BRIEFING MATERIALS

FOR

JOINT MEETING OF

THE ARTHRITIS ADVISORY COMMITTEE

AND

THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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1 INTRODUCTION AND KEY POINTS

1.1 Introduction

These briefing materials are provided by McNeil Consumer Healthcare Division of McNEIL-PPC, Inc. (McNeil) for the FDA and Advisory Committee Members in advance of the joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee on February 10-11, 2014.[1] The committees will discuss data and analyses published in 2006 or later that are relevant to further understanding the relationship between nonsteroidal anti-inflammatory drugs (NSAIDs) and cardiovascular thrombotic risk that is currently described in NSAID class labeling. These materials provide data and analysis of information published in 2005 or later that are relevant to daily ibuprofen doses of ≤1200 mg.

McNeil is a major manufacturer of over-the-counter (OTC) drug products, including MOTRIN® IB (ibuprofen) and TYLENOL® (acetaminophen) analgesic and antipyretic products, as well as BENADRYL® (diphenhydramine), SUDAFED® (pseudoephedrine), SUDAFED PE® (phenylephrine), and ZYRTEC® (cetirizine).

Ibuprofen (200 mg) has been marketed as an OTC medicine in the United States since 1984.[2] OTC ibuprofen medicines are labeled for use by consumers at single doses up to 400 mg and daily doses of ≤1200 mg for the temporary reduction, up to 3 days, of fever and the temporary relief, up to 10 days, of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, and menstrual cramps. According to data from the 2006 Slone Survey,™ ibuprofen is a commonly used drug among US adults, with 17% of adults taking an ibuprofen-containing medicine in any given week [1]. More recently, according to Information Resources Inc (IRI) National Household Panel data, 40.6% of US households purchased single-ingredient ibuprofen in the 52-week period ending in the third quarter of 2013.

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[1] Cited publications have been provided on a separate CD.

[2] Ibuprofen has been widely used as a prescription product in the United States for almost 40 years. Prescription Motrin® (ibuprofen) tablets have been approved for strengths of 300, 400, 600, and 800 mg. In May 1984, FDA approved NDA 19-012 for OTC Motrin IB 200 mg tablets. On June 9, 1997, McNeil Consumer & Specialty Pharmaceuticals (McNeil) acquired OTC Motrin IB NDA 19-012 and prescription Motrin NDA 17-463 from Pharmacia & Upjohn Company (now Pfizer, Inc). The prescription Motrin suspension NDA (19-842) was approved in September 1989, and the OTC Children's Motrin suspension NDA (20-516) was approved in June 1995.

FDA held a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee on February 16-18, 2005 to review cardiovascular risk considerations for cyclo-oxygenase-2 (COX-2) selective NSAIDs and related agents.[3] In April 2005, FDA issued a public health advisory [2] that included the Agency's conclusions and recommendations for market and label changes related to cardiovascular risk [3]. The recommendations for non-prescription NSAIDs were as follows:

> "We recommend that the NSAIDs that are currently available without a prescription for the short-term treatment of acute pain continue to be available to consumers. While this would apparently represent the first time that products that have a boxed warning in the prescription package insert would also be available for non-prescription use, we believe the available data support a conclusion that short-term use of low doses of the available non-prescription NSAIDs is not associated with an increased risk of serious adverse CV events. The overall benefit versus risk profile for the non-prescription NSAIDs remains very favorable when they are used according to the labeled instructions, and we believe that it is important to maintain a range of therapeutic options for the short-term relief of pain in the OTC market. Further, the other available non-prescription drugs for short-term relief of pain and fever can also be associated with serious, and potentially life-threatening, adverse events in certain settings and patient populations."
>
> "To further encourage the safe use of the non-prescription NSAIDs, we believe that the labeling for these products should be revised to include more specific information about the potential CV and GI risks, instructions about which patients should seek the advice of a physician before using these drugs, and stronger reminders about limiting the dose and duration of treatment in accordance with the package instructions unless otherwise advised by a physician. In addition, as noted earlier, the agency has determined that the labeling for non-prescription NSAIDs should be revised to warn of the potential for skin reactions. We also recommend that the Agency continue its current consumer education efforts regarding the safe and effective use of non-prescription pain relievers and that this new information be highlighted in those campaigns."

[3] Following the meeting, FDA requested relevant clinical study information from all NSAID NDA holders. McNeil submitted information to the FDA on July 27, 2005 and on October 28, 2005 mainly summarizing company clinical trial study report results available as of April 2005.

FDA subsequently recommended changes to labeling for non-prescription NSAIDs. Attachment 1 provides current OTC labeling for MOTRIN® IB in a tabular format which includes FDA's recommended changes.

1.2 Key Points

Ibuprofen, which has been available OTC in the United States for almost 30 years, is an important analgesic and antipyretic medicine that provides relief of mild-to-moderate pain and fever reduction. The current OTC labeling, which includes FDA's recommendations, appropriately reflects the current knowledge of potential cardiovascular risk. This conclusion is based on review of data from observational studies since 2005, clinical trial data since 2005, and post-marketing safety data since 2003. Data from these sources continue to support FDA's 2005 conclusion that short-term use of low doses of the available non-prescription NSAIDs is not associated with an increased risk of serious cardiovascular adverse events.

- **Current OTC Ibuprofen Label Warnings.** Current OTC labeling (pertinent bullets shown below) for ibuprofen appropriately directs the consumer on product use given current knowledge of potential cardiovascular risk.
    - Ask a doctor before use if you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
    - Ask a doctor before use if you are taking a diuretic
    - Ask a doctor or pharmacist before use if you are taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
    - When using this product the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

- **Observational Studies.** Observational studies published since 2005 evaluating the potential cardiovascular (CV) risk of ibuprofen daily doses ≤1200 mg, in which the majority of patients used ibuprofen beyond the labeled OTC duration of ten days, are consistent with prior findings and support FDA's conclusion for OTC NSAIDs that "Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events"[3]. (See Section 2)

Consistent with the Federal Register Notice of the Advisory Committee Meeting, the focus of our analysis was on publications from 2005 or later that addressed the overall relationship between OTC ibuprofen doses and cardiovascular risk. In addition, McNeil evaluated

adverse events from clinical trials of OTC doses of ibuprofen, clinical trial data on the concomitant use of ibuprofen and aspirin, and ibuprofen post-marketing safety data. Conclusions from McNeil's review of these data and associated reference citations are provided below. Additional details regarding these data are not provided, since the focus of this submission is published observational studies of use of ibuprofen at daily doses ≤1200 mg.

- **Adverse Events from Published Clinical Trials.** Adverse event data from published clinical trials since 2005 [4,5,6,7,8,9,10,11,12,13,14,15][4] of at least four weeks duration of single-ingredient ibuprofen at OTC doses (≤1200 mg daily) indicated no clinically important patterns in cardiovascular or thrombotic adverse events and were consistent with the findings summarized and reported in 2005. Limited and variable adverse event data were available for these studies from the published literature.

- **Concomitant Use of Ibuprofen and Aspirin from Published Clinical Trials.** Published clinical trial data since 2005 [16,17,18,19,20,21][4] are consistent with previous conclusions and suggest that concomitant use of ibuprofen with aspirin inhibits aspirin's cardioprotective benefit, as described in the current OTC Drug Facts label (see bullet below).
    - Ask a doctor or pharmacist before use if you are taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin

- **McNeil's Post-marketing Safety Data.** Review of the Company's ibuprofen post-marketing safety data does not indicate a changing trend in cardiovascular adverse event reporting over the last 10 years. The number of these events reported to the Company annually remains low; this observation supports current labeling and is consistent with FDA's 2005 conclusion that short-term use of low doses of the available non-prescription NSAIDs is not associated with an increased risk of serious adverse cardiovascular events.

[4] These studies were not conducted or financially supported by McNeil.

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2 EPIDEMIOLOGIC OR OTHER OBSERVATIONAL STUDIES EVALUATING THE CARDIOVASCULAR RISK OF IBUPROFEN INCLUDING SEPARATE REPORTING OF OVER-THE-COUNTER DOSAGE OF IBUPROFEN

This section provides a summary of published studies on cardiovascular events from epidemiologic or other observational studies on daily doses of ibuprofen ≤1200 mg (OTC dose). McNeil's literature search covered the period from 1946 through November 2013; however, the only studies that reported on cardiovascular risk for ibuprofen at doses ≤1200 mg daily were those published since the 2005 Advisory Committee meeting. These studies were the focus of this assessment and were not conducted or financially supported by McNeil.

2.1 Key Point

- Observational studies published since 2005 evaluating the potential cardiovascular (CV) risk of ibuprofen daily doses ≤1200 mg, in which the majority of patients used ibuprofen beyond the labeled OTC duration of ten days, are consistent with prior findings and support FDA's conclusion for OTC NSAIDs that "Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events"[1].

2.2 Introduction

In preparation for the February 10-11, 2014 Advisory Committee meeting, FDA provided sponsors with a list of references (Attachment 2) to be considered at the meeting. McNeil reviewed the list of references for epidemiologic or other observational studies that included information on daily doses of ibuprofen ≤1200 mg (1200 mg is the maximum daily OTC dose). In addition, we conducted a literature search covering articles from 1946 through November 2013[1]. Articles from the published literature are included in this section if they provided epidemiologic or other observational study results on daily doses of ibuprofen ≤1200 mg. Based on these criteria, eight articles from the published literature were identified for inclusion. These studies were not conducted or financially supported by McNeil. Cited publications are provided in the reference list at the end of this section.

[1] Three online bibliographic databases, MEDLINE® from 1946 through November 20, 2013, EMBASE® from 1988 through November 21, 2013, and Derwent Drug File® from 1964 to Week 47, 2013 were searched for publications using the search terms (observational, case-control, prospective, retrospective, or epidemiologic), and (NSAIDs and cardiovascular outcomes). There were no language limitations on the search.

2.3 Overview of the Literature

A summary of the eight observational studies discussed in this section is presented in Table 2- 1. The table provides information on the lead study author and year of publication, data source, study population and age range, outcomes, and study design. Four of the studies use the Danish population registry [2,3,4,5], however each was based on a different patient cohort. The Danish studies [2,3,4,5] investigated more than one cardiovascular outcome and used two study designs to assess each outcome: 1) cohort and 2) case-crossover design. The remaining studies implemented one study design—either case-control [6,7,8] or cohort [9].

Table 2- 1. Published Observational Studies With a Calculated Daily Dose ≤1200 mg Ibuprofen

First author and year	Data source	Study population	Outcomes 1	Outcomes 2	Outcomes 3	Study Design 1	Study Design 2
Fosbøl, 2010 [2]	Danish registry	Healthy, age ≥10 y; 1st users	CV death	Coronary death + MI	Stroke	Cohort	Case-crossover
Fosbøl, 2009 [3]	Danish registry	Healthy, age ≥10 y	CV death	CV death + MI		Cohort	Case-crossover
Gislason, 2009 [4]	Danish registry	Heart failure patients, age ≥30 y	Death	Hosp. for HF	Hosp. for AMI	Cohort	Case-crossover
Gislason, 2006 [5]	Danish registry	AMI patients, age ≥30 y	Death	Rehosp. for MI		Cohort	Case-crossover
van der Linden, 2009 [6]	PHARMO, Netherlands	Age ≥40 y	Nonfatal MI			Case-control	
García Rodríguez, 2008 [7]	THIN, UK database	Age 50-84 y	Nonfatal MI			Case-control	
van Staa, 2008 [9]	GPRD, UK database	Age ≥40 y	Any MI			Cohort	
Andersohn, 2006 [8]	GPRD, UK database	Age ≥40 y	Any AMI+CHD death			Case-control	

Abbreviations: CV = cardiovascular, AMI = acute myocardial infarction, CHD = coronary heart disease, GPRD = General Practice Research Database, HF = heart failure, MI = myocardial infarction, THIN = The Health Improvement Network, UK = United Kingdom, Hosp = hospitalization.

2.4 Summary of Study Results

This section provides a summary of the results of the eight observational studies. Section 2.4.1 provides information on duration of ibuprofen use for each study. Section 2.4.2 provides forest plots by cardiovascular outcome. For reference, Attachment 3 Table 1 contains study results in greater detail including results for all medications and daily doses studied.

2.4.1 Duration of Ibuprofen Use

The labeled maximum recommended duration of use of OTC ibuprofen is ten days, unless directed by a doctor. The eight observational studies reviewed used prescription dispensing data from which duration of use could be estimated. None of the studies analyzed duration of ibuprofen use according to the US OTC label, i.e., ≤ ten days. Table 2- 2 presents summary information for duration of ibuprofen use for the studies which reported it.

Table 2- 2. Estimated Duration of Ibuprofen[a] Use in Selected Observational Studies

1st author and year	Study population	Estimated Duration of Use of Ibuprofen in Days Median (IQR)[b,c]
Fosbøl, 2010 [2]	Healthy, age ≥10 y	14 (14-24)
Fosbøl, 2009 [3]	Healthy, age ≥10 y	14 (14-24)
Gislason, 2009 [4]	Heart failure patients, age ≥30 y	97 (30-211)
Gislason, 2006 [5]	AMI patients, age ≥30 y	37 (10-463)
van der Linden, 2009 [6]	Age ≥40 y	-[d]
García Rodríguez, 2008 [7]	Age 50-84 y	-[d]
van Staa, 2008 [9]	Age ≥40 y	No. of prior prescriptions 0-4 47.9% 5-9 14.8% 10+ 37.3%
Andersohn, 2006 [8]	Age ≥40 y	<3 mo 69.3% 3-12 mo 26.9% >12 mo 3.8%

a: Includes all ibuprofen users, regardless of daily dose.
b: Unless otherwise specified
c: IQR=interquartile range: 25th - 75th percentiles
d: Duration of use for ibuprofen not reported separately in this study.
Abbreviations: AMI = acute myocardial infarction

The maximum recommended duration of OTC ibuprofen use was exceeded for the majority of participants for all studies which reported duration of use, with the possible exception of the study by Andersohn et al [8]. The data were not detailed enough in the study to determine the percentage using ibuprofen for ten days or less since the shortest duration category was less than three months. While still largely exceeding ten days duration, the duration of use was substantially lower in the two studies in healthy populations aged 10

years and older [2,3] compared to the six other studies. In these studies by Fosbøl et al [2,3], the 25th percentile and the median duration of ibuprofen use was 14 days. Another way to interpret this is that at least 75% of ibuprofen users in the study population used ibuprofen for 14 days or more.

2.4.2 Cardiovascular Risk for Daily Ibuprofen Doses Less Than or Equal to 1200 mg: Forest Plots by Cardiovascular Outcome

Since duration of use was not investigated separately at ibuprofen daily dose ≤1200 mg in the observational studies, results for this daily dose (≤1200 mg) regardless of duration of ibuprofen use are presented in this section. Forest plots are used to visualize the data. No observational studies investigating CV risk at ibuprofen daily doses ≤1200 mg were published prior to 2006.

Forest plots are useful for the visualization of relative risk estimates and 95% confidence intervals. Point estimates are represented by a point and the 95% confidence interval is represented by a horizontal line through the estimate. A relative risk (RR) of 1.0 is interpreted as no difference in risk between the exposure (≤1200 mg daily ibuprofen, in this case) and the comparator. If the 95% confidence interval crosses the vertical line at 1.0, then the risk estimate cannot be considered statistically different from a RR of 1.0. An estimate with a corresponding confidence interval that is either entirely above or below 1.0, represents a RR that is statistically increased (right of 1.0) or decreased (left of 1.0).

Results are grouped in each plot by study design to compare consistency of findings in studies with similar design features as well as strengths and limitations. Forest plots are provided for the following cardiovascular endpoints: nonfatal myocardial infarction (Figure 2-1), fatal and nonfatal myocardial infarction (Figure 2- 2), coronary death and nonfatal myocardial infarction (Figure 2- 3), cardiovascular death (Figure 2- 4), fatal and nonfatal stroke (Figure 2- 5), hospitalized heart failure (Figure 2- 6), and all cause death (Figure 2-7). While there were only eight studies, a study may appear multiple times in one plot indicating multiple types of analysis or subpopulations within the study, as well as in multiple plots indicating evaluation of multiple endpoints within the study. Four of the eight studies were based on one data source, the Danish population registry [2,3,4,5], and examined multiple cardiovascular outcomes and analytical methods.

Results from these eight epidemiologic observational studies were variable across studies, outcome, study design, and study population. Point estimates ranged from 0.57 to 1.51,

with 95% confidence intervals that frequently included 1.0. No studies reported a point estimate of 2.0 or greater. These point estimates are not within the range (greater than 2 or 3) that would suggest a potential change in our understanding of the risk profile. This is consistent with the 2005 FDA Advisory Committee meeting minutes that state:

> ""Observational studies are most helpful if they find a strong and consistent association across studies, with a hazard ratio greater than 2 or 3; Observational studies with hazard ratios under 2, even if statistically significant, are difficult to interpret since low but precise estimates of risk may be due to residual confounding or biases. Observational studies can be classified as "hypothesis generating"; they provide clues as to whether and if to conduct RCTs but observational studies do not establish causality.[10]"

Figure 2- 1. Relative Risks for Ibuprofen ≤1200 mg for Nonfatal Myocardial Infarction

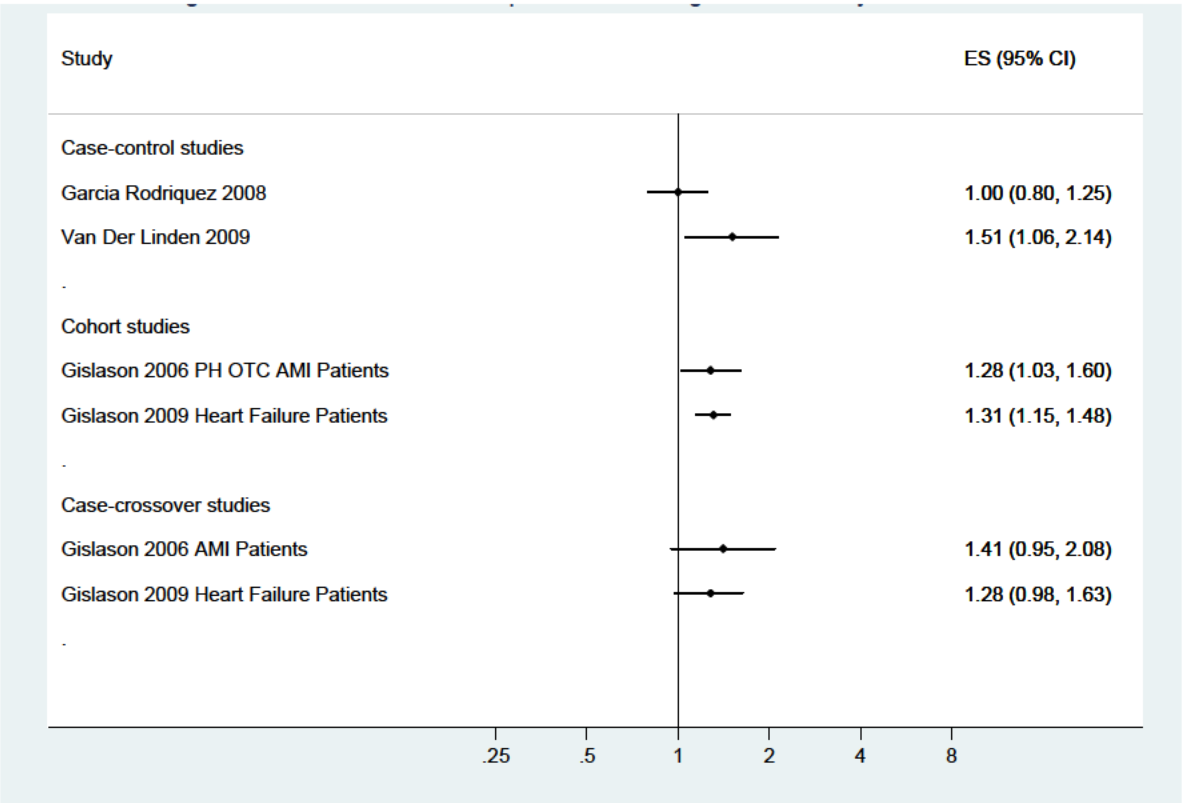


Figure 2- 2. Relative Risks for Ibuprofen ≤1200 mg for Fatal and Nonfatal Myocardial Infarction

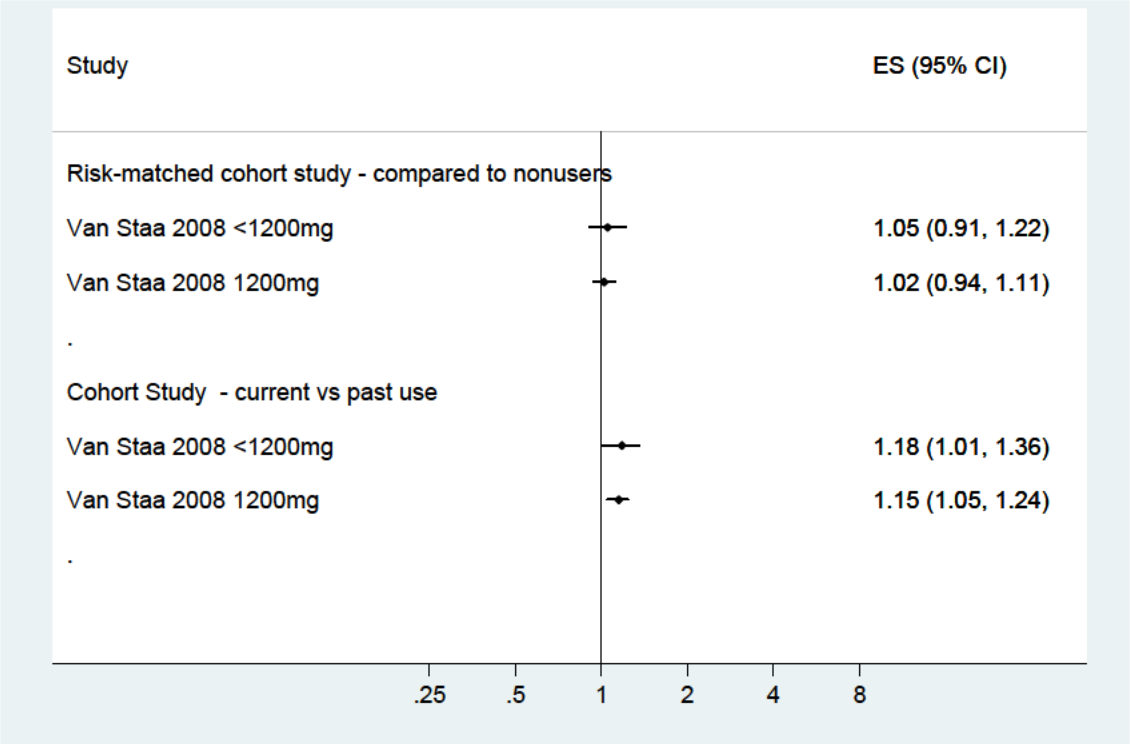
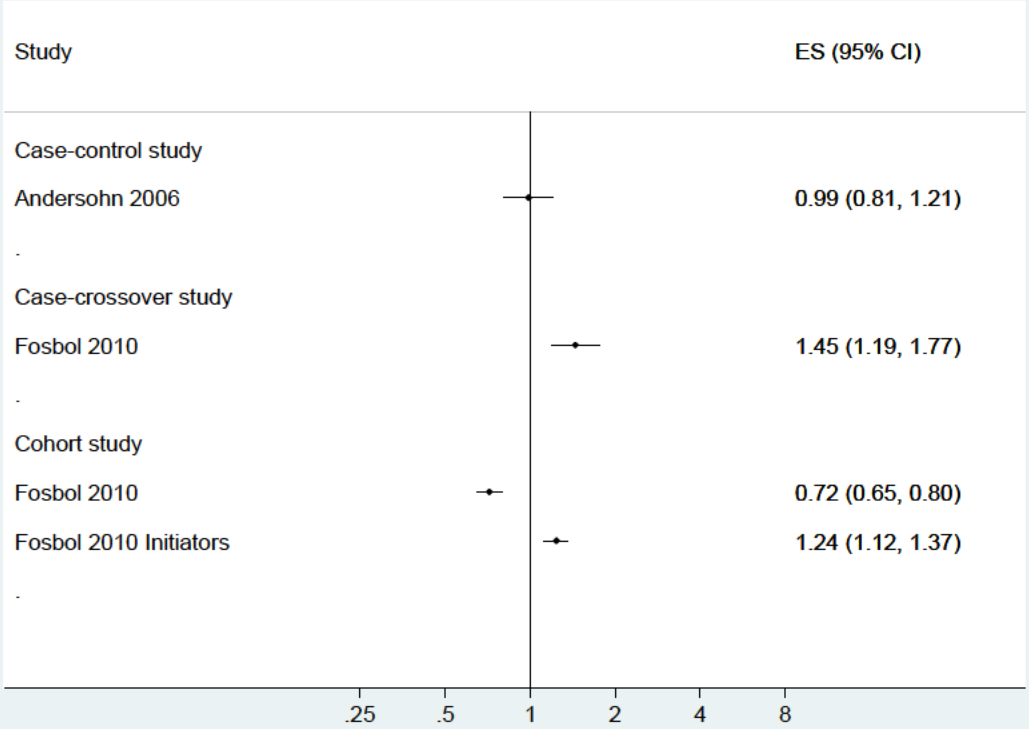
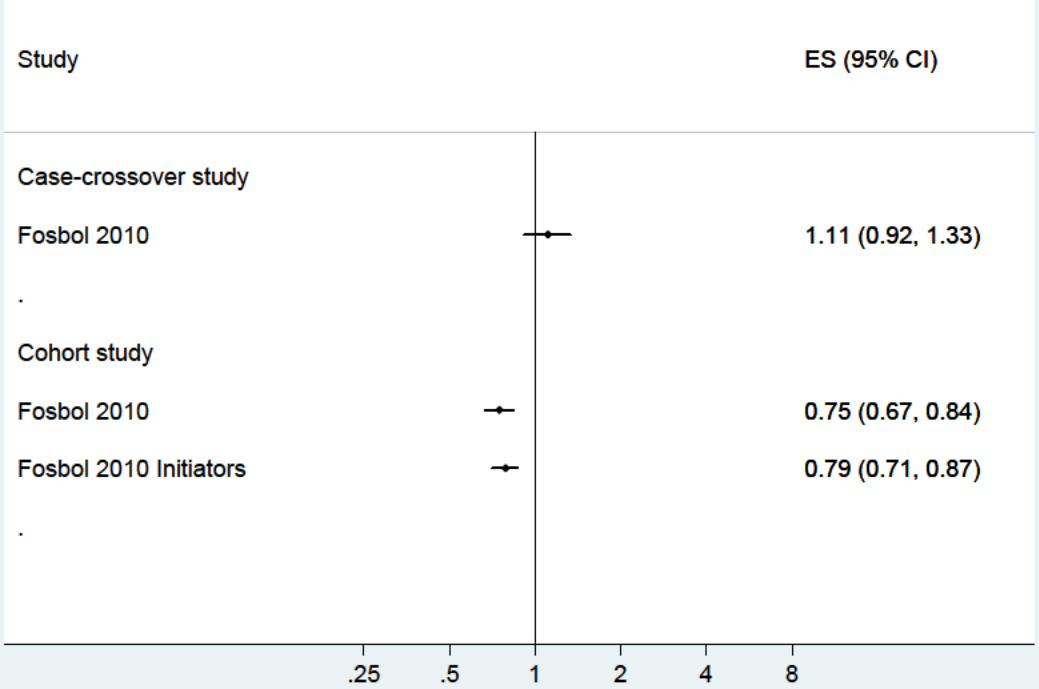


Figure 2- 3. Relative Risks for Ibuprofen ≤1200 mg for Coronary Death and Nonfatal Myocardial Infarction



Note: Coronary death is defined as death from ischemic heart disease and sudden cardiac death.

Figure 2- 4. Relative Risks for Ibuprofen ≤1200 mg for Cardiovascular Death



Note: Cardiovascular death includes death due to stroke, thrombotic events, and myocardial infarction.

Figure 2- 5. Relative Risks for Ibuprofen ≤1200 mg for Fatal and Nonfatal Stroke

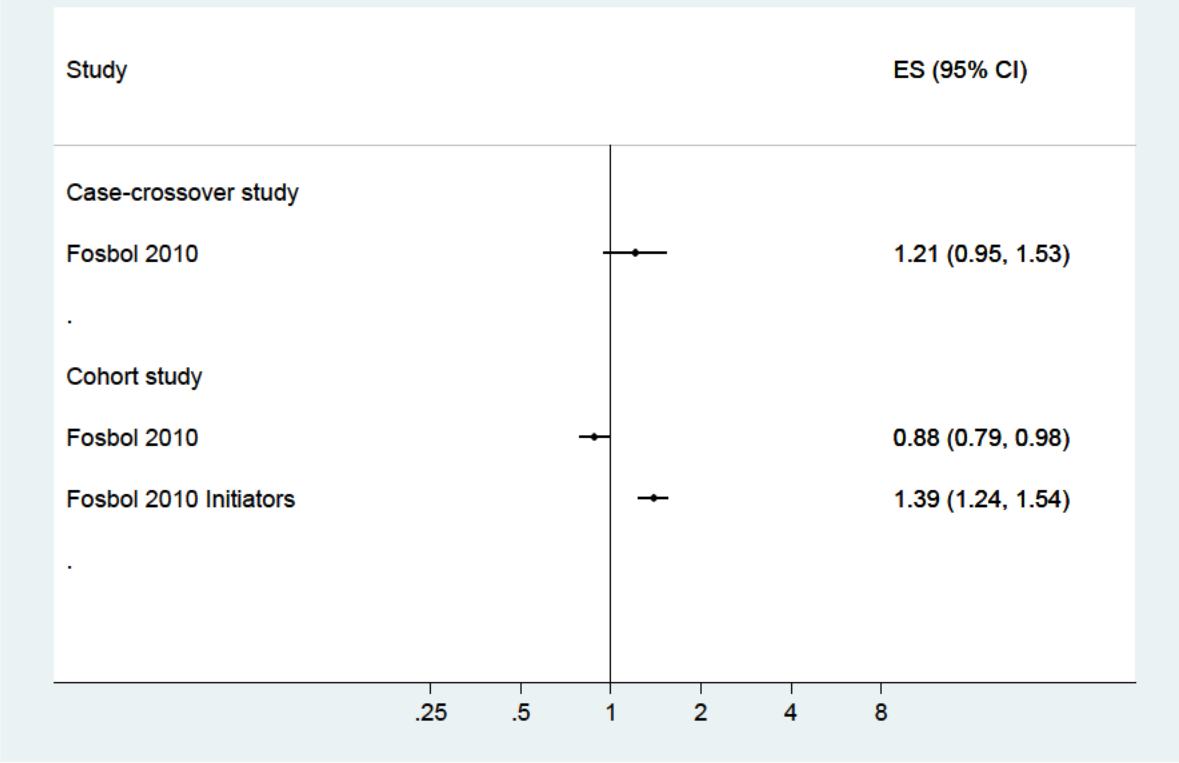


Figure 2- 6. Relative Risks for Ibuprofen ≤1200 mg for Hospitalized Heart Failure

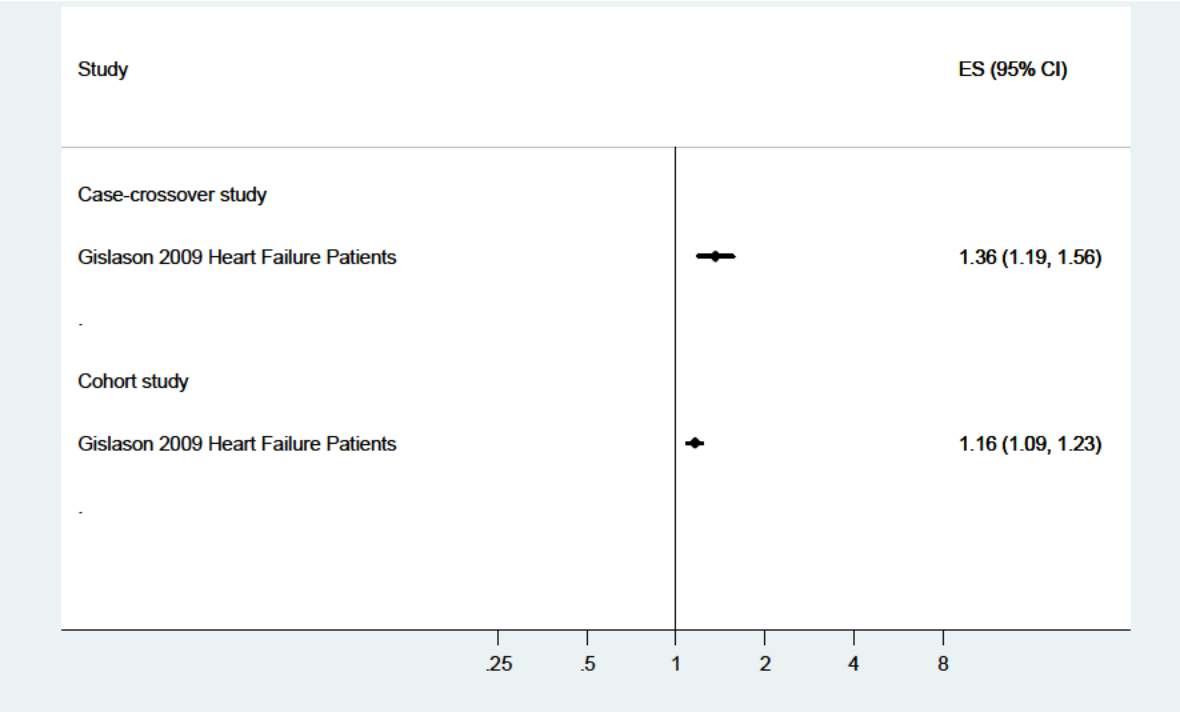
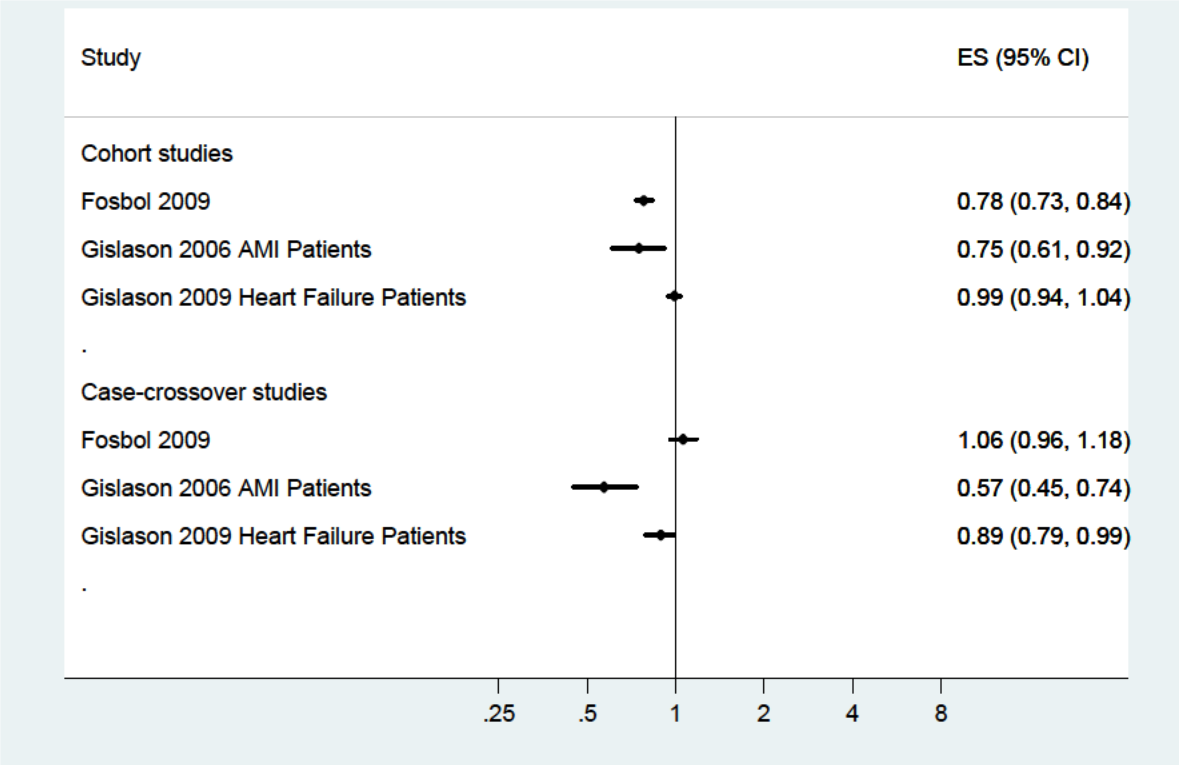


Figure 2- 7. Relative Risks for Ibuprofen ≤1200 mg for All Cause Death



2.5 Methodological Considerations

The randomized clinical trial is widely considered to be the gold standard of evidence in assessing treatment effects. However no large, long-term clinical trials have been published since 2005 that assessed the cardiovascular risk of ibuprofen at a dose of ≤1200 mg daily. In contrast, over 70 observational studies have been published since 2005 assessing cardiovascular risk in NSAIDs often reporting results separately for each NSAID; eight of these studies included information on daily doses of ibuprofen ≤1200 mg.

Daily dose in observational database studies is a measure derived from prescription dispensing information available in observational databases (e.g., drug strength, quantity and the number of days of supply). There are several algorithms that may be used to calculate daily dose resulting in more than a 10-fold difference in the percentage of estimates exceeding a given threshold such as daily dose [11]. Additionally, there is little information about how medicine is actually consumed because consumption is estimated only from the timing of subsequent dispensings.

An important limitation of any database study that is restricted to prescription dispensing of medication is the omission of information on OTC medication use. In the case of ibuprofen, omission may result in substantial misclassification of exposure, particularly among controls. Ilkhanoff et al [12] found that in a US study, ibuprofen obtained without a prescription accounted for over 90% of ibuprofen exposure among controls. Therefore, in a prescription database study, those assumed to be non-users may include those who actually were exposed. Such misclassification would tend to bias risk estimates toward the null, i.e., towards showing no risk difference between nonusers and users. The amount of misclassification will vary with the extent to which access to or use of OTC ibuprofen is limited. For example, four of the observational studies were conducted in Denmark, where ibuprofen is available OTC without prescription only in a low dose (200 mg) and limited quantities [4], perhaps reducing the likelihood of misclassification.

Another limitation and source of bias in database studies is the failure to capture and record important confounders. In particular, confounders that increase cardiovascular risk and may be more common in prescription NSAIDs users than in non-users are frequently not available in electronic databases and could include body mass index, physical activity, family history and smoking. Ilkhanoff et al [12] replicated analyses of nonaspirin NSAIDs and myocardial infarction in electronic databases by adjusting their data only for confounders typically found in electronic databases. After adjustment for OTC ibuprofen, physical activity and BMI, and omitting aspirin users, the odds ratio was reduced by 30% from 1.24 to 0.83.

One study design that effectively reduces this kind of confounding is the case-crossover design in which individuals serve as their own control, whose potential unmeasured confounders would not be expected to bias results [13]. Note, though, that the implicit control of confounding in case-crossover studies only applies to attributes that do not change over time. If, for example, physical activity level changes over time, there could be residual confounding even within an individual. The studies by Fosbøl et al [2,3] and Gislason et al [4,5] included a case-crossover analysis.

A recent large-scale research effort to better understand the use of observational databases for active drug safety and benefit monitoring [14] has found that results of observational studies are sensitive to choice of study design [15,16], implementation of method [16], definition of outcome [17,18] and choice of database [19]. The variation among the identified studies may be partially the result of these. In particular, results of case-crossover and case-control studies have a tendency to be biased upward [20,21] where results would

be overstated. In addition, bias and unmeasured confounding in database characteristics and study design and implementation have a substantive impact on the ability of observational studies to identify true statistical significance [22], especially if relative risk is increased only slightly, e.g., RR = 1.25. Observational studies may obtain more appropriate effect estimation by incorporating what is known about the underlying biases in the database through the use of an empirically generated null distribution to calibrate p-values [22]. Empirically generating a null distribution in an observational database is a computationally intensive undertaking and was not performed in the studies selected for review.

In summary, these methodological considerations contribute to the need for a strong and consistent association across observational studies (with risk estimates on the order of 2 to 3) in order to consider a potential change in our understanding of the risk profile. The studies in this submission did not meet this criterion.

2.6 Conclusions

- Observational studies published since 2005 evaluating the potential cardiovascular (CV) risk of ibuprofen daily doses ≤1200 mg, in which the majority of patients used ibuprofen beyond the labeled OTC duration of ten days, are consistent with prior findings and support FDA's conclusion for OTC NSAIDs that "Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events"[1].

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3 ATTACHMENTS

ATTACHMENT 1: OTC MOTRIN® IB LABELING

Motrin® IB

Drug Facts

Active ingredient (in each caplet) ***Purpose***

Ibuprofen 200 mg (NSAID)* ..... Pain reliever/fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - headache
  - muscular aches
  - minor pain of arthritis
  - toothache
  - backache
  - the common cold
  - menstrual cramps
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- you have problems or serious side effects from taking pain relievers or fever reducers
- the stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
- you have asthma
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are

- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- under a doctor's care for any serious condition
- taking any other drug

Motrin® IB

When using this product
- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if
- you experience any of the following signs of stomach bleeding
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. (1-800-222-1222)

Directions
- **do not take more than directed**
- **the smallest effective dose should be used**

adults and children 12 years and older	■ take 1 caplet every 4 to 6 hours while symptoms persist ■ if pain or fever does not respond to 1 caplet, 2 caplets may be used ■ do not exceed 6 caplets in 24 hours, unless directed by a doctor
children under 12 years	■ ask a doctor

Other information
- store between 20-25°C (68-77°F)
- **tamper evident statement**

Inactive ingredients carnauba wax, colloidal silicon dioxide, corn starch, FD&C yellow no. 6, hypromellose, iron oxide, magnesium stearate, polydextrose, polyethylene glycol, pregelatinized starch, propylene glycol, shellac, stearic acid, titanium dioxide

Questions or comments? Call **1-877-895-3665** (toll-free) or **215-273-8755** (collect)

ATTACHMENT 2: LIST OF REFERENCES PROVIDED BY FDA

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ATTACHMENT 3: TABULAR SUMMARY OF PUBLISHED EPIDEMIOLOGIC OR OBSERVATIONAL STUDIES EVALUATING THE CARDIOVASCULAR RISKS OF OVER-THE-COUNTER DOSES OF IBUPROFEN

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results	
Andersohn F, Suissa S, Garbe E. Circulation 2006;113(16):1950-1957. [1]	General Practice Research Database (GPRD) managed by the Medicines and Healthcare Products Regulatory Agency in the UK. Nested case-control	Patients ≥ 40 y old with at least one Rx NSAID between June 1, 2000 and Oct 31 2004	Registered in database, N=486,378; AMI, N=3,643; controls, N= 13,918 Mean age=69 y 59% M	AMI, death from AMI, and sudden or unexpected death from coronary heart disease	**Relative risk of AMI according to current NSAID use compared to nonuse of any NSAID**	
					Rofecoxib	
					Any use	1.29 (1.02–1.63)
					<25 mg/d	1.01 (0.74–1.40)
					≥25 mg/d	1.58 (1.16–2.15)
					Celecoxib	
					Any use	1.56 (1.22–2.00)
					≤200 mg/d	1.44 (1.12–1.87)
					>200 mg/d	2.46 (1.26–4.81)
					Etoricoxib	
					Any use	2.09 (1.10–3.97)
					≤60 mg/d	1.51 (0.61–3.76)
					>60 mg/d	2.80 (1.15–6.81)
					Valdecoxib	
					Any use	4.60 (0.61–34.51)
					≤10 mg/d	Not calculated
					>10 mg/d	Not calculated
					Diclofenac	
					Any use	1.37 (1.17–1.59)
					≤100 mg/d	1.31 (1.06–1.62)
					>100 mg/d	1.35 (1.13–1.61)
					Ibuprofen	
					Any use	1.04 (0.86–1.25)
					≤1200 mg/d	0.99 (0.81–1.21)
					>1200 mg/d	1.14 (0.74–1.77)
					Naproxen	
					Any use	1.15 (0.84–1.58)
					≤750 mg/d	1.19 (0.79–1.80)
					>750 mg/d	1.05 (0.66–1.66)

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results		
Fosbøl EL, Gislason GH, Jacobsen S, et al. Clin Pharmacol Ther 2009;85:190-197. [2]	Danish population registries Case-crossover and cohort	"Healthy" Danish residents, i.e., ≥10 y on Jan. 1, 1997 with no contact with hospital system 5 y before index date and with no use of serious pharmaco-logic treatments in the prior 2 y (Beta-blockers, digoxin, diuretics, glucose-lowering agents, etc.).	N=1,028,437 Median age = 39 58% male	Death & composite of death and MI	**Cox proportional hazard ratios**:		
						CV Death	**CV Death and MI**
					Ibu		
					No use	1.00	
					Any use	0.89 (0.83–0.94)	1.01 (0.96–1.07)
					≤1200 mg/d	0.78 (0.73–0.84)	0.92 (0.86–0.97)
					>1200 mg/d	1.77 (1.55–2.02)	1.84 (1.62–2.08)
					Diclofenac		
					No use	1.00	
					Any use	1.47 (1.35–1.59)	1.63 (1.52–1.76)
					<100 mg/d	0.87 (0.73–1.03)	1.05 (0.90–1.21)
					≥100 mg/d	1.83 (1.67–2.01)	1.99 (1.83–2.17)
					Rofecoxib		
					No use	1.00	
					Any use	2.12 (1.87–2.40)	2.13 (1.89–2.41)
					≤25 mg /d	1.97 (1.72–2.25)	2.00 (1.76–2.27)
					>25 mg/d	6.02 (4.10–8.85)	5.59 (3.81–8.21)
					Celecoxib		
					No use	1.00	
					Any use	2.05 (1.81–2.32)	2.01 (1.78–2.27)
					≤200 mg/d	1.65 (1.42–1.92)	1.64 (1.42–1.90)
					>200 mg/d	4.38 (3.50–5.47)	4.16 (3.34–5.19)
					Naproxen		
					No use	1.00	
					Any use	0.80 (0.67–0.94)	0.97 (0.83–1.12)
					≤500 mg/d	0.70 (0.58–0.86)	0.90 (0.76–1.06)
					>500 mg/d	1.25 (0.90–1.72)	1.28 (0.95–1.74)

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results		
Fosbøl EL, Gislason GH, Jacobsen S, et al. 2009.					**Case-crossover Odds ratios:**		
						CV Death	**CV Death and MI**
(continued)					Ibu		
					No use	1.00	
					Any use	1.06 (0.96–1.17)	1.14 (1.04–1.24)
					≤1200 mg/d	1.06 (0.96–1.18)	1.12 (1.02–1.23)
					>1200 mg/d	1.04 (0.88–1.23)	1.10 (0.94–1.30)
					Diclofenac		
					No use	1.00	
					Any use	1.81 (1.61–2.04)	1.81 (1.62–2.01
					<100 mg/d	1.34 (1.07–1.69)	1.37 (1.11–1.69)
					≥100 mg/d	1.83 (1.62–2.07)	1.82 (1.63–2.04)
					Rofecoxib		
					No use	1.00	
					Any use	2.74 (2.20–3.43)	2.59 (2.09–3.22)
					≤25 mg/d	2.22 (1.78–2.78)	2.12 (1.71–2.63)
					>25 mg/d	4.99 (3.11–7.99)	4.66 (2.92–7.42)
					Celecoxib		
					No use	1.00	
					Any use	1.95 (1.56–2.43)	2.07 (1.67–2.57)
					≤200 mg/d	1.46 (1.16–1.84)	1.60 (1.27–2.01)
					>200 mg/d	2.12 (1.52–2.95)	2.08 (1.49–2.89)
					Naproxen		
					No use	1.00	
					Any use	0.75 (0.56–1.00)	0.99 (0.76–1.28)
					≤500 mg/d	0.78 (0.58–1.05)	1.03 (0.78–1.35)
					>500 mg/d	0.80 (0.47–1.37)	0.91 (0.54–1.54)

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results
Fosbøl EL, Folke F, Jacobsen S, et al. Circ Cardiovasc Qual Outcome 2010;3(4):395-405. [3] **[Fosbøl 2009 has different outcomes (death and death + MI) and includes analyses in a cohort of new NSAIDs users]**	Danish National Registries Case-crossover and cohort	Danish residents; age, ≥ 10 y on Jan. 1, 1997 having no contact with hospital system 5 y before index date and with no use of serious pharmaco-logic treatments prior 2 years (Beta-blockers, digoxin, diuretics, glucose-lowering agents, etc.)	Individuals meeting criteria, N=1,028,437 Median age=39 y 58% M	CV death Coronary death or nonfatal MI Fatal or nonfatal stroke Composite of fatal and nonfatal bleedings	**Adjusted odds ratios for case-crossover analysis: Cardiovascular Death**

	CV Death	Coronary death MI	Fatal/nonfatal Stroke
Ibu			
No use	1.00	1.00	1.00
Any use	1.08 (0.90–1.29)	1.52 (1.25–1.85)	1.29 (1.02–1.63)
≤1200 mg/d	1.11 (0.92–1.33)	1.45 (1.19–1.77)	1.21 (0.95–1.53)
>1200 mg/d	1.04 (0.74-147)	1.44 (0.91–2.27)	1.36 (0.84–2.19)
Diclofenac			
No use	1.00	1.00	1.00
Any use	1.91 (1.62–2.42)	1.82 (1.43–2.33)	1.71 (1.29–2.25)
<100 mg/d	1.23 (0.76–1.98)	0.96 (0.59–1.57)	1.16 (0.65–2.08)
≥100 mg/d	2.04 (1.60–2.60)	2.01 (1.56–2.59)	1.70 (1.27–2.27)
Rofecoxib			
No use	1.00	1.00	1.00
Any use	1.66 (1.06–2.59)	1.72 (0.95–3.12)	1.14 (0.62–2.12)
≤25 mg/d	1.52 (0.96–2.41)	1.60 (1.23–2.06)	1.11 (0.59–2.07)
>25 mg/d	1.73 (0.75–3.98)	3.02 (1.91–4.78)	1.62 (0.31–8.40)
Celecoxib			
No use	1.00	1.00	1.00
Any use	0.92 (0.56–1.51)	1.93 (1.06–3.51)	1.20 (0.59–2.46)
≤200 mg/d	1.42 (0.86–2.36)	2.13 (1.13–4.02)	1.16 (0.55–2.42)
>200 mg/d	0.37 (0.16–0.87)	0.91 (0.31–2.67)	0.74 (0.20–2.72)
Naproxen			
No use	1.00	1.00	1.00
Any use	0.84 (0.50–1.42)	0.98 (0.59–1.63)	1.91 (1.04–3.50)
≤500 mg/d	1.25 (0.75–2.11)	1.37 (0.83–2.27)	1.52 (0.81–2.87)
>500 mg/d	0.30 (0.08–1.11)	0.24 (0.06–1.03)	2.50 (0.57–10.96)

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results			
Fosbøl EL, Folke F, Jacobsen S, et al. 2010. (continued)					**Hazard ratios estimated by Cox proportional hazard analysis:**			
						Coronary death	**Fatal/nonfatal**	
						CV Death	**MI**	**Stroke**
					Ibuprofen			
					No use	1.00	1.00	1.00
					Any use	0.83 (0.75–0.92)	0.77 (0.70–0.84)	0.94 (0.85–1.03)
					≤1200 mg/d	0.75 (0.67–0.84)	0.72 (0.65–0.80)	0.88 (0.79–0.98)
					>1200 mg/d	0.93 (0.75-1.14)	1.16 (0.92–1.47)	1.45 (1.14–1.86)
					Diclofenac			
					No use	1.00	1.00	1.00
					Any use	1.03 (0.88–1.20)	1.13 (1.00–1.29)	1.34 (1.16–1.55)
					<100 mg/d	0.62 (0.45-0.86)	0.88 (0.69–1.12)	0.93 (0.71–1.73)
					≥100 mg/d	1.28 (1.08–1.53)	1.28 (1.10–1.50)	1.59 (1.35–1.88)
					Rofecoxib			
					No use	1.00	1.00	1.00
					Any use	1.42 (1.09–1.84)	1.34 (1.04–1.73)	0.90 (0.64–1.27)
					≤25 mg/d	1.34 (1.02-1.76)	1.32 (1.02–1.71)	0.88 (0.61–1.25)
					>25 mg/d	3.43 (1.43-8.24)	1.89 (0.61–5.87)	1.55 (0.39–6.20)
					Celecoxib			
					No use	1.00	1.00	1.00
					Any use	0.95 (0.70–1.30)	1.15 (0.87–1.51)	1.12 (0.82–1.53)
					≤200 mg/d	0.85 (0.65-1.11)	1.15 (0.85–1.54)	1.02 (0.72–1.45)
					>200 mg/d	1.02 (0.58-1.80)	1.19 (0.59–2.38)	1.73 (0.90–3.34)
					Naproxen			
					No use	1.00	1.00	1.00
					Any use	0.74 (0.46–0.98)	0.76 (0.60–0.96)	0.89 (0.69–1.15)
					≤500 mg/d	0.73 (0.53-0.99)	0.79 (0.62–1.02)	0.89 (0.67–1.18)
					>500 mg/d	0.83 (0.44-1.53)	0.58 (0.30–1.13)	0.89 (0.48–1.66)

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results
Fosbøl EL, Folke F, Jacobsen S, et al. 2010. (continued)					**Population of NSAID initiators and sex-, age-, and time-matched controls of non-NSAID Initiators: Hazard ratios estimated by Cox proportional hazard analysis (N=901,596)**

Coronary death or Fatal/nonfatal

	CV Death	MI	Stroke
Ibuprofen			
No use	1.00	1.00	1.00
Any use	0.88 (0.80–0.96)	1.31 (1.20–1.44)	1.47 (1.33–1.63)
≤1200 mg/d	0.79 (0.71–0.87)	1.24 (1.12–1.37)	1.39 (1.24–1.54)
>1200 mg/d	1.63 (1.32–2.00)	1.94 (1.54–2.45)	2.22 (1.74–2.84)
Diclofenac			
No use	1.00	1.00	1.00
Any use	1.20 (1.06–1.38)	1.83 (1.61–2.09)	2.00 (1.73–2.30)
<100 mg/d	0.80 (0.62–1.05)	1.39 (1.09–1.77)	1.33 (1.00–1.75)
≥100 mg/d	1.46 (1.25–1.70)	2.10 (1.81–2.45)	2.41 (2.04–2.84)
Rofecoxib			
No use	1.00	1.00	1.00
Any use	1.64 (1.31–2.05)	1.84 (1.43–2.37)	1.12 (0.80–1.58)
≤25 mg/d	1.60 (1.27–2.01)	1.82 (1.41–2.36)	1.10 (0.77–1.56)
>25 mg/d	2.77 (1.15–6.66)	2.36 (0.76–7.32)	1.79 (0.45–7.15)
Celecoxib			
No use	1.00	1.00	1.00
Any use	1.24 (0.97–1.58)	1.44 (1.10–1.87)	1.27 (0.93–1.74)
≤200 mg/d	1.19 (0.91–1.56)	1.44 (1.07–1.93)	1.16 (0.82–1.65)
>200 mg/d	1.51 (0.86–2.65)	1.49 (0.74–2.98)	1.95 (1.01–3.75)
Naproxen			
No use	1.00	1.00	1.00
Any use	0.86 (0.67–1.10)	0.78 (0.61–1.00)	1.54 (1.19–1.99)
≤500 mg/d	0.84 (0.64–1.11)	0.69 (0.51–0.93)	1.55 (1.17–1.05)
>500 mg/d	0.92 (0.52–1.62)	1.22 (0.75–2.00)	1.48 (0.80–2.76)

Table 1. Published Epidemiologic or Observational Studies of Ibuprofen Including Over-the-Counter Dosage

Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results
Garcia Rodríguez LA, Tacconelli S, Patrignani P. J Am Coll Cardiol 2008;52:1628-1636.[4]	The Health Improvement Network (THIN), a United Kingdom database Population based, nested case-control study	Patients 50-84 y with ≥ 2 years of enrollment, and ≥1 health contact in the prior 3 y before their start date	Cohort, N=716,395; cases of nonfatal MI, N=8,852; controls, N=20,000	Nonfatal MI	**Adjusted relative risk of nonfatal MI according to daily dose of individual NSAIDS RR (95% CI)** No use 1.00 Celecoxib (200 mg cutoff) Low-medium dose 1.35 (1.00–1.82) High dose 1.05 (0.33–3.35) Diclofenac (100 mg cutoff) Low-medium dose 1.51 1.20–1.89) High dose 1.80 (1.49–2.18) Ibu (1,200 mg cutoff) Low-medium dose 1.00 (0.80–1.25) High dose 1.56 (0.90–2.71) Indomethacin (75 mg cutoff) Low-medium dose 1.58 (0.80–3.10) High dose 1.36 (0.67–2.79) Meloxicam (7.5 mg cutoff) Low-medium dose 1.40 (0.87–2.27) High dose 1.21 (0.75–1.94) Naproxen (750 mg cutoff) Low-medium dose 0.90 (0.50–1.60) High dose 1.12 (0.74–1.69) Rofecoxib (25 mg cutoff) Low-medium dose 1.41 (1.07–1.87) High dose 6.50 (0.70–60.33)

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Gislason GH, Jacobsen S, Rasmussen JN, et al. Circulation 2006;113(25):2906-2913. [5]	Danish National Patient Registry Cohort and case-crossover	Aged ≥ 30 years, hospitalized with a first acute MI during 1995-2002 and alive at discharge	Total with first MI discharged alive, N=58,432; Ibu, N=10,230 Mean age=68 y 62.8% M	Death and re-hospitalization for MI	**Hazard Ratios for Death and Rehospitalization for MI; Cox Proportional Hazards Analysis**		
						Death	**Rehospitalization for MI**
					Rofecoxib		
					No use	1.00	1.00
					Any use	2.80 (2.41–3.25)	1.63 (1.27–2.10)
					≤ 25 mg/d	2.49 (2.11–2.94)	1.68 (1.30–2.17)
					> 25 mg/d	5.26 (3.90–7.09)	1.27 (0.57–2.86)
					Celecoxib		
					Any use	2.57 (2.15–3.08)	1.50 (1.10–2.05)
					≤ 200 mg/d	1.92 (1.52–2.43)	1.47 (1.03–2.09)
					> 200 mg/d	4.69 (3.58–6.14)	1.64 (0.91–2.90)
					Ibu		
					Any use	1.50 (1.36–1.67)	1.25 (1.07–1.46)
					≤ 1200 mg/d	0.75 (0.61–0.92)	1.28 (1.03–1.60)
					> 1200 mg/d	2.20 (1.95–2.48)	1.22 (0.99–1.51)
					Diclofenac		
					Any use	2.40 (2.09–2.80)	1.54 (1.23–1.93)
					< 100 mg/d	0.89 (0.66–1.20)	1.27 (0.92–1.76)
					≥ 100 mg/d	4.44 (3.79–5.19)	1.89 (1.40–2.55)
					Other NSAIDs		
					Any use	1.29 (1.16–1.43)	1.27 (1.09–1.47)

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Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results		
Gislason GH, Jacobsen S, Rasmussen JN, et al. 2006. (continued)					**Odds ratios for death and rehospitalization for MI: Conditional logistic regression analysis by the case-crossover design**		
						Death	**Rehospitalization for MI**
					Rofecoxib		
					No use	1.00	1.00
					Any use	2.36 (1.75–3.19)	2.46 (1.42–4.24)
					≤ 25 mg/d	1.96 (1.43–2.69)	2.37 (1.35–4.16)
					> 25 mg/d	8.65 (3.71–20.1)	3.73 (0.67–20.6)
					Celecoxib		
					Any use	2.37 (1.68–3.35)	1.36 (0.73–2.53)
					≤ 200 mg/d	1.97 (1.33–2.93)	1.01 (0.50–2.02)
					> 200 mg/d	3.88 (2.04–7.36)	5.27 (1.07–25.9)
					Ibuprofen		
					Any use	1.05 (0.88–1.24)	1.32 (1.02–1.72)
					≤ 1200 mg/d	0.57 (0.45–0.74)	1.41 (0.95–2.08)
					> 1200 mg/d	1.65 (1.33–2.04)	1.26 (0.89–1.78)
					Diclofenac		
					Any use	1.59 (1.28–1.98)	1.67 (1.15–2.42)
					< 100 mg/d	0.86 (0.63–1.17)	1.66 (1.04–2.63)
					≥ 100 mg/d	2.82 (2.08–3.83)	1.69 (0.96–2.98)
					Other NSAIDs		
					Any use	1.14 (0.93–1.39)	1.07 (0.77–1.48)

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Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results			
Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Arch Intern Med. 2009;169(2):141-149.[6] **[Gislason 2006 has a different study population: those surviving 1st MI during 1995-2002]**	Danish National Patient Registry Observational cohort and case-crossover	Patients ≥ 30 y with a first hospitalization for heart failure Jan. 1, 1995 to Dec. 31, 2004	Cohort, N=107,092 Mean age=75 y 51% M	Death and hospitalization because of MI or heart failure	**Hazard Ratio**	**Death**	**Hospitalization for Heart Failure**	**Hospitalization for AMI**
					Rofecoxib			
					Any use	1.70 (1.58-1.82)	1.40 (1.26-1.55)	1.30 (1.07-1.59)
					≤ 25 mg/d	1.42 (1.31-1.54)	1.33 (1.20-149)	1.26 (1.01-1.57)
					> 25 mg/d	3.54 (3.12-4.02)	1.86 (1.46-2.35)	1.59 (0.97-2.61)
					Celecoxib			
					Any use	1.75 (1.63-1.88)	1.24 (1.12-1.39)	1.38 (1.13-1.69)
					≤ 200 mg/d	1.34 (1.22-1.48)	1.24 (1.09-1.41)	1.33 (1.05-1.69)
					> 200 mg/d	2.72 (2.45-3.02)	1.26 (1.04-1.53)	1.50 (1.08-2.10)
					Ibuprofen			
					Any use	1.31 (1.25-1.37)	1.16 (1.10-1.23)	1.33 (1.19-1.50)
					≤ 1200 mg/d	0.99 (0.94-1.04)	1.16 (1.09-1.23)	1.31 (1.15-1.48)
					> 1200 mg/d	2.83 (2.64-3.02)	1.18 (1.04-1.33)	1.47 (1.15-1.89)
					Diclofenac			
					Any use	2.08 (1.95-2.21)	1.35 (1.24-1.48)	1.36 (1.12-1.64)
					≤ 100 mg/d	1.31 (1.20-1.42)	1.34 (1.21-1.48)	1.14 (0.91-1.43)
					> 100 mg/d	5.54 (5.08-6.03)	1.42 (1.17-1.73)	2.43 (1.74-3.40)
					Naproxen			
					Any use	1.22 (1.07-1.39)	1.18 (1.00-1.40)	1.52 (1.11-2.06)
					≤ 500 mg/d	0.88 (0.73-1.05)	1.18 (0.97-1.44)	1.47 (1.02-2.10)
					> 500 mg/d	1.97 (1.64-2.36)	1.18 (0.88-1.57)	1.62 (0.97-2.72)
					Other NSAID	1.28 (1.21-1.35)	1.27 (1.18-1.36)	1.32 (1.13-1.54)

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Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results			
Gislason GH, Rasmussen JN, Abildstrom SZ, et al. 2009. (continued)					**Adjusted odds ratio from case-crossover analysis**			
						Death	**Hospitalization for HF**	**Hospitalization for AMI**
					Rofecoxib			
					Any use	1.62 (1.40-1.88)	2.39 (1.89-3.01)	1.39 (0.93-2.06)
					≤ 25 mg/d	1.19 (1.01-1.40)	2.12 (1.67-2.70)	1.32 (0.88-1.98)
					> 25 mg/d	4.99 (3.65-6.84)	6.17 (3.22-11.82)	2.73 (0.66-11.32)
					Celecoxib			
					Any use	1.89 (1.60-2.23)	1.86 (1.45-2.40)	1.31 (0.85-2.04)
					≤ 200 mg/d	1.21 (0.99-1.48)	1.95 (1.49-2.56)	1.26 (0.77-2.04)
					> 200 mg/d	4.11 (3.15-5.38)	1.48 (0.87-2.54)	1.51 (0.70-3.27)
					Ibuprofen			
					Any use	1.50 (1.36-1.65)	1.41 (1.24-1.61)	1.47 (1.15-1.88)
					≤ 1200 mg/d	0.89 (0.79-0.99)	1.36 (1.19-1.56)	1.28 (0.98-1.63)
					> 1200 mg/d	6.43 (5.26-7.86)	1.86 (1.33-2.60)	4.51 (2.28-8.91)
					Diclofenac			
					Any use	2.50 (2.21-2.82)	1.97 (1.64-2.34)	1.64 (1.16-2.30)
					≤ 100 mg/d	1.21 (1.04-1.40)	1.85 (1.52-2.25)	1.18 (0.81-1.72)
					> 100 mg/d	14.69 (10.9-19.7)	2.90 (1.81-4.64)	9.10 (3.45-23.98)
					Naproxen			
					Any use	1.20 (0.91-1.58)	1.02 (0.72-1.46)	1.31 (0.64-2.71)
					≤ 500 mg/d	0.84 (0.60-1.17)	1.03 (0.69-1.53)	1.31 (0.56-3.05)
					> 500 mg/d	2.35 (1.51-3.65)	1.01 (0.53-1.89)	1.33 (0.39-4.50)
					Other NSAID	1.29 (1.15-1.44)	1.68 (1.44-1.97)	1.56 (1.16-2.08)

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Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results
Van Der Linden MW, Van Der Bij S, Welsing P, et al Ann Rheum Dis 2009;68(5):668-673. [7]	Netherlands: case-control study	Users of NSAIDs and COX-2 inhibitors between 2001 and 2004	Subjects, N =485,059; AMI, N=2,165; controls, N= 8,653 Mean age=66.6 y AMI: 61% M Controls: 40% M	Hospitalization for acute myocardial infarction	**Adjusted ORs: AMI risk current versus remote use** Celecoxib Overall 2.53 (1.53-4.18) Low dose 1.41 (0.62-3.17) High dose 3.04 (1.31-7.04) Rofecoxib Overall 1.60 (1.22-2.10) Low dose 1.58 (1.14-2.19) High dose 2.12 (0.50-9.03) Naproxen Overall 1.21 (0.87-1.68) Low dose Not reported High dose Not reported Ibuprofen Overall 1.56 (1.19-2.05) Low dose 1.51 (1.06-2.14) High dose 1.66 (0.92-3.00) Diclofenac Overall 1.51 (1.22-1.87) Low dose 1.13 (0.79-1.61) High dose 1.75 (1.29-2.38)

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Citation [Reference]	Database and Study Design	Study Population	N Mean age Gender	Outcomes	Study Results	
Van Staa TP, Rietbrock S, Setakis E, et al. J Intern Med (GBR) 2008;264(5):481-492.[8]	GPRD, a general practice electronic database managed by the Medicines and Healthcare Products Regulatory Agency in the UK Retrospective cohort study	Patients age ≥ 40 y prescribed a traditional NSAID; Control cohort was matched by gender, 10-year age stratum and disease risk score for risk of MI	NSAID cohort, N= 729,294 Mean age=58.0 y 46% M Control cohort, N= 443,047 Mean age=58.2 y 46% M	MI	**Results: NSAID vs. control adjusted Relative Rate (95% CI)**	
					Ibu	1.04 (0.98–1.09)
					≤1200 mg/d	1.05 (0.91–1.22)
					1200 mg/d	1.02 (0.94–1.11)
					1201–2399 mg/d	1.22 (1.03–1.44)
					≥2400 mg/d	1.96 (1.05–3.65)
					Diclofenac	1.21 (1.15–1.28)
					<150 mg/d	1.13 (1.04–1.22)
					150 mg/d	1.28 (1.18–1.39)
					151–299 mg/d	1.18 (0.85–1.65)
					≥300 mg/d	2.03 (1.09–3.77)
					Naproxen	1.03 (0.94–1.13)
					<1000 mg/d	0.99 (0.85–1.17)
					1000 mg/d	1.12 (0.98–1.27)
					>1000 mg/d	0.92 (0.49–1.71)
					Mefenamic acid	1.18 (0.97–1.45)
					Indomethacin	1.27 (1.13–1.43)
					Meloxicam	1.12 (0.94–1.32)
					Piroxicam	1.01 (0.84–1.21)

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Van Staa TP, Rietbrock S, Setakis E, et al. 2008. (continued)					**Current vs. past NSAID use adjusted RR (95% CI)**	
					Ibu	1.16 (1.11–1.22)
					<1200 mg/d	1.18 (1.01–1.36)
					1200 mg/d	1.15 (1.05–1.24)
					1201–2399 mg/d	1.38 (1.17–1.62)
					≥2400 mg/d	2.16 (1.16–4.01)
					Diclofenac	1.34 (1.28–1.40)
					<150 mg/d	1.26 (1.16–1.36)
					150 mg/d	1.40 (1.29–1.51)
					151–299 mg/d	1.29 (0.92–1.79)
					≥300 mg/d	2.19 (1.18–4.07)
					Naproxen	1.16 (1.06–1.27)
					<1000 mg/d	1.12 (0.95–1.31)
					1000 mg/d	1.25 (1.10–1.42)
					>1000 mg/d	1.00 (0.54–1.87)
					Mefenamic acid	1.36 (1.06–1.27)
					Indomethacin	1.44 (1.29–1.61)
					Meloxicam	1.19 (1.01–1.41)
					Piroxicam	1.15 (0.96–1.37)

Abbreviations: AMI = acute myocardial infarction, CV = cardiovascular, M = male, mg/d = milligrams per day, Rx = prescription, y = years

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