength NSAIDs and OTC-Strength NSAIDs, 7 days for low-dose aspirin (LDA). The additional time is because of the latency of actual use, which might be longer for paracetamol and Prescription-Strength NSAIDs (corresponding to chronic disorders like OA or RA) than for OTC—Strength NSAIDs (corresponding acute pain). Total number of DDD dispensed one year before t0 were also calculated.

OTC- Strength NSAIDs DDD were defined as the maximal daily dose recommended for OTC use: 1200mg for ibuprofen, 75mg for OTC diclofenac, 500mg for OTC naproxen (or 660mg for naproxen sodium), 75mg for OTC ketoprofen. The DDD of paracetamol was 3g. DDD of other prescription-only NSAIDs were defined according to WHO ATC/DDD Index 2013. The DDD of low-dose aspirin is one tablet per day.

For study drugs and low-dose aspirin, current, recent, past and nonusers were defined. “Current users” were those with exposure at the index date, “recent users” if the exposure time ended within 60 days before t0, “past users” if the exposure time ended within 60 and 365 days before t0. “Non-users” were those with **no dispensation of either NSAIDs or paracetamol** within one year preceding t0. Patients were also classified into different subgroups: OTC-Strength NSAIDs, Prescription-Strength NSAIDs only, paracetamol only, and mix exposure. In the second analysis, we separated LDA current users and LDA non-current users (including recent, past and nonusers). In each group, we compared patients with co-dispensed paracetamol/ibuprofen to patients without co-dispensed paracetamol/ibuprofen. **Exclusive nonusers** were those without any dispensing of either NSAIDs or paracetamol in the preceding year.

Covariates

Other covariates were obtained including the prevalent long term illness (Affection de Longue Durée (list of major chronic diseases with full insurance cover of all claims related to the disease

- ALD) at t0 (stroke, lower-limb arterial disease with ischemia, severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects, diabetes type 1 and 2, severe arterial hypertension, and coronary artery diseases); drugs dispensed within 3 months prior to t0 (high-dose aspirin, antithrombotic agents (not including LDA), antidiabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, vasoprotectors, β -blockers, calcium channel inhibitors, agents acting on the renin-angiotensin system and serum lipid reducing agents), type of low-dose aspirin users (current, recent, past, nonusers) and hospital admission within 3 months prior to t0.

Statistical analysis

For the age-gender matched sample, we used univariate logistic regression models to estimate the crude odds ratios (ORs) and their 95% CI. Adjusted odds ratios (aORs) and their 95% CI were estimated by including all abovementioned covariates in the multivariate logistic regression models. Exclusive nonusers were used as reference for all sub-groups. The multivariable logistic regression models included all aforementioned covariates.

To create the DRS matched- sample, we first estimate the DRS for each patient (both users and nonusers of study drugs) by including all aforementioned covariates in a logistic model and specifying a forward variable selection with an alpha-value of 0.3. Since the DRS was established, we used the greedy matching method with ratio 1:1 and calipers set at 0.2 standard deviations of the logit of the DRS to match cases and controls. We compared the balance in baseline covariates between selected cases and controls after matching by using the standardized difference; a standardized difference that is less than 5% has been taken to indicate a negligible difference in the mean or prevalence of a covariate. Finally, we built a logistic regression models for the matched sample and estimated the odd ratios (ORs) and their 95% CI to compare current use with non-users.

To evaluate the effect of interaction of LDA and paracetamol/ ibuprofen, we separated current LDA users and estimate the risk associated with co-dispensed paracetamol or ibuprofen compared patients without paracetamol/ ibuprofen co-dispensed. Because the restriction might break the balance of the DRS matched sample, we included all covariates in the multivariable regression model.

All statistical analyses and data management were performed with the SAS statistical software package, version 9.4 (SAS Institute Inc, Cary, NC).

Sensitivity analysis

Because we found an increase of ACS risk after 2 weeks after dispensing of OTC-Strength ibuprofen in the PS-matched study, we wanted to test this short-term effect in a nested case-control study. To do that, exposure times were defined as the total dose dispensed divided by the DDD plus 7 days for paracetamol, prescription-Strength NSAIDs and OTC-Strength NSAIDs (30 days in the main analysis).

3.3. Results

The study cohort was made up of 596 029 users without history of ACS, in which we identified 4460 (0.75%) with at least one hospitalisation with ACS as the primary discharge diagnosis in 2009-2012. The age-gender matched sample included 4 193 cases and 36 158 controls (Figure 30).

Cases presented a higher proportion of prevalent long-term illnesses and cardiovascular drugs use in the 3 preceding months (Table 34). The DRS- matched sample included 3 955 cases and 3 955 controls. The characteristics of cases and controls were well balanced after matching with DRS. No variables had standardized difference more than 5%. Distributions of DRS in the cases and controls group are shown in Appendix 12.

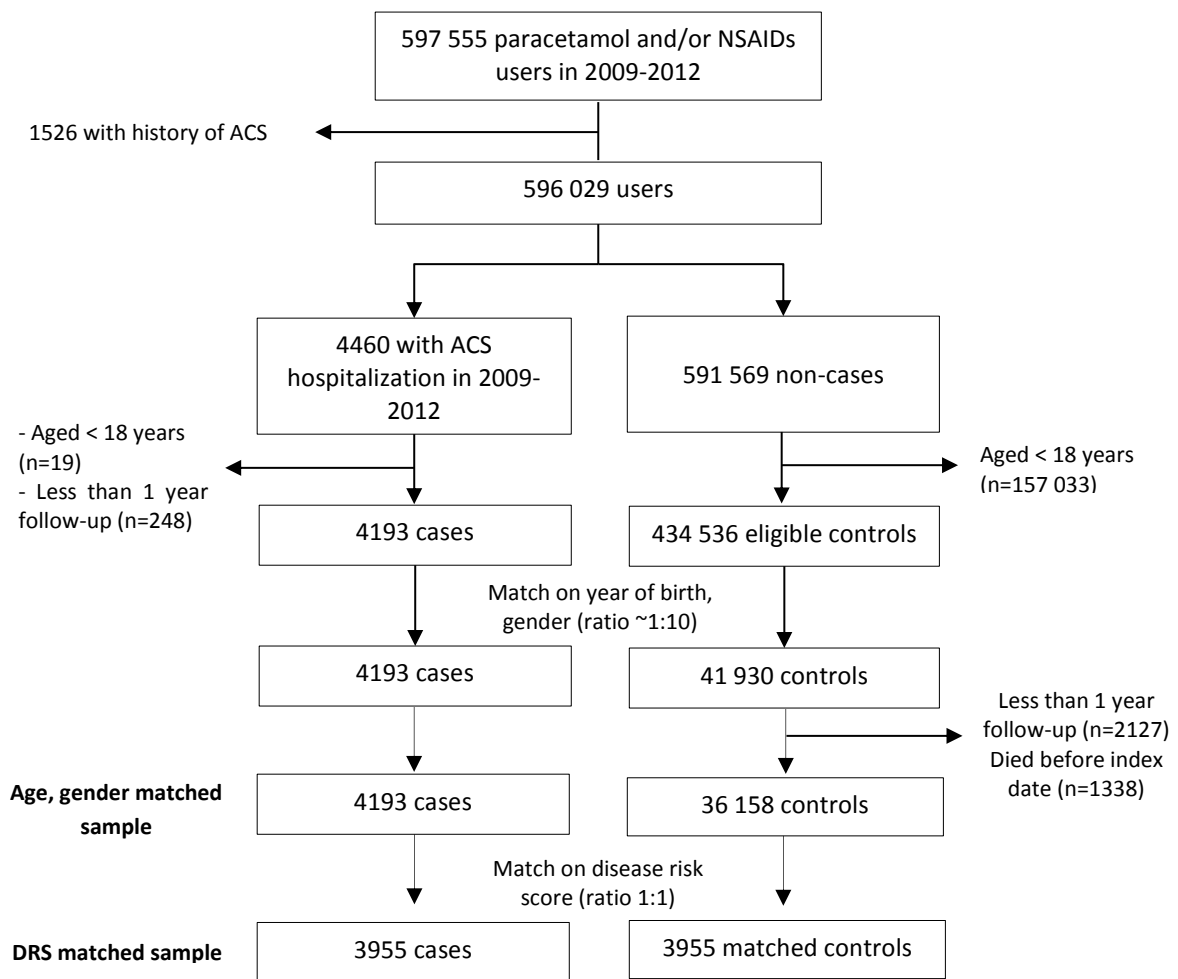


Figure 30. Cases and controls selection flowchart

Table 34. Characteristics of cases and controls in the age-gender matched and disease risk score matched- sample

	Age, gender matched sample		Age, gender, DRS matched sample		
	Controls n = 36158	Cases n = 4193	Controls n = 3955	Cases n = 3955	Standardized difference (%)
Mean age, years (\pm SD)	66.5 (14.2)	67.6 (14.4)	68.4 (14.0)	68.4 (14.0)	0
Median	67.0	68.0	69.0	69.0	
Female, n (%)	12269 (33.9)	1434 (34.2)	1344 (34.0)	1344 (34.0)	0
Prevalent long-term illnesses, n (%)					
Stroke	721 (2.0)	93 (2.2)	90 (2.3)	108 (2.7)	-2.56
Lower-limb arterial disease with ischemia	1064 (2.9)	247 (5.9)	228 (5.8)	252 (6.4)	-2.51
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	1823 (5.0)	246 (5.9)	239 (6.0)	242 (6.1)	-0.42
Diabetes type I, II	3588 (9.9)	722 (17.2)	674 (17.0)	724 (18.3)	-3.41
Severe arterial hypertension	2244 (6.2)	393 (9.4)	380 (9.6)	393 (9.9)	-1.01
Coronary artery diseases	1874 (5.2)	1103 (26.3)	889 (22.5)	849 (21.5)	2.41
Drug use in the 3 preceding months, n (%)					
High-dose aspirin	505 (1.4)	92 (2.2)	82 (2.1)	82 (2.1)	0.00
Antithrombotic agents	4094 (11.3)	1043 (24.9)	952 (24.1)	945 (23.9)	0.47
Anti-diabetes	4044 (11.2)	824 (19.7)	774 (19.6)	824 (20.8)	-2.99
Cardiac therapies	3279 (9.1)	971 (23.2)	887 (22.4)	881 (22.3)	-0.24
Antihypertensive agents	1070 (3.0)	189 (4.5)	182 (4.6)	187 (4.7)	-0.47
Diuretics	4034 (11.2)	753 (18.0)	721 (18.2)	747 (18.9)	-1.80
Peripheral vasodilators	584 (1.6)	95 (2.3)	92 (2.3)	98 (2.5)	-1.31
Vasoprotectors	234 (0.6)	28 (0.7)	27 (0.7)	32 (0.8)	-1.16
β -blockers	6166 (17.1)	1271 (30.3)	1172 (29.6)	1169 (29.6)	0.00
Calcium channel inhibitors	4324 (12.0)	839 (20.0)	795 (20.1)	820 (20.7)	-1.49
Agents acting on the renin- angiotensin system	10820 (29.9)	1760 (42.0)	1671 (42.3)	1699 (43.0)	-1.42
Serum lipid reducing agents	9958 (27.5)	1645 (39.2)	1546 (39.1)	1526 (38.6)	1.03
Current use of low-dose aspirin	4197 (11.6)	1009 (24.1)	924 (23.4)	958 (24.2)	-1.88
Any hospital admission in the 3 preceding months	2936 (8.1)	655 (15.6)	599 (15.1)	609 (15.4)	-0.83

Paracetamol and risk of ACS

Current exclusive use of paracetamol was associated with an increase of ACS risk in both matched samples (aOR 1.36 [95%CI 1.23–1.50]; DRS matched OR 1.38 [1.21–1.56]) (Table 35).

In patients with fewer than 15 DDD of paracetamol dispensed in the last year, there were higher increases of risk (aOR 1.38 [1.14 – 1.69], DRS matched OR 1.69 [1.28–2.23]) compared with more than 15 DDD..

Recent use of paracetamol was associated with a slight increase of ACS risk (aOR 1.18 [1.04-1.34], DRS matched OR 1.12 [0.95-1.32]). ACS risk in patients aged less than 60 years increased less than in patients older than 60 years (DRS matched OR 1.24 [0.95 – 1.64] vs. 1.45 [1.25 – 1.68], <60 and ≥ 60 years old respectively).

In current LDA users with co-dispensed paracetamol, ACS risk was insignificant decreased compared with current LDA users without paracetamol (aOR 0.92 [0.75–1.14], DRS matched OR 0.82 [0.64–1.06])

Table 36).

Table 35. Risk of acute coronary syndrome associated with paracetamol, OTC-Strength NSAIDs and Prescription-Strength NSAIDs in the nested case-control study

	Age-gender matched sample				Disease risk score matched sample		
	Controls n = 36158	Cases n = 4193	Crude OR (95% CI)	Adjusted OR (95% CI)	Controls n = 3929	Cases n = 3929	OR (95% CI)
Exclusive non-users*	10259 (28.4)	940 (22.4)	1 (Ref.)	1 (Ref.)	1041 (26.3)	887 (22.4)	1 (Ref.)
Current exclusive users							
Paracetamol	7091 (19.6)	1106 (26.4)	1.70 (1.55 – 1.87)	1.36 (1.23 – 1.50)	894 (22.6)	1050 (26.5)	1.38 (1.21 – 1.56)
< 15 DDD	989 (2.7)	144 (3.4)	1.59 (1.32 – 1.92)	1.38 (1.14 – 1.69)	94 (2.4)	135 (3.4)	1.69 (1.28 – 2.23)
15-90 DDD	2833 (7.8)	445 (10.6)	1.71 (1.52 – 1.93)	1.28 (1.12 – 1.46)	361 (9.1)	415 (10.5)	1.35 (1.14 – 1.59)
> 90 DDD	3269 (9.1)	517 (12.3)	1.73 (1.54 – 1.94)	1.24 (1.09 – 1.41)	439 (11.1)	500 (12.6)	1.34 (1.14 – 1.56)
Age <60	1210 (3.3)	198 (4.7)	1.77 (1.47 – 2.13)	1.21 (0.98 – 1.50)	139 (3.5)	162 (4.1)	1.24 (0.95 – 1.64)
Age ≥60	5881 (16.3)	908 (21.7)	1.70 (1.52 – 1.89)	1.34 (1.20 – 1.51)	755 (19.1)	888 (22.4)	1.45 (1.25 – 1.68)
OTC-Strength NSAIDs	283 (0.8)	29 (0.7)	1.12 (0.76 – 1.65)	1.16 (0.78 – 1.72)	29 (0.7)	27 (0.7)	1.09 (0.64 – 1.86)
Ibuprofen	189 (0.5)	22 (0.5)	1.27 (0.81 – 1.98)	1.22 (0.77 – 1.93)	20 (0.5)	20 (0.5)	1.17 (0.63 – 2.19)
Age <60	117 (0.3)	16 (0.4)	1.48 (0.87 – 2.52)	1.56 (0.89 – 2.74)	7 (0.2)	14 (0.4)	2.13 (0.85 – 5.36)
Age ≥60	116 (0.5)	13 (0.3)	0.86 (0.48 – 1.52)	0.87 (0.48 – 1.56)	22 (0.5)	13 (0.3)	0.73 (0.36 – 1.46)
Prescription-strength NSAIDs	1336 (3.7)	150 (3.6)	1.23 (1.02 – 1.47)	1.27 (1.05 – 1.54)	116 (2.9)	139 (3.5)	1.41 (1.08 – 1.83)
Ibuprofen	97 (0.3)	5 (0.1)	0.56 (0.23 – 1.39)	0.46 (0.18 – 1.18)	5 (0.1)	5 (0.1)	1.17 (0.34 – 4.07)
Diclofenac	346 (1.0)	41 (1.0)	1.29 (0.93 – 1.80)	1.19 (0.84 – 1.68)	33 (0.8)	38 (1.0)	1.35 (0.84 – 2.17)
Naproxen	136 (0.4)	11 (0.3)	0.88 (0.48 – 1.64)	0.81 (0.42 – 1.54)	10 (0.3)	9 (0.2)	1.06 (0.43 – 2.61)

	Age-gender matched sample				Disease risk score matched sample						
	Controls n = 36158		Cases n = 4193		Crude OR (95% CI)	Adjusted OR (95% CI)	Controls n = 3929		Cases n = 3929	OR (95% CI)	
Paracetamol + OTC-Strength NSAIDs	87	(0.2)	22	(0.5)	2.76 (1.72 – 4.43)	2.43 (1.48 – 4.00)	9	(0.2)	17	(0.4)	2.22 (0.98 – 5.00)
Paracetamol + Prescription-strength NSAIDs	200	(0.6)	24	(0.6)	1.31 (0.85 – 2.01)	1.34 (0.86 – 2.08)	17	(0.4)	23	(0.6)	1.59 (0.84 – 2.99)
OTC + Prescription-strength NSAIDs	14	(0.0)	3	(0.1)	2.34 (0.97 – 5.66)	2.51 (1.00 – 6.27)	1	(0.0)	5	(0.1)	5.87 (0.68 – 50.3)
Recent users											
Paracetamol only	3352	(9.3)	435	(10.4)	1.42 (1.26 – 1.60)	1.18 (1.04 – 1.34)	427	(10.8)	407	(10.3)	1.12 (0.95 – 1.32)
OTC-Strength NSAIDs only	196	(0.5)	17	(0.4)	0.95 (0.57 – 1.56)	0.91 (0.54 – 1.53)	12	(0.3)	16	(0.4)	1.56 (0.74 – 3.32)
Ibuprofen	188	(0.5)	13	(0.3)	0.75 (0.43 – 1.33)	0.60 (0.33 – 1.09)	14	(0.4)	12	(0.3)	1.01 (0.46 – 2.19)
Prescription-strength NSAIDs only	930	(2.6)	91	(2.2)	1.23 (1.02 – 1.47)	1.10 (0.87 – 1.38)	68	(1.7)	83	(2.1)	1.43 (1.03 – 2.00)
Ibuprofen	103	(0.3)	11	(0.3)	1.16 (0.62 – 2.18)	1.14 (0.59 – 2.19)	9	(0.2)	10	(0.3)	1.30 (0.53 – 3.22)
Diclofenac	266	(0.7)	19	(0.5)	0.78 (0.49 – 1.25)	0.77 (0.47 – 1.24)	23	(0.6)	18	(0.5)	0.92 (0.49 – 1.71)
Naproxen	99	(0.3)	8	(0.2)	0.88 (0.43 – 1.82)	0.92 (0.44 – 1.92)	12	(0.3)	8	(0.2)	0.78 (0.32 – 1.92)
Recent mixed users	946	(2.6)	95	(2.3)	1.10 (0.88 – 1.37)	1.09 (0.86 – 1.36)	86	(2.2)	87	(2.2)	1.19 (0.87 – 1.62)
Past users of any substance	11450	(31.7)	1278	(30.5)	1.22 (1.11 – 1.33)	1.15 (1.05 – 1.26)	1255	(31.7)	1214	(30.7)	1.13 (1.01 – 1.28)

* No dispensing of paracetamol or NSAIDs in the previous year

Table 36. Risk of acute coronary syndrome associated with paracetamol, OTC-Strength ibuprofen in current low-dose aspirin users in the nested case-control study

	Age-gender matched sample				Age-gender-disease risk score matched sample		
	Controls	Cases	Crude OR	Adjusted OR	Controls	Cases	OR
	n = 5707	n = 1322	(95% CI)	(95% CI)	n = 3122	n = 3008	(95% CI)
No Paracetamol co-dispensed	4886 (85.6)	1160 (87.7)	1 (Ref.)	1 (Ref.)	797 (83.2)	794 (85.9)	1 (Ref.)
Paracetamol co-dispensed	821 (14.4)	162 (12.2)	0.82 (0.68 – 1.00)	0.92 (0.75 – 1.14) ^Ø	161 (16.8)	130 (14.1)	0.82 (0.64 – 1.06) ^Ø
No OSI co-dispensed	5679 (99.5)	1316 (99.5)	1 (Ref.)	1 (Ref.)	956 (99.8)	920 (99.6)	1 (Ref.)
OSI co-dispensed	28 (0.5)	6 (0.5)	0.93 (0.38 – 2.24)	0.92 (0.36 – 2.34)*	2 (0.2)	4 (0.4)	2.39 (0.43 – 13.3)*

^Ø The multivariable regression model included all covariates and the type of OTC-Strength NSAIDs and Prescription-Strength NSAIDs users

* The multivariable regression model included all covariates and the type of paracetamol users

OSI, OTC-Strength ibuprofen; LDA, low-dose aspirin;

Current use of low-dose aspirin: exposure on the index date

OTC-Strength NSAIDs and risk of ACS

There was no increase of ACS risk in OTC-Strength NSAIDs exclusive users (aOR 1.16 [0.78–1.72], DRS matched OR 1.09 [0.64–1.86]) (Table 35). OTC-Strength Ibuprofen (OSI) was also not associated with any increase of ACS risk in both analyses (aOR 1.22 [0.77–1.93], DRS matched OR 1.17 [0.63–2.19]).

ACS risk increased in users less than 60 year-old (aOR 1.56 (0.89 – 2.74, DRS matched OR 2.13 [0.85–5.36])), but not in patients older than 60 years (aOR 0.87 [0.48–1.56], DRS matched OR 0.73 [0.36–1.46]) (Table 35).

Recent use of OTC-Strength NSAIDs was not associated with increase of risk (aOR 0.91 [0.54 – 1.53], DRS matched OR 1.56 [0.74 – 3.32]).

In LDA users with co-dispensed OSI, risk of ACS increased in the DRS matched analysis but not significantly (aOR 2.92 [0.76-11.2]) (

Table 36).

Prescription-Strength NSAIDs

Prescription NSAIDs were associated with a slight increase of risk overall (aOR 1.27 [1.05 – 1.54], DRS matched OR 1.41 [1.08 – 1.83]). However, none of ibuprofen, diclofenac or naproxen was associated with an increase of ACS risk in both analyses (Table 35). None of recent use of OSI, PSI, diclofenac or naproxen was related with increase of ACS risk.

Results of the sensitivity analysis are presented in Table 37. The aOR increased in all sub-groups of current use (paracetamol: 1.46 [1.31 – 1.63]; OTC-Strength NSAIDs 1.70 ([1.11 – 2.62]; Prescription-strength NSAIDs: 1.44 [1.18 – 1.75]). OTC-Strength Ibuprofen was associated with significant increase of risk in patients younger than 60 year-old (aOR 2.50 [1.35 – 4.62]) but Prescription-Strength Ibuprofen was not (aOR 1.04 [0.47 – 2.28]). There was a small decrease of risk in patients with recent use of OSI and PSI (OSI aOR 0.64 [0.34 – 1.19] and PSI OR 0.63 [0.27 – 1.46]).

Concomitant use of paracetamol and OSI

Concomitant use of paracetamol and OTC-Strength NSAIDs was associated with a significantly higher risk of ACS (aOR 2.43 [1.48–4.00])

Table 37. Sensitivity analysis - Risk of acute coronary syndrome associated with paracetamol, OTC-Strength NSAIDs and Prescription-Strength NSAIDs in the nested case-control study

	Age-gender matched sample			
	Controls n = 36158	Cases n = 4193	Crude OR (95% CI)	Adjusted OR (95% CI)
Exclusive non-users*	10597 (29.3)	971 (23.2)	1 (Ref.)	1 (Ref.)
Current exclusive users				
Paracetamol	4244 (11.7)	727 (17.3)	1.87 (1.69 – 2.07)	1.46 (1.31 – 1.63)
Age <60	1210 (3.3)	198 (4.7)	1.96 (1.55 – 2.46)	1.28 (0.98 – 2.38)
Age ≥60	5881 (16.3)	908 (21.7)	1.86 (1.65 – 2.10)	1.45 (1.27 – 1.64)

	Age-gender matched sample					
	Controls		Cases		Crude OR	Adjusted OR
	n = 36158		n = 4193		(95% CI)	(95% CI)
OTC-Strength NSAIDs	166	(0.5)	26	(0.6)	1.71 (1.12 – 2.60)	1.70 (1.11 – 2.62)
Ibuprofen	112	(0.3)	18	(0.4)	1.75 (1.06 – 2.90)	1.62 (0.97 – 2.72)
Age <60	117	(0.3)	16	(0.4)	2.57 (1.45 – 4.57)	2.50 (1.35 – 4.62)
Age ≥60	116	(0.5)	13	(0.3)	1.17 (0.63 – 2.19)	1.12 (0.59 – 2.12)
Prescription-strength NSAIDs	1070	(3.0)	135	(3.2)	1.38 (1.14 – 1.67)	1.44 (1.18 – 1.75)
Ibuprofen	64	(0.2)	8	(0.2)	1.36 (0.65 – 2.85)	1.04 (0.47 – 2.28)
Recent users						
Paracetamol only	4995	(13.8)	669	(16.0)	1.46 (1.32 – 1.62)	1.21 (1.08 – 1.35)
OTC-Strength NSAIDs only	263	(0.7)	17	(0.4)	0.70 (0.43 – 1.16)	0.73 (0.44 – 1.20)
Ibuprofen	171	(0.5)	12	(0.3)	0.77 (0.42 – 1.38)	0.64 (0.34 – 1.19)
Prescription-strength NSAIDs only	1089	(3.0)	101	(2.4)	1.01 (0.82 – 1.25)	1.07 (0.86 – 1.33)
Ibuprofen	105	(0.3)	6	(0.1)	0.62 (0.27 – 1.42)	0.63 (0.27 – 1.46)

3.4. Discussion

Paracetamol and risk of ACS

Using a nested case-control design, we found an increase of ACS associated with paracetamol overall, especially in patients aged 60 and older. This is consistent with the results of the self-controlled (SCC) design, in which we found an adjusted HR of 1.32 [1.16 – 1.49] in non LDA users and 1.38 [1.19 – 1.61] in non-LDA users aged older than 60. Again, this nested case control study raises concern about cardiovascular risk of paracetamol, in the elderly. In addition, the increase of risk that we found in patients with less than 15 DDD dispensed in the previous year (aOR 1.38 [1.14 – 1.69]) is consistent with what we found in the self-controlled cohort study in episodes with ≤ 7 DDD (aHR 1.31 [1.06 – 1.62]) and 8-14 DDD (aHR 1.36 [1.08– 1.71]). These results suggest that paracetamol should be taken with caution, even in short duration.

This study also confirms the effect of concomitant use of paracetamol with low-dose aspirin that we had found in the SCC study of paracetamol.

In addition, the increase of ACS risk when paracetamol was used concomitantly with OTC-Strength NSAIDs that we found in this study is consistent with the results of the SCC study of OTC-Strength Ibuprofen (ERR 1.96 [0.98 – 3.93]).

OTC-Strength ibuprofen and risk of ACS

In this study, an increase of ACS associated to OSI was not found. This finding is similar to what we found in the PS-matched cohort study (HR 0.97 [0.71-1.32] in 3 months follow-up and HR 1.24 [0.81-1.88] in 1 month follow-up). The early increase of ACS risk associated with OSI in the first two weeks in the PS-matched study (HR 1.75 [1.08-2.82]) is consistent with results of the sensitivity analysis (OSI aOR 1.62 [0.97 – 2.72]).

The age relationship in this study is consistent with the SCC study. Both studies found higher increase of risk in patients younger than 60 years-old (SCC event rate ratio 1.88 [1.15 – 3.07]).

The interaction of low-dose aspirin and OSI in this study is not clear. The traditional analysis shows no increase of ACS risk but the DRS matched analysis shows an increase (not significant). In the SCC study of OSI, that effect was clearer especially in the first 2 weeks after dispensing. However, because of the small number of concomitant LDA-OSI users, the interaction needs to be evaluated in a larger population.

We did not find an increased risk of ACS associated Prescription strength ibuprofen. As we can see in the descriptive study, there is no difference of OSI and PSI users regarding their characteristics (concomitant diseases, etc.) and their usage pattern. The explanation to this difference might be the latency of use in real-life, which is related to different indications of ibuprofen. OSI's indication is for acute pain, so the actual use is likely right after dispensing. PSI is prescribed for chronic condition such as OR or RA, thus there might be some latency of use after dispensing. There might be some protopathic or indication bias, if the acute pain episodes treated with OSI were associated more with acute MI than the chronic diseases treated with PSI.

The slight decrease of risk in patients with recent use of PSI and OSI in the sensitivity analysis, as well as the decrease of risk that we found in the second fortnight in the PS-matched study, suggest a typical effect of ibuprofen. However, the underlying mechanism is not clear.

Strength and weakness of study design

The nested case-control design is better than cohort design to evaluate the multi-exposure effect of OTC NSAIDs, POM NSAIDs, paracetamol. The effect of drug/drug interactions can be easily studied by stratifying users. However with the case-control design we cannot generalize the risk to the general population. The findings represent only the high-risk population of cases and matched controls. Secondly, we cannot readily compare head to head two drugs (e.g. OTC NSAIDs vs. paracetamol) like we did in the PS-matched cohort study. Thus, the indication and protopathic bias cannot be addressed.

Regarding the two methods used to adjust for confounding factors, we found that the results of the DRS matched- analysis was likely to produce a larger (or stronger) adjustment than the traditional adjustment by the multivariable regression, by looking at the difference of the crude

ORs and aORs. We cannot conclude which methods did better. However, with the DRS method the balance of the case and control groups after matching is can be estimated by the standardized difference, we cannot do the same with the traditional adjustment. One disadvantage of the DRS matching method is the decline of the study sample size. This can be limited by stratification on DRS. In this study, the decline of the sample size is minor (6% lost cases after matching).

3.5. Conclusion

The use of paracetamol was associated with a 36% increased risk of ACS. Use of OTC-strength NSAIDs was not associated with an increase of risk in main analysis, however results of the sensitivity analysis showed an early increase of 62%. At prescription dose strength, neither Ibuprofen, nor diclofenac or naproxen was associated with an increase of risk. However these conclusions are limited by the small number of cases exposed to NSAIDs.

CHAPTER VI - General discussions and conclusions

1. Discussions on main results

OTC-Strength NSAIDs, paracetamol and cardiovascular risk

WHAT IS ALREADY KNOWN

- An increased occurrence of acute coronary events has been associated with the use of NSAIDs, especially in relation to the potency of COX-2 inhibition.
- The cardiovascular risks of NSAIDs seem to be dose-dependent, but the correlation between the duration of treatment and cardiovascular risk is not clear, especially for traditional NSAIDs such as diclofenac or ibuprofen.
- In the high-risk population with prior history of coronary heart disease, the use of diclofenac or ibuprofen, even at low-doses or in short duration, may increase the cardiovascular risk.
- The cardiovascular safety varies between individual NSAIDs. Among NSAIDs available OTC (ibuprofen, diclofenac and naproxen) naproxen seems to be the safest, at prescription doses.
- The concomitant use of ibuprofen might interfere with the cardioprotective effects of low-dose aspirin.
- Data have suggested a preferential COX-2 inhibitory action of paracetamol, which may confer a cardiovascular risk.
- According to observational studies, paracetamol seems to be not related with an increased risk of myocardial infarction or stroke. However, some studies have reported increased risk of other cardiovascular outcomes such as coronary heart diseases or death.

An increase of risk with paracetamol may be proportional with the frequency of use.

WHAT IS UNKNOWN

- The CV risk associated with OTC-Strength NSAIDs in real-life conditions of use.
- The CV risk associated with paracetamol, a drugs with similar indications.
- The relative risks of paracetamol and low-dose Ibuprofen

WHAT THIS THESIS ADDS

There are no clinical trials of either paracetamol or low-dose ibuprofen with the power to study cardiovascular events in these patients, and for these indications. The large individual patient data meta-analysis of clinical trials (345) had in fact little power, especially to study ibuprofen. There was no dose-reponse information available from these clinical trials, where all doses were essentially the same. All clinical trials selected were of at least 4 weeks minimal duration and no information on the timing of the events relative to start of treatment was shown. There was no information on paracetamol. The PAIN Study, the only randomized clinical trial comparing directly paracetamol and ibuprofen in adults as used for common acute painful episodes, designed to look at safety issues in 8644 matients, had no cardiovascular events. From the event rates observed in our studies, a clinical trial designed to ascertain risk in this patient population would need to include several hundred thousands (or million) patients. Such patient numbers require the use of epidemiological methods and data sources.

There are three major difficulties in studying these drugs and their association with cardiovascular risk using pharmacoepidemiological approaches:

a) The first is the absence or uncertainty of the ascertainment or exposure to these drugs and doses. In most claims databases, neither drug will appear if they are not reimbursed. In electronic health records, they will only appear if the patient notifies the physician. In our case though there is probably a measure of uncertainty related to the possibility of unmeasured exposure because of true unrecorded OTC usage, this is limited, and would not alter the conclusions drawn from those episodes that were identified. Exposure after prescription and dispensing is always uncertain expecially if the drugs are prescribed for chronic diseases in elder patients. However in

the PAIN study, where these drugs were prescribed for acute painful episodes for which the patient had consulted, the beginning of exposure were with 24 hours after dispensing. The same was found in the Norwegian pharmacy-based diclofenac study. We therefore believe that in most cases exposure follows dispensing, especially in younger patients with few concomitant diseases.

b) The second issue is the extreme rarity of outcomes in the user population, at least in those patients not using concomitant low-dose aspirin. During the control period, the patients on LDA had 20 (paracetamol) to 100 times the event rate of patients not on LDA. Even though there were 220 000 treatment episodes (66 000 patient-years) with OSI, there were only 16 events, and 397 events in 673 000 episodes (168 000 person-years) for paracetamol. In the nested case-control study again 20 cases only were exposed to OSI: to specify risk factors and dose- or duration-dependence one will have to move to the full national database of 66 million persons to have 2000 exposed cases in the same circumstances; the event rates are so low that the public health impact of any risks we may observe remains of dubious importance, for ibuprofen and for paracetamol.

c) The third issue is the very specific biases related to the event under study, protopathic or indication biases: Indication bias can be suspected when the event that causes the prescription (pain and fever) may itself be a risk factor for the event (myocardial ischemia); alternatively there is the possibility of protopathic bias, where the drug is prescribed for pain related to the event under study, be it deferred pain in myocardial ischemia, or headache for stroke. None of the epidemiological studies to date have attempted to control for these biases, and most use non-use as the reference. Non-use is highly vulnerable to indication bias, when the risk is acute and transient.

The best way to control for indication bias would be a very large randomized placebo-controlled trial, which as seen has not been done and would involve considerable numbers of patients (and costs). Among our studies, the self-controlled cohort studies (SCC) and nested case-control (NCC) are exposed to these biases. The propensity score matched cohort study is less vulnerable, especially if a difference is found between the study arms: since these drugs are used for the

same indications, they should have the same indication and protopathic biases. Finding no difference could indicate similar risk, with or without bias. Of course the indication bias might be differential, with a channelling of the drug perceived as more effective as a painkiller to the more severe events, with greater chance of an indication-related rather than drug-related event. This may be the case for the higher risk found in the NCC when paracetamol is associated with ibuprofen. A similar higher risk related to the association of ibuprofen and paracetamol but not to either drug alone was found for soft-tissue infection, which was later shown to be related to channelling of the drug association to the more severe tonsillitis and ENT infections that were more at risk of soft tissue extension (Lesko SM, O'Brien KL, Schwartz B, Vezina R and Mitchell AA. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. *Pediatrics*. 2001;107:1108-15.). Indication bias would not explain the increased risk found shortly after ibuprofen was dispensed, compared to paracetamol in the propensity score matched study, unless more severe pain were channelled to ibuprofen rather than paracetamol, which might well be the case considering the poorer efficacy of paracetamol.

We probably identified another bias: when LDA patients are studied in the SCC studies, we found a decrease of risk of ACS with paracetamol, and an increase with ibuprofen. The latter might be related to the documented interaction between ibuprofen and aspirin, but the former has no obvious biological or pharmacological basis, especially when considering its magnitude. The greatest effect seems to be during the control period: the event rate in the control period of the paracetamol cohort was about twice that of the control ibuprofen period, and the event rates during the exposed periods were similar: this suggests a channelling of patients with ACS or MI to paracetamol rather than ibuprofen, as might be expected from the warnings concerning NSAIDs. This could explain the large difference in pre-exposure event rates. The lower post-exposure rate would then simply be regression to the mean: even though the event rate is greated in the pretreatment period, this only represents at best a few percent of the patients. Even if these were indeed at high risk, it would not change the risks for the other 98% of the population, and would have no perceivable impact on the post-exposure risk. In the same way, the increased risk after ibuprofen dispensing might simply be regression to the mean in a population depleted in pre-exposure events. In the NCC, the extremely small number of cases or controls exposed to ibuprofen and LDA (respectively 4 and 2) preclude any analysis.

The time course of risk

Our first finding is that the risk of acute coronary syndrome or myocardial infarction associated with OTC-Strength ibuprofen depends on the time after dispensing (PS-matched study and SCC). In the first 2 weeks, the risks increased sharply, then decreased quickly in the second fortnight, so that at the end of the first month after dispensing no excess risk was observed.

Previous observational studies also found an association of short-term prescription strength ibuprofen use and cardiovascular risk. (149,248,250) In the study of Schjerning Olsen *et al.* (149) the risk increased in the first month, then continued increasing in the 2nd and 3rd month. We did not find any increase beyond the first month. This difference might be because of the shorter duration of use of OTC NSAIDs in our descriptive studies. (27,127) The sharp increase in the first 2 weeks might be the result of indication and protopathic bias. Although the indication bias was limited in our propensity score matched study, there is still a possibility that OTC-strength ibuprofen might be preferred to paracetamol in some acute conditions that might be associated with cardiovascular events. This effect need to be confirmed in a larger study population.

Concomitant use with low-dose aspirin

Our second finding is that the use of OTC-Strength ibuprofen in low-dose aspirin users might increase the risk of myocardial infarction or acute coronary syndrome. We found this interaction in the self-controlled cohort study, where the indication and protopathic bias were not controlled, and where there may be channeling of patients with MI or ACS away from ibuprofen, resulting in a spuriously low pre-exposure event rate. That might overestimate the risk associated with OTC-Strength ibuprofen in this SCC study. In the PS-matched study, subjects with concomitant low-dose aspirin were excluded. In the nested case-control study, the number of cases was too low to confirm the effect of concomitant aspirin use.

The hypothesis that ibuprofen may interact with the cardioprotective effects of aspirin has been reported by MacDonald and Wei, (171) and in some experimental studies.

(139,168,171,344) Three other observational studies, however, did not find significant interactions of those two substances. (133,172,245)

Concerning paracetamol, our first important finding about the cardiovascular risk was the effect of concomitant low-dose aspirin use. We found a strong separation of risk profiles when we stratified patients by concomitant low-dose aspirin. There was a decrease of ACS risk when the two drugs were dispensed together, but an increase of risk when paracetamol was dispensed alone. This could be the result of a channeling bias, as we explained earlier. The use of low-dose aspirin suggests a prior MI and therefore might underestimate the risk after vs. before dispensing. The channeling bias, however, is less likely to affect LDA non-users, and could not explain the increase of risk in this sub-group.

Regarding the mechanism of action underlying this effect, there is no known pharmacodynamic interaction of LDA and paracetamol. (168) However, there is no data about pharmacokinetic interactions of those two drugs, which could be important in the elderly. The study of de Abajo *et al.* (245) is the only observational study that evaluated the effect of paracetamol in current low-dose aspirin users. But they compared paracetamol and low-dose aspirin concomitant use with nonuser of NSAIDs but not with users of low-dose aspirin alone. Therefore, the effect of the interaction has not been fully explored.

Because of the uncertainty about a possible channelling bias and its impact on the observed apparent risk, it might be more prudent to consider these effects in low-dose aspirin users with extreme caution.

Risk in relation to age

In the SCC study, we found that OTC-Strength ibuprofen users younger than 60 year-old whether with or without low-dose aspirin (83% of the total population) were associated with higher increase of ACS and MI risk. This phenomenon could be due to the low baseline risk of young OTC-Strength ibuprofen users. A small increase of the absolute risk can lead to a high increase of the relative risk. Another explanation could be that young users are more susceptible because they don't use medicines to prevent thrombotic events.

Concerning paracetamol, the risk ratios of CV events were generally higher in the elderly across different study design. In the SCC study, we found a significant increase of acute coronary syndrome risks in users aged 60 years or older not using low-dose aspirin. In the nested case-control study, which included mainly the elderly (mean age 67 year-old), we also found an increased of ACS risk associated with paracetamol. Fulton *et al.* (266) found no increase of myocardial infarction associated with paracetamol in patients with hypertension aged 65 years and older. However, this study did not report the effect of concomitant low-dose aspirin. In a hypertensive population, the high frequency use of low-dose aspirin might conceal the true effect of paracetamol.

Risk of the association of OSI and paracetamol

We found an increase of acute coronary syndrome risk when paracetamol and OTC-Strength NSAIDs were used concomitantly in the nested case-controlled study, and in the self-controlled study of OTC-Strength Ibuprofen. Even though the increases were not significant and our study design might not be appropriate for that kind of comparison, because paracetamol was dispensed with OTC-Strength NSAIDs in about 33% of all OTC-Strength NSAIDs episodes in France, this effect should be confirmed in further studies. In France, there is no combined paracetamol and ibuprofen product. It is also possible that the combination was used in patients with more severe pain, therefore more at risk of having an event related to the pain (confounding by indication, see above).

Risk of death

We did not evaluate the risk of death in the self-controlled cohort study because of the immortal time bias. Risk of death was only measured in the propensity score matched study. We found a lower risk of all-cause death associated with OTC-Strength Ibuprofen compared with paracetamol. Patients in the propensity score adjusted cohort were younger than the average paracetamol user, so that this risk cannot be generalized to all paracetamol users. Together with findings of previous observational studies, (264,267) there is a concern about the

risk of death associated to paracetamol, especially since the comparison with ibuprofen has somewhat limited the indication bias.

Risk of OSI compared with paracetamol

By matching on propensity score, the PS-matched study can address confounding by indication and protopathic bias. In this design, the channeling bias was also limited because we compared the event rate after dispensing and all subjects with prior ACS or stroke were excluded. What we found in this study is, though there was a higher risk of ACS with OSI in the first fortnight there was no difference between paracetamol and OTC-Strength Ibuprofen over the complete duration of the study, nor from the first month on.

In the SCC studies we found, in LDA non users, an increase in risk in patients on OSI under the age of 60, and an increase for paracetamol above the age of 60.

The PS cohort study included patients that were mostly young, similar to the OSI users, most of whom were included in this study. In the PS study, overall there was no difference between OSI and paracetamol, taking into account the very low event rates in this population. The 3-month HR was 0.97 (0.71 to 1.32). This is within the usual equivalence band (0.7-1.43), rejecting a risk greater than 1.33 at the 0.025 level.

Information on the risk in older patients can be found in the NCC study: this was based on events, not exposures, and the average age was 67. In these cases, the risk associated with paracetamol was 1.38 (1.21-1.56), which is consistent with the risk associated with NSAIDs in population observation studies, where the usual RR or OR is between 1.3 and 1.5, a little higher for rofecoxib or diclofenac (1.5-1.7). This might be affected by indication bias since the comparator was non-use. In the same circumstance OSI had an OR of 1.09 (0.64-1.36). In the DRS-matched analysis, this represents an OR for OSI vs paracetamol of 0.79 (0.47-1.35). This is not significant but merits further exploration with more power: there were only 27 OSI-exposed cases and 29 controls.

In summary, the risk of acute coronary syndrome with OSI was greater than for paracetamol within the first 2 weeks in the PS matched cohort, but not thereafter or over the course of the study. In older patients, the NCC confirmed an increased risk with paracetamol, not with ibuprofen, though the difference between the two did not reach significance.

Public health implications

There are in average 70,000 episodes of OTC-strength ibuprofen per year in the EGB database, this can be generalized to 7 million episodes per year over all French population. In the self-control cohort study, the excess increase of risk of myocardial infarction after OTC-strength ibuprofen dispensing was 24 cases per 316,265 episodes, i.e. approximately 7.6 cases per 100,000 episodes. This can be translated to an excess increase of about 500 cases of myocardial infarction per year over all the population, compared to the non-use period before dispensing. This should be put in perspective with about 100 000 ACS overall per year in France, so that the risk related to the use of OTC-strength ibuprofen would represent about 0.5% of all ACS. The increase of absolute risk cannot be all attributed to OTC-strength ibuprofen without considering indication and protopathic bias.

Paracetamol is the most prescribed and bought drug in France. In other countries where most of the paracetamol is bought in supermarkets and drugstores. Any risk associated with paracetamol might be a major public health issue.

There was no overall difference in myocardial infarction risk with paracetamol over 3 months after dispensing compared to the 3 months before dispensing. This includes a probable channelling bias with low-dose aspirin that apparently increased the predispensing event rate. In the 95% of patients not using low-dose aspirin, paracetamol was associated with a slight increase in the risk of coronary events, especially above the age of 60. The relative risk found overall was 1.3 in the SCC, similar to that found in the NCC, which included only non-LDA patients. Overall this represents an absolute risk of 0.21 cases of ACS per 1000 non-LDA episodes of paracetamol dispensing. Considering about 58 million episodes of paracetamol dispensing per year in France, this would represent an excess risk of 12500 cases, i.e. 12.5% of

all ACS. Of course this cannot be entirely attributable to paracetamol, without taking into account indication and protopathic biases, and probably some channelling.

The increase of MI risk was higher in the elderly not using low-dose aspirin. The excess risk was about one per 10,000 person-months during the paracetamol risk period. This number looks small but in France about 6 million persons above the age of 60 use paracetamol each year. (272) This might translate into as many as 1800 to 2000 paracetamol-related extra cases of myocardial infarction in low-risk older patients yearly in France.

Compared with paracetamol, the myocardial infarction risk of OTC-strength ibuprofen only increased in the first 2 weeks after dispensing, the excess risk was 3.6 cases per 100,000 episodes, i.e. about 250 cases in the total population per year. However, the risk quickly decreased in the second fortnight. In one month follow-up, OTC-strength ibuprofen use was associated with a slight increase of 2.2 cases per 100,000 episodes compared with paracetamol, i.e. ~ 150 cases in the total population (0.15% of all ACS). We also have to underline that this slight increase of risk might fluctuate because of the uncertainty of the propensity matching method that we used.

2. Conclusion

Since paracetamol is the most prescribed and bought drug in France, and it can be easily purchased in supermarkets and drugstores in other countries, any risk associated with paracetamol might become a major public health issue, even though one might wonder about the real public health impact of risks that require populations of millions of users to be measured: our calculations concerning the impact of the population puts the excess risk at several thousand extra cases per year.

Our findings add to the increasing evidence that paracetamol is not quite as safe as generally thought. (224,226) This was especially true in patients above the age of 60, not using low-dose aspirin. Since in parallel there are arguments for the lack of benefit of paracetamol in acute or chronic painful conditions, (75,335,337,364) there is a need to further explore and specify the real risks associated with paracetamol, while continuing to look for other painkillers.

As yet our results do not provide strong arguments to prefer paracetamol to OSl or reciprocally based on safety considerations.

3. Research perspectives

Although our self-controlled cohort study included million of episodes of paracetamol use, there was a risk of indication and protopathic bias when we compared paracetamol use to nonuse periods. When paracetamol is compared to ibuprofen in mostly young patients, there was no difference in risk beyond one month. The nested case-control, which concerned essentially elderly patients, confirmed the results of teh self-controlle cohort, in showing a risk of about 1.3 compred to pretreatment or non-use of paracetamol.

At this point there were not enough events exposed to low-dose NSAIDs in the elderly to be able to conclude as to the comparative risks of paracetamol and ibuprofen. In the same way there were too few events exposed to individual prescription-strength NSAIDs to be able to compute individual drug risks. In France, ibuprofen is the most used OTC-strength NSAIDs. (27) Any increase of cardiovascular risk associated with other OTC-strength NSAIDs like diclofenac or naproxen may not be a big concern because of a small number of users and a low rate of thrombotic events in the user population. Our study population represent about 1% of the French population. Because OTC-Strength ibuprofen users are generally young, even in over 300 thousand episodes of use, we only identified 54 myocardial infarction events in the three months after dispensing. Given these small numbers of events it was not possible to explore the impact of dose or duration of exposure, or some risk factors that may be of importance.

To study these aspects, it is proposed to conduct case-based studies in the national database, which would increase 100-fold the power of the present study. Cohort-based studies may also be considered, despite the massive data they represent.

Because of the potential indication and protopathic biases, further studies should concentrate on comparative studies with drugs sharing the same indications, primarily paracetamol and ibuprofen, possibly also antibiotics or other drugs used for instance in the treatments of flu. Considering the very low event rates, the most efficient designs could be the case-control

design and its variants (case-crossover, self-controlled case series, case-population), even in very large population databases. For instance in France there are about 100 000 ACS per year, which should provide a solid case base for studies, even if the association is rare as is certainly the case.

Further studies may also focus on other risks associated with prescription-strength NSAIDs such as stroke, GI bleeding or renal failure.

Résumé en français

Contexte

Le Paracétamol est utilisé dans le monde entier pour traiter la douleur et la fièvre. Il est recommandé comme antalgique de première ligne en raison de réputation de meilleure tolérance gastro-intestinale (GI) et cardiovasculaire (CV) que les AINS, en particulier chez les personnes âgées. Cependant, des travaux récents ont mis en évidence que le paracétamol pourrait ne pas être aussi sûr (224,225) ou efficace (75,335–339) que l'on croit.

Son mécanisme d'action reste incertain, probablement lié à une inhibition préférentielle de la COX-2. (186,187,352,353)(264,267)

Certains anti-inflammatoires non-stéroïdiens (AINS) comme l'ibuprofène et le diclofénac sont disponibles à faibles doses en vente libre (over-the-counter, OTC), comme antalgique et antipyrétiques. Les données ont montré que environ 70% des utilisateurs d'AINS les prennent pour la douleur, seulement 30% prennent les AINS pour l'arthrose ou la polyarthrite rhumatoïde (PR). (310,319)

Malgré l'utilisation fréquente des AINS OTC, la plupart des données publiées sur la sécurité CV des AINS fait référence aux AINS à prescription obligatoire (AINS POM) plutôt qu'aux AINS à faible dose en vente libre. Les médicaments en vente libre sont difficiles à étudier en raison du manque de données dans les dossiers médicaux électroniques ainsi que dans des bases de données d'assurance maladie. en dehors de la France.(27,272) En France, l'ibuprofène à dose antalgique remboursé représente environ 70% de toutes les ventes d'ibuprofène. (273) Il en est de même pour le paracétamol, dont les ventes remboursées représentent environ 84% des ventes totales (272)

Profitant des nombreuses données sur l'ibuprofène à dose antalgique et le paracétamol disponibles dans la base de données nationale, l'objectif de cette thèse était d'évaluer le risque CV associé au paracétamol et aux AINS à dose antalgique.

Revue des études publiées sur les risques cardiovasculaires du paracétamol et des AINS à dose antalgique

Objectif

Revoir toutes les études publiées au sujet des risques cardiovasculaires du paracétamol et des AINS à dose antalgique en vente libre

Méthode

Recherche dans PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) des publications en langue anglaise des sujets humains, qui contiennent des expositions et des critères de jugement d'intérêt pendant la période du 1er Janvier 1990 au 12 mai 2016, en utilisant des « *medical subject headings* » (MeSH) et des termes de texte libre.

Résultats

AINS à dose antalgique en vente libre

Aucune étude n'a étudié le risque CV des AINS en vente libre. Cependant, nous avons identifié 18 études observationnelles qui ont évalué l'effet de doses faibles et / ou de durées courtes d'utilisation des AINS qui étaient disponibles en vente libre.

Les rapports de cotes (RC) ou les risques relatifs (RR) d'infarctus du myocarde (IdM) associés à l'ibuprofène à faible dose étaient de 0,63 à 1,51. Trois études ont montré des augmentations significatives du risque d'IdM. Il y avait une diminution du risque de décès dans deux études (0,79 [0,71-0,87] (247) et 0,75 [0,61–0,92] (257)).

Le risque d'IdM/ IdM récurrent / décès CV lié à l'utilisation d'ibuprofène à court terme variait entre 0,91 et 2,49.

Le risque CV associé au diclofénac à faible dose variait entre 0,91 et 1,80. La plupart des études ont rapporté une augmentation à court terme du risque CV. Schjerning Olsen *et al.* (149) ont trouvé une augmentation du risque d'IdM récurrent ou de décès de 3,26 [2,75 à 3,86] dans la première semaine.

La plupart des études n'ont pas trouvé une augmentation du risque CV associé au naproxène à faible dose, excepté une étude qui a trouvé une augmentation de risque d'IdM (RR 1,47 [1,03 à 2,10]) (251) et une autre qui a révélé une augmentation du risque d'accident vasculaire cérébral (AVC) (Hazard rate (HR) 1,55 [1,17 à 2,05]). (247) Une des études a trouvé une augmentation du risque d'IdM dans le premier mois (2,84 [1,43 à 5,63]) (250) et d'IdM récurrent/ décès dans la première semaine (1,76 [1,04 à 2,98]). (149)

Paracétamol

Nous avons identifié 7 études qui concernent le risque CV du paracétamol. Le paracétamol n'a pas été associé à une augmentation du risque global d'IdM parmi les études trouvées. Le risque d'IdM n'a pas été clairement dépendant de la dose ou la durée ou la fréquence d'utilisation. Il n'y avait pas d'augmentation du risque d'AVC global dans toutes les études. La seule augmentation du risque d'AVC était chez les patients qui ont très souvent utilisé le paracétamol (RR 1,30 [1,19 à 1,41]). (267)

Cependant, les études qui ont inclus le décès comme un critère de jugement d'intérêt ont trouvé des augmentations de risque. Le risque de décès de toutes causes a augmenté significativement dans une étude (RR 1,28 [1,26 à 1,30]). (267) Une autre étude a signalé une augmentation du risque d'IdM / AVC / décès CV chez les patients avec des hautes fréquences d'utilisation (≥ 6 jours / semaine: 1,50 [1,10 à 2,04]; ≥ 15 comprimés / semaine 1,68 [1,10 à 2,58]). (264)

Conclusion

La plupart des études ont évalué les AINS utilisés sur ordonnance sous une faible dose ou à court terme. Aucune étude n'a montré le risque CV des «vrais» AINS en vente libre. L'ibuprofène, le diclofénac et le naproxène ont généralement eu des bons profils de tolérance CV à faible dose. Cependant, le risque CV pourrait augmenter très tôt, dès les premières semaines d'utilisation. Parce que les vrais AINS en vente libre peuvent être utilisés différemment par rapport aux AINS sur ordonnance, il n'est pas certain comment ces résultats sont appliqués à l'utilisation réelle des AINS en vente libre.

Les études qui ont analysé le risque d'IdM ou d'AVC seul du paracétamol n'ont signalé aucune augmentation du risque, alors que les études qui comprenaient le décès/ décès CV ont trouvé une augmentation plus marquée du risque, en particulier avec une fréquence d'utilisation élevée. Il y avait un risque de biais de classification erronée dans la plupart des études, lorsque les non-utilisateurs de paracétamol peuvent être les utilisateurs des AINS, du fait que ces deux groupes ont des indications similaires.

Les AINS à dose antalgique et le paracétamol sont les deux groupes d'antalgique les plus utilisés. N'importe quel risque peut avoir un impact important de santé publique.

En conclusion, dans le contexte du manque de preuves concernant les risques CV des AINS à dose antalgique et le paracétamol dans les conditions d'utilisation réelles, des études observationnelles sont essentielles pour proposer des recommandations pour la pratique clinique.

Études analytiques

Étude de cohorte autocontrôlée du paracétamol

Objectif

Evaluer le risque de survenue d'un Syndrome Coronaire Aigu (SCA), d'infarctus du myocarde (IdM), d'accident vasculaire cérébral (AVC) et d'hémorragie digestive haute (UGIB) associé au paracétamol.

Méthodes

Etude de cohorte autocontrôlée dans l'EGB, qui comprend 84% des ventes de paracétamol. Toutes les dispensations de paracétamol (codes ATC N02BE01, N02BE51, N02BE71 et N02AA59) entre 2009 et 2012 ont été identifiées dans l'EGB. Seuls les épisodes d'utilisation exclusive du paracétamol (sans AINS), chez les sujets de plus de 15 ans ont été conservés. Chaque épisode comportait une période à risque de 3 mois après la dispensation et une période contrôle symétrique avant la dispensation. Les événements d'intérêt étaient les hospitalisations identifiées dans le PMSI, en rapport avec un IdM (I21), un angor instable (I20.0), les deux étant regroupés sous le terme de SCA; d'AVC (I63); d'UGIB (K250, K254, K260,

K270, K290, K920, K921, ou K922). Les analyses ont été réalisées sur la population totale des épisodes inclus, puis en stratifiant sur la présence d'aspirine à faible dose (AFD), selon l'âge, la quantité dispensée de paracétamol, le niveau de risque cardiovasculaire.

Résultats

Il y avait 1 026 041 épisodes d'exposition au paracétamol, chez 342 561 patients (âge moyen 47.2 ans; 55.8% féminins). Les risques relatifs globaux ajustés de survenue d'IDM, SCA, AVC et UGIB [IC95%] étaient de 1.01 [0.85 – 1.21], 0.91 [0.82 – 1.01], 0.85 [0.73 – 0.98] et 1.34 [1.08 – 1.66]. Chez les utilisateurs d'AFD (5% des épisodes), les risques d'IdM, de SCA ou d'AVC étaient réduits (0.29 [0.20 – 0.42], 0.39 [0.32 – 0.47], 0.35 [0.26 – 0.48]). Chez les non-utilisateurs d'AFD ayant plus de 60 ans les risques étaient notablement élevés (IdM 1.91 [1.43 – 2.54], SCA 1.38 [1.19 – 1.61]; AVC 1.13 [0.93 – 1.37], UGIB 1.45 [1.08-1.95]).

Conclusions

La dispensation de paracétamol s'accompagne d'un risque diminué d'événement cardiovasculaire chez les patients co-utilisateurs d'aspirine à faible dose, qui pourrait être lié à un biais de channelling du paracetammol chez les sujet ayant eu un infarctus récent, et traités par aspirine. En revanche, chez les non-utilisateurs d'aspirine, l'accroissement notable des risques cardiovasculaires et digestifs devrait faire rediscuter de l'utilité réelle d'encourager l'utilisation de paracétamol, en particulier chez le sujet âgé de plus de 60 ans.

Étude de cohorte autocontrôlée de l'ibuprofène à dose antalgique

Objectif

Evaluer le risque de SCA, d'IM et d'AVC associé à l'ibuprofène à dose antalgique (IDA).

Méthodes

Etude de cohorte autocontrôlée dans l'EGB, échantillon à 1/97 représentatif de la base de données nationale français d'assurance maladie, qui comprend 70% des ventes d'ibuprofène. L'ibuprofène à dose OTC a été identifié par une combinaison de sa classification ATC (anatomique, thérapeutique et chimique) de M01AE01 (correspondent les AINS) et EphMRA

(*European Pharmaceutical Marketing Research Association*) de N02B (correspondant aux antalgiques).

Toutes les dispensations d'ibuprofène à dose antalgique (IDA) entre 2009 et 2014 ont été extraites. Les patients âgés de moins de 18 ans ont été éliminés. Les critères de jugement principaux étaient le SCA, l'IdM et l'AVC, identifiés par leurs codes CIM-10 (Classification internationale des maladies, 10e révision) du diagnostic principal. La période à risques était la période de 3 mois après la délivrance (date de référence). La période contrôle était la période de 3 mois avant la délivrance. Le rapport de taux d'événements (RTE) a été calculé comme le taux d'événements (TE) pendant la période à risque divisé par le TE pendant la période de contrôle. Une régression de Poisson conditionnelle a été utilisée pour les estimations des RTE et ses intervalles de confiances (IC) à 95%. Des analyses stratifiées ont également été réalisées pour tester l'effet de l'utilisation d'aspirine à faible dose (AFD). L'évolution temporelle des risque de SCA a été décrite chez les utilisateurs d'AFD et les non-utilisateurs d'AFD.

Résultats

Il y avait 316 265 épisodes d'IDA chez 168 407 utilisateurs (âge moyen 43,0 ans, 58,2% de femmes). Pendant les périodes de contrôle et à risque, il y avait 67 et 100 SCA identifiés (TE 0,8 et 1,2 par 10 000 personnes-mois (10KPM), RTE 1,46 - IC 95% [1,07 à 1,99]); 30 et 54 IdM (TE 0,4 et 0,6 par 10 KPM, RTE 1,76, [1,13 à 2,75]), 22 et 50 AVC (TE 0,3 et 0,6 pour 10 KPM, RTE 2,22, [1,34 à 3,67]). Chez les utilisateurs de AFD (3.5% de la population), la délivrance d'IDA a été associée à une augmentation du risque de SCA (RTE 1,52, [1,07 à 2,16]); IdM (RTE 1,98 [1.19 à 3.31]). Chez les non-utilisateurs d'AFD (96,5%), il n'y avait pas d'augmentation du risque CV (RTE SCA 1,22 [0,63 à 2,36]; IdM 1,10 [0,42 à 2,85]). Le risque d'AVC a été augmenté chez les non-utilisateurs d'AFD (RTE 3,91 [1,47 à 10,4]). Quel que soit AFD ou non-AFD utilisateurs, il y avait une augmentation de risque de SCA pendant les deux semaines après la dispensation (RTE 3,52 [2,28 à 5,44] et 1,98 [0,78 à 5,08], AFD et non-AFD respectivement), et puis une diminution dans la deuxième quinzaine (RTE 0,53 [0,21 à 1,34] et 1,02 [0,30 à 3,52]).

Conclusion

L'utilisation d'Ibuprofène à dose antalgique a été associée à une augmentation du risque de SCA et d'IdM par rapport à la période de non-utilisation avant la dispensation chez les

utilisateurs de l'aspirine à faible dose, en particulier dans les deux premières semaines, mais pas chez les non-utilisateurs d'aspirine à faible dose.

Étude de cohorte appariée sur le score de propension

Objectif

Comparer le risque de SCA, d'IdM, d'AVC et de décès associé à l'Ibuprofène à dose antalgique (IDA) par rapport au paracétamol.

Méthodes

Tous les épisodes de traitement exclusifs de paracétamol seul (sans AINS) et d'Ibuprofène à dose antalgique (IDA) entre 2009 et 2014 chez les utilisateurs âgés ≥ 18 ans ont été identifiés dans la base de données EGB. L'IDA a été identifiée par son code ATC M01AE01 en association avec son code EphMRA N02B. Le paracétamol seul a été identifié par son code ATC N02BE01. Les épisodes avec aspirine (à faible ou forte dose) ont été éliminés pour limiter l'effet d'interaction.

Les scores de propension (SP) d'être traité par IDA ont été estimés pour chaque patient dans son épisode d'utilisation. L'appariement sur le SP a été fait avec un ratio de 2 : 1.

Les critères de jugement étaient les diagnostics principaux de SCA, IdM, d'AVC et le décès de toutes causes confondues. Les patients ont été suivis à partir de la dispensation d'IDA ou de paracétamol (t0) jusqu'à la survenue d'un des événements suivants : trois mois après t0, le prochain épisode de traitement de Paracétamol ou d'AINS, une dispensation de l'aspirine à faible dose (AFD), une hospitalisation, la fin de la période d'étude (31 décembre 2014), ou le décès du patient.

Les risques relatifs instantanés (HRs) et ses IC à 95% sont estimés par un modèle de COX univarié (le paracétamol a été pris comme référence). Des covariables dont la différence standardisée significative (au seuil de 5%) ont été prises dans un modèle de Cox multivarié.

Une analyse de sensibilité a été réalisée pour le suivi sans arrêt à la dispensation de l'AFD ou l'admission à l'hôpital, en prenant en compte l'exposition à l'AFD comme une variable dépendant du temps.

Résultats

La cohorte initiale comprenait au total 1 368 664 épisodes de paracétamol et 209 566 épisodes d'IDA, chez 372 089 et 125 964 sujets respectivement. La cohorte appariée a inclus 208 518 épisodes d'IDA pour 482 192 personnes-mois (PM) de suivi et 416 958 épisodes de paracétamol pour 1 035 668 PM de suivi. Il y avait 57 (IDA) et 125 (P) événements de SCA identifiés (taux d'évènement (TE) 1,18 vs 1,21 / 10,000PM (10KPM), HR 0,97 [IC 95% 0,71 à 1,32]), 34 et 70 IdM (TE 0,70 vs 0,67 / 10KPM, HR 1,04 [0,69 à 1,57]); 26 et 74 AVC (TE 0,54 vs 0,71 / 10KPM, HR 0,75 [0,48 à 1,17]); 65 et 166 décès toutes causes (TE 1,35 vs 1,60 / 10KPM, HR 0,84 [0,63 à 1,12]). Le risque d'IdM était plus élevé pendant les deux premières semaines (HR 1,91 [0,96 à 3,78]), puis plus faible dans la quinzaine suivante (0,60 [0,20 à 1,83]).

Dans l'analyse de sensibilité, les HRs n'ont pas changé pour IdM et SCA par rapport à l'analyse principale. Plus de décès ont été identifiés et on a trouvé une diminution significative de risque de décès lié à l'IDA (HR 0,74 [0,62 à 0,89]).

Conclusion

L'augmentation initiale du risque d'IdM associé à l'ibuprofène à dose antalgique nécessite une exploration plus approfondie. Une étude dans une population plus large est nécessaire pour analyser les effets de la dose et de la durée.

Étude cas-témoin nichée

Objective

Evaluer le risque de SCA liés au paracétamol, aux AINS à dose antalgique ou à dose de prescription.

Méthodes

C'est une étude de cas-témoins nichée dans la cohorte des utilisateurs d'AINS ou paracétamol entre 2005-2012, âge ≥ 18 ans, sans hospitalisation pour SCA pendant la période 2005-2008.

Tous les cas de SCA pendant la période 2009-2012 ont été identifiés par les codes CIM-10 I21 (IdM) et I20.0 (angine de poitrine). Pour chaque patient, seulement la première hospitalisation de SCA a été incluse. La date de référence était la date de la première hospitalisation. Des cas avec moins d'un an de suivi ont été exclus.

Deux échantillons de cas-témoins ont été créés. Dans le 1er échantillon, les témoins ont été appariés par l'âge et le sexe avec les cas. Dans le 2ème échantillon, les témoins ont été appariés par l'âge, le sexe et le « *disease risk score* » (DRS). Les mêmes dates de référence ont été définies pour les témoins et les cas.

L'exposition aux médicaments d'intérêt a été identifiée pendant l'année précédente. La durée d'exposition a été calculée comme le nombre total de doses délivrées divisé par le DDD (*Defined Daily Dose*) de la molécule, plus 30 jours. Les patients avec une exposition actuelle (en cours d'exposition au t0) et récente (l'exposition terminée dans les 60 jours avant t0) ont été comparés avec les patients sans exposition exclusive pendant l'année précédente.

Co-variables : les Affections de Longue Durée (ALD), les médicaments cardiovasculaires utilisés pendant les 3 mois précédents.

Dans l'échantillon apparié par l'âge et le sexe, les rapports de cotes (RCs) ajustés et ses IC à 95% ont été estimés par la régression logistique multivariée qui a pris en compte les autres co-variables. Dans l'échantillon apparié par l'âge, le sexe et le DRS, les RCs bruts ont été estimés par régression logistique univariée.

Analyse de sensibilité

Une période de 7 jours (au lieu de 30 jours) a été ajoutée à la fin de l'approvisionnement des médicaments pour tester le risque à court terme.

Résultats

La cohorte originale a inclus 4193 cas de SCA et 41 930 non-cas. Le 1e échantillon a inclus 4193 cas et 36 158 témoins. Le 2e (DRS) échantillon a inclus 3955 cas et 3955 témoins.

L'utilisation exclusive actuelle de paracétamol a été associée à une augmentation du risque de SCA dans les deux échantillons (1e échantillon : RC ajusté 1,36 [IC 95% 1,23 à 1,50]; 2e échantillon : DRS RC 1,38 [1,21 à 1,56]). Chez les utilisateurs actuels d'aspirine à faible dose (AFD) avec paracétamol co-délivré, le risque de SCA a diminué légèrement par rapport aux utilisateurs actuels AFD sans paracétamol (RC ajusté 0,92 [0,75 à 1,14], DRS RC 0,82 [0,64 à 1,06]).

Il n'y avait pas d'augmentation du risque de SCA associé à l'utilisation exclusive des AINS à dose antalgique (RC ajusté 1,16 [0,78 à 1,72] ; DRS RC 1,09 [0,64 à 1,86]). À dose de prescription les AINS ont été liés à une légère augmentation du risque (RC ajusté 1,27 [1,05 à 1,54]). Il n'y avait pas d'augmentation du risque associé à l'ibuprofène à dose antalgique (RC ajusté 1,22 [0,77 à 1,93]). À dose de prescription, ni ibuprofène, ni diclofénac ou naproxène était lié à une augmentation du risque de SCA.

Dans l'analyse de sensibilité, on a trouvé une augmentation du risque de SCA associé au paracétamol, aux AINS à dose antalgique et aux AINS à dose de prescription (Paracétamol: RC ajusté 1,46 [1,31 à 1,63]; AINS à dose antalgique 1,70 [1,11 à 2,62]); AINS à dose de prescription: 1,44 [1,18 à 1,75]).

Conclusion

L'utilisation du paracétamol est liée à une augmentation du risque de SCA d'environ 30%, que l'on ne retrouve pas avec les AINS à dose antalgique. L'ibuprofène, le diclofénac et le naproxène à dose de prescription n'étaient pas liés à une augmentation du risque de SCA.

Conclusions générales

Nos résultats s'ajoutent aux indications croissantes que le paracétamol n'est pas tout à fait aussi sûr qu'on le pense généralement, en particulier chez les patients âgés sans aspirine à faible dose co-délivrée. Le paracétamol étant l'un des médicaments les plus fréquemment prescrits et achetés, n'importe quel risque associé au paracétamol pourrait être un problème majeur de santé publique.

Dans notre étude autocontrôlée, on trouve que l'ibuprofène à dose antalgique a été associé à une augmentation à court terme du risque cardiovasculaire par rapport à la non-utilisation. Cependant, en comparaison avec le paracétamol, l'ibuprofène à dose antalgique n'a pas été associé à une augmentation du risque CV ou de décès de toutes causes confondues. L'augmentation initiale du risque d'IdM associé à l'ibuprofène à dose antalgique ainsi que l'effet d'interaction avec l'aspirine à faible dose justifie une exploration plus approfondie.

Des études plus approfondies sur une base plus importante, reprenant l'ensemble de la population française, permettront de préciser les points d'incertitude de cette étude, et en particulier l'effet de l'âge ou de la dose et la durée, ou d'autres facteurs de risques associés, ainsi que l'impact de ces produits sur d'autres risques, par exemple digestifs, rénaux ou neurologiques.

APPENDIX

Appendix 1. List of publication

1. **Duong M**, Gulmez SE, Salvo F, Abouelfath A, Lassalle R, Droz C, *et al.* Usage patterns of paracetamol in France. *Br J Clin Pharmacol.* 2016 Jan 1;n/a – n/a.
2. **Duong M**, Salvo F, Pariente A, Abouelfath A, Lassalle R, Droz C, *et al.* Usage patterns of “over-the-counter” vs. prescription-strength nonsteroidal anti-inflammatory drugs in France. *Br J Clin Pharmacol.* 2014 May;77(5):887–95.
3. Moore N, Salvo F, **Duong M**, Gulmez SE. Does paracetamol still have a future in osteoarthritis? *Lancet Lond Engl.* 2016 Mar 17;
4. Moore N, Salvo F, **Duong M**, Blin P, Pariente A. Cardiovascular risks associated with low-dose ibuprofen and diclofenac as used OTC. *Expert Opin Drug Saf.* 2013 Nov 21;1–13.
5. Salvo F, Antoniazzi S, **Duong M**, Molimard M, Bazin F, Fourrier-Réglat A, *et al.* Cardiovascular events associated with the long-term use of NSAIDs: a review of randomized controlled trials and observational studies. *Expert Opin Drug Saf.* 2014 May;13(5):573–85.
6. **Duong M**, Abouelfath A, Lassalle R, Blin P, Moore N. Cardiovascular and Gastrointestinal events in over One million Paracetamol Treatment Episodes in the French Population: a Self-Controlled Cohort Study. Submitted to *British Medical Journal*.
7. **Duong M**, Abouelfath A, Lassalle R, Blin P, Moore N. Cardiovascular events associated with Ibuprofen-Strength use in the French Population: a Self-Controlled Cohort Study. In preparation.
8. **Duong M**, Abouelfath A, Lassalle R, Blin P, Moore N. OTC-Strength Ibuprofen use in France and risk of cardiovascular events compared with paracetamol: a propensity score matched cohort study. In preparation.

Appendix 2. List of communication

Oral presentations

1. Risk of thrombotic events associated with OTC NSAIDs and paracetamol in French population: a self-controlled cohort study. The ISPE 9th Asian Conference on Pharmacoepidemiology; 2015 Nov 15; Bangkok, Thailand.
2. Cardiovascular risk associated with OTC and prescription-strength NSAIDs: a self-controlled cohort study. Journée scientifique du Service de pharmacologie; Jul 2015; Bordeaux, France.
3. Cardiovascular risk associated with OTC and prescription-strength NSAIDs and paracetamol: a nested case control study applying disease risk score. Periodical Seminar of Research unit 1219 "Bordeaux Population Health Research Center"; Apr 2016; Bordeaux, France.
4. Application of self-controlled study designs in risk identification. Seminar of methodology, Bordeaux Pharmacoepi; Feb 2016; Bordeaux, France.
5. Cardiovascular and gastrointestinal safety of paracetamol in French population. The 16th ISoP Annual Meeting. 16-19 Oct 2016; Agra, India.

Posters

1. Duong M. Cardiovascular Risk of Over-The-Counter Non-Steroidal Anti-Inflammatory Drugs in the French National Claims Database. Poster presented at: 31st international conference on pharmacoepidemiology and therapeutic risk management; 2015 Aug 26; Boston, MA, USA.
2. Duong M. Cardiovascular risk of OTC NSAIDs and Paracetamol in the French national claims database. Poster presented at: 19th Congress of French Society of Pharmacology and Therapeutics; 2015 Apr 22; Caen, France.
3. Duong M. Usage pattern of Paracetamol in France. Poster presented at: 31st international conference on pharmacoepidemiology and therapeutic risk management; 2015 Aug 26; Boston, MA, USA.
4. Duong M. Usage patterns of single-ingredient and combined analgesic paracetamol in France. 15th Annual Meeting of the International Society of Pharmacovigilance; 2015 Oct 28; Prague, Czech Republic.
5. Duong M. Risque cardiovasculaire et digestif associé à la prise de paracétamol : une étude de cohorte autocontrôlée dans l'EGB. Poster presented at: 8ème Colloque Données de Santé en vie réelle; 2016 Feb 6; Paris, France.
6. Duong M. Cardiovascular and gastrointestinal safety of paracetamol in a representative sample of the French population: a self-controlled cohort study. Poster presented at: 20th Congress of the French Society of Pharmacology and Therapeutics; 2016 Apr 21; Nancy, France.

7. Duong M. Cardiovascular and Gastrointestinal Safety of Paracetamol in French Population: A Self-Controlled Cohort Study. Poster presented at: 32nd international conference on pharmacoepidemiology and therapeutic risk management; 2016 Aug 27; Dublin, Ireland.
8. Duong M. Cardiovascular and Gastrointestinal Safety of OTC and Prescription-Only Ibuprofen versus Paracetamol in French Population. Poster presented at: 32nd international conference on pharmacoepidemiology and therapeutic risk management; 2016 Aug 27; Dublin, Ireland.
9. Duong M. Cardiovascular and Gastrointestinal Safety of and Prescription-Only NSAIDs versus Paracetamol in French Population. Poster presented at: 32nd international conference on pharmacoepidemiology and therapeutic risk management; 2016 Aug 27; Dublin, Ireland.

Appendix 3. Search strategy for literature review of cardiovascular risk associated with NSAIDs in OTC-like conditions

1. stroke [Tiab] OR "myocardial infarction" [Tiab] OR "heart failure" [Tiab] OR "cardiac failure" [Tiab] OR "acute coronary syndrome" [Tiab] OR cerebrovascular disease* [Tiab] OR coronary heart disease* [Tiab] OR "sudden cardiac death" [Tiab] OR "cardiovascular mortality" [Tiab] OR "coronary heart disease" [Tiab] OR "cardiorenal syndrome" [Tiab] OR stroke [MeSH] OR myocardial infarction [MeSH] OR heart failure [MeSH] OR acute coronary syndrome [MeSH] OR death, sudden, cardiac [MeSH]
2. nsaid OR "non-steroidal anti-inflammatory" OR "Anti-Inflammatory Agents, Non-Steroidal" [Mesh] OR diclofenac OR ibuprofen OR naproxen OR ketoprofen OR dexketoprofen
3. "low dose*" OR "dose effect" OR "dose response" OR "dose-dependent" OR "dose relationship" OR "traditional" OR "non selective" OR OTC OR "over-the-counter" OR "non prescription") NOT ("aspirin"[Title] OR acetylsalicylic[Title])
4. "short duration" OR duration-dependent OR "short term" OR "low frequency" OR "onset" OR "time to event" NOT (aspirin[Title] OR acetylsalicylic[Title])
5. cohort stud* OR case-control stud* OR cohort OR epidemiologic methods OR "nested case-control" OR "case cohort" OR "self-controlled" OR "case crossover" OR "Observational Study"[PT] OR observational
6. "news"[Publication Type] OR "guideline"[Publication Type] OR letter [Publication Type] OR editorial [Publication Type] OR comment [Publication Type] OR review [Publication Type] OR "meta-analysis" [Publication Type] OR letter[Title] OR editorial[Title] OR comment[Title] OR review[Title] OR "meta-analysis"[Title]
7. "clinical trial"[Publication Type] OR "clinical trial, phase i"[Publication Type] OR "clinical trial, phase ii"[Publication Type] OR "clinical trial, phase iii"[Publication Type] OR "clinical trial, phase iv"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "pragmatic clinical trial"[Publication Type] OR trial [Title]

Search terms to identify clinical trials: ((#1 AND #2 AND (#3 OR #4) AND #7) NOT #5) AND limits Publication Date from January, 1st 1990 to May, 5th 2016; Humans, English

Search terms to identify observational studies with dose effect assessments: ((#1 AND #2 AND #3 AND #5) NOT (#6 OR #7)) AND limits Publication Date from January, 1st 1990 to May, 5th 2016; Humans, English

Search terms to identify observational studies with duration of exposure assessments: ((#1 AND #2 AND #4 AND #5) NOT (#6 OR #7)) AND limits Publication Date from January, 1st 1990 to May, 5th 2016; Humans, English

Appendix 4. Search strategy for literature review of cardiovascular risk associated with paracetamol

1. stroke [Tiab] OR “myocardial infarction” [Tiab] OR “heart failure” [Tiab] OR “cardiac failure” [Tiab] OR “acute coronary syndrome” [Tiab] OR cerebrovascular disease* [Tiab] OR coronary heart disease* [Tiab] OR “sudden cardiac death” [Tiab] OR “cardiovascular mortality” [Tiab] OR “coronary heart disease” [Tiab] OR “cardiorenal syndrome” [Tiab] OR stroke [MeSH] OR myocardial infarction [MeSH] OR heart failure [MeSH] OR acute coronary syndrome [MeSH] OR death, sudden, cardiac [MeSH]
2. paracetamol OR acetaminophen OR paracetamol [Mesh] OR acetaminophen[Mesh]
3. cohort stud* OR case-control stud* OR cohort OR epidemiologic methods OR “nested case-control” OR “case cohort” or “self-controlled” OR “case crossover” OR “Observational Study”[PT] OR observational
4. "news"[Publication Type] OR "guideline"[Publication Type] OR letter [Publication Type] OR editorial [Publication Type] OR comment [Publication Type] OR review [Publication Type] OR “meta-analysis” [Publication Type] OR letter[Title] OR editorial[Title] OR comment[Title] OR review[Title] OR “meta-analysis”[Title]
5. "clinical trial"[Publication Type] OR "clinical trial, phase i"[Publication Type] OR "clinical trial, phase ii"[Publication Type] OR "clinical trial, phase iii"[Publication Type] OR "clinical trial, phase iv"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "pragmatic clinical trial"[Publication Type] OR trial [Title]

Search terms to identify clinical trials: ((#1 AND #2 AND #5) NOT (#3 OR #4)) AND limits Publication Date from January, 1st 1990 to May, 5th 2016; Humans, English

Search terms to identify observational studies: ((#1 AND #2 AND #3 NOT (#4 OR #5)) AND limits Publication Date from January, 1st 1990 to May, 5th 2016; Humans, English

Appendix 5. OTC-dosage preparations that can prescribed and reimbursed in France

INN	Dosage per tablet (mg)	Number of DDD per pack	DDD (mg)
DICLOFENAC	12.5	3.75	100
FENOPROFEN	300	4	1200
IBUPROFEN	100	2.5 to 3.3	1200
IBUPROFEN	200	3.33 to 5	1200
IBUPROFEN	400	6.66 to 10	1200
KETOPROFEN	25	3.33	150
MEFENAMIC ACID	250	5	1000
NAPROXEN	220	8.8	500

DDD: Defined Daily Dose

Appendix 6. OTC-dosage preparations that can prescribed and reimbursed in France

INN	Dosage per tablet (mg)	Number of DDD per Pack	DDD (mg)
ACECLOFENAC	100	15	200
ALMINOPROFEN	300	15	300
CELECOXIB	100, 200	15 to 30	200
DICLOFENAC	25, 50, 75, 100	7.5 to 22.5	100
DICLOFENAC + MISOPROSTOL	50, 75	15	100
ETODOLAC	100, 200, 300, 400	7.5 to 15	400
ETORICOXIB	30, 60	14 to 28	60
FLURBIPROFEN	50, 100, 200	6 to 16	200
IBUPROFEN	400	8 or 10	1200
INDOMETHACIN	25, 50, 75, 100	5 to 15	100
KETOPROFEN	50, 100, 150, 200	6.7 to 20	150
MELOXICAM	7.5, 15	7 - 14	15
NABUMETONE	500, 1000	14, 28	1000
NAPROXEN	250, 275, 500, 550, 750, 1000	2.5 to 11.25	1000
NIFLUMIC ACID	250	10	750
NIMESULIDE	100	5 to 15	200
PIROXICAM	10, 20	14 to 15	20
SULINDAC	100, 200	3 to 15	400
TENOXICAM	20	15	20
TIAPROFENIC ACID	100, 200	5	600

Appendix 7. Individual drug utilisation in number of DDD dispensed in France over 1 year in the SALT study

Drug	mean (SD)	Median	25% - 75%
Any NSAID	36.1 (57.1)	20	[10.0;37.5]
Nimesulide	24.8 (30.8)	15	[15.0;15.0]
Diclofenac	35.3 (53.0)	22.5	[15.0;30.0]
Ibuprofen	13.4 (20.8)	6.7	[6.7;13.3]
Ketoprofen	35.6 (55.6)	20	[20.0;40.0]
Meloxicam	27.0 (45.4)	14	[7.0;28.0]
Niflumic acid	12.0 (8.4)	10	[10.0;10.0]
Aceclofenac	26.3 (35.4)	15	[15.0;30.0]
Alminoprofen	14.0 (15.7)	7.5	[7.5;15.0]
Celecoxib	70.4 (89.8)	30	[30.0;60.0]
Diclofenac associations	32.9 (51.1)	15	[15.0;30.0]
Etodolac	26.5 (40.4)	15	[15.0;30.0]
Fenoprofen	7.8 (12.3)	4.8	[2.4;7.2]
Flurbiprofen	21.2 (39.3)	7.5	[7.5;22.5]
Indomethacin	59.0 (96.1)	20	[10.0;57.5]
Mefenamic acid	11.6 (14.6)	5	[5.0;10.0]
Morniflumate	10.9 (19.9)	7.5	[7.5;14.9]
Nabumetone	32.0 (48.4)	14	[14.0;28.0]
Naproxen	36.7 (62.7)	17.6	[17.6;35.2]
Phenylbutazone	97.1 (139.1)	40	[13.3;120.0]
Piroxicam	25.4 (36.4)	14	[14.0;28.0]
Sulindac	51.8 (76.8)	22.5	[15.0;45.0]
Tenoxicam	29.5 (46.9)	15	[15.0;30.0]
Tiaprofenic acid	6.8 (7.1)	5	[5.0;5.0]

Appendix 8. Risk of ACS, stroke and GI bleeding associated with paracetamol in 1 and 2 months follow-up periods (sensitivity analysis)

	1 month		2 months	
	Crude HR (95%CI)	Adjusted HR (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)
ACS				
All episodes	0.99 (0.85 – 1.15)	0.95 (0.81 – 1.10)	0.95 (0.84 – 1.06)	0.88 (0.79 – 0.99)
With co-dispensed LDA	0.39 (0.29 – 0.52)	0.39 (0.29 – 0.52)	0.36 (0.29 – 0.45)	0.36 (0.29 – 0.45)
Without co-dispensed LDA	1.41 (1.17 – 1.70)	1.38 (1.14 – 1.66)	1.35 (1.17 – 1.56)	1.30 (1.13 – 1.50)
Only MI				
All episodes	1.12 (0.87 – 1.46)	1.08 (0.83 – 1.40)	1.01 (0.83 – 1.24)	0.95 (0.77 – 1.16)
With co-dispensed LDA	0.31 (0.18 – 0.54)	0.31 (0.18 – 0.54)	0.26 (0.17 – 0.40)	0.26 (0.17 – 0.41)
Without co-dispensed LDA	1.72 (1.26 – 2.37)	1.68 (1.22 – 2.31)	1.56 (1.22 – 2.00)	1.50 (1.17 – 1.93)
Stroke				
All episodes	0.95 (0.76 – 1.19)	0.92 (0.74 – 1.15)	0.95 (0.80 – 1.12)	0.90 (0.46 – 1.06)
With co-dispensed LDA	0.41 (0.26 – 0.64)	0.41 (0.26 – 0.64)	0.39 (0.27 – 0.55)	0.39 (0.28 – 0.55)
Without co-dispensed LDA	1.24 (0.96 – 1.61)	1.21 (0.93 – 1.57)	1.22 (1.00 – 1.49)	1.17 (0.96 – 1.42)
GI bleeding				
All episodes	1.40 (1.02 – 1.91)	1.37 (1.00 – 1.87)	1.32 (1.04 – 1.68)	1.27 (1.00 – 1.62)
With co-dispensed LDA	0.76 (0.32 – 1.82)	0.76 (0.31 – 1.82)	0.87 (0.42 – 1.80)	0.86 (0.41 – 1.80)
Without co-dispensed LDA	1.50 (1.07 – 2.11)	1.47 (1.05 – 2.06)	1.37 (1.06 – 1.77)	1.32 (1.02 – 1.71)

ACS, Acute Coronary Syndrome; MI, Myocardial infarction; GI, Gastrointestinal; LDA: low-dose aspirin

Appendix 9. Hazard ratios of ACS, stroke and GI bleeding risk associated with paracetamol, stratified by co-dispensing of any platelet aggregation inhibitors and aspirin (low- or high-dose)

	Crude HR (95%CI)	
	Platelet aggregation inhibitors	Aspirin (low- or high-dose)
ACS		
Yes	0.48 (0.41 – 0.57)	0.41 (0.34 – 0.49)
No	1.33 (1.17 – 1.51)	1.41 (1.24 – 1.60)
Only MI		
Yes	0.41 (0.30 – 0.54)	0.32 (0.22 – 0.45)
No	1.93 (1.52 – 2.47)	1.69 (1.35 – 2.10)
Stroke		
Yes	0.37 (0.29 – 0.49)	0.35 (0.26 – 0.47)
No	1.24 (1.03 – 1.49)	1.22 (1.02 – 1.45)
GI bleeding		
Yes	0.97 (0.58 – 1.62)	1.09 (0.57 – 2.07)
No	1.45 (1.15 – 1.84)	<i>1.42</i> 1.13 – 1.79)

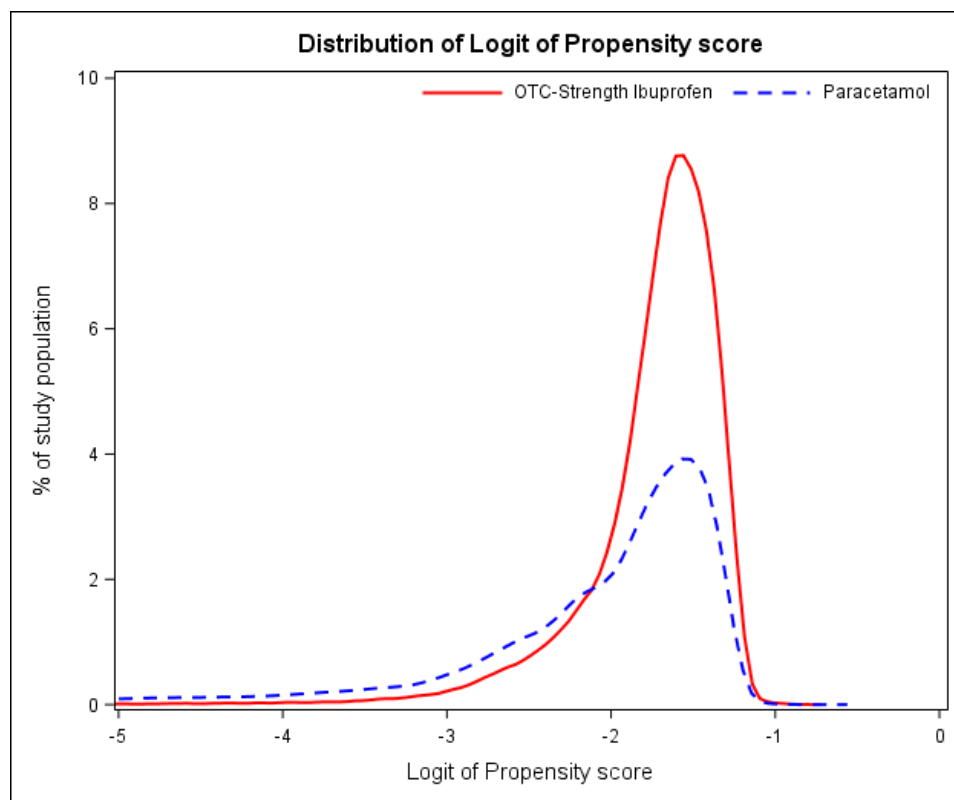
ACS, Acute Coronary Syndrome; MI, Myocardial infarction; GI, Gastrointestinal; LDA: low-dose aspirin

Appendix 10. ACS, stroke and GI bleeding risk associated to paracetamol estimated by Poisson regression

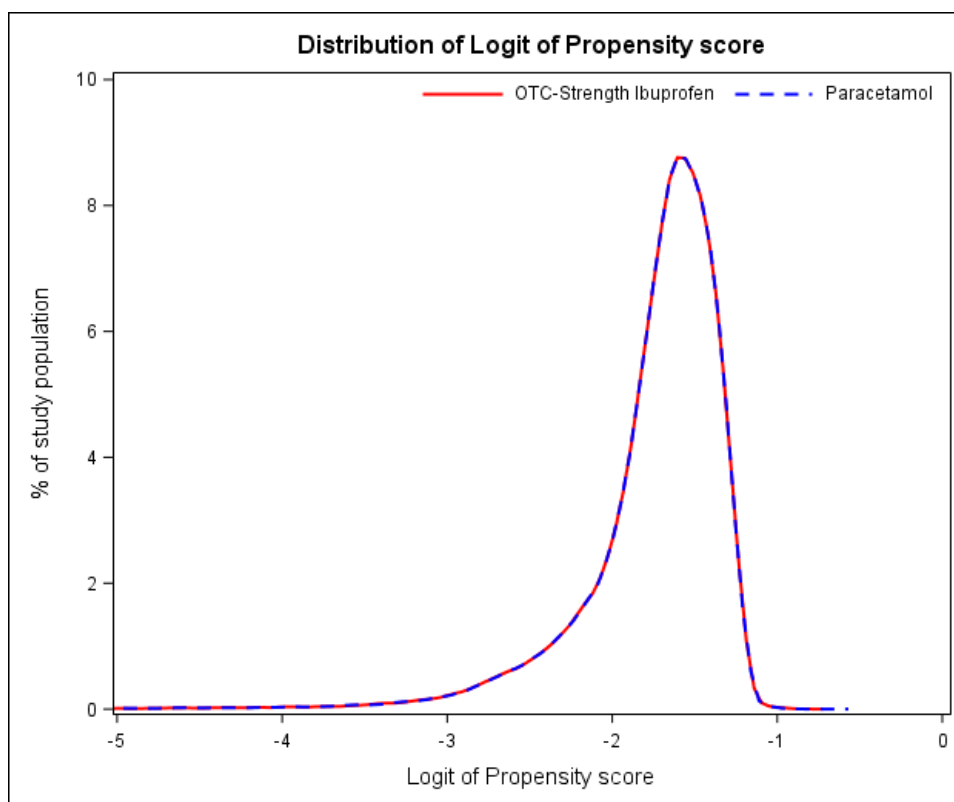
	Crude ERR (95%CI)	Adjusted ERR (95%CI)
ACS		
All episodes	0.97 (0.88 – 1.07)	0.89 (0.79 – 0.98)
With LDA	0.38 (0.19 – 0.57)	0.38 (0.20 – 0.57)
Without LDA	1.34 (1.23 – 1.46)	1.28 (1.17 – 1.40)
Only MI		
All episodes	1.09 (0.91 – 1.30)	1.00 (0.84 – 1.17)
With LDA	0.28 (0.19 – 0.41)	0.29 (0.19 – 0.42)
Without LDA	1.62 (1.31 – 2.01)	1.55 (1.34 – 1.75)
Stroke		
All episodes	0.90 (0.76 – 1.03)	0.83 (0.69 – 0.97)
With LDA	0.34 (0.03 – 0.64)	0.34 (0.03 – 0.64)
Without LDA	1.16 (1.00 – 1.32)	1.10 (0.93 – 1.26)
GI bleeding		
All episodes	1.36 (1.17 – 1.56)	1.30 (1.11 – 1.50)
With LDA	0.95 (0.37 – 1.53)	0.95 (0.37 – 1.53)
Without LDA	1.40 (1.19 – 1.61)	1.34 (1.13 – 1.55)

LDA: low-dose aspirin; ERR, Event Rate Ratio

Appendix 11. Distribution of logit of propensity score before and after matching in the Paracetamol and OTC-Strength Ibuprofen group (PS-matched cohort study)

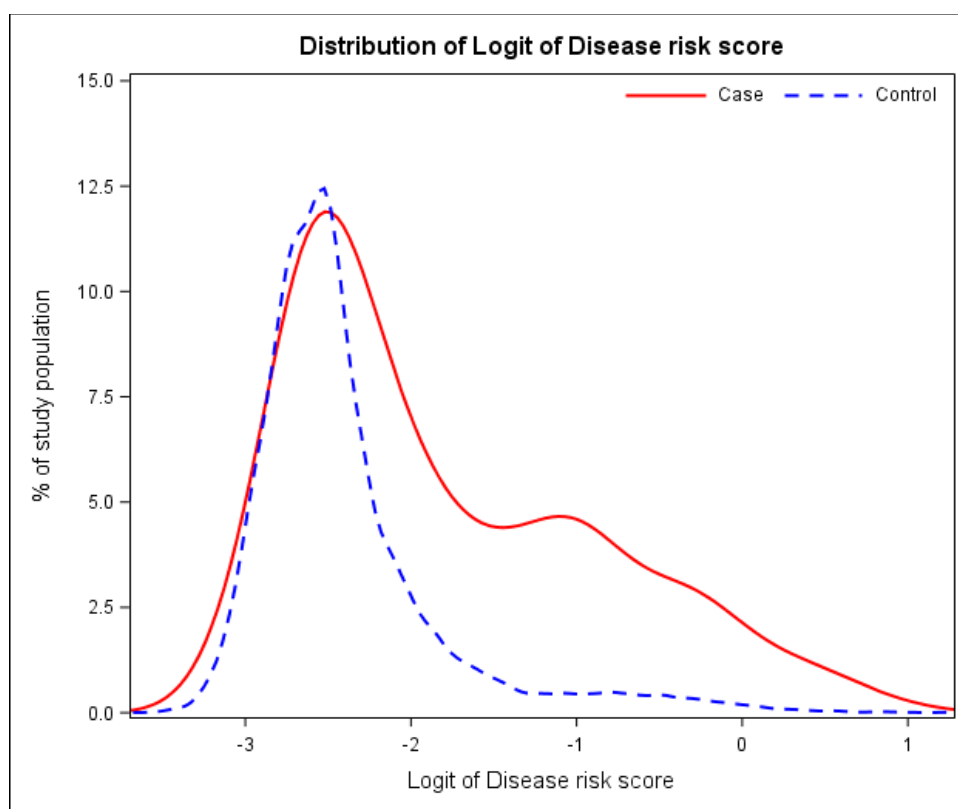


a. Before matching

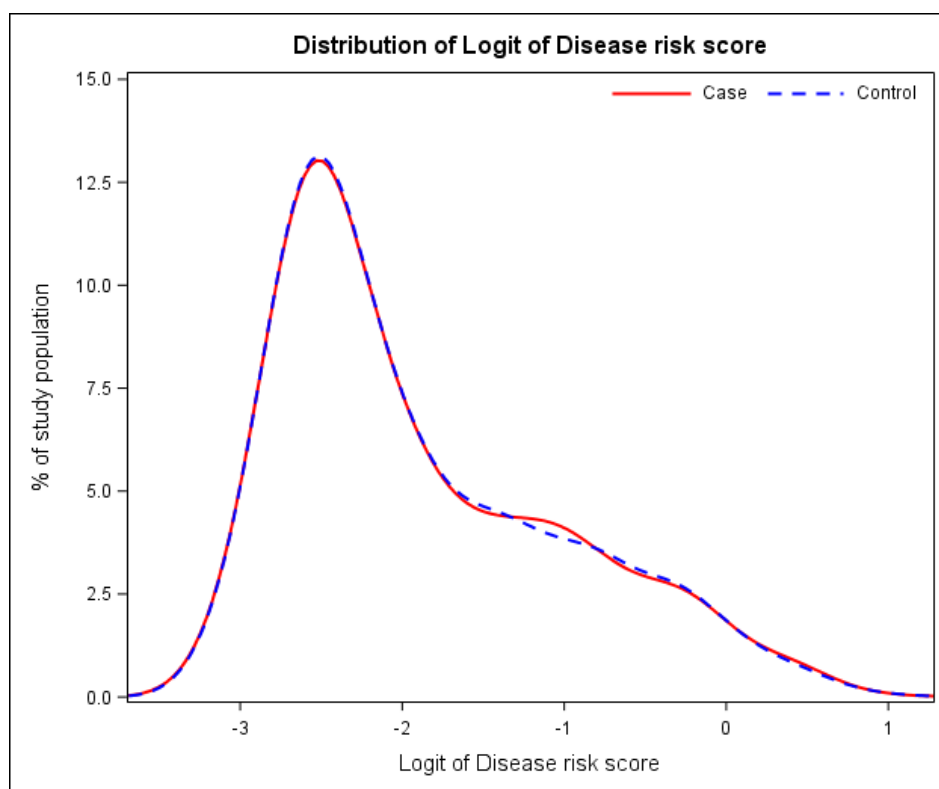


b. After matching

Appendix 12. Distribution of disease risk score before and after matching in the nested case-control study



a. Before matching



b. After matching

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