1. Introduction

1.1 What is Pharmacoepidemiology?

Pharmacoepidemiology is a scientifc discipline which studies the use and the effects of drugs in large groups of people [Strom, 1994]. It can be seen as a specialized discipline of epidemiology with a particular focus on drugs. Pharmacoepidemiology builds a bridge between epidemiology and clinical pharmacology. Studies using pharmacoepidemiologic methods are widely used for drug safety, drug utilization, pharmacoeconomic and other research questions. In other words, pharmacoepidemiologists explore "what people do with drugs and what drugs do to people". The most efficient way to conduct pharmacoepidemiologic studies is the use of automated databases with patient records including both, information on drug use as well as medical diagnoses in chronological order. Several databases with comprehensive recording of drug therapy and outcome for large populations from various parts of the world have proven to be of high quality and useful for pharmacoepidemiological research. These databases are, when used judiciously, an important tool for pharmacoepidemiological studies to investigate, relatively quickly and inexpensively, potential adverse as well as beneficial drug effects [Hallas, 2001].

1.2 Cardiovascular Diseases in the General Population

Cardiovascular diseases are a growing public health problem, particularly in the industrialized western world, becoming the leading cause of death in developing countries [Yusuf, 2001]. Atherosclerosis, leading to coronary heart disease (CHD) and ultimately to myocardial infarction (MI), plays a major role. The classical risk factors for myocardial infarction, coronary heart disease and atherosclerosis are well documented. These are high cholesterol, hypertension, diabetes mellitus, smoking, physical inactivity, family history of

CHD or MI and others. Their modification (e.g. lowering LDL cholesterol, lowering blood pressure) can reduce the risk of myocardial infarction substantially, as well as changes of lifestyle habits such as weight reduction, cessation of smoking or enhanced physical activity [Lloyd-Jones, 2002; Kenchaiah, 2002]. Many risk factors interact with each other and lead - if present concomitantly - to an ever higher risk for adverse cardiovascular outcomes. A report of the Framingham Heart Study showed that obesity is a direct and indirect risk factor for CHD by promoting high blood pressure, diabetes, dyslipidaemia and atherosclerosis [Yusuf, 2001]. Furthermore, it is suggested that the risk of cardiovascular diseases and the mortality of acute myocardial infarction (AMI) is increased among individuals with low socioeconomic status [Alboni, 2003]. However, these known risk factors do not fully explain all new cases of myocardial infarction; there is a substantial number of cases without diagnosed pre-existing diseases predisposing to coronary atherosclerosis or ischaemic heart disease, and therefore additional risk factors may play a role in the etiology of acute coronary syndromes. More than 19 million people worldwide experience a severe cardiac event every year [Myerburg, 1997]. In Switzerland in the year 2000 cardiovascular diseases caused 43.3% of all deaths in women and 36.2% in men (not age adjusted). Deaths due to heart disease, myocardial infarction and other ischaemic diseases rose up to 57.2% (men and women) compared to 46.5% in 1980 [Pharma Information, 2003]. On the basis of the 1991 Framingham study risk appraisal models, approximately 32% of men and 7% of women in England (between 35 - 74 years at age) are at more than 15% risk of developing heart disease in the next 10 years [Nanchahal, 2002]. Current estimates showed that almost 62 million Americans have at least one type of cardiovascular disease. Cardiovascular diseases are also the leading cause of hospitalizations in the United States [American Heart Association, 2002].

1.3 Myocardial Infarction, Rheumatoid Arthritis and Systemic Lupus Erythematosus

A thrombotic occlusion of a coronary artery causes an acute myocardial infarction (AMI) after prolonged ischaemia. The size of the infarction is a major determinant of subsequent heart failure and of life expectancy. The severity and duration of reduced coronary blood flow are of major importance and early diagnosis and therapeutic thrombolysis are crucial. AMI is often preceded by unstable angina which is an attributable factor to thrombus formation and is part of the acute coronary syndrome. Additionally, ventricular fibrillation is not an unusual complication after severe ischaemia. The diagnosis of an AMI is based on specific clinical features, characteristic changes in laboratory parameters, particularly an elevation of cardiac enzymes (e.g. creatinkinase), as well as an altered electrocardiogram (ECG) [Henderson, 1996].

Rheumatoid arthritis (RA) is an inflammatory disease of joints and connective tissue. The prevalence is around 2%-3% in the general population. The pathophysiology of the disease is not fully understood yet. A pathological dysregulation of the immune system, genetic predisposition as well as an infectious etiology may play a role for the development of the disease. Rheumatoid arthritis leads to an inflammatory response where cytokines (e.g. interleukin-1, tumor necrosis factor-alpha) are released. These stimulate the expression of cyclooxygenase-2 (COX-2), followed by the synthesis of prostaglandins. The ongoing inflammation leads to a degeneration of the fibrocartilage and bone tissue of the corresponding joint. Severe pain and limited mobility are characteristic features for the disease. The main therapeutic options against symptoms are non-steroidal antiinflammatory drugs (NSAIDs), including selective COX-2 inhibitors, glucocorticoids and disease-modifying antirheumatic drugs (DMARDs), synthetic or biologic ones (e.g. infliximab, methotrexate) [O`Dell 2004].

Systemic lupus erythematosus (SLE) is a generalized autoimmune disease. The etiology is also not yet fully understood. Genetic predisposition and both endogenous and exogenous factors (e.g. sunlight, hormones) are playing a key role. The disease is characterized by flares typically affecting young adults; women have an approximately nine-fold increased risk compared to men. SLE promotes the formation of autoantibodies and immune complexes which trigger an inflammatory response. The disease affects various organs, joints and the skin in variable frequency and intensity. Arthritis and skin eruption as well as psychic disorders are further associated with SLE. The therapeutic options to reduce symptoms are also NSAIDs and glucocorticoids.

NSAIDs influence the synthesis of prostaglandins (PGs). This is of major importance to understand efficacy and side effects of NSAIDs. NSAIDs decrease the activity of the cyclooxygenase-system (COX) which regulates the formation of PGs (elevated during inflammation) and thromboxanes (TXs). The COX can be divided into two isoforms COX-1 and COX-2. There exists a significant overlap between expression patterns and functions of the two isoforms. The selectivity for both COX isoforms is different for each individual NSAID. COX-1 can be found in nearly all body tissues and as the only isoform in platelets catalyzing the transformation of arachidonic acid into TXA2 and in the gastric mucosa catalyzing the synthesis of cytoprotective PGs. The expression of both COX-1 and COX-2 is increased in inflammatory diseases. Animal experiments with lipoprotein receptor deficient mice indicate that the decrease of TXA2 by COX-1 inhibition could alter the progression of atherogenesis [FitzGerald, 2002].

1.4 Atherosclerosis and Inflammation

A large body of results from extensive basic, clinical and epidemiological research in recent years indicate that atherosclerosis is the consequence of chronic inflammation - a real paradigmatic shift in cardiology. Free radicals caused for example by smoking, hypertension, diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations, infectious microorganisms (such as herpesviruses or Chlamydia pneumoniae) and combinations of these or other factors are possible causes of endothelial dysfunction; endothelial dysfunction may promote atherosclerosis, particularly in combination with elevated low density lipoprotein (LDL) levels. Injury induced endothelial dysfunction increases the adhesiveness of platelets and leukocytes to the endothelium. The inflammatory response stimulates the proliferation and migration of smooth-muscle cells, followed by formation of an intermediate lesion in the area of inflammation. Ongoing inflammation causes an increasing number of macrophages and lymphocytes to emigrate from the blood and to multiply within the lesion. After activation of these cells, a release of hydrolytic enzymes, cytokines, chemokines and growth factors is characteristic [Ross, 1999]. Monocyte-chemoattractant protein-1 and interleukin-8 favour the penetration of monocytes and macrophages into the blood vessel wall [Libby, 2002]. Cycles of accumulation of mononuclear cells, migration of smooth-muscle cells and formation of fibrous tissue lead to further enlargement of the lesion. More advanced lesions can be covered by a fibrous cap – called plaque – that overlies a cove of lipid and necrotic tissue. The blood flow in the artery may be reduced and the lesion may intrude into the lumen and alter the nature of blood flow [Ross, 1999]. The mechanisms of the superficial erosion of atherosclerotic plaques are not yet fully understood. Local production of inflammatory mediators or an attack of activated T-killer cells could provoke an endothelial cell decline that would be due to apoptosis. Furthermore, oxidized lipoproteins and inflammatory mediators stimulate the expression and activation of matrix metalloproteinases (MMPs), which are capable to destroy the subendothelial basement membrane. From this point of view, inflammation promotes the loss of

endothelium, a crucial moment of superficial erosion [Libby, 2002; Ross, 1999]. Lesions of atherosclerosis have an influence on platelet adhesion and mural thrombosis. The activated platelets lead to the formation of arachidonic acid which can be transformed into PGs (such as thromboxane A2, a potent vasoconstricting and platelet-aggregating substance) or into leukotrienes, which can amplify the inflammatory response. Plaque rupture and thrombosis, both complications of an advanced lesion may lead to unstable angina pectoris or myocardial infarction (MI) [Libby, 2002; Ross, 1999]

In two recently published papers, Naghavi and co-workers describe a model of a vulnerable patient (with or without atherosclerosis), characterized by the plaque vulnerability and/or the vulnerable blood (a proneness to thrombosis) and/or the vulnerable myocardium (proneness to fatal arrhythmias). The overlap of these three characteristics increases the risk of MI. However, about in every second of all fatal MIs, plaque rupture is the most common cause. The authors described various types and phases of vulnerable plaque. The final phase is characterized by a critically stenotic condition when the blood vessel is seriously narrowed. The detection of vulnerable plaque remains a major difficulty whereby active inflammation is supposed to be a major marker [Naghavi I and II, 2003]

Patients with AMI and unstable angina show an increased level of proinflammatory cytokines. Tumor necrosis factor (TNF) is the best studied one, others are interleukin-(IL)-1, IL-2, IL-6 and interferon-gamma [Murray, 2003]. The plasma concentration of IL-6, a serum inflammation marker, is elevated in patients with acute coronary syndromes. The C-reactive protein (CRP) – its hepatic byproduct – is an independent predictor for future coronary events. A case control study with 369 cases and 1348 controls showed after 20-years of follow-up that the risk of MI increased with increasing levels of CRP [Sakkinen, 2002]. A significant positive trend between increasing CRP levels and progressively higher Framingham Coronary Heart Disease Risk Score (FCRS) was reported in a cross-sectional survey of 1666 individuals free of cardiovascular disease [Albert, 2003]. A prospective study following 27,939 subjects for a mean of eight years showed that the measured base-line levels of CRP and LDL cholesterol had a strong linear correlation with the incidence of

cardiovascular events [Ridker, 2002]. The question arises how far the inflammatory response in arteries differs from that in other tissues.

Certain parallels between atherosclerosis and systemic inflammatory disease (e.g. rheumatoid arthritis) are perceptible. It is not yet fully understood how far chronic inflammatory response can be assigned to a specific tissue or organ. Specific characteristics of RA and atherosclerosis are displayed in Table 1. About 50% of patients with cardiovascular disease have hyperlipidaemia [Shepherd, 1995]. The combination of chronic intravascular inflammation with hyperlipidaemia seems to be particularly harmful.

Table 1.1:

Characteristics of atherosclerosis and rheumatoid arthritis (from: Russell R, Atherosclerosis – an inflammatory disease; NEJM; 340(2), 115-126)

Disease	**a)**	**b)**	**c)**	Connective tissue	Extracellular matrix	Pathogenetic
Atherosclerosis	+	+	-	Smooth-muscle cells	Collagen types I, III, IV, elastin, fibronectin, proteoglycan	Endothelial-cell injury and dysfunction, fibrous Cap, new matrix formation and
Rheum. Arthr.	+	+	+/-	Synovial fibroblasts	Collagen types I, IV, fibronectin, proteoglycan	Synovial-cell injury, erosion of cartilage, new Matrix scarring (pannus)

a) Monocytes and Macrophages b) Lymphocytes c) Granulocytes

1.5 Myocardial Infarction, Non-Steroidal Antiinflammatory Drugs (NSAIDs) and Rheumatic Diseases in Pharmacoepidemiology

Several studies - pharmacoepidemiological and experimental ones - have been published since the late 1990`s, investigating the association between AMI risk, NSAID exposure and chronic inflammatory diseases. Five observational studies were published alone in 2002 examining the risk of MI in current NSAID users. Most of them used large databases from various different health care systems. Schlienger et al. published a population based case-control study. They included 3319 cases (at age 75 years and younger) with a diagnosis of a first-time MI, and 13139 matched controls [Schlienger, 2002]. Findings from this study suggested that current NSAID exposure in patients free of diagnosed cardiovascular and other predisposing diseases does not decrease the risk of MI. A further case-control study encompassed 4425 patients hospitalized for MI and 17700 control subjects. The authors found no overall protective effect of NSAIDs against MI, but reported that use of one specific NSAID, naproxen, was associated with a reduced MI risk [Solomon, 2002]. Naproxen was also examined in a Canadian case-control study with 4163 cases (≤ 65 years) who had been hospitalized for MI. The 14,160 control subjects were selected at random from a sample of 82,000 patients obtained from a local drug and physician claims database. The authors reported for naproxen a protective effect against MI [Rahme, 2002].

Furthermore, White et al. performed a pooled analysis with data from the Celecoxib Long-term Arthritis Safety Study; pooled and described as one trial, 3987 persons randomized to celecoxib, and 3981 persons randomized to either ibuprofen or diclofenac were included. No increased risk of serious cardiovascular thrombotic events was found in subjects who have taken the specific cyclooxygenase-2 inhibitor celecoxib compared with non-selective NSAIDs [White, 2002]. The background risk for MI may be very different in patients aggregated in a pooled analysis, a natural limitation of such a study design. Recent discussion emerged regarding the cardiovascular safety of rofecoxib. The VIGOR trial, published in 2000, randomized 8076 subjects with RA to rofecoxib or naproxen. The authors reported a four-fold increased MI risk in patients with RA taking rofecoxib [Bombardier, 2000]. It was not clear

whether this association was due to an increased risk in association with rofecoxib or because the comparison drug naproxen in fact is associated with a decrease of risk. Two recently published studies reported an elevated risk estimate for MI or congestive heart failure for current rofecoxib use compared with celecoxib use and no NSAID use for subjects aged 65 years or older. [Solomon, 2004; Mamdani, 2004]. The findings of an observational study in the elderly suggested no increased MI risk for users of selective COX-2 inhibitors (celecoxib and rofecoxib) compared to naproxen and non-naproxen, non-selective NSAID users [Mamdani, 2003].

An observational cohort study identified a cohort of 181,441 new non-aspirin NSAID users and an equal number of matched non users. Both groups were 50 - 84 years of age. The authors defined hospital admission for MI or death from coronary heart disease as study endpoint. They found 11.9 cases of serious coronary heart disease per 1000 person-years. The- MI-risk was not lower for current long-term NSAID users (> 60 days) than for non-users, but they reported a reduced MI risk for naproxen compared to ibuprofen [Ray, 2002(359)]. After following a cohort of 164,769 women (50 - 74 years of age), Garcia-Rodriguez et al. examined in a nested case-control analysis the risk of MI in both current aspirin and NSAID users. While they reported a significant reduction of the risk for MI in aspirin users, they found no risk reduction for chronic NSAID users compared to non-users [Garcia Rodriguez, 2000]. Recently, they also investigated NSAIDs and the risk of myocardial infarction in a cohort study with a nested case-control analysis. They identified 4975 cases (AMI and death from coronary heart disease) and 20,000 controls in the UK in the general population and found no risk reduction for current NSAID users – independent of treatment duration and daily dose - on the occurrence of MI. The incidence rate of MI was 5 per 1000 person-years [Garcia-Rodriguez, 2004]

In 2002 and 2003 several studies were published examining severe cardiovascular events in patients with a chronic inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and osteoarthritis (OA). The cardiovascular safety was assessed in 5435 participants in various osteoarthritis trials. The risk of any arterial or venous thrombotic cardiovascular adverse event (AE) was the primary endpoint. The

investigators reported in this pooled analysis a lower incidence for AEs for rofecoxib compared to non-selective NSAIDs, and for the rofecoxib and placebo group a nearly identical risk [Reicin, 2002]. Several studies suggest that the risk of cardiovascular events is increased in patients with RA. Epidemiologic data provide prevalence for RA of 0.5% to 1% in the general population, although the annual incidence is highly variable [Sangha, 2000]. An observational cohort study using a database in England showed not only a significantly increased risk of mortality and thromboembolic events in patients with RA but also with osteoarthritis (OA) [Watson, 2001]. A retrospective cohort study followed patients (40 years and older) after excluding subjects with a prior history of AMI or cerebrovascular events. They analyzed 2.37 million patients (1.11 million men and 1.26 million women) and found after a follow-up of almost 5 years age- and gender-adjusted all-cause mortality rates which were 60 to 70% higher in patients with RA compared to patients with OA and those without arthritis [Watson, 2003]. In a large prospective cohort study among 114,342 women participating in the Nurses` Health Study, the authors reported a significantly two-fold increased MI risk in women with RA compared to those without. The risk was 30% higher in women with a RA history of 10 years or more [Solomon, 2003].Very similar findings were reported in an other study published in 1999; this survey showed that RA is associated with an elevated risk for MI and probably cerebrovascular accidents. The study was based on 11,572 patients (9093 with RA, 2479 with OA) who were patients of rheumatology practices [Wolfe, 2003]. The examination of acute thromboembolic events (TCEs) in rheumatoid arthritis patients with current naproxen exposure was the objective of a case-control study. Current naproxen use was associated with a lower risk for TCEs in patients who had a prescription for naproxen in the past year compared to non-naproxen users. The authors analyzed 809 cases (40 to 79 years of age) from a computer database [Watson, 2002]. Two recently published papers explored atherosclerosis in association with SLE, encompassing some 250 patients with SLE and controls. Both teams found premature atherosclerosis in the SLE patients at all ages. The majority of patients were white women who had had SLE for 10 to 15 years [Asanuma, 2003; Roman, 2003].

2. Goal and Objectives

2.1. Goal

- To contribute to the understanding of the association between acute myocardial infarction and inflammatory diseases, using the General Practice Research Database (GPRD) for a pharmacoepidemiological study.

2.2. Objectives

- To compare the risk of developing an acute first-time myocardial infarction between subjects with or without rheumatoid arthritis or systemic lupus erythematosus

- To investigate the effect of use of non-steroidal anti-inflammatory drugs on the risk of developing a first-time myocardial infarction with particular emphasis on the timing of use as well as on the duration or dosage of use

3. Effect of Rheumatoid Arthritis or Systemic Lupus Erythematosus on the Risk of First-Time Acute Myocardial Infarction

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We explored the association between diagnosed rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) and the risk of developing a first-time acute myocardial infarction (AMI) by conducting a population-based case-control analysis using data from the United-Kingdom-based General Practice Research Database (GPRD). Among 8,688 cases with AMI and 33,329 matched controls the adjusted odds ratios (ORs) of AMI for subjects with RA was 1.47 (95% CI 1.23-1.76), and in subjects with both RA and diagnosed hyperlipidemia 7.12 (95% CI 4.16-12.18). The risk associated with SLE was 2.67 (95% CI 1.34-5.34). The results underline that RA and SLE increase the AMI risk.

The association of diseases with systemic inflammation – such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) – and cardiovascular disease has gained much attention since evidence has increased that inflammation is a direct risk factor for atherosclerosis[1]. A recent observational study reported a two-fold increased risk of acute myocardial infarction (AMI) in women with diagnosed RA[2]. In previous studies, increased rates of cardiovascular diseases in patients with RA[2-4] or SLE[5,6] have been observed. The authors of a recent study used data from the Nurses' Health Study to explore the association between diagnosed RA and myocardial infarction in females only [2], while we explored the risk of developing a first-time AMI associated with RA or SLE in a large case-control analysis including both men and women < 90 years of age.

We used the large and well-validated General Practice Research Database (GPRD) to conduct this population-based case-control analysis. The GPRD has been previously described in detail.[7,8] It encompasses more than 3 million residents in the UK that have been registered with selected general practitioners. The information electronically recorded by general practitioners includes patient demographics and characteristics (e.g., height, weight, smoking status), symptoms, clinical diagnoses, consultant referrals, hospitalizations, and drug prescriptions. The database has been the source for numerous epidemiological studies in recent years, and the accuracy and completeness of these data have been well

documented and validated.[9,10] GPRD data have been used in several recent studies investigating risk factors for AMI.[11-13]

Cases with a first-time diagnosis of AMI were identified via computer-recorded Oxford Medical Information System [OXMIS] codes, mapped onto *International Classification of Diseases [ICD]* codes). We searched for subjects who had a first-time AMI at 89 years of age or younger between January, 1995 and April, 2002. We excluded subjects registered on the database for less than 3 years before the date of the AMI (subsequently referred to as index date). In previous studies using GPRD data[11,12,14,15] the computer-recorded diagnosis of a first-time AMI was validated for a random sample of approximately 450 patients by reviewing hospital discharge letters. The documented high validation rate (>90%) led us to include all potential cases that we identified through manual review of computerized patient records.

We identified at random 4 controls per case, matched to cases on age (± 1 year), sex, general practice attended, number of years of recorded history in the database, and calendar time (by using the same index date as for the corresponding case). We excluded controls with a GPRD history of less than 3 years. We compared the proportion of diagnosed RA or SLE as well as of various risk factors for AMI prior to the index date between cases and controls. We conducted a matched analysis (conditional logistic regression model) using the software program SAS, Version 8.1 (SAS Institute Inc., Cary, NC). Relative risk estimates (odds ratios, OR) are presented with 95% confidence intervals (95% CI).

The association between RA or SLE and the AMI-risk was adjusted for body mass index (<25, 25-29.9, ≥30 kg/m^2, unknown), smoking status (never, ex, current, unknown), aspirin use (current, past, non), use of non-aspirin non-steroidal anti-inflammatory drugs (current, past, non), a history of diagnosed hypertension, hyperlipidemia, diabetes mellitus, angina pectoris, other cardiac diseases (arrhythmias or congestive heart failure), arterial vascular diseases (claudication, stroke, transient ischemic attack, arterial thromboembolic events), and kidney diseases.

The analysis encompassed 8688 cases with a first-time AMI and 33,923 matched controls. Among the AMI cases, 62.9% were males. Table 1 displays the age and sex distribution and the distribution of known risk factors for AMI in cases and controls. After adjusting for the above mentioned covariates, the relative risk estimates (ORs) of developing a first-time AMI for subjects with RA or SLE were 1.47 (95% CI 1.23-1.76) and 2.67 (95% CI 1.34-5.34), respectively (Table 2). The AMI risk associated with RA was higher in females than in males (p-value test for effect modification 0.049) (Table 2), while it tended to be higher in males than in females for SLE (p-value test for effect modification 0.281). The risks of developing a first-time AMI were particularly high in subjects with RA or SLE if they also had diagnosed hyperlipidemia (Table 2). More cases than controls ever used statins (5.1% and 2.5%, respectively) or oral corticosteroids (15.6% and 12.9%, respectively) prior to the index date, and cases tended to have slightly more practice visits in their medical history than controls; however, adjusting the analysis for these parameters did not materially change the results.

The findings of this large observational study support recent findings by Solomon et al. reporting an approximately 2-fold increased AMI risk in females with diagnosed RA.[2] However, we also included males in our analysis and studied the association between RA or SLE and AMI. Furthermore, we found a substantially increased risk for subjects with both hyperlipidemia and inflammatory diseases. The association between diagnosed SLE and the risk of AMI was even more pronounced than the one for RA; the OR was around 4 for males and 2 for females, the difference between genders not being statistically significant. All these findings have been adjusted for age, sex, geography and calendar time (by matching) and for a variety of known clinical risk factors and drugs potentially affecting the AMI risk in multivariate regression models. These results from a large, population-based case-control analysis using a well-validated database from the UK fit well in the concept that systemic inflammation accelerates atherosclerosis and increases the risk for cardiovascular disease. The results of the current study support the statement by Solomon et al.[2] that subjects with chronic systemic inflammatory diseases may profit from aggressive strategies to prevent

from ischemic heart disease. This seems to be particularly important for subjects with both inflammatory diseases and hyperlipidemia.

Key words: myocardial infarction; rheumatoid arthritis; systemic lupus erythematosus

3.1 Miniabstract for table of contents

In a large population-based case-control analysis using data from the United-Kingdom-based General Practice Research Database, we studied the association between diagnosed rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) and the risk of developing a first-time acute myocardial infarction (AMI). The risk of AMI was elevated for subjects with RA (OR 1.47, 95% CI 1.23-1.76) or SLE (OR 2.67, 95% CI 1.34-5.34).

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TABLE 3.1 Characteristics of cases with acute myocardial infarction and controls

Parameter	**Cases (%)** (n=8688)	**Controls (%)** (n=33,923)	**Adjusted* OR** (95% CI)	**P-value**
Age (years)				
< 50	662 (7.6)	2611 (7.7)	--	--
50-69	3681 (42.4)	14,521 (42.8)	--	--
70-89	4345 (50.0)	16,791 (49.5)	--	--
Sex				
male	5463 (62.9)	21,310 (62.8)	--	--
female	3225 (37.1)	12,613 (37.2)	--	--
Smoking status				
non	3952 (45.5)	18,555 (54.7)	1.00 (Referent)	
current	2192 (25.2)	5559 (16.4)	2.08 (1.94-2.23)	< 0.001
ex	1363 (15.7)	4697 (13.9)	1.31 (1.21-1.42)	< 0.001
unknown	1181 (13.6)	5112 (15.0)	1.18 (1.07-1.30)	< 0.001
Body mass index (kg/m^2)				
< 25	2376 (27.4)	10,174 (30.0)	1.00 (Referent)	
25-29.9	2711 (31.2)	10,426 (30.7)	1.06 (0.99-1.13)	0.104
$\geq$ 30	1219 (14.0)	3893 (11.5)	1.20 (1.10-1.31)	< 0.001
unknown	2382 (27.4)	9430 (27.8)	1.20 (1.11-1.31)	< 0.001

TABLE 3.1 (cont') Characteristics of cases with acute myocardial infarction and controls

Hypertension	3045 (35.1)	9275 (27.3)	1.26 (1.19-1.33)	< 0.001
Hyperlipidemia †	1957 (22.5)	2027 (6.0)	4.19 (3.88-4.53)	< 0.001
Diabetes mellitus	1185 (13.6)	2276 (6.7)	1.85 (1.70-2.01)	< 0.001
Angina pectoris	2616 (30.1)	4090 (12.1)	2.73 (2.55-2.92)	< 0.001
Arrhythmias/Congestive heart failure	1691 (19.5)	4019 (11.9)	1.48 (1.37-1.59)	< 0.001
Arterial thrombosis	1408 (16.2)	3655 (10.8)	1.26 (1.16-1.37)	< 0.001
Kidney diseases	349 (4.0)	845 (2.5)	1.25 (1.08-1.44)	0.003

* adjusted for all covariates in the table, aspirin and use of non-steroidal antiinflammatory drugs
† defined as having a diagnosis of hypercholesterolemia and/or treatment with statins or fibrates

TABLE 3.2 Distribution of rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) in cases with acute myocardial infarction and controls

Parameter	**Cases** (n=8688)	**Controls** (n=33,923)	**Adjusted* OR** (95% CI)	**P-value**
No RA, no SLE	8465	33,335	1.0 (Referent)	
RA	208	562	1.47 (1.23-1.76)	< 0.001
Males	79	263	1.22 (0.93-1.60)	0.160
Females	129	299	1.72 (1.36-2.18)	< 0.001
Age < 70 years	100	249	1.79 (1.37-2.34)	< 0.001
Age ≥ 70 years	108	313	1.31 (1.04-1.66)	0.025
Hyperlipidemia	38	25	7.12 (4.16-12.18)	< 0.001
no hyperlipidemia	170	537	1.45 (1.20-1.74)	< 0.001
SLE	15	26	2.67 (1.34-5.34)	0.006
Males	8	7	4.61 (1.50-14.18)	0.008
Females	7	19	2.10 (0.84-5.28)	0.113
Age < 70 years	12	15	3.47 (1.49-8.06)	0.004
Age ≥ 70 years	3	11	1.39 (0.35-5.58)	0.643
Hyperlipidemia	3	1	18.26 (1.48-225)	0.024
no hyperlipidemia	12	25	2.55 (1.23-5.30)	0.012

* adjusted for all covariates from Table 1, aspirin and use of non-steroidal antiinflammatory drugs

4. Discontinuation of Nonsteroidal Anti-Inflammatory Drugs is Associated with Increased Risk of Acute Myocardial Infarction

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4.1 Abstract

Background Systemic inflammation has been shown to be associated with an increased risk of acute myocardial infarction (AMI). However, the effect of use of nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of AMI has not been well defined yet. We therefore studied the risk of AMI during NSAID exposure and after cessation of NSAIDs.

Methods We conducted a large case-control analysis on the British General Practice Research Database (GPRD). The study included 8,688 cases with a first-time AMI between 1995 and 2001, and 33,923 controls, matched to cases on age, sex, calendar time and general practice attended.

Results After adjusting for hypertension, hyperlipidaemia, diabetes mellitus, ischaemic heart disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), acute chest infection, body mass index, smoking and aspirin use, the risk of AMI was 1.52 (95% CI 1.33-1.74) for subjects who stopped taking NSAIDs 1-29 days prior to the index date, as compared to non-users. The risk was highest in subjects with rheumatoid arthritis or SLE (adjusted OR 3.68, 95% CI 2.36-5.74) and for subjects who stopped NSAIDs after previous long-term use (adjusted OR 2.60, 95% CI 1.84-3.68). Current and past NSAID use (therapy stop $\geq$ 60 days prior to the index date) were not associated with an increased risk of AMI (adjusted OR 1.07, 95% CI 0.96-1.19, and 1.05, 95% CI 0.99-1.12, respectively).

Conclusions Our findings suggest that the risk of AMI is substantially increased during several weeks after cessation of NSAIDs.

4.2 Introduction

There is increasing evidence that intravascular inflammation plays a key role in the development of atherosclerosis and acute coronary events.[1-3] Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation. They exert their effect by reversible, competitive inhibition of cyclooxygenase (COX), an important enzyme in the regulation of molecular pathways of pain and inflammation.[4] In addition to COX inhibition, NSAIDs also decrease thromboxane A_2 (TXA_2) production, potentially leading to an inhibition of platelet aggregation.[4] In theory, these two pharmacological mechanisms could reduce the risk of AMI during exposure to non-aspirin NSAIDs.

In fact, several recent observational studies explored the risk of AMI in subjects taking non-aspirin NSAIDs.[5-10] The risk estimates for current NSAID use in these studies were consistently reported to be around one, and most authors concluded that current exposure to non-aspirin-NSAIDs does not substantially lower the risk of AMI.[5-8]

However, a possible limitation of these studies is that it is difficult to distinguish between the effect of the underlying inflammation – a main reason for using NSAIDs – and the potential NSAID effect on the AMI risk, since the two are highly correlated. Relative risks around one for current NSAID use may also be the result of a NSAID effect; in other words, current NSAID exposure may lower an inflammation-induced increased risk of AMI risk towards one, but not below.

In a recent study, we explored the effect of current NSAID use on the risk of AMI in 3319 cases with a first-time AMI between 1992 and 1997 and 13,139 controls using the UK-based General Practice Research Database (GPRD). Study subjects were free of diagnosed cardiovascular or metabolic risk factors. We reported a relative risk close to one for current NSAID use, but observed a more than two-fold increased risk of AMI for long-term users of NSAIDs who stopped their NSAIDs before the AMI.[6]

The aim of this study was to further explore in detail the association between timing of discontinuation of NSAID exposure and the risk of first-time AMI. For this purpose, we

conducted another large case-control analysis on the GPRD, including incident AMI cases from 1995 to 2001 with or without clinical risk factors for AMI.

4.3 Methods

Study population and data source

The GPRD is a large and well-validated database which has been previously described in detail.[11, 12] Briefly, more than 3 million residents in the United Kingdom (UK) have been registered with selected general practitioners (GPs) who agreed to provide data for research purposes to the GPRD. The database has been the source of numerous epidemiological studies, and the accuracy and completeness of the data have been well documented and validated.[13, 14] GPRD data have been used in several recent studies on AMI.[6, 15-19] The age- and sex-distribution of patients in the GPRD is representative of the UK-population. The information electronically recorded by GPs includes patient demographics and characteristics (e.g., height, weight, smoking status), symptoms, clinical diagnoses, referrals to consultants, hospitalizations, and drug prescriptions. Drug prescriptions are recorded in detail using a drug dictionary based on the UK Prescription Pricing Authority. These codes define for each prescription the active compound, the route of administration, the dose of a single unit, the number of units prescribed, and in most instances the intake regimen prescribed by the GP (e.g. 3 tablets per day). Drug prescriptions are generated directly from the computer and recorded in each patient's computerized profile. On request, hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record.

Case definition and ascertainment

We identified potential cases with a first-time diagnosis of AMI via computer-recorded Oxford Medical Information System [OXMIS] codes, mapped onto *International Classification*

of Diseases [ICD] codes. We searched for subjects who had a first-time AMI < 90 years of age between 1995 and 2001. We excluded subjects who were registered on the database for less than 3 years before the date of the AMI (subsequently referred to as index date). We reviewed the computer records of all potential cases, whereby any information regarding NSAID exposure was concealed. In previous studies using GPRD data,[16-18] the computer-recorded diagnosis of a first-time AMI was validated for a random sample of approximately 450 patients by reviewing hospital discharge letters. When we selected cases based on a manual review of computer records and sent for hospital discharge letters, > 90% of cases were confirmed by the presence of characteristic diagnostic criteria.[16-18] Based on these previous extensive validation procedures, we included all potential cases that we identified through manual review of patient records.

Controls

We identified at random four controls without AMI, matched to cases on age (± 1 year), sex, general practice attended, number of years of recorded history in the database, and calendar time (by using the same index date, i.e. the date of the AMI-diagnosis of the corresponding case). We also excluded controls with a history of less than 3 years in the GPRD.

Exposure definition

Based on the number of tablets and the GPs intake regimen of the last NSAID prescription prior to the index date, we assessed the number of days between the NSAID stop and the index date for each case and control. A subject was defined as 'current user' if the supply of the last prescription for an NSAID lasted up to the index date or beyond. Subjects whose therapy ended before the index date were categorized according to the time lag between the end of therapy and the index date (1-29, 30-59, ≥ 60 days). Subjects were further classified according to the number of prescriptions for NSAIDs (i.e. 1-19, 20-

39, ≥ 40 prescriptions for acemetacin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, sulindac, tenoxicam or tiaprofenic acid).

Statistical analysis

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, Version 8.1 (SAS Institute Inc., Cary, NC). Relative risk estimates (odds ratios, OR) are presented with 95% confidence intervals (95% CI).

For each case and control, the independent effects of various potential confounders on the AMI risk were assessed, such as body mass index (BMI) (<25, 25-29.9, ≥30 kg/m^2, unknown), smoking status (never, ex, current, unknown), aspirin use, hypertension, hyperlipidaemia, diabetes mellitus, ischaemic heart disease, other cardiac diseases (arrhythmias or congestive heart failure), arterial vascular diseases (claudication, stroke, transient ischaemic attack, arterial thromboembolic events), kidney diseases, acute chest infection, and diseases with systemic inflammation (rheumatoid arthritis or systemic lupus erythematosus [SLE]).

4.4 Results

The analysis encompassed 8688 cases with a first-time AMI and 33,923 matched controls. Table 1 displays the age- and sex-distribution of cases and controls as well as their smoking status, BMI and presence of cardiovascular or metabolic diseases related to an altered AMI risk. Cases were predominantly male (62.9%), and 50.0% were at or above the age of 70 years at the date of the AMI.

Increased risk of first-time AMI after discontinuation of NSAIDs

As compared to non-users of NSAIDs, the OR of developing a first-time AMI during current NSAID exposure was 1.07 (95% CI 0.96-1.19), adjusted for BMI, smoking, hypertension, hyperlipidaemia, diabetes mellitus, ischaemic heart disease, arrhythmias or congestive heart failure, vascular diseases, kidney diseases, acute chest infection, and aspirin use. The adjusted ORs for subjects who stopped taking NSAIDs 1-29, 30-59 or ≥ 60 days prior to the index date were 1.52 (95% CI 1.33-1.74), 1.44 (95% CI 1.21-1.70) and 1.05 (95% CI 0.99-1.12), respectively (Table 2).

Additional stratification by duration of NSAID use showed that the risk of AMI after stopping NSAIDs 1-29 days before the index date was highest for long-term NSAID users (≥ 40 NSAID prescriptions, adjusted OR 2.60, 95% CI 1.84-3.68) and lower for users of 1-19 prescriptions (adjusted OR 1.22, 95% CI 1.01-1.48) (Table 2).

In order to test for effect modification, we further stratified the analysis by sex, age (<70 vs. ≥ 70 years of age at the index date), a history of diagnosed hypertension, hyperlipidaemia, diabetes mellitus, or ischaemic heart disease. There was no suggestion of effect modification by age, sex or underlying diseases except for ischaemic heart disease; the adjusted OR for subjects who stopped NSAIDs 1-29 days prior to the index date was 1.46 (95% CI 1.23-1.73) for subjects without and 2.85 (95% CI 1.79-4.54) for subjects with ischaemic heart disease.

We also stratified cases and controls who stopped NSAIDs 1-29 days prior to the index date by individual NSAIDs. The ORs for the most frequently used NSAIDs (diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, and piroxicam) were all similar (data not shown). As compared to non-use, current aspirin use yielded an adjusted OR of 0.83 (95% CI 0.76-0.91).

Increased risk of first-time AMI related to diseases with systemic inflammation

Diseases with systemic vascular inflammation were more prevalent in cases than controls. There were 208 AMI-cases with a history of rheumatoid arthritis (79 males and 129 females), and 15 cases with a history of SLE (8 males, 7 females). Rheumatoid arthritis (OR 1.47, 95% CI 1.23-1.76) or SLE (OR 2.80, 95% CI 1.40-5.60) were associated with a higher AMI risk, adjusted for the same parameters as listed above (Table 1). An acute chest infection within 1-4, 5-9, 10-14 or ≥ 15 days prior to the index date yielded adjusted ORs of 3.49 (95% CI 2.76-4.41), 1.77 (95% CI 1.34-2.35), 1.47 (95% CI 1.11-1.94) and 0.98 (95% CI 0.92-1.04), respectively.

We further explored the risk of AMI with cessation of NSAID use in subjects with and without rheumatoid arthritis or SLE. The reference group were subjects without rheumatoid arthritis/SLE and without NSAID use. As compared to those, the adjusted OR for subjects with rheumatoid arthritis/SLE who were non-users of NSAIDs was 1.66 (95% CI 1.01-2.75). For subjects with rheumatoid arthritis/SLE who stopped NSAIDs 1-29 days before the index date, it was 3.68 (95% CI 2.36-5.74), and for those who stopped NSAIDs ≥ 60 days before the index date 1.64 (95% CI 1.27-2.21). For subjects with rheumatoid arthritis/SLE who currently used NSAIDs at the index date, the adjusted OR was 1.26 (95% CI 0.91-1.75).

4.5 Discussion

In recent years, the role of vascular inflammation in the development of atherosclerosis and subsequent cardiovascular events has been recognised.[1-3] In fact, the plasma concentration of C-reactive protein (CRP), a marker for systemic inflammation, has been shown to predict the risk of future acute myocardial infarction (AMI) and stroke in men and women.[20-22] With the exception of newer, selective COX-2 inhibitors, most currently used NSAIDs inhibit non-selectively both COX-1 and COX-2,[23] thereby decreasing systemic

inflammation. NSAIDs also decrease thromboxane A_2 (TXA_2) production,[4] whereby the clinical relevance of the partial inhibition of platelet aggregation by non-aspirin NSAIDs is not fully understood.[4, 24]

The results of this large case-control analysis suggest that the risk of developing a first-time AMI is increased for a time period of several weeks after discontinuation of NSAID use, particularly in subjects who used NSAIDs on a long-term basis. The risk of AMI was not increased for subjects who currently used NSAIDs at the index date nor for past users who stopped NSAIDs more than two months before.

The causes for the observed association between recent cessation of NSAIDs and increased risk of AMI remain to be defined. It may be the result of an inflammatory rebound effect in the vascular tissue and/or the consequence of activated platelet aggregation after termination of the pharmacological inhibition of COX and TXA_2. It has been shown that patients with acute coronary syndromes exhibit signs of systemic and widespread coronary inflammation[25, 26]. Furthermore, a recent study reported a lower one-year mortality for patients who regularly used NSAIDs after an AMI as compared to AMI-patients not taking NSAIDs.[27] Thus, it is conceivable that NSAIDs suppress inflammation in coronary arteries and that cessation of NSAID use may allow a flaring up of the inflammation in the vessel wall, thereby resulting in plaque instability and subsequent AMI.

The increased risk of AMI shortly after stopping NSAIDs was found to be independent of sex, age or underlying diseases, with the exception of a previous history of ischaemic heart disease. We observed that the risk was highest in subjects who stopped NSAIDs after long-term exposure (i.e. $\geq$ 40 NSAID prescriptions, presumably those with the longest history of systemic inflammation), and that the risk of AMI was higher with recent discontinuation of NSAID use in subjects with inflammatory diseases (i.e. rheumatoid arthritis or SLE), supporting the proposition that inflammatory diseases increase the risk of AMI and that current NSAID exposure may suppress this risk. As we recently reported, rheumatoid arthritis or SLE were both independent risk factors for AMI in this study population.[28]

A spurious association may have resulted from a bias that could be called "inverse confounding by indication". In other words, cessation of NSAID use may be the consequence of clinical symptoms related to the future AMI. To address this potential problem, we reviewed case records of cases who stopped NSAIDs at various time points. Even though in many case records no obvious reason for the cessation of NSAID therapy was available, there was no evidence that clinical symptoms directly or indirectly related to AMI were more frequent in recent than in past NSAID users. In addition, we quantified all practice visits in the two months immediately preceding the index date for cases and controls to explore whether cases were less likely than controls to see the GP shortly prior to the index date (and thus be less likely to get a prescription for NSAIDs). However, the opposite was true, cases had substantially more practice visits recorded than controls prior to the index date, and adjusting the analysis for this parameter did not materially alter the results. It is a limitation of this observational study that we were not in a position to clearly distinguish between various indications for NSAIDs in the study population, and indications may have overlapped or may have changed over time. This as well as the lack of recorded laboratory parameters, particularly C-reactive protein, did not allow us to classify patients according to timing or extent of systemic inflammation.

The classification of exposed subjects according to the date of the end of therapy is less perfect in clinical practice than in our model, since subjects may not take drugs exactly as prescribed by the GP. However, we categorized all users by the same algorithm and regardless of case-control status, and therefore exposure misclassification was likely to be random. On the other hand, it is a particular strength of the current study that the detailed recording of drug exposure in the GPRD allowed us to estimate the date of the end of the NSAID therapy.

During the time period we sampled cases and controls for this study, there was too little exposure to selective COX-2-inhibitors for a meaningful analysis. Thus, this analysis does not contribute to the discussion whether COX-2 inhibitors alter the AMI risk.[29-32]

We found an increased risk of AMI in patients with rheumatoid arthritis or SLE, both diseases with increased systemic (including vascular) inflammation. Indeed, rheumatoid arthritis has been associated with coronary artery disease[33-35] as well as intimal and medial thickening of carotid arteries.[36, 37]. SLE has also been related to an increased risk of atherosclerosis and coronary heart disease. [38-40] Furthermore, associations between chronic chest infections and AMI have been described, [41, 42] and the previously reported increased risk of AMI for subjects with acute chest infections [17] has again been observed in this study.

In summary, this large case-control analysis suggests that there is a vulnerable time period of several weeks with an increased risk of first-time AMI after discontinuation of prolonged NSAID use. The risk of AMI was not elevated for current NSAID users, suggesting that NSAIDs may counterbalance an increased risk caused by inflammation. This interpretation is contrary to previous studies reporting no effect of current NSAID exposure on the risk of AMI.[5-8] Our results suggest that abrupt discontinuation of NSAID therapy may have to be avoided and that physicians should carefully review the disease status and the current medication profile before terminating a therapy with NSAIDs. This may be particularly valid for patients with chronic inflammatory diseases and/or for subjects who used NSAIDs for a long time. The current findings need to be confirmed by additional studies given their potential clinical implications.

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Table 4.1: **Characteristics of cases with acute myocardial infarction (AMI) and controls**

Parameter	**Categories**	**Cases, No (%) (N=8,688)**	**Controls, No (%) (N=33,923)**	**Adjusted* OR (95% CI)**
Age, years	< 50	662 (7.6)	2611 (7.7)	--
	50-69	3681 (42.4)	14,521 (42.8)	--
	70-89	4345 (50.0)	16,791 (49.5)	--
Sex	Male	5463 (62.9)	21,310 (62.8)	--
	Female	3225 (37.1)	12,613 (37.2)	--
Smoking status	Non	3952 (45.5)	18,555 (54.7)	1.0 (Referent)
	Current	2192 (25.2)	5559 (16.4)	2.07 (1.93-2.22)
	Ex	1363 (15.7)	4697 (13.9)	1.31 (1.21-1.41)
Body Mass Index (kg/m^2)	< 25	2376 (27.4)	10,174 (30.0)	1.0 (Referent)
	25-29.9	2711 (31.2)	10,426 (30.7)	1.06 (0.99-1.14)
	≥ 30	1219 (14.0)	3893 (11.5)	1.21 (1.11-1.32)
Diagnosed risks	Hypertension	3045 (35.1)	9275 (27.3)	1.26 (1.19-1.34)
	Hyperlipidemia	1957 (22.5)	2027 (6.0)	4.21 (3.89-4.55)
	Diabetes mellitus	1185 (13.6)	2276 (6.7)	1.84 (1.69-2.00)
	IHD †	2616 (30.1)	4090 (12.1)	2.72 (2.54-2.92)
	Arrhythmias / CHF‡	1691 (19.5)	4019 (11.9)	1.46 (1.36-1.57)
	Arterial Thrombosis	1408 (16.2)	3655 (10.8)	1.25 (1.15-1.36)
	Kidney diseases	349 (4.0)	845 (2.5)	1.23 (1.07-1.43)
	SLE	15 (0.2)	26 (0.1)	2.80 (1.40-5.60)
	Rheumatoid arthritis	208 (2.4)	562 (1.7)	1.47 (1.23-1.76)

* adjusted for all covariates in the table, acute chest infections, aspirin and NSAID use
† IHD ischaemic heart disease
‡ CHF congestive heart failure

Table 4.2: **Timing of NSAID exposure by duration and relative risk estimates**

NSAID exposure	**Cases (N=8688)**	**Controls (N=33,923)**	**Adjusted* Odds Ratio (95% CI)**
Non users	**3203**	**13,551**	**1.0 (Referent)**
Current use at index date	**650**	**2339**	**1.07 (0.96-1.19)**
1-19 Rx	231	906	1.04 (0.88-1.24)
20-39 Rx	165	606	1.08 (0.85-1.37)
≥ 40 Rx	254	827	1.23 (0.99-1.53)
NSAID stop 1-29 days †	**405**	**1065**	**1.52 (1.33-1.74)**
1-19 Rx	195	632	1.22 (1.01-1.48)
20-39 Rx	96	227	1.85 (1.31-2.61)
≥ 40 Rx	114	206	2.60 (1.84-3.68)
NSAID stop 30-59 days †	**241**	**677**	**1.44 (1.21-1.70)**
1-19 Rx	175	501	1.48 (1.21-1.81)
20-39 Rx	35	117	1.23 (0.74-2.04)
≥ 40 Rx	31	59	1.55 (0.83-2.88)
NSAID stop ≥ 60 days †	**4189**	**16,291**	**1.05 (0.99-1.12)**
1-19 Rx	3784	15,077	1.03 (0.97-1.10)
20-39 Rx	255	784	1.21 (0.99-1.49)
≥ 40 Rx	150	430	1.36 (1.02-1.81)

* adjusted for parameters in Table 1, acute chest infection and aspirin use
† before the index date

5. Current Use of Nonsteroidal Anti-Inflammatory Drugs and the Risk of Acute Myocardial Infarction

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Short running head: NSAIDs and myocardial infarction

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5.1 Abstract

Background Systemic inflammation has been shown to be associated with an increased risk of acute myocardial infarction (AMI). Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation while taken. The effect of current NSAID use on the risk of AMI has been discussed controversially. We studied the risk of AMI during current NSAID exposure in subjects 89 years of age or younger.

Methods We performed a population-based case-control analysis using the General Practice Research Database (GPRD). We included 8688 cases with a first-time AMI between 1995 and 2001 and 33,923 controls matched to cases on age, sex, calendar time and general practice attended.

Results After adjusting for various risk factors for AMI (e.g. hypertension, hyperlipidaemia, diabetes mellitus, ischemic heart disease, body mass index, smoking and aspirin use), the relative risk (expressed as odds ratio [OR]) of AMI was 1.07 (95% confidence interval [CI] 0.96 - 1.19) for subjects with current NSAID exposure compared to non-users. The adjusted OR for current diclofenac use was 1.23 (95% CI 1.00 - 1.51), for current ibuprofen use 1.15 (95% CI 0.91 - 1.46), and for current naproxen use 0.95 (95% CI 0.66 - 1.37), compared to non-use of NSAIDs.

Current aspirin use combined with current NSAID use was associated with a statistically significant risk reduction (adjusted OR 0.74 [95% CI 0.57 - 0.97]), compared to non-use of NSAIDs and aspirin. Current use of aspirin together with current use of ibuprofen yielded an adjusted OR of 0.69 (95% CI 0.42 - 1.15).

Conclusions Our results provide additional evidence that the risk of first-time AMI during current use of NSAIDs is around 1. We found no evidence for a reduced cardioprotective effect of aspirin with concomitant NSAID use.

5.2 Introduction

Recent studies highlighted the association between intravascular inflammation, atherosclerosis and acute coronary events (1-4). Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation. Older NSAIDs non-selectively inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). In general, the COX enzyme system plays an important role in the regulation of pain and inflammation at a molecular level (5). Inhibition of COX-2 is followed by decreased prostaglandin E2 production, which is associated with anti-inflammatory as well as analgesic and antipyretic effects. In addition, COX-1 inhibition decreases thromboxane A2 (TXA2) production, thereby reducing platelet aggregation (6). These well-documented effects may lead to a reduced risk of acute myocardial infarction (AMI) during exposure to non-aspirin NSAIDs.

Several recent studies explored the risk of AMI in association with non-aspirin NSAIDs (7-16). The reported risk estimates of developing myocardial infarction for current users of non-aspirin NSAIDs were consistently around one. Most authors concluded that current use of non-aspirin NSAIDs does not substantially affect the AMI risk (7-10). There is evidence from several observational studies that naproxen use may be associated with a reduced AMI risk, but these results have been inconclusive (8, 9, 11, 12, 15, 16). Furthermore, it has been suggested that simultaneous exposure to both NSAIDs and aspirin may reduce the cardioprotective effects of aspirin (17-19).

In a previous study we explored the effect of discontinuation of NSAID use. We found a statistically increased AMI risk for subjects who stopped taking NSAIDs in the month immediately preceding the AMI. The risk was highest for subjects who stopped taking NSAIDs after previous long-term use (20). With this study we aimed at further exploring in detail a possible effect of current NSAID exposure on the risk of first-time AMI. The main focus was on the elaboration of possible interindividual differences between NSAIDs, on potential duration and dose effects, on the role of underlying clinical risk factors for AMI and on possible interactions between NSAIDs and aspirin use on cardiovascular protection.

5.3 Methods

Study population and data source

The General Practice Research Database (GPRD) is a large and well-validated database which has been previously described in more detail (21-23). Briefly, more than three million residents in England and Wales have been registered with selected general practitioners (GPs). The GPs agreed to provide data for research purposes to the GPRD. The accuracy and the completeness of this database has been well documented and validated (24-26) and it has been previously used to study risk factors for AMI (8, 11, 27-30). The electronic data records include patient demographics and characteristics (e.g. smoking, weight, height), symptoms, clinical diagnoses, referrals to consultants and to hospital as well as drug prescriptions. For each prescription the active compound, the route of administration, the dose of a single unit, the number of units prescribed and the intake regimen (e.g. 2 tablets per day prescribed by the GP) are defined. Additional information such as hospital discharge or referral letters are available on request, if needed for the validation of a recorded diagnosis. Originally a modification of the Oxford Medical Information System classification (similar to the International Classification of Diseases, Eighth Revision [ICD-8]) was used to enter medical diagnoses, and a coded drug dictionary based on the United Kingdom's Prescription Pricing Authority dictionary was used for recording prescriptions. More recently, the data has been encoded using Read codes for diseases and Multilex codes for drugs.

Case definition and ascertainment

We identified on computer potential cases with a first-time AMI between January 1995 and April 2001 at age of 89 years or younger. Subjects with a database history of less than 3 years before the index date (the date of the AMI) were excluded. We reviewed the computer records of all potential cases, blinded to any information on NSAID exposure.

According to previous validation studies, a high percentage (more than 90%) of selected potential cases with AMI can be confirmed by the presence of specific diagnostic criteria in hospital discharge letters (27-29). Due to this fact, we included all potential cases after identifying them by manual review of patient profiles.

Controls

Four controls (i.e. subjects without AMI) were identified at random and matched to cases on age (±1 year), sex, general practice attended, number of years of recorded history in the database and calendar time (by using the same index date, i.e. the date of the AMI-diagnosis of the corresponding case). Controls with a history of less than three years in the database were excluded.

Exposure definition

For each case and control patient, the exposure history to NSAIDs (i.e. acemetacin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid) was assessed. Patients without exposure to NSAIDs recorded in the medical history before the index date were defined as ‘non-users’. ‘Current users’ were subjects whose supply of the last prescription for an NSAID prior to the index date ended at or after the index date. Additionally, subjects with current use were classified according to the last prescription for the individual NSAID prior to the index date. Current users were further grouped according to the number of NSAID prescriptions received and according to the dose of the last NSAID taken prior to the index date.

Statistical analysis

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, Version 8.1 (SAS Institute Inc., Cary, NC). Relative risk estimates (odds ratios, OR) are presented with 95% confidence intervals (95% CI).

We assessed the independent effects of various potential confounders on the AMI risk such as body mass index (BMI; <25, 25-29.9, >30 kg/m^2, unknown), smoking status (never, ex, current, unknown), aspirin use, hypertension, hyperlipidaemia, diabetes mellitus, ischemic heart disease, other cardiac diseases (arrhythmias or congestive heart failure), arterial vascular diseases (claudication, stroke, transient ischemic attack, arterial thromboembolic events), kidney diseases, acute chest infection and diseases with systemic inflammation (rheumatoid arthritis or systemic lupus erythematosus [SLE]) (31).

5.4 Results

We identified 8688 cases with a first-time AMI and 33,923 matched controls. Table 1 shows the age and sex distribution of cases and controls as well as their smoking status, BMI and the presence of cardiovascular or metabolic diseases prior to the index date. Cases were predominantly male (62.9%) and 50.0% were 70 years or older at the date of the AMI. Of the 8688 cases, 2124 (24.4%) did not have prior to the AMI a computer-recorded diagnosis of a cardiovascular or metabolic disorder predisposing to AMI.

The overall risk estimate (OR) of developing a first-time AMI during current NSAID exposure was 1.07 (95% CI 0.96-1.19), compared to non-users of NSAIDs, adjusted for BMI, smoking, hypertension, hyperlipidaemia, diabetes mellitus, ischemic heart disease, arrhythmias or congestive heart failure, vascular diseases, kidney diseases, acute chest infection, rheumatoid arthritis, systemic lupus erythematosus, and aspirin use. Table 2 shows the relative risk estimates of developing a first-time AMI during current NSAID exposure (all ages, 650 cases and 2339 controls), stratified by individual NSAIDs. The NSAIDs used most often, i.e. diclofenac, ibuprofen, naproxen, indomethacin and piroxicam, all yielded relative risk estimates around 1. Stratification by sex yielded different results for ibuprofen and naproxen; the adjusted ORs for current naproxen use were 0.70 (95% CI 0.42 - 1.15) for males and 1.58 (95% CI 0.88 - 2.82) for females, and 1.43 (95% CI 1.06 - 1.92) for male

ibuprofen users and 0.82 (95% CI 0.53 - 1.22) for female ibuprofen users, as compared to non-users of NSAIDs. We also compared the effect of current NSAID exposure between subjects with or without predisposing diseases for AMI. Current naproxen exposure in comparison with non-use of NSAIDs was associated with a risk estimate of 0.84 (95% CI 0.52 - 1.35) in subjects with diagnosed risk factors for AMI, and 0.69 (95% CI 0.21 - 2.25) for subjects without risk factors. The AMI risk for current diclofenac exposure in apparently healthy subjects was 2.01 (95% CI 1.19 - 3.40), compared to non-users of NSAIDs.

In an additional analysis we assessed the effect of current use of individual agents by dose and duration (Table 3). A comparison of the AMI risk during current naproxen exposure, taking current users of all other NSAIDs as the reference group, yielded an adjusted OR of 0.81 (95% CI 0.55 - 1.19).

We further investigated whether current NSAID exposure influences the cardioprotective effect of aspirin. Concomitant use of aspirin and NSAIDs was associated with a statistically significantly decreased risk of 0.74 (95% CI 0.57 - 0.97), as compared to subjects without NSAID and/or aspirin use. The adjusted OR for current aspirin exposure together with current ibuprofen use yielded an adjusted risk estimate of 0.69 (95% CI 0.42 - 1.15). For current aspirin use in the absence of any other NSAID exposure we found an adjusted OR of 0.87 (95% CI 0.75 - 1.00), as compared to non-users of aspirin.

5.5 Discussion

This large case- control analysis provides evidence that current NSAID exposure in subjects below the age of 90 years with or without cardiovascular or metabolic risk factors for AMI is not associated with a substantially altered risk of developing a first-time AMI. The overall relative risk for current NSAID users (OR 1.07; 95% CI 0.96 - 1.19) was closely similar to findings of other authors (7-10,16). However, in two recently published studies we found an increased risk for developing a first-time AMI after stopping NSAIDs 1-29 days prior

to the index date (20) and also a risk elevation in subjects with diagnosed rheumatoid arthritis or SLE (31). Taking the results of these two previous findings together with the results of the present study, it may mean that current NSAID exposure in subjects with chronic inflammation reduces the elevated AMI risk towards 1, but not below 1. It is speculative what a possible potential mechanism may be; there may be some rebound inflammation after stopping NSAIDs for the duration of approximately one month.

Several recent studies explored whether use of NSAIDs is associated with a reduced risk of developing coronary heart disease. NSAIDs may reduce vascular inflammation and atheroma formation (3). C-reactive protein (CRP) - a marker for systemic inflammation - has been shown to be associated with the risk of future AMI in both men and women (32-34). The most commonly used NSAIDs are both non selective COX -1- and COX-2-inhibitors and decrease systemic inflammation. Secondly, NSAIDs lead to decreased thromboxane A2 (TXA2) production, which is followed by a partial inhibition of platelet aggregation (35, 36). Nevertheless, the role of inhibition of platelet aggregation by non-aspirin NSAIDs is not fully understood (36, 37).

In our analysis we did not find a substantially altered AMI risk for any individual NSAID. Current naproxen has been reported to be associated with a possibly decreased risk of developing AMI (9, 11, 12). The risk estimate found in our study was closely similar to the ones found by Rahme and colleagues (12) and Solomon and colleagues (9) which were 0.79 and 0.84, respectively. However, in contrast to these two studies, our study did not reach statistical significance despite the relatively large number of exposed subjects.

Aspirin is known to reduce the risk of thrombotic cardiovascular disease due to its ability to inhibit platelet aggregation. In a recent in-vivo study Catella-Lawson and co-authors found a substantially decreased inhibition of platelet aggregation in subjects who had taken a single dose of ibuprofen two hours before aspirin (17). It was suggested that ingestion of ibuprofen before aspirin - within a specific time range - might limit the cardioprotective effect of aspirin in patients who are at increased risk for cardiovascular diseases (17), which might be associated with a decreased cardioprotective effect of

aspirin (18, 19). In contrast to theses findings, we found a statistically significant decrease in the AMI risk for simultaneous exposure to both aspirin and NSAIDs (adjusted OR 0.74; 95% CI 0.57 - 0.97) at the index date compared to patients without exposure to aspirin and/or NSAIDs prior to the index date. In a subanalysis we also found a suggestion of a decreased AMI risk for subjects who used aspirin and ibuprofen concomitantly at the index date (adjusted OR 0.69; 95% CI 0.42 - 1.15) (see Table 4). However, in our study - as in any other retrospective observational study - it was not possible to take the exact timing of ingestion of aspirin and NSAIDs into account, since this is not known.

Several other recent studies also investigated the potential effects of concomitant aspirin and ibuprofen or NSAID use. Curtis and colleagues determined in a retrospective cohort study whether prescribing of aspirin and ibuprofen was associated with an increased risk of death in patients ≤ 65 years of age discharged with myocardial infarction (38). They found that patients co-prescribed aspirin and ibuprofen on discharge had a similar risk of death within one year of discharge compared to patients prescribed aspirin alone (hazard ratio 0.84; 95% CI 0.70-1.01) or prescribed aspirin and an NSAID other than ibuprofen (hazard ratio 0.96; 95% CI 0.86-1.06). Due to the observational design, residual confounding cannot be excluded. Furthermore, additional OTC use of NSAIDs including ibuprofen may have been underestimated which could bias the results toward the null.

In a retrospective cohort study using a Scottish record-linkage database, MacDonald and Wei (18) evaluated the risk of cardiovascular and all-cause mortality in patients with known cardiovascular disease who used either aspirin alone or aspirin combined with ibuprofen, diclofenac or other NSAIDs. They found an adjusted hazard ratio for cardiovascular mortality in users of both aspirin and ibuprofen of 1.73 (95% CI 1.05-2.84) compared to users of aspirin alone, while the relative risk was 0.80 (95% CI 0.49-1.31) in users of aspirin and diclofenac, and 1.03 (95% CI 0.77-1.37) in those using aspirin and other NSAIDs, respectively. The study is limited due to the lack of information on OTC NSAID use and on severity of cardiovascular disease or other comorbidities.

Kurth and colleagues (19) performed a subgroup analysis of the Physicians' Health Study (a 5-year randomized, double-blind, placebo-controlled trial of aspirin 325 mg on alternate days) among 22,071 apparently healthy males with prospective observational data on use of NSAIDs collected with follow-up questionnaires. Compared to use of aspirin without additional NSAID exposure, use of aspirin with NSAIDs was associated with a non-significant increased relative risk of myocardial infarction if NSAID use was between 1-59 days per year (adjusted RR 1.21; 95% CI 0.79-1.87) and a significantly increased relative risk of 2.86 (95% CI 1.25-6.56) in those patients with longer NSAID exposure (i.e. $\geq$ 60 days/year). The authors concluded that regular but not intermittent NSAID use may inhibit the beneficial effects of aspirin. Since these data are derived from a post-hoc analysis and no specific data on specific types of NSAIDs are provided, the results have to be interpreted cautiously.

In a case-control study Kimmel and colleagues (15) assessed the risk of a first, nonfatal MI associated with the combined use of aspirin and NSAIDs including ibuprofen versus aspirin alone. Information on exposure and other covariates was collected with a standard structured telephone interview in both cases and controls. The OR of MI among users of aspirin and NSAIDs versus users of aspirin alone was 0.92 (95% CI 0.46-1.81). The corresponding OR of those using ibuprofen and aspirin compared to aspirin alone was 0.61 (95% CI 0.17-2.21). Stratification by frequency of ibuprofen use suggested an increased MI risk in aspirin users with frequent ibuprofen use versus aspirin only users (OR 2.03; 95% CI 0.60-6.84). However, recall bias or other potential biases need to be considered as potential limitations.

In another observational study, Patel and Goldberg (39) assessed the rate ratio of experiencing an MI in a group of patients using both aspirin and ibuprofen versus a group of patients using aspirin alone. The rate ratio of MI in the group of combined users versus aspirin users alone was significantly decreased at 0.69 (95% CI 0.50-0.73).

Furthermore, García Rodríguez and colleagues (16) used a nested case-control design to explore the potential negative effect of combined aspirin and ibuprofen use on

cardioprotection (i.e. risk of fatal and nonfatal AMI). As compared to aspirin users only, patients using aspirin and NSAIDs had a non-significantly increased AMI risk (OR 1.10; 95% CI 0.89-1.37); stratification by dose suggested higher risks in association with high NSAID doses. Further stratification by individual NSAID use yielded an adjusted OR of 1.08 (95% CI 0.74-1.58) for patients using aspirin plus ibuprofen compared to aspirin users alone.

In the present study it was not possible to adjust for socioeconomic status or life style habits such as physical activity or diet since this is not routinely recorded in the GPRD. These factors are known to be associated with the risk of cardiovascular diseases. Theoretically, they may also be related to NSAID use and could be potential confounders in the association between NSAID use and AMI. Another limitation of this study is the fact that we were not able to measure over-the-counter (OTC) NSAID use. Various NSAIDs (e.g. aspirin, ibuprofen or naproxen) are widely used as OTC products. According to previous investigations, most subjects with regular use of NSAIDs on prescription do not additionally purchase OTC NSAIDs on a regular basis. On the other hand, subjects who have no NSAID use recorded on prescription may be more likely to use NSAIDs from time to time without a prescription (40). This may lead to some exposure misclassification, a limitation which is a potential problem for all observational studies on NSAIDs using prescription databases.

In the present study we had too little information on rofecoxib, celecoxib and no information on valdecoxib since these drugs were only restrictively used or not yet marketed in the UK during the time of the study. Future studies may address the question whether selective COX-2 inhibitors affect the risk of developing a first-time AMI.

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Table 5.1 Characteristics of cases with acute myocardial infarction (AMI) and controls

Parameter	**Cases, No (%) (n=8,688)**	**Controls, No (%) (n=33,923)**	**Adjusted* OR (95% CI)**
Age, years			
< 50	662 (7.6)	2611 (7.7)	--
50-69	3681 (42.4)	14,521 (42.8)	--
70-89	4345 (50.0)	16,791 (49.5)	--
Sex			
Male	5463 (62.9)	21,310 (62.8)	--
Female	3225 (37.1)	12,613 (37.2)	--
Smoking status			
non	3952 (45.5)	18,555 (54.7)	1.00 (Referent)
current	2192 (25.2)	5559 (16.4)	2.07 (1.93-2.22)
ex	1363 (15.7)	4697 (13.9)	1.31 (1.21-1.41)
Body Mass Index (kg/m²)			
< 25	2376 (27.4)	10,174 (30.0)	1.00 (Referent)
25-29.9	2711 (31.2)	10,426 (30.7)	1.06 (0.99-1.14)
≥ 30	1219 (14.0)	3893 (11.5)	1.21 (1.11-1.32)
Diagnosed risks			
hypertension	3045 (35.1)	9275 (27.3)	1.26 (1.19-1.34)
hyperlipidemia	1957 (22.5)	2027 (6.0)	4.21 (3.89-4.55)
diabetes mellitus	1185 (13.6)	2276 (6.7)	1.84 (1.69-2.00)
IHD	2616 (30.1)	4090 (12.1)	2.72 (2.54-2.92)
arrhythmias / CHF	1691 (19.5)	4019 (11.9)	1.46 (1.36-1.57)
arterial thrombosis	1408 (16.2)	3655 (10.8)	1.25 (1.15-1.36)
kidney diseases	349 (4.0)	845 (2.5)	1.23 (1.07-1.43)

* adjusted for all covariates in the table, acute chest infections, aspirin and non-steroidal anti-inflammatory drugs use

IHD = ischemic heart disease, CHF = congestive heart failure, OR = odds ratio

Table 5.2 Risk of first-time AMI in current NSAID users, stratified by individual agents*

NSAID exposure	Cases (n) (n=8`688)	Controls (n=33`923)	Adjusted OR † (95% CI) (95% CI)
Non users	**3203**	**13,551**	**1.00 (Referent)**
Current NSAID use at the index date	**650**	**2339**	**1.07 (0.96 – 1.19)**
diclofenac	260	834	1.23 (1.00 – 1.51)
ibuprofen	176	656	1.15 (0.91 – 1.46)
naproxen	63	251	0.95 (0.66 – 1.37)
indomethacin	36	124	1.35 (0.81 – 2.25)
piroxicam	30	114	0.94 (0.53 – 1.68)
ketoprofen	18	109	0.86 (0.43 – 1.70)
fenbufen	16	19	3.08 (1.17 – 8.05)
nabumetone	10	56	0.62 (0.25 – 1.52)
mefenamic acid	9	26	2.29 (0.79 – 5.65)
etodolac	8	43	1.13 (0.39 – 3.21)
flurbiprofen	6	34	0.67 (0.21 – 2.11)
tiaprofenic acid*	6	26	0.64 (0.16 – 2.51)
NSAID stop 1-29 days**	**405**	**1065**	**1.52 (1.33 – 1.74)**
NSAID stop 30-59 days**	**241**	**677**	**1.44 (1.21 – 1.70)**
NSAID stop ≥60days**	**4189**	**16`291**	**1.05 (0.99 – 1.12)**

* only NSAIDs presented with ≥ 5 exposed cases and controls
** before the index date
† adjusted for all covariates in table 1, acute chest infections, and aspirin use

Table 5.3 Risk of first-time AMI in current diclofenac, ibuprofen or naproxen users, stratified by predisposing diseases, gender, age, exposure time and dosage*

Exposure	Diclofenac			Ibuprofen			Naproxen		
	Cases	*Controls*	*Adj. OR** (95% CI)*	*Cases*	*Controls*	*Adj. OR** (95% CI)*	*Cases*	*Controls*	*Adj. OR** (95% CI)*
Idiopathic	60	335	2.01 (1.19-3.40)	36	271	0.86 (0.48-1.54)	12	95	0.69 (0.22-2.25)
Non-idiopathic	200	499	1.09 (0.82-1.45)	140	385	1.15 (0.84-1.59)	51	156	0.84 (0.52-1.35)
Males	133	481	1.04 (0.78-1.38)	110	359	1.43 (1.06-1.92)	32	155	0.70 (0.42-1.15)
Females	127	353	1.56 (1.13-2.16)	66	297	0.82 (0.53-1.22)	31	96	1.58 (0.88-2.82)
<70 years	124	381	1.04 (0.75-1.45)	73	267	1.11 (0.76-1.61)	29	108	1.22 (0.69-2.15)
≥70 years	136	453	1.34 (1.02-1.76)	103	389	1.24 (0.92-1.98)	34	143	1.85 (0.52-1.38)
Low dose	186	608	1.22 (0.95-1.55)	17	71	1.03 (0.51-2.05)	24	98	0.80 (0.45-1.44)
High dose	74	226	1.25 (0.85-1.83)	159	585	1.18 (0.92-1.51)	39	153	1.07 (0.67-1.71)
Short duration	67	207	1.14 (0.77-1.70)	55	209	1.22 (0.82-1.83)	12	52	1.28 (0.58-2.81)
Long duration	193	627	1.24 (0.98-1.58)	121	447	1.12 (0.84-1.48)	51	199	0.85 (0.56-1.28)

* reference group: non-users of NSAIDs
** adjusted for all covariates in table 1, acute chest infections, and aspirin use

Idiopathic: without risk factors

Non-idiopathic: with risk factors

Low dose (dose per tablet): Diclofenac <100mg, Ibuprofen ≤200mg, Naproxen 275mg

High dose (dose per tablet): Diclofenac 100mg, Ibuprofen >200mg, Naproxen 500mg

Short duration: <10 prescriptions before the index date

Long duration: ≥10 prescriptions before the index date

Table 5.4 Risk of first-time acute myocardial infarction in current aspirin users with or without concomitant NSAID use compared with non-users of aspirin and/or NSAIDs

NSAID Exposure	**Cases, No (%) (n=8,688)**	**Controls, No (%) (n=33,923)**	**Adjusted* OR (95% CI)**
Non- use of aspirin and/or NSAIDs	6706 (77.2)	28,744 (84.3)	1.00 (Referent)
Current aspirin / never NSAIDs	383 (4.4)	1000 (2.95)	0.87 (0.75-1.00)
Current aspirin / current NSAIDs	96 (1.1)	250 (0.7)	0.74 (0.57-0.97)
Current aspirin / current ibuprofen	27 (0.3)	68 (0.2)	0.69 (0.42-1.15)
Current aspirin / current NSAID other than ibuprofen	69 (0.8)	182 (0.5)	0.76 (0.56-1.04)
Current aspirin / past NSAIDs	604 (7.0)	1635 (4.5)	0.82 (0.73-0.93)

† adjusted for all covariates in table 1, acute chest infections, and inflammatory diseases

6. Discussion and Conclusions

Detailed discussions of the main findings are found in each of the respective chapters. This section will focus on the study population and methodologies used, followed by a discussion of possible suggestions for future research and final conclusions.

6.1 Study Population and Data Source

The General Practice Research Database (GPRD)

This thesis was conducted with data of the GPRD, one of the best and most important databases for pharmacoepidemiological research worldwide. It contains detailed recorded information on prescriptions, diagnoses and many other individual characteristics of patients such as smoking, weight or height [Garcia-Rodriguez, 1998].

The installation of a general practice office computer system in the late 1980 in offices of general practitioners (GPs) in England, developed by the commercial company VAMP Health (Value Added Medical Product Health), was the beginning of a patient-based recording of medical information what is known as the General Practice Research Database (GPRD). GPs who agreed to contribute data to this data-system received 12 months of instruction and training on data entry in a standard manner and they had to agree to supply the collected data anonymously to researchers on a continuing basis. GPs who did not comply with the required quality standards were excluded. The recorded data contains details on the clinical history, diagnoses, prescribed medication, vaccinations and other important information about demographics, referrals and hospitalizations. A detailed prescription history (dosage, instructions and quantity) is useful and important to determine dosage and duration of drug exposure used by a particular patient. Various code systems are used for data entry. Medical diagnoses are recorded with a modification of the Oxford Medical Information System

(OXMIS) classification, drug prescriptions are recorded based on the Prescription and Pricing Authority`s dictionary (PPA). Since 1987 more than three million patients in England and Wales were included anonymously and are available for epidemiologic research purposes [Jick, 1997; Walley, 1997; Garcia-Rodriguez, 1998].

Validation Procedure

In the early 90`s the Boston Collaborative Drug Surveillance Program (BCDSP) conducted validation studies aiming at verifying diagnoses made by referring physicians and those made during hospitalizations. They determined a high concordance between the notations on the computer and the notations on the paper records within the 600 medical practices obtaining a complete teaching program [Jick, 1991; Jick, 1992]. The BCDSP keeps evaluating the GPRD continuously at various levels. Medical practices are reviewed for the consistency of the recorded information on drugs prescribed and on diagnoses recorded, and practices with irregular reporting or obvious underreporting over time were removed from the GPRD, since poor data recording negatively affects data quality and the validity of research projects [Jick S, 2003]

They also compared the data on disease incidence from the GPRD with confirmed “gold standards” from reliable sources such as national health statistics in the United Kingdom. It has been shown in two large validation studies that information, existent in the manual medical records in the general practitioners` offices, was recorded on the computer over 90% of the time [Jick, 1991; Jick, 1992]. The indication for the first drug use was recorded in more than 95% of instances and for acute myocardial infarction hospitalizations were recorded on computer in 100% of instances.

An additional ascertainment of cases was made in a study evaluating the risk of myocardial infarction in association with antihypertensive drug treatment. Hospital discharge letters of some 450 cases were compared to the computer records and an additional questionnaire was sent to the general practitioner requesting information on the reliability of the diagnosis. In order for a diagnosis to be considered valid, it was required that the case with of AMI had

at least two of the following criteria fulfilled: characteristic cardiac pain, an electrocardiogram consistent with the diagnosis, serial cardiac enzyme levels consistent with the diagnosis, an arteriogram documenting a recent coronary occlusion or a given fibrinolytic therapy. The reviewing process was done by three authors blinded to exposure, and total agreement on case status was necessary. Subjects were excluded as cases with a missing confirmation of the diagnosis, with a myocardial infarction reflecting an old event or with an incomplete computer record. The same restrictions were valid for patients who died after admission to the hospital or already died before reaching hospital to evaluate their case status. Subjects with an other cause of death than MI were excluded. The results of this validation study showed a high degree of validity of the computer-recorded information in the GPRD for MI diagnoses [Jick S, 2003; Jick, 1996].

6.2 Methodology

The main goal of this thesis was to contribute to the current knowledge on the association between inflammatory diseases, exposure to non-steroidal anti-inflammatory drugs and the risk of developing an acute myocardial infarction. The protocol of the study was sent to the Scientific and Ethical Advisory Group (SEAG) in London (UK) for appraisal. The thesis encompasses three retrospective case-control analyses. In general, case control studies are efficient and well-suited for the investigation of risk factors of rare diseases. They are mostly conducted retrospectively since this is the most inexpensive and most efficient possibility to get data on the association between risk factors and a disease of interest.

This large project was conducted in close collaboration with the BCDSP. Computer programmers from the BCDSP extracted the relevant information on patients with myocardial infarction and sent us patient profiles electronically; these were reviewed manually to validate the first-time diagnosis of myocardial infarction. Patient records were reviewed after

anonymization and the reviewer was blinded to any exposure of interest. A patient profile is attached in the Appendix 1. Cases with an uncertain diagnosis were excluded.

In all three studies four controls per case were randomly selected from the database. Controls were matched to cases on age, gender, general practice attended, calendar time and time since entering the database. Inclusion as well as exclusion criteria for both, cases and controls as well as further information on case and control selection have been described in detail within the three presented papers.

The description of the dataset was essential for the characterization of each case and the matched controls to analyze them in this large MI-study. For both cases and controls, a large number of variables regarding the nature and timing of use of drugs of interest were extracted by the specialized programmer at the BCDSP upon our detailed instructions. NSAID exposure was characterized by the following four variables:

1. Number of NSAID-prescriptions prior to the index date
2. Number of days between the first prescription in the profile for any drug (= start of active recording) and the first prescription for this drug
3. Number of days between the last prescription for this individual NSAID prior to the index date and the index date
4. PPA-code of the last prescription prior to the index date (PPA = Prescription and Pricing Authority in the UK, defines the individual NSAID), reflecting the number of tablets and the tablet dose

The information on the date of the last prescription prior to the index date and the number of tablets prescribed, together with the GPs instructions on how to take the tablet (e.g. 3 tablets per day) allowed to calculate the theoretical end of the therapy, i.e. the date when the tablet supply ended, given that the patient followed the therapy instructions perfectly.

The BCDSP programmer created a text-file (see ASCII file in the Appendix 2) with all the relevant parameters which allowed a detailed analysis with the computer program SAS.

In a case-control study it is not possible to directly assess the absolute and relative risk because the case-control design does not allow to get an incidence of the outcome in both the exposed and the non-exposed study population. The subjects in the analysis are either diseased (cases) or undiseased (controls). In other words, cases have the outcome of interest (in this case an acute myocardial infarction), and controls don't. Otherwise, they can and should be similar. The logistic regression analysis was used to calculate odds ratios and 95% confidence intervals of developing a first-time diagnosis of AMI in relation to previous use of the drugs of interest, taking non-users as the reference group. These matched analyses (multivariate conditional logistic regression models) were conducted using the software program SAS (Version 8.1, SAS Institute Inc., Cary NC). Furthermore, for each case and control, the independent effects of various potential confounders on the AMI risk were assessed from the patient profiles, and their potential effect on the risk of developing AMI as well as their potential to confound the association between drug use and AMI-risk was analyzed. Stratified analyses allowed the identification of potential effect modification by age, gender and the presence of underlying diseases potentially predisposing to AMI.

A phenomenon which is typical and particular in pharmacoepidemiology is the possibility of confounding by indication. Nowadays aspirin is much more often prescribed in low daily doses to high-risk patients with atherosclerosis than analgesic. Thus, aspirin exposure is strongly associated with the study outcome (i.e. AMI), and we obviously had to take aspirin exposure carefully into account in the analysis to control this potential problem of confounding by indication [Teicher, 1990, Psaty, 1995].

Lifestyle factors

Adjusting the analysis for lifestyle habits (e.g. nutrition, physical activity) or socioeconomic status was not possible in our study because such information is not recorded in the GPRD at an individual level. As an example, it is known that moderate alcohol intake decreases the risk of cardiovascular disease [Walsh, 2002]. Thus, it would be desirable to have information on alcohol consumption for cases and controls to be in a position to estimate the effect of alcohol consumption on the AMI-risk. This parameter, however, acts only as confounder if alcohol consumption is also directly linked to NSAID intake (if NSAID exposure is the parameter of interest in the analysis). Furthermore it is known that a strong adherence to the traditional Mediterranean diet (e.g. high intake of fruits, vegetables, nuts, minimally processed grains, olive oil) is associated with a decreased mortality due to coronary heart disease and cancer [Trichopoulou, 2003], which again might be a problem if diet is also directly and strongly linked to NSAID intake.

Recent debate concerned with socioeconomic status (SES) as a major determinant of coronary heart disease. The question arises in what way high or low SES is associated with a higher NSAID intake. In general, people in a low socioeconomic group have a low educational level and are forced to look after a job with strong and monotonous physical work. They probably have higher odds for developing bodily ailments which are responsible for higher NSAID use due to pain, distress and degenerative diseases.

6.3 Suggestions for future Research

Databases

The development of large databases has been one of the main and most important steps in the development of pharmacoepidemiology. Recording individual drug use and clinical outcomes are aimed to be as complete as possible to make systematic information available on large groups of drug users. In general, using well validated databases has important advantages for pharmacoepidemiological research in comparison to an old approach of hospital-based research with patient interviews:

- Data are free of recall or interviewer bias
- The costs of the study are usually low (except licence costs to use the database)
- Data are recorded by the doctor at the time an event occurs and on an ongoing level, free of any study hypothesis.
- Studies can be conducted in a short time to provide a quick answer on an arising controversy.

On the other hand, pharmacoepidemiological databases have several limitations:

- There is no direct and reliable information on drug compliance of the patients; an uncertainty remains whether the patients actually used the prescribed drug which was recorded by the GP
- There is no comprehensive information about additional medication bought over the counter in community pharmacies
- Most often there is no information on socioeconomic factors and lifestyle habits such as nutrition or physical activity

- Studying drug effects when the timing of drug intake is absolutely crucial (e.g. drug safety after having taken a drug before or after a meal) cannot be done retrospectively using a database since such information is not known to the GP and therefore cannot be recorded and analyzed.
- Ongoing validation of the recorded data is essential for pharmacoepidemiological research. Errors, biases and incompleteness might limit the usefulness and validity of pharmacoepidemiological studies

Electronic databases are increasingly used for pharmacoepidemiologic research. There are well-known databases in England (e.g. GPRD), Northern America (e.g. Medicare) and some smaller ones in the Scandinavian countries, but not in Switzerland.

The medical system and the way drugs are prescribed are similar in Switzerland and Scandinavian countries. Both use a system with prescribers (physicians in different settings), dispensers/sellers of drugs (pharmacies), and payers (reimbursement companies such as health insurances), often with an annual maximum amount which has to be paid by the patient him- or herself. The Nordic countries (Denmark, Finland, Norway and Sweden) generate detailed statistics on the consumption of medicines, and they work with national prescription databases. A standardized unit of measurement (defined daily dose, DDD) is used in these countries since the late 1970s [Sorensen, 2001]. Sales statistics allow studies about time trends and geographical variety in drug consumption, but they do not provide any information about the population or about the prescribers. Postal questionnaires, incidence and prevalence studies as well as trends of diseases and economic factors are the researchers` primary objectives [Klaukka, 2001; Straand, 2001; Bingefors, 2001; Bergman, 2001].

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Selective Cyclooxygenase-2 (COX-2) Inhibitors

The newer group of NSAIDs, the selective cyclooxygenase (COX)-2 inhibitors have been shown to have comparable efficacy to non-selective, non-steroidal antiinflammatory drugs in the treatment of patients reducing pain and general inflammation. They have become enormously popular in the meanwhile. Selective COX-2 inhibitors have little or no effect on platelet aggregation or platelet derived thromboxane synthesis but they are capable to reduce systemic prostacyclin synthesis.

Recent debate raised concern about the cardiovascular safety of selective COX-2 inhibitors, of rofecoxib in particular. The VIGOR Study reported that myocardial infarctions were more frequent in patients treated with rofecoxib (0.4%) than in patients assigned to naproxen (0.1%) [Bombardier, 2000]. Mukherjee and co-workers reported in their analysis that selective COX-2 inhibitors may be associated with an increased risk of thrombosis and AMI [Mukherjee, 2001].

Recently published studies explored the relationship between selective COX-2 inhibitors and the risk of MI in older adults. The findings in a case-control study showed an elevated MI risk for current rofecoxib use compared with celecoxib and no NSAID use [Solomon, 2004], findings in a retrospective cohort study suggested a higher risk for congestive heart failure in rofecoxib and non-selective NSAID users compared to celecoxib relative to non-NSAID controls [Mamdani, 2004].

As mentioned earlier, during the time of our investigations only rofecoxib and celecoxib were marketed and available but there was not enough information about them for a meaningful analysis. Valdecoxib and parecoxib (prodrug of valdecoxib) are new selective COX-2 inhibitors that have been marketed in the meanwhile.

A careful and detailed evaluation of all aspects of cardiovascular safety in regard to the newly introduced selective COX-2 inhibitors is needed to explore the relationship between specific non-selective and selective NSAIDs and the risk of MI.

Aspirin plus Ibuprofen

A field of controversial discussion is the potential inhibition of the clinical benefits of aspirin on cardioprotection by concomitant intake of NSAIDs. Several observational studies as well as in-vivo experiments suggested that the cardioprotective effects of aspirin may be reduced if non-aspirin NSAIDs (particularly ibuprofen) are taken together with aspirin. As previously mentioned, the discussion started with a publication in the NEJM in December 2001, in which the results of a randomized, crossover study of combinations of single daily doses (aspirin plus ibuprofen) suggested that the concomitant administration of ibuprofen might antagonize the irreversible platelet inhibition of aspirin [Catella-Lawson, 2001]. Subsequent studies, however, provided no consistent results. MacDonald & Wei found a nearly two-fold increased risk of all-cause mortality in patients who used ibuprofen plus aspirin compared to users of aspirin alone [MacDonald, 2003]. The small number (n=187) of patients and the missing adjustment for severity of cardiovascular disease as well as for possible confounders such as smoking or BMI are limitations of this study. Data from a subgroup analysis of a randomized trial suggested a three-fold increased MI risk for people – randomized to aspirin – taking any NSAIDs during more than 60 days per year [Kurth, 2003]. This large observational study used randomized data for aspirin exposure, adjusted for important covariates. The authors used cases with confirmed MI diagnoses, but they could not generate any evidence for effects of an individual NSAID exposure. Bias, confounding by indication (higher consumption of NSAIDs around the index date) or residual confounding may have occurred and may be plausible alternative explanations of these overall findings. The possibility of missclassification was previously mentioned in the context of availability of ibuprofen and other NSAIDs over the counter. Thus, overall use of ibuprofen could be underestimated in a prescription database. Kimmel and colleagues found in a recently published observational study a two-fold increased MI risk among current aspirin plus frequent (4 times/week) ibuprofen users compared to aspirin-only users [Kimmel, 2004].

In contrary to these findings a very large cohort study (with Medicare data) compared the baseline characteristics of aspirin-alone users, aspirin plus ibuprofen users and aspirin plus any NSAID users after adjustment for severity of cardiovascular disease. The authors found a comparable risk of death between the three investigated exposure groups and concluded that aspirin and ibuprofen did not adversely interact in the analyzed cohort with MI in patients at ≥ 65 years of age [Curtis, 2003]. These findings have been supported by Patel & Goldberg who suggested – based on their results of an observational study with 52,139 patient-months of combined (aspirin plus ibuprofen) medication – that the MI risk does not seem to be increased among patients simultaneously consuming aspirin plus ibuprofen, compared with aspirin alone [Patel, 2004]. Garcia-Rodriguez and co-workers conducted a retrospective cohort study and reported no increased or decreased risk estimates for developing MI for simultaneous aspirin and NSAID use (including ibuprofen). They examined 4975 cases of acute MI and death from coronary heart disease and 20,000 controls in a nested case-control analysis. Their findings do not support the suggested interaction between aspirin and NSAIDs [Garcia Rodriguez, 2004]. Additional studies are needed to determine the clinical relevance of the overall findings and whether patients at risk who are taking aspirin for cardioprotection should really avoid taking ibuprofen.

6.4 Final Conclusions

In the three published case-control analyses we investigated the association between the risk of developing an acute myocardial infarction (AMI) and the use of non-steroidal antiinflammatory drugs (NSAIDs) or chronic inflammatory diseases, using data from the British General Practice Research Database (GPRD). Based on the main findings we conclude the following:

1. Patients who currently take NSAIDs have no substantially increased or decreased risk of AMI. Risk estimates for individual NSAIDs were all comparable.
2. The MI risk was increased for a period of several weeks after cessation of NSAIDs, in particular after long-term use and in patients with systemic inflammation (i.e. RA or SLE).
3. There does not seem to be an increased risk of MI among patients using simultaneously aspirin and ibuprofen (or other non-aspirin NSAIDs) compared with aspirin alone.
4. Abrupt discontinuation of the therapy with the investigated NSAIDs may have to be avoided in patients with and without existing chronic inflammatory diseases.
5. The findings support the existence of SLE and RA as risk factors for MI, particularly with simultaneously existing hyperlipidaemia. Early treatment of RA and SLE with disease-modifying antiinflammatory drugs and strong therapy of traditional risk factors (e.g. cholesterol lowering) may decrease the risk of a future MI and the burden of disease.
6. Further research is needed on the effects on selective COX-2 inhibitors on cardiovascular risk. It is of importance to consider the clinical implications within the treatment of patients with chronic inflammatory disease who are at risk for cardiovascular events.

APPENDIX 1

Example of a patient profile in the General Practice Research Database

```
#  353  ID:0069-003658    FAM.ID:0001649 Practice Start:05/01/1989  REG:07/20/1977  PERMANENT
FEMALE  DOB: 01/01/1943  Age in 99: 56  Marit.Stat: ?        DRAWDOWN:02/98  Rxs:  33  Evs:  49  Fds:  26  Dtl:  2

                                                    05/01/1989
51019  09/08/1989    9240    BRUISE LEG                          HAEMATOMA.ADVICED     [O ] ( 927 BL)
52054  07/09/1992    -----   CERVICAL CYTOLOGY EXAMINATION       SMEAR TAKEN           [R ] (L9161  )
52102  08/26/1992    -----   BREAST EXAMINATION                  ADVISED MM            [O ] (Y600 BE)
52102  08/26/1992    -----   THYROXINE ESTIMATION                                      [O ] (L4000TE)
52102  08/26/1992    -----   CERVICAL CYTOLOGY EXAMINATION       SMEAR SENT            [R ] (L9161  )
52149  10/12/1992    -----   CHOLESTEROL CLINIC                  ADVISED RE DIET ETC   [O ] (Y060 JV)
52313  03/25/1993    -----   BLOOD TEST                          T4                    [R ] (L8899  )
52332  04/13/1993     2440   HYPOTHYROIDISM                      BORDERLINE            [O ] ( 244 A )
52531  10/29/1993    -----   THYROID FUNCTION TEST                                     [R ] (L4033F )
52629  02/04/1994     7881   PAIN FOOT                                                 [O ] ( 7871FP)
53019  03/01/1995     7704   VERTIGO                             GONE NOW              [O ] ( 7805A )
53019  03/01/1995     7881   PAIN FOOT                                                 [R ] ( 7871FP)
53028  03/10/1995    -----   BLOOD PRESSURE NORMAL                                     [O ] ( 4010N )
53083  05/04/1995     7881   PAIN FOOT                           BETTER ON IBUPROFEN   [O ] ( 7871FP)
53241  10/09/1995    -----   ADVICE GIVEN                        SC2 RESPITE TCA PRN   [ON] (T3301A )
53241  10/09/1995     7011   KERATOSIS                           BACK FOR EXCISION     [ON] ( 7011K )
53241  10/09/1995     3173   STRESS REACTION                     TSB UNCLE DEMENTED    [ON] ( 307 TR)
53256  10/24/1995    -----   HISTOLOGY                           REQ.                  [RN] (L 161  )
53256  10/24/1995    S 885   EXCISION SKIN LESION                OVER L SCAPULA        [MN] (K914 D )
53264  11/01/1995    S 963   REMOVAL SUTURES                     RETAPED  MM          [O ] (K921 RT)
53264  11/01/1995    -----   BLOOD PRESSURE CHECK                ALLS WELL  MM         [O ] ( 4010C )
53773  03/24/1997    -----   THYROID FUNCTION TEST                                     [R ] (L4033F )
53773  03/24/1997    -----   BLOOD PRESSURE NORMAL                                     [O ] ( 4010N )
53788  04/08/1997     4130   ANGINA EFFORT                       ECG                   [O ] ( 4139E )
53788  04/08/1997     4130   ANGINA                                                    [R ] ( 4139N )

53791  04/11/1997 ----------------------------------------------------------------------------------
53791  04/11/1997 [redacted]                                                         [H ] ( 4109N )
53796  04/16/1997    -----   DISCHARGED FROM HOSPITAL                                  [D ] (T932   )
53796  04/16/1997     4130   ANGINA UNSTABLE                                           [DF] ( 4139U )
53803  04/23/1997    -----   CERTIFICATE MEDICAL INTERMEDIATE    5W                    [O ] (T304   )
53803  04/23/1997     4130   ANGINA                                                    [O ] ( 4139N )
53816  05/06/1997    -----   ATHEROSCLEROSIS PREVENTION CLINIC                         [R ] (Y060 LB)
53816  05/06/1997    -----   MEDICATION STOPPED                  ASPIRIN REVIEW 2 52   [O ] (T914   )
53816  05/06/1997     7817   DYSPEPSIA                                                 [O ] ( 5369CD)
53825  05/15/1997     5301   OESOPHAGITIS                                              [O ] ( 5309A )
 3838  05/28/1997    -----   CERTIFICATE MEDICAL                 4W                    [O ] (T302   )
53847  06/06/1997     5301   OESOPHAGITIS                        NOT SETTLED           [O ] ( 5309A )
53860  06/19/1997    -----   CERTIFICATE MEDICAL FINAL           23 6                  [O ] (T305   )
53860  06/19/1997    -----   BETTER                              CT                    [O ] (T92321A)
53928  08/26/1997    -----   WELL                                STILL SOME DYSPEPSI   [O ] (T9232A )
53928  08/26/1997    -----   FAMILY HISTORY                      POLYCYTHAEMIA         [O ] (T9490  )
53957  09/24/1997    -----   PROPHYLACTIC INOCULATION            BST TETANUS.269250A   [O ] (Y42  AD)
53957  09/24/1997    -----   CERVICAL CYTOLOGY EXAMINATION       TAKEN.MB.             [R ] (L9161  )
53957  09/24/1997    -----   URINE TEST                          NAD.                  [O ] (L7890T )
53957  09/24/1997    -----   BLOOD PRESSURE CHECK                ALL OK.TCA 6M.MB.     [O ] ( 4010C )
54060  01/05/1998     7740   CHEST PAIN                          CENT LEFT.SINCE SAT   [O ] ( 7837B )
54060  01/05/1998    -----   THYROID FUNCTION TEST               RPT. PREV.TSH RAISE   [R ] (L4033F )
54060  01/05/1998    -----   BLOOD PRESSURE CHECK                BP OK.PULSE 56.MB.    [O ] ( 4010C )
54060  01/05/1998     4130   ANGINA                              NOW SETTLED           [O ] ( 4139N )
54060  01/05/1998    -----   ECG                                 PERFORMED.MB.         [O ] (D2600  )

09/22/2000  13:52        Patient with First-Time Myocardial Infarction On or After 1/1/95        Page 358
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APPENDIX 2

ASCII-file for the MI-study

patient ID	
set number	
case-control status	0=control, 1=case
age at index date	continuous
sex	1=male, 2=female
index date	
height in cm	at anytime in the profile after age 20; first choice is closest prior to the index date; second choice anytime after the index date; if not available at all, record 0
weight in kg	closest recording prior to the index date; if not available before index date, record 0
smoking status	0=non, 1=current, 2=past, 9=unknown prior to index date
died at index date	0=no, 1=yes, based on OXMIS code for death within (plus/ minus) 1 week of the index date
history of hypertension	1=yes anytime prior to the index date, 2=yes if first-time diagnosis (ICD-code ICD 400.x - 403.x) is recorded within 6 months after index date, or 0 if not before and not within 6 months after index date.
history of diabetes	1=yes anytime prior to the index date, 2=yes if first-time diagnosis (ICD-code ICD 250.x) is recorded within 6 months after index date, or 0 if not before and not within 6 months after index date.
history of hyperlipidemia	1=yes anytime prior to the index date, 2=yes if first-time diagnosis (ICD-code ICD 272.x) is recorded within 6 months after index date, or 0 if not before and not within 6 months after index date.
prescription for insulin	1=yes anytime prior to the index date, 2=yes if a BCDSP-code 2103, 2104, 2106, 2107, 2112, 2119, 2124, 2125, 2128, 2129, 2136, 2138, 2141, 2144, 2145, 2146, 2149, 2151, 2152, 2154, 2155, 2156, 2158 ir recorded for the first time within 6 months after the index date, or 0 if not before and not within 6 months after index date.
prescription for oral antidiabetics	1=yes anytime prior to the index date, 2=yes if first-time prescription for 2116 (Glibenclamide), 2148 (Gliclazide), 2159 (Glimepiride), 2139 (Glipizide), 2140 (Gliquidone), 2122 (Metformin), 7762001 or 7762002 (Pioglitazone), 2160 (Troglitazone), 10236001 or 10236002 or 8075003 Rosiglitazone, 8075001 or 8075002 or 8075003 (Repaglinide), 2157 (Acarbose) is recorded within 6 months after index date, or 0 if not before and not within 6 months after index date.
prescription for lipid-lowering drugs	1=yes anytime prior to the index date, 2=yes if first-time prescription for 19103 (Simvastatin), 1214 (Pravastatin), 1218 (Atorvastatin), 1217 (Fluvastatine), 1219 (Cerivastatin), 1201 (Clofibrate), 1208 (Bezafibrate), 1213 (Fenofibrate), 1215 (Gemfibrozil), 1216 (Ciprofibrate) is recorded

	within 6 months after index date, or 0 if not before and not within 6 months after index date.
history of ischaemic heart disease	0=no; if yes (ICD-code 410.x-414.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date
ischemic heart disease ICD-code	0=no; if yes (ICD-code 410.x-414.x) at anytime prior to the index date, record the ICD-code (4 digits, e.g. 4105) of the last recording prior to the index date.
history of cardiac arrhythmias	0=no; if yes (ICD-code 415.x-416.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile prior to the index date.
arrhythmias ICD-code	0=no; if yes (ICD-code 415.x-416.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of congestive heart failure	0=no; if yes (ICD-code 427.x or 429.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
congestive heart failure ICD-code	0=no; if yes (ICD-code 427.x or 429.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of stroke	0=no; if yes (ICD-code 433.x-438.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
stroke ICD-code	0=no; if yes (ICD-code 433.x-438.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of arterial thromboembolism	0=no; if yes (ICD-code 444.x-445.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
arterial thromboembolism ICD-code	0=no; if yes (ICD-code 444.x-445.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of venous thromboembolism	0=no; if yes (ICD-code 451.x-453.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the prfile and the index date.
venous thromboembolism ICD-code	0=no; if yes (ICD-code 451.x-453.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of intermittent claudication	0=no; if yes (OXMIS-code 4439A) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
history of pulm. heart disease	0=no; if yes (ICD-code 426.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
pulm. heart disease ICD-code	0=no; if yes (ICD-code 426.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of asthma	0=no; if yes (ICD-code 493.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
asthma ICD-code	0=no; if yes (ICD-code 493.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last

	recording prior to the index date.
history of COPD	0=no; if yes (ICD-code 496.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
COPD ICD-code	0=no; if yes (ICD-code 496.x) at anytime prior to the index date, record the ICD-code (4 digits) of the last recording prior to the index date.
history of renal disease	0=no; if yes (ICD-code 447.x, 580.x-586.x, 590.x, 591.x, 593.x, 753.-x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
renal disease ICD-code	0=no; if yes (ICD-code 447.x, 580.x-586.x, 590.x, 591.x, 593.x, 753.-x) at anytime prior to the index date, record the ICD-code of the last recording prior to the index date.
history of connective tissue disorders	0=no; if yes (ICD-code 446.x, 695.4, 701.0, 711.x, 712.x, 716.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
conn. tissue disease ICD-code	0=no; if yes (ICD-code 446.x, 695.4, 701.0, 711.x, 712.x, 716.x) at anytime prior to the index date, record the ICD-code of the last recording prior to the index date.
history of abdominal bleeding	0=no; if yes (ICD-code 781.5, 782.0, 782.7) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
abdominal bleeding ICD-code	0=no; if yes (ICD-code 781.5, 782.0, 782.7) at anytime prior to the index date, record the ICD-code of the last recording prior to the index date.
history of buccal inflammation	0=no; if yes (ICD-code 523.x) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
buccal inflammation ICD-code	0=no; if yes (ICD-code 523.x) at anytime prior to the index date, record the ICD-code of the last recording prior to the index date.
history of gout	0=no; if yes (ICD-code 274.0) at anytime prior to the index date, record the number of days between the first-time diagnosis in the profile and the index date.
practice visits ever	number of practice visits prior to the index date (count only visits at separate dates) from the beginning of the active prescription history, and record it as a continuous variable for each subject. Do not include the index date itself in the count, and do not include „historical“ entries (i.e. before the first non-finding drug date).
practice visits last year	number of practice visits in the last 365 days preceding the index date (count only visits at separate dates), continuous variable for each subject. Don't include index date in count.
prescription history	the number of days of prescription history, i.e. the number of days from the first prescription in the profile up to the index date (continuous variable).
history of chest infection	if a code for chest infection was recorded at or prior to the index date, please record the number of days between the last infection prior to the index date and the index date itself. If the last infection is recorded at the index date, record 1. If there is no such code at any time prior to the index date, record 0.

	ICD	460.x - 470.x
	ICD	480.x - 486.x
	ICD	489.x - 491.x
	ICD	779.3
	OXMIS	5199E
	OXMIS	5199RN

code of this chest infection	please record the OXMIS-code of the last infection prior to the index date. If no such infection, record again 0.

For all the following individual drugs or drug groups (an individual drug or a drug group has a title printed bold and in capitals), please record the following 4 variables:

- number of prescriptions prior to the index date
- number of days between the first prescription in the profile for any drug (=start of active recording) and the first prescription for this drug (please record 1 if the first prescription for the study happens to be the first study drug in the profile ever, and 0 if there is no prescription prior to the index date for this drug)
- number of days between the last prescription for this drug prior to the index date and the index date (if no prescription at all, or if the first prescriptions is at the index date itself, record 0)
- ppa-code of the last prescription prior to the index date

ACETYLSALICYLIC ACID	902, 4902, 4908
CELECOXIB	4824
ROFEXOCIB	4823
PARACETAMOL	941, 946, 4995, 5002, 5092

OTHER NSAIDs

• Acemetacin	4812
• Diclofenac	4816 / 16235
• Diflunisal	5047
• Etodolac	4804
• Fenbufen	5071
• Fenoprofen	5049
• Flurbiprofen	5081
• Ibuprofen	4817 / 4980
• Indomethacin	956 / 20913
• Ketoprofen	5006
• Mefenamic acid	955
• Nabumetone	4802
• Naproxen	4813 / 5034
• Piroxicam	5055
• Sulindac	16236
• Tenoxicam	4801
• Tiaprofenic acid	4803

SSRIs

• citalopram	4158
• fluoxetine	4149
• fluvoxamine	4152
• paroxetine	4154
• sertraline	4155
• venlafaxine	4157

NON-SSRI ANTIDEPRESSANTS

• Amitriptyline	4117
• Clomipramine	4122
• Dothiepin	4133
• Doxepin	13535
• Imipramine	13510
• Lofepramine	4147
• Nefazodone	4160
• Trazodone	4142
• Trimipramine	4123

OTHER ANTIDEPRESSANTS

- Amoxapine 4144
- Desipramine 4114
- Lithium 4116
- Maprotiline 4131
- Mianserin 4137
- Moclobemide 4156
- Nortriptyline 4119
- Protriptyline 4106

BETA-2-AGONISTS

- Fenoterol 6604
- Fenoterol w Ipratropium 6619
- Reproterol 6637
- Salbutamol 6565
- Salbutamol w Ipratropium 6664
- Terbutaline 6582
- Terbutaline w Guaiphenesin 6648
- Tulobuterol 6658
- Bambuterol 6662
- Eformoterol 6598
- Salmeterol 6657
- Isoproterenol 6507, 6545, 6595
- Pirbuterol 6628
- Rimiterol 6652
- Metaproterenol 6559

XANTHINES

- Aminophylline 6503
- Theophylline 6539, 6649

ANTICHOLINERGICS

- Ipratropium brom 6650
- Oxitropium 6659

MASTCELL-STABILIZERS

- Sodium Cromoglycate 6555
- Sodium Cromoglycate w Salbutamol 6663
- Sodium Cromoglycate w Isoprenalin 6647
- Nedocromil sodium 6653

STATINS

- Atorvastatin 1218
- Cerivastatin 1219
- Fluvastatin 1217
- Pravastatin 1214
- Simvastatin 19103

FIBRATES

- Clofibrate 1201
- Bezafibrate 1208
- Fenofibrate 1213
- Gemfibrozil 1215
- Ciprofibrate 1216

OTHER LIPID-LOWERING AGENTS

- Colestipol 1204
- Cholestyramine 12203
- Acipimox 1211
- Niacin/Nicot Ac. 14511

ESTROGENS UNOPPOSED

- 7703 / 7720 / 7723 / 7731 / 7735 / 7752 / 7755

ESTROGENS UNOPPOSED

- 7743 / 7747 / 7753 / 7761 / 7762 / 7763 / 7764 / 7765 / 7766 / 8955 / 8957

In addition: if any of the unopposed estrogens is used in combination with 7727 or 7729 within 365 days of the last prescription for the estrogen before the index date, it is also opposed estrogen use.

ANTIPSYCHOTICS

• Chlorpromazine	13501, 13561, 2150 (with phenformin)
• Thioridazine	13506
• Pericyazine	13564
• Methotrimeprazine	944
• Pipothiazine	23515
• Promazine	13514, 13538 (with meprobamate)
• Trifluoperazine	13508
• Prochlorperazine	2317
• Zuclopenthixol	13576
• Flupentixol	13588
• Benperidol	23513
• Haloperidol	13519
• Droperidol	13554
• Sertindole	23519
• Sulpiride	13584
• Clozapine	4135
• Chlormethiazole	9149
• Loxapine	23505
• Pimozide	13518
• Risperidone	23517

BENZODIAZEPINES

• Alprazolam	4143
• Bromazepam	13595
• Clobazam	23502
• Clonazepam	1724
• Clorazepate potassium	13566
• Diazepam	13546
• Flurazepam	9140
• Flunitrazepam	9184
• Ketazolam	23514
• Loprazolam	19102
• Lorazepam	13569
• Lormetazepam	9189
• Midazolam	23508
• Nitrazepam	9124
• Oxazepam	13550
• Temazepam	9183
• Triazolam	9185

ALLOPURINOL 13603

MACROLIDES

Erythromycin	3715, 3773, 3795, 3837, 3838
Clarithromycin	23887
Azithromycin	23888

TETRACYCLINES

Tetracycline	3741, 3823, 23882, 3704
Doxycycline	3792
Minocycline	3834
Demeclocycline	3714
Lymecycline	3824

SULFONAMIDES

Cotrimoxazol SMX/TMP	3814
Sulfasalazine	3790
Trimethoprime	3834

QUINOLONES

Ciprofloxacine	23876
Ofloxacine	23886
Norfloxacine	23843
Levofloxacine	33708
Cinoxacin	23838
Enoxacin	23862
Temafloxacin	23889

PENICILLINS

Ampicilline	3702
Penicilline	3731, 3819
Dicloxacilline	3770, 3755
Peni V	3784
Amoxicilline	3843
Pivampicilline	3847
Floxacillin	3863
Bacampillin	23801
Amox / clav	23829
Pivampicillin / pivmecillin	23860

CEPHALOSPORINS

Cephalexin	3816
Cefadroxil	23817
Cefaclor	23820
Cefixime	23884
Cefpodoxime	23897
Cephradine	3126

CLINDAMYCIN 3815

For the following corticosteroids, we need to separate oral from inhaled use. Thus, we have to take ppa-codes rather than BCDSP-codes alone. Please note that you have used the same list when you programmed the ASCII-file for the study on fractures and corticosteroids.

INHALED STEROIDS

BECLOMETHASONE DIPROPIONATE (6345) including the following ppa-codes:

80701
80801
576601
576603
576801
5777001
577101
577102
577105
577106
577109
577110
577111
577116
577119
577120
577121
577122
577701
577801
584101
584102
584103
584104
584105
584106
584107
584108
584109
584112
584113

584199
584401
584601
5771114
8501387
8501388
8501389
8502624
8502625
8502626
8502780
9900347
9900558
9900655
9901307
9901308
9901309
9910526
9910529
9910530
9910640
9910650
9910672
9910673
9910674
9910675
9910706
9910707
9910708
9910812
9910813
9910814
9910815
9911159
9911160
9911161

BUDESONIDE (6620) including the following ppa-codes:

849601
849602
849603
849604
849616
5938601
5938602
5938603
5938604
5938605
5938606
5938701
5938702
8496106
9900042
9900043
9900298
9900299
9900551
9910459
9910460
9911123

BECLOMETHASONE W SALBUTAMOL (6635) including the following ppa-codes:

578301
3433909
3438501
7636601
7636602
7636603
9910966

FLUTICASONE (6661) including the following ppa-codes:

2614407

2614408
2614409
2659608
2659609
2659610
2659614
2659616
2659617
2659619
2659620
2659621
2659622
9901113
9901114
9901115
9901116
9901117
9901118
9901119
9901120
9901121
9901122
9901123
9901124
9910482
9910483
9910485
9910841
9910842
9910843
9910844

ORAL STEROIDS

BETAMETHASONE (6301) including the following ppa-codes:
682110
682502
682503
686301
686601
693101
694104
CORTISONE (6303) including the following ppa-codes:
1491101
1495601
1495602
1496102
1496103
1496401
1497101
1497102
1498102
1498103
1499101
HYDROCORTISONE (6306) including the following ppa-codes:
1487101
3237130
3237131
3238706
3254107
3256103
3256104
METHYLPREDNISOLONE (6308) including the following ppa-codes:
4403103
4403104
4403105
4514101
4514111
4514112

4514113
4514114
9900607

PREDNISOLONE (6311) including the following ppa-codes:

1731101
1731102
1731103
1738101
1742101
1742102
1742103
1744102
1744103
1744105
1744107
5793101
5793102
5793103
5793301
5794101
5795106
5795107
5795109
5795110
5795111
5795112
5795202
5795501
5795701
5796503
5796504
5796902
5799901
5803107

PREDNISONE (6312) including the following ppa-codes:

5800101
5800102
5800701
5800901
5802301
5802401

DEXAMETHASONE (6333) including the following ppa-codes:

1723103
1723104
1791101
1791102
1791103
1793102
1793103
1793104
1793301
5183102
5183103
5183104
9901155

FLUDROCORTISONE (6335) including the following ppa-codes:

2617101
2617103
2623801
2623802
2623803
2623804
2624101
2624102
2624301
2624501

PREDNISOLONE STEAGLATE (6344) including the following ppa-codes:

5799601
6585101

BETAMETHASONE SOD PHOSPHATE (6349) including the following ppa-codes:
682111
684104
BUDESONIDE (6360 or 6620) including the following ppa-codes:
2231901
849617

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