Taking Care

NSAIDs in the treatment of musculoskeletal complaints in primary care

Aafke R. Koffeman

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TAKING CARE
NSAIDS IN THE TREATMENT OF MUSCULOSKELETAL COMPLAINTS IN PRIMARY CARE

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CONTENT

Chapter 1
General introduction

Musculoskeletal complaints

Musculoskeletal complaints form a common problem in the general population. A 2006 study into self-reported chronic complaints of the musculoskeletal system found a prevalence of around 40%. When asked whether any musculoskeletal pain had been experienced over the past 14 days, around 60% of respondents answered yes.[1] It is unsurprising, therefore, that musculoskeletal disorders form the most common reason for consulting the general practitioner (GP) in the Netherlands. In 2001 the incidence of musculoskeletal disorders in GP practices was 267 per 1000 patients, and the prevalence 397 per 1000. These increased with age, with an estimated incidence of 350 per 1000 and prevalence of 600 per 1000 in patients over 75 years of age.[1] In the UK, musculoskeletal problems account for 14% of all primary care consultations, and each year at least a quarter of the registered population consult their GP for a musculoskeletal complaint.[2] The types and severity of complaints presented vary greatly. The majority are mild and self-limiting in nature, but chronic conditions such as osteoarthritis are also common.[1 3] The one common feature that these various musculoskeletal disorders share is that their most burdensome component is pain.

Depending on the type of complaint presented, there are various treatment options available to the GP. Non-pharmaceutical interventions, such as physiotherapy, tend to be targeted at improving function and reducing fear of movement. In many cases, the GP will also wish to prescribe an analgesic aimed at reducing the pain associated with the complaint. Treatment guidelines recommend a stepped approach to such analgesic therapy. Paracetamol is recommended as a first step, as it is effective in many painful conditions and is considered relatively safe. When paracetamol fails, GPs can prescribe non-steroidal anti-inflammatory drugs (NSAIDs).[4-10]

Non-steroidal anti-inflammatory drugs

NSAIDs are a group medicines with analgesic, anti-inflammatory and anti-pyretic properties. They inhibit the action of the cyclooxygenase (COX), which is a central enzyme in the synthesis of prostaglandins. Prostaglandins play an important role in the pain process, causing local vasodilatation and oedema, and leading to increased sensitivity of sensible nerve ends. Various isoforms of cyclooxygenase exist, of which COX-1 and COX-2 have been studied the most extensively. COX-1 is thought to be responsible for the production of prostaglandins with a general regulating function, such as autoregulation of renal perfusion and gastroprotection. This isoform is present in most body tissues and does not play a major role in pain awareness. COX-2, on the other hand, is only present in certain tissues under normal circumstances. Its concentration in other cells increases strongly during inflammatory processes, and it is thought to play an important role in pain processes. Traditional non-selective NSAIDs such as ibuprofen, naproxen and diclofenac, inhibit the

action of both cyclooxygenase isoforms. More recently, selective COX-2 inhibitors (coxibs), such as etoricoxib and valdecoxib, have been developed.[11]

Adverse effects of NSAIDs

The use of NSAIDs is known to be associated with various unintended adverse effects. These adverse effects can be severe, leading to hospitalization and even death. Two Dutch studies examining the occurrence of avoidable hospital admissions due to adverse events of medication, found NSAIDs to be one of ten groups of medications responsible for half of such avoidable hospital admissions.[12-14]

Gastrointestinal events

The most important and well-known adverse drug reaction (ADR) associated with NSAID use is the occurrence of peptic ulcer disease and its complications, most notably upper gastrointestinal bleeding, obstruction and perforation.[15 16] Many risk factors which lead to an increase of such upper gastrointestinal events have been identified, including increasing age, a history of peptic ulcer or ulcer complication, concomitant use of ulcerogenic drugs such as antithrombotics, corticosteroids and selective serotonin-reuptake inhibitors, and a history of diabetes mellitus, heart failure and severe rheumatoid arthritis.[14] In order to reduce the risk of gastrointestinal complications in patients prescribed NSAIDs, guidelines have been developed with recommendations regarding the prescription of these drugs and preventive measures which can be taken to reduce the risk, such as concomitant prescription of a gastroprotective agent or prescription of a coxib.[17 18]

Ischaemic cardiovascular events

Over the course of the last decade, it was discovered that use of NSAIDs is also associated with ischaemic cardiovascular events. This association was first found in several large trials assessing the efficacy and safety of rofecoxib.[19] As a result, rofecoxib was taken off the market in 2004. Since then, however, it has been demonstrated that not only coxibs, but also traditional non-selective NSAIDs are associated with an increased risk of myocardial infarction and stroke.[20-23] As of yet, no national guideline has been published specifically on this topic, but a consensus report published in definitive form in 2009 warned against this risk of ischaemic adverse events and recommended avoiding NSAIDs in patients with a prior ischaemic cardiovascular history.[14]

Renal insufficiency and heart failure

Other adverse events known to be associated with NSAID use include a deterioration of renal function and heart failure.[14 24-26] The use of NSAIDs is therefore contraindicated in patients with severe chronic renal insufficiency and in those with heart failure.[27 28]

Non-serious adverse events

In addition to the serious adverse events described above, NSAIDs are associated with non-serious adverse drug reactions, such as dyspepsia, diarrhoea and dyspnea. In randomized controlled trials (RCTs) these complaints have been shown to frequently occur.[11] These RCTs consist of select populations of relatively healthy patients, however, and don't correspond with the population of patients seen by the GP.

Over-the-counter NSAIDs

In many countries, including the Netherlands, NSAIDs are available without prescription, or over-the-counter (OTC). In general, short-term use of NSAIDs is considered relatively safe, provided it is used in OTC-doses by adults without contraindications or interacting medications.[29] However, previous studies have shown that OTC NSAIDs are often used in high dosages and by people with a contraindication for use.[30 31] A consensus report published in 2009, aimed at reducing the number of medication-related hospital admissions, contained the general recommendation to consider a 'Pharmacy Only' status for OTC NSAIDs.[14] This would still allow people to purchase NSAIDs without prescription, but only at pharmacies. As a consequence, the Dutch Medicines Evaluation Board reconsidered the legal status of OTC products of NSAIDs, and changed the status of high dose NSAIDs and large package sizes to 'Pharmacy Only'.[32] However, lower doses of these drugs and smaller package sizes are still freely available in drugstores in the Netherlands and, in the case of ibuprofen 200mg, in supermarkets.

Outline of this thesis

This thesis aims to provide an insight into various efficacy and safety aspects of NSAIDs in primary care patients with musculoskeletal complaints. **Chapter 2** provides a literature review of the efficacy of NSAIDs versus placebo and paracetamol, in musculoskeletal complaints common in primary care. In **chapter 3** we focus on the prescribing behaviour of GPs, examining the frequency of NSAID prescription in patients with various types of musculoskeletal complaints. In particular, we examine the prescription of these drugs in patients with a high risk of ischaemic cardiovascular events, over the course of the last decade in which knowledge about these effects first became available. In **chapter 4**, we examine how often patients who are treated with an NSAID by their GP because of a musculoskeletal complaint, subsequently consult their GP because of a non-serious adverse drug reaction. **Chapter 5** examines the effect of guidelines on the prescribing behaviour of GPs, by comparing the frequency of gastropreventive measures in high-risk patients prescribed NSAIDs to those prescribed lowdose acetylsalicylic acid. The use of over-the-counter NSAIDs is investigated in **chapter 6**, both in the general population and in patients with a high risk of developing an adverse drug reaction. Finally, in **chapter 7**

the key findings of the previous chapters are summarized and discussed in the context of current knowledge and evidence, and directions for future research are provided.

REFERENCES

1. Van der Linden MW, Westert GP, De Bakker DH, Schellevis FG. Second national survey of general practice. Morbidity in the population and in general practice. [Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk]. Utrecht/Bilthoven: NIVEL/RIVM; 2004. Available at: http://www.nivel.nl/sites/default/files/bestanden/ns2_r1_h02.pdf.
2. Jordan KP, Kadam UT, Hayward R, Porcheret M, Young C, Croft P. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC Musculoskelet Disord* 2010;11:144.
3. Rijksinstituut voor Volksgezondheid en Milieu. National Compass Public Health. Diseases of the musculoskeletal system. [Nationaal Kompas Volksgezondheid. Ziekten van het bewegingsstelsel en bindweefsel]. Available at: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/bewegingsstelsel-en-bindweefsel/.
4. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15:S192-300.
5. Chavannes AW, Mens JMA, Koes BW, Lubbers WJ, Ostelo R, Spinnewijn WEM, et al. NHG guideline non-specific low back pain. [NHG-standaard aspecifieke lagerugpijn]. *Huisarts Wet* 2005;48:113-23.
6. Conaghan PG, Dickson J, Grant RL, Guideline Development G. Care and management of osteoarthritis in adults: summary of NICE guidance. *BMJ* 2008;336:502-3.
7. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014 Jan 24 [Epub ahead of print].
8. Van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J* 2006;15:S169-91.
9. Winters JC, Van der Windt DAWM, Spinnewijn WEM, De Jongh AC, Van der Heijden GJMG, Buis PAJ, et al. NHG guideline shoulder complaints. [NHG-standaard schouderklachten]. *Huisarts Wet* 2008;51:555-65.
10. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
11. Health Care Insurance Board (CVZ). Pharmacotherapeutic compass. [Farmacotherapeutisch kompas]. Diemen: CVZ; 2013. Available at: http://www.fk.cvz.nl.
12. van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. *Pharmacoepidemiol Drug Saf* 2008;17:365-71.
13. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, Group HS. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008;168(17):1890-6.
14. Warlé-Van Herwaarden MF KC, Sturkenboom MCJM, Van den Bemt PMLA, De Smet PAGM. Targeting outpatient drug safety: recommendations of the Dutch Harm-Wrestling Task Force. Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie; 2010.

Available at: http://www.knmp.nl/downloads/medicijnen-zorgverlening/medicatieveiligheid/rapport-harm-wrestling-english.pdf.

15. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
16. Hernandez-Diaz S, Rodriguez LA. Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-99.
17. The Dutch Institute for Health Care Improvement CBO. Guideline NSAID use and prevention of gastric damage. [NSAID-gebruik en preventie van maagschade]. Utrecht: The Dutch Institute for Health Care Improvement CBO; 2003. Available at: http://www.cbo.nl/Downloads/259/richtlijnnsaid.pdf.
18. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:728-38.
19. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-1102.
20. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.
21. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011;8:e1001098.
22. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
23. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf. 2011;20:1225-36.
24. Evans JM, McGregor E, McMahon AD, McGilchrist MM, Jones MC, White G, et al. Non-steroidal anti-inflammatory drugs and hospitalization for acute renal failure. *Qjm* 1995;88(8):551-7.
25. Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Arch Intern Med* 2002;162(3):265-70.
26. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis* 2005;45(3):531-9.
27. De Grauw WJC, Kaasjager HAH, Bilo HJG, Faber EF, Flikweert S, Gaillard CAJM, et al. National Transmural Consensus Chronic Renal Insufficiency. [Landelijke Transmurale Afspraak Chronische Nierschade]. *Huisarts Wet* 2009;52(12):586-97.
28. Hoes AW, Walma EP, Rutten FH, Twickler TB, Rohling R, Jansen RWMM, et al. Multidisciplinary guideline heart failure. [Multidisciplinaire richtlijn hartfalen]. The Dutch College of General Practice, the Dutch Society for Cardiology and the Dutch College of Internal Medicine; 2010. Available at: http://www.cbo.nl/Downloads/1081/rl_hartfalen_2010.pdf.
29. Moore N, Van Ganse E, Le Parc JM, Wall R, Schneid H, Fahran M, et al. The PAIN Study: Paracetamol, Aspirin and Ibuprofen New Tolerability Study. A large scale randomised clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. *Clin Drug Invest* 1999;18(2):89-98.

30. French DP, James DH. Reasons for the use of mild analgesics among English students. *Pharm World Sci* 2008;30(1):79-85.
31. Stosic R, Dunagan F, Palmer H, Fowler T, Adams I. Responsible self-medication: perceived risks and benefits of over-the-counter analgesic use. *Int J Pharm Pract* 2011;19:236-45.
32. Motivation for classification system of legal status of supply for anti-inflammatories (NSAIDs) and acetylsalicylic acid, defined by the MEB on 2 July 2009. The Hague: Medicines Evaluation Board; 2010. Available at: http://www.cbg-meb.nl/NR/rdonlyres/D97C7481-5C4E-4488-851C-A3D3DE371DCB/0/UKMotiveringNSAIDs20090820.pdf.

Chapter 2
The efficacy of non-steroidal anti-inflammatory drugs in musculoskeletal disorders common in primary care: an overview of the evidence

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(under review)

ABSTRACT

Background

Much research has been performed into the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) in specific musculoskeletal disorders, but an overview of the evidence is lacking.

Methods

We searched Pubmed and Embase for systematic reviews of randomized clinical trials (RCTs) assessing the efficacy of oral NSAIDs versus placebo or paracetamol, in the treatment of musculoskeletal disorders commonly presented in primary care. Outcomes of interest were pain and proportion improved. For pain the magnitude of group differences was classified as negligible, small, moderate, or large, for improvement the number needed to treat (NNT) was calculated where possible.

Findings

Our search yielded 5370 studies, 58 systematic reviews met our inclusion criteria. 19 reviews, including studies on neck pain and shoulder disorders, did not find any RCTs. The remaining 39 reviews presented results of 122 RCTs, 22 reviews reported sufficient data to assess magnitudes of effect. Most reviews focused on NSAIDs versus placebo. Results for pain varied greatly, a moderate group difference was found in some reviews, but the majority found a small difference or no significant difference versus placebo. NNT for improvement ranged from 4 to 10 for NSAIDs compared to placebo. For paracetamol as a comparison, only reviews on low back pain and osteoarthritis were found, the majority of these found a small group difference for pain in favour of NSAIDs. NNT for improvement ranged from 5 to 9 for NSAIDs versus paracetamol.

Interpretation

For many musculoskeletal conditions common in primary care, the efficacy of NSAIDs compared to placebo or paracetamol appears to be limited. For some highly prevalent conditions evidence from RCTs on NSAID efficacy is lacking. Considering the potential harms of NSAID treatment, these findings suggest a smaller role for NSAIDs in the treatment of musculoskeletal pain in primary care may be more appropriate.

INTRODUCTION

Musculoskeletal disorders form a common problem in the general population, with a prevalence of self-reported chronic complaints of around 40%.[1] Disorders of the musculoskeletal system are the most common reason for consulting the general practitioner (GP). In 2001 the incidence of musculoskeletal disorders in Dutch GP-practices was 267 per 1000 patients, and the prevalence 397 per 1000.[1] In the UK, musculoskeletal disorders account for 14% of all primary care consultations, and each year at least a quarter of the registered population consult their GP for a musculoskeletal disorder.[2]

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory properties and are frequently used in the treatment of musculoskeletal disorders. Around a quarter of patients newly consulting their GP for a musculoskeletal disorder are prescribed an NSAID.[3] In addition, musculoskeletal pain forms one of the main reasons for over-the-counter use of NSAIDs, especially in older adults.[4] The use of NSAIDs is associated with the occurrence of serious adverse drug reactions (ADRs), particularly of the gastrointestinal, cardiovascular, and renal tract.[5-12] Thus, careful weighing of the benefits and harms of NSAIDs is required. Treatment guidelines have been developed for various musculoskeletal disorders, such as back pain, shoulder pain, and osteoarthritis, and many recommend paracetamol as a first choice analgesic, advising NSAIDs only if treatment with paracetamol fails.[13-18]

Much research has been performed into the efficacy of NSAIDs in specific musculoskeletal disorders, but a full overview of the evidence for musculoskeletal disorders is lacking. The objective of this systematic review is to summarize and review the available evidence on the efficacy of oral NSAIDs in the treatment of musculoskeletal disorders commonly presented in primary care, compared to placebo or paracetamol. Considering the broad scope of this overview, only systematic reviews of RCTs will be included.

METHODS

Protocol

Methods were specified in advance and documented in a protocol (not published, available on request).

Criteria for considering studies for this review

Types of studies

Systematic reviews of RCTs published between January 1st 2000 and 28th November 2013 were included. If several reviews were found on one topic, these were all included, unless

it concerned updated versions of one review, in which case only the most recent version was included. Systematic reviews of systematic reviews were not included in this study, but their content was evaluated to establish which systematic reviews they included.

Types of participants

Subjects aged 16 or over were included. All types of painful musculoskeletal disorders commonly treated in primary care were included, including disorders of the neck, back, upper extremity, lower extremity and osteoarthritis. Both hospital-based and community-based studies were eligible for inclusion, as were studies involving only a subset of the population (e.g. elderly).

Excluded were studies on types of arthritis other than osteoarthritis, such as rheumatoid arthritis, as these are generally referred to secondary care for treatment, and studies on bone diseases (such as osteoporosis), malignancies, and congenital musculoskeletal malformations.

Types of intervention

Any dosage amount of NSAIDs administered via oral route. All types of NSAIDs, including cyclo-oxygenase inhibitors (coxibs), were included. Additional interventions were not allowed. For example, studies comparing NSAIDs plus physiotherapy to one of the comparisons mentioned below were excluded.

Types of comparison

Included were placebo and any dosage amount of paracetamol.

Types of outcomes

Included outcome measures were pain (pain severity on a pain scale) and proportion of patients improved. All types of patient improvement measures were eligible, including those defined according to responder criteria, and those based on self-reported improvement. Other outcomes such as function, return to work, and adverse events were not considered for inclusion.

Search strategy for identification of studies

We performed a literature search in Medline and Embase. The search terms used are shown in appendix I. In addition, references of identified systematic reviews and of other potentially relevant studies were screened. Papers published in English or Dutch were eligible.

Data collection and analyses

Study selection

Two independent reviewers (AK and PL) selected the studies. Title and abstract were screened, and subsequently full reports were retrieved and assessed on final eligibility. Any disagreements that arose between the reviewers were resolved through a consensus meeting.

Methodological quality assessment

Two independent reviewers assessed the methodological quality of each study selected for inclusion. We divided the studies across all authors so they did not assess any studies they co-authored. Any disagreements were resolved through a consensus meeting. Assessment of methodological quality was performed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (box 1).[19] The AMSTAR tool is an 11-item instrument that addresses key domains in methodological quality of systematic reviews.[19] It has been shown to have good inter-observer agreement, reliability and construct validity.[20 21] After quality assessment, the initial interobserver agreement for all items was evaluated by calculating Cohen's kappa.

Box 1. AMSTAR evaluation of methodological quality[19]

AMSTAR items
1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

AMSTAR: assessment of multiple systematic reviews.

Data extraction and synthesis

Data extraction was performed by AK and checked by a second reviewer (PL). For each included systematic review, we extracted data on the type of musculoskeletal disorder (diagnosis), number of included RCTs and subjects, conduct of a meta-analysis, and duration of follow-up (immediate follow-up: < 2 weeks; short-term follow-up: 2-6 weeks; long-term follow-up: > 6 weeks). If the authors of the systematic review performed a quality assessment, these scores as reported in the review were recorded. The prescribed

daily dosage (PDD) of the NSAID studied was also recorded where possible. This PDD was then divided by the defined daily dosage (DDD) of the NSAID studied, so that the dosage of the NSAID given could be expressed as the number of DDDs for each study. For studies with paracetamol as a comparison, the same was done for the PDD of paracetamol. Finally, where possible, quantitative results on pain and on the proportion of patients improved were extracted from the systematic reviews. For studies reporting on pain on a scale other than a 100-point scale, the standardized mean difference (SMD) was calculated if sufficient data were available. For those systematic reviews providing quantitative results on pain as a continuous outcome, the magnitude of the group difference found was classified by us as negligible, small, moderate, or large, according to the definitions shown in box 2.[22 23] For the outcome proportion of patients improved, the number needed to treat (NNT) was calculated where possible.

Box 2. Definitions for estimating magnitude of group difference[22 23]

Size of group difference	Mean improvement on 100-point VAS or equivalent	SMD/ES
Negligible	< 5-points	< 0.2
Small	5- to 10-points	0.2-0.49
Moderate	10- to 20-points	0.5-0.79
Large	> 20-points	≥ 0.8

ES: effect size; SMD: standardised mean difference; VAS: visual analogue scale.

RESULTS

Study selection

The initial search yielded 5370 studies, 5052 were screened on title and abstract and 233 papers were assessed for eligibility in full-text (figure 1). Of these, 175 did not meet our inclusion criteria, including 23 systematic reviews of systematic reviews.[22 24-45] Two Cochrane reviews could not be included because they had been withdrawn and updated versions have not yet been published.[46 47] In total, 58 systematic reviews were included. However, 19 of these did perform a search meeting our inclusion criteria for population, intervention, comparison and outcomes, but did not find any RCTs (figure 1).[48-64] Data could therefore only be extracted from the remaining 39 systematic reviews.[65-103]

Methodological quality of included studies

The AMSTAR scores of the included systematic reviews are shown in table 1. Total quality scores varied widely, from 0 to 9 out of 11. The authors agreed on 81% of the AMSTAR items scored, Cohen's kappa for inter-observer agreement was 0.62. The inter-observer agreement was also determined per AMSTAR item. It was highest for AMSTAR item 7, with

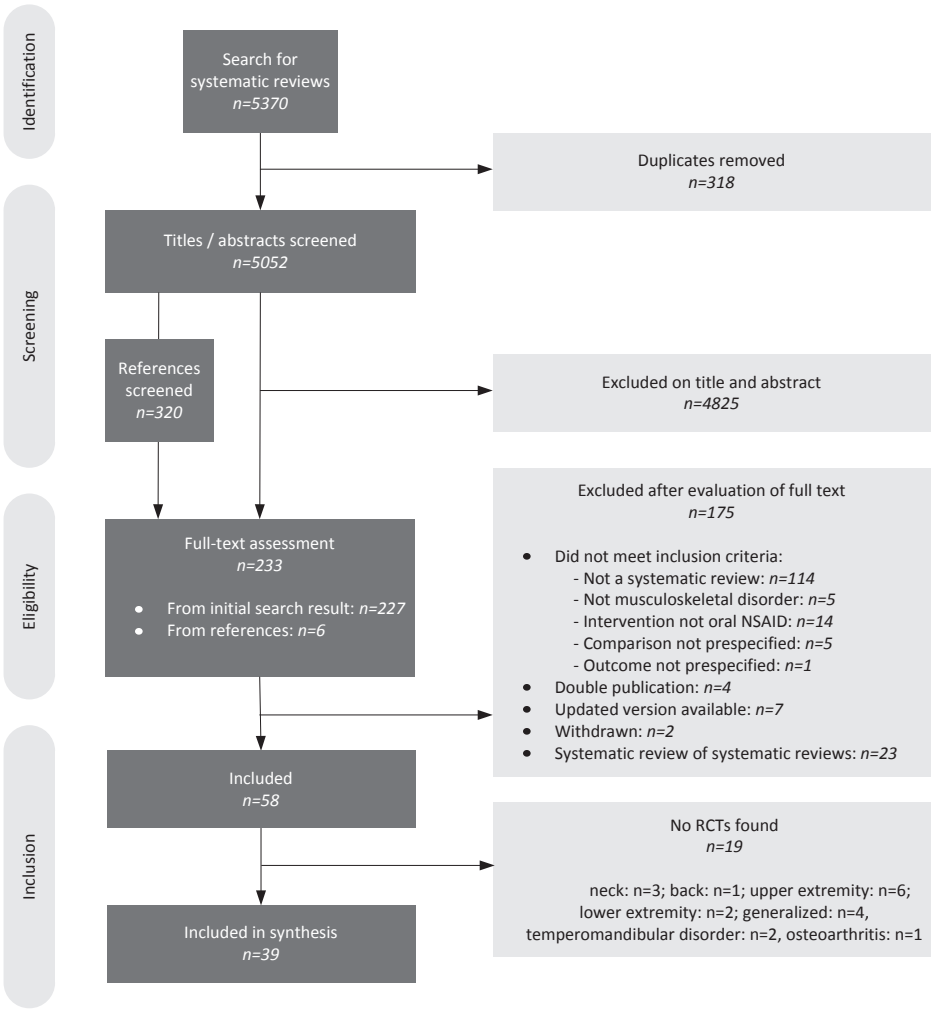

Figure 1. Flow-chart of selection of studies.

an agreement of 95% and Cohen's kappa of 0.89, and lowest for item 4, agreement 69% and Cohen's kappa 0.31.

Characteristics and results of included studies

Of the 39 reviews, 30 presented only results for the efficacy of NSAID versus placebo, five examined only NSAIDs versus paracetamol, and four included results for both comparisons. A strong overlap between reviews was found with regards to the included RCTs, when combined the 39 reviews presented results of 122 RCTs. Characteristics and results of all systematic reviews are shown in detail in appendix II for NSAIDs versus placebo, and in appendix III for NSAIDs versus paracetamol. 17 of the 39 reviews did not report any data

Table 1. AMSTAR quality assessment of included systematic reviews

Systematic review	Score per AMSTAR item											Total score
	1	2	3	4	5	6	7	8	9	10	11	
DISORDERS OF THE BACK												
Keller, 2007[79]	0	0	0	0	0	1	1	1	1	0	0	4
Kuijpers, 2011[80]	1	0	1	0	1	1	1	1	1	0	0	7
Lewis, 2011[83]	1	0	1	1	0	1	1	1	1	1	0	8
Machado, 2009[85]	0	0	1	0	0	0	1	0	1	0	0	3
McCarbergh, 2010[87]	0	0	0	0	0	1	0	0	0	0	0	1
Pinto, 2012[94]	0	1	1	0	0	1	1	1	1	1	0	7
Roelofs, 2008[96]	0	1	1	0	1	1	1	1	1	1	0	8
Schnitzer, 2004[97]	0	0	0	0	0	1	1	1	0	0	0	3
Vroomen, 2000[102]	0	0	1	0	0	1	1	0	1	0	0	4
DISORDERS OF THE UPPER EXTREMITY												
Gerritsen, 2002[76]	0	1	1	0	0	1	1	1	1	0	0	6
Goodyear-Smith, 2004[77]	0	0	1	1	0	0	1	1	0	0	0	4
O'Connor, 2003[90]	1	1	1	0	1	1	1	1	1	0	0	8
Pattanittum, 2013[91]	1	1	1	0	1	1	1	1	1	1	0	9
Piazzini, 2007[93]	0	1	0	0	0	1	1	1	1	0	0	5
DISORDERS OF THE LOWER EXTREMITY												
Heintjes, 2004[78]	1	1	1	1	1	1	1	1	1	0	0	9
Reurink, 2011[95]	0	1	1	0	1	1	1	1	1	0	0	7
Snijders, 2008[98]	0	0	1	0	0	0	0	0	0	0	0	1
GENERALIZED DISORDERS												
Abeles, 2008[65]	0	0	0	0	0	0	0	0	0	0	0	0
TEMPOROMANDIBULAR DISORDERS												
List, 2003[84]	0	1	1	1	1	1	1	0	0	0	0	6
Mujakperuo, 2010[89]	1	1	1	0	1	1	1	1	1	0	1	9
OSTEOARTHRITIS												
Adatia, 2012[66]	0	0	1	0	0	0	0	0	0	0	0	1
Altman, 2010[67]	0	0	0	0	0	0	0	0	0	0	0	0
Argoff, 2011[68]	0	0	0	0	0	0	0	0	0	0	0	0
Bjordal, 2004[70]	1	0	1	1	0	0	1	1	1	0	1	7
Bjordal, 2007[69]	1	0	1	1	0	0	1	1	1	0	0	6
Chavez, 2003[71]	0	0	1	0	0	0	0	0	0	0	0	1
Deeks, 2002[72]	0	0	1	1	0	1	1	1	1	0	0	6
Delafuente, 2004[73]	0	0	0	0	0	1	0	0	0	0	0	1
Edwards, 2004[74]	0	1	0	1	1	1	1	1	0	0	1	7
Garner, 2005[75]	1	1	1	0	1	1	1	1	1	0	1	9
Lee, 2004[82]	0	1	1	1	1	0	1	1	1	0	1	8
Lee, 2005[81]	0	0	1	0	0	1	0	0	1	0	1	4
Mahendira, 2009[86]	0	0	1	0	1	0	1	1	1	0	0	5
McCormack, 2011[88]	0	0	1	1	0	0	0	0	0	0	0	2
Pavelka, 2012[92]	0	0	0	0	0	0	0	0	0	0	0	0
Stam, 2012[99]	0	1	1	0	1	1	0	0	1	0	0	5
Trijau, 2010[100]	0	0	1	0	0	0	1	1	0	0	0	3
Verkleij, 2011[101]	1	1	1	0	0	1	1	0	1	1	1	8
Wegman, 2004[103]	0	0	1	0	0	1	1	0	1	0	0	4

AMSTAR: assessment of multiple systematic reviews.

from the RCTs, therefore the magnitude of effects found could not be assessed (appendix II and III). Among these 17 reviews were four on carpal tunnel syndrome,[76 77 90 93] one on acute ankle sprain,[98] and one on fibromyalgia,[65] the others studied topics also covered in other included reviews.[66-68 71 73 84 86-88 92 97] The main findings of the 22 included reviews that provided sufficient data to determine the magnitude of effects found, are summarized in table 2 and in the text below.

NSAIDs versus placebo – pain

For acute low back pain, three reviews reporting on this comparison presented data on pain; the group difference was found to be small in two,[85 96] and moderate in one.[79] Each of these reviews reported on three RCTs but overlap was present; combined they presented data from four RCTs. For chronic low back pain, four reviews were included, combined they reported on 5 RCTs and all found a moderate effect on pain.[79 80 85 96] For sciatica the results varied: one review reported a negligible effect based on three RCTs,[94] a second review included two of these three RCTs and reported no significant difference,[96] a third included a different combination of two of the three RCTs and found a small effect.[83]

For each of the following musculoskeletal disorders, one review was included for NSAIDs versus placebo: lateral elbow pain (moderate effect),[91] patellofemoral pain syndrome (moderate effect),[78] acute hamstring injury (no significant difference),[95] and temporomandibular disorder (negligible effect).[89] Each of these reviews included only one RCT for this comparison and outcome.

Seven reviews on osteoarthritis reported data on the efficacy of NSAIDs versus placebo for pain, combined these reviews reported on 56 RCTs. The magnitude of effects found varied between and within these reviews. Three reported a small effect[70 72 81] and one a moderate effect.[69] The remaining three reviews reported more than one effect size (appendix II): one found a small to moderate effect depending on whether a flare design was applied,[100] one a negligible to moderate effect depending on the NSAID type and dosage studied,[99] and one a small to large effect depending on NSAID dosage.[75] The large effect reported in this last review was based on the findings of one RCT, which studied NSAIDs in a dosage five times the DDD (appendix II).

NSAIDs versus placebo – proportion improved

One review on acute low back pain reported on the proportion of patients improved and found a NNT for improvement of 10, after pooling the results of seven RCTs.[96] Two reviews on sciatica also reported on this outcome. One pooled the findings of three RCTs and found no significant difference between NSAIDs and placebo.[102] The second, which included one of these three RCTs and two additional RCTs, did not pool the findings, and effects found in individual RCTs ranged from no significant difference to a NNT of 10.[83] A review on lateral elbow pain reported no significant difference of the proportion of patients improved

Table 2. Summary of main findings

Diagnosis	Outcome	Number of SRs	Number of RCTs	Results		
				Magnitude of group difference / NNT	Number of SRs	Mean AMSTAR score (range)
NSAID VERSUS PLACEBO						
Acute LBP	Pain	3	4	Small	2	6 (3-8)
				Moderate	1	4
	Proportion improved	1	7	NNT: 10	1	8
Chronic LBP	Pain	4	5	Moderate	4	6 (3-8)
Sciatica	Pain	3	3	No significant difference	1	8
				Negligible	1	7
				Small	1	8
	Proportion improved	2	6	No significant difference NNT: 6-10	2 1	6 (4-8) 8
Lateral elbow pain	Pain	1	1	Moderate	1	9
	Proportion improved	1	1	No significant difference	1	9
PFPS	Pain	1	1	Moderate	1	9
	Proportion improved	1	1	No significant difference	1	9
Acute hamstring injury	Pain	1	1	No significant difference	1	7
Temporomandibular disorder	Pain	1	1	Negligible	1	9
Osteoarthritis	Pain	7	56	Negligible	1	5
				Small	6	6 (3-9)
				Moderate	4	6 (3-9)
				Large	1	9
	Proportion improved	1	4	NNT: 4	1	9
NSAID VERSUS PARACETAMOL						
Acute LBP	Pain	1	3	No significant difference	1	8
	Proportion improved	1	3	NNT: 9	1	8
Osteoarthritis	Pain	5	21	No significant difference	1	9
				Small	4	7 (4-9)
				Moderate	1	5
	Proportion improved	1	1	NNT: 5-6	1	9

AMSTAR: assessment of multiple systematic reviews; LBP: low back pain; NNT: number needed to treat; NSAID: non-steroidal anti-inflammatory drug; RCT: randomised clinical trial; SR: systematic review.
17 SRs did not report data and are not shown in table (magnitude of between-group difference not assessable), including SRs on carpal tunnel syndrome (n=4), acute ankle sprain (n=1) and fibromyalgia (n=1).

based on one RCT,[91] as did a review on patellofemoral pain syndrome.[78] One review on osteoarthritis reported on proportion improved as an outcome and found a NNT of 4.[75]

NSAIDs versus paracetamol – pain

One review on acute low back pain was included for this comparison and outcome, it included three RCTs and found no significant difference in pain.[96] For osteoarthritis, five reviews reported on this comparison and outcome, reporting on a total of 21 RCTs.[75 82 99 101 103] Three of these reported a small effect in favour of NSAIDs,[82 101 103] and one a moderate effect.[99] The last review reported different results depending on the dosage of NSAIDs studied, its findings ranged from no significant difference to a small effect in favour of NSAIDs.[75]

NSAID versus paracetamol – proportion improved

One review on acute low back pain found a NNT of 9 for improvement for NSAID versus paracetamol,[96] a review on osteoarthritis also reported on this comparison and outcome and found a NNT of 5 to 6 depending on the NSAID dosage studied.[75]

DISCUSSION

This systematic review provides a comprehensive overview of the available evidence on the efficacy of NSAIDs versus placebo and paracetamol in musculoskeletal conditions commonly presented in primary care, by summarizing the results of previous systematic reviews of RCTs. Of the 58 included reviews, 19 studies did not find any RCTs. Among these were reviews focusing on highly prevalent disorders such as neck pain and shoulder disorders, which are often treated with NSAIDs in primary care.[1 3] In contrast to this lack of evidence for these disorders, 19 reviews on osteoarthritis were found, reporting on a total of 72 RCTs. Although osteoarthritis is an important chronic condition, it is notable that far fewer studies were found on other disorders of the musculoskeletal system such as back disorders, even though these are far more prevalent in primary care.[94] The majority of included reviews focused on NSAIDs versus placebo, far fewer studies were found for paracetamol as a comparison. From a clinical perspective, this last comparison is extremely relevant as paracetamol forms a safer alternative to NSAIDs and is often recommended as a first-choice analgesic before NSAIDs.[13-18]

In reviews that reported on NSAIDs versus placebo, results for pain varied. A moderate group difference was found in some reviews on chronic low back pain, lateral elbow pain, patellofemoral pain syndrome and osteoarthritis, but the majority of included reviews found only a small difference or no significant difference compared to placebo. NNT for improvement could only be calculated in five reviews, results ranged from no significant

difference in the proportion improved, to a NNT of 10 for NSAIDs versus placebo. For paracetamol as a comparison, one review on acute low back pain was found, the remaining studies focused on osteoarthritis. The majority of these found a small group difference for pain in favour of NSAIDs. NNT for improvement ranged from 5 to 9 for NSAIDs versus paracetamol.

When interpreting these findings on efficacy, it is important to note that a strong overlap was present between reviews, with several reviews often reporting findings from the same RCTs. This limitation is inherent to our method of conducting a review of systematic reviews, rather than including and assessing individual RCTs. However, this method also comes with distinct advantages, as it allows for a broad overview of the available evidence on the efficacy of NSAIDs in all musculoskeletal disorders common in primary care, thereby providing an aid for GPs in clinical practice and identifying gaps in current evidence. The overlap between reviews is clearly visible and is in itself of interest, as it shows that for some conditions of the musculoskeletal system, such as low back pain, there are actually far fewer RCTs available than the large number of published systematic reviews on this topic might suggest. In addition, one important conclusion on the efficacy of NSAIDs which can certainly be drawn from our results, is that large effects were not found in any of the included reviews, except for one on osteoarthritis which based this finding on data from only one RCT.

Several additional limitations require attention. Firstly, our method of including only systematic reviews means that data from RCTs published after the most recent systematic review, or on a topic for which no systematic review exists, was missed. It also means that we could not systematically assess the underlying RCTs included in the reviews, and were therefore unable to address methodological issues relating to these RCTs. Secondly, we limited our inclusion criteria to placebo or paracetamol as a comparison, choosing the latter because of its incorporation into several treatment guidelines.[13-18] From a clinical perspective, comparisons with other treatment options such as topical NSAIDs are also of interest, as they may also form a safer alternative to oral NSAIDs.[28 28] In addition, we limited our outcomes to pain and proportion improved. As our objective was to summarize studies on the efficacy of NSAIDs, the occurrence of adverse events was not included as an outcome. Some of the reviews included in our study did report on adverse events. For instance, a review on low back pain reported sufficient data on this outcome to determine the number needed to harm, which was found to range from 11 to 23 for NSAIDs versus placebo and 10 for NSAIDs versus paracetamol.[80]

Finally, we summarized the results on pain reduction from the included reviews, by categorizing the magnitude of the group difference in pain reduction as negligible, small, moderate, or large, using criteria from previous studies.[22 23] While these criteria are conventional, the level of change in pain that is considered relevant in clinical practice may vary depending on factors such as baseline pain, age, the patient's clinical condition, and

prior treatment response.[104] In addition, even if a small group difference of limited clinical importance is found, there may still be a sizable percentage of individual patients who experience a clinically important pain reduction within the groups.[104] We therefore also included studies reporting on the proportion of patients improved. However, the definitions of what constituted a sufficient patient improvement varied between the included reviews, which should be taken into account when interpreting these results.

This systematic review focused on the efficacy of NSAIDs and did not examine effectiveness within specifically the primary care population. Nonetheless, our results draw into question the current strong emphasis on and frequent use of NSAIDs in the treatment of musculoskeletal pain in general practice. For some prevalent conditions, little evidence on efficacy is available to support such treatment. For many non-arthritic conditions for which systematic reviews were found, no significant difference or only small effects relative to placebo or paracetamol were reported. Even for conditions which have been studied extensively, such as osteoarthritis, large effects were rarely found, especially when compared to paracetamol. Considering the fact that NSAIDs are associated with serious adverse drug reactions, these findings suggest that a smaller role for NSAIDs in the treatment of musculoskeletal pain in primary care may be more appropriate.

REFERENCES

1. Van der Linden MW, Westert GP, De Bakker DH, Schellevis FG. Second national survey of general practice. Morbidity in the population and in general practice. [Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk]. Utrecht/Bilthoven: NIVEL/RIVM; 2004. Available at: http://www.nivel.nl/sites/default/files/bestanden/ns2_r1_h02.pdf.
2. Jordan KP, Kadam UT, Hayward R, Porcheret M, Young C, Croft P. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC Musculoskelet Disord* 2010;11:144.
3. Koffeman AR, Valkhoff VE, Jong GW, Warle-van Herwaarden MF, Bindels PJ, Sturkenboom MC, et al. Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints. *Scand J Prim Health Care* 2014;32:90-8.
4. Koffeman AR, Valkhoff VE, Celik S, W'T Jong G, Sturkenboom MC, Bindels PJ, et al. High-risk use of over-the-counter non-steroidal anti-inflammatory drugs: a population-based cross-sectional study. *Br J Gen Pract* 2014;64:e191-8.
5. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
6. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-9.
7. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296:1633-44.
8. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
9. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiology and drug safety* 2011;20:1225-36.
10. Evans JM, McGregor E, McMahon AD, McGilchrist MM, Jones MC, White G, et al. Non-steroidal anti-inflammatory drugs and hospitalization for acute renal failure. *Qjm* 1995;88:551-7.
11. Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Arch Intern Med* 2002;162:265-70.
12. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis* 2005;45:531-9.
13. van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J* 2006;15:S169-91.
14. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15:S192-300.
15. Chavannes AW, Mens JMA, Koes BW, Lubbers WJ, Ostelo R, Spinnewijn WEM, et al. NHG guideline non-specific low back pain [NHG-standaard aspecifieke lagerugpijn]. *Huisarts Wet* 2005;48:113-23.

16. Winters JC, Van der Windt DAWM, Spinnewijn WEM, De Jongh AC, Van der Heijden GJMG, Buis PAJ, et al. NHG guideline shoulder complaints. [NHG-standaard schouderklachten]. *Huisarts Wet* 2008;51:555-65.
17. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363-88.
18. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66):377-88.
19. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
20. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One* 2007;2:e1350.
21. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol* 2009;62:1013-20.
22. Chou R, Huffman LH, American Pain S, American College of P. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007;147:505-14.
23. Cohen J. Statistical power analysis for the behavioral sciences. NJ: Lawrence Erlbaum Associates, Inc; 1988.
24. Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res* 2008;466:1539-54.
25. Ashworth NL. Carpal tunnel syndrome. *Clin Evid (Online)* 2011;pii1114.
26. Bisset L, Coombes B, Vicenzino B. Tennis elbow. *Clin Evid (Online)* 2011;pii1117.
27. Chou R. Low back pain (chronic). *Clin Evid (Online)* 2010;pii1116.
28. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Rockville: Agency for Healthcare Research and Quality; 2011.
29. Crawford JO, Laiou E. Conservative treatment of work-related upper limb disorders - A review. *Occupational Medicine* 2007;57:4-17.
30. Fajardo M, Di Cesare PE. Disease-modifying therapies for osteoarthritis : current status. *Drugs Aging* 2005;22:141-61.
31. Huisstede BM, Hoogvliet P, Randsdorp MS, Glerum S, van Middelkoop M, Koes BW. Carpal Tunnel Syndrome. Part I: Effectiveness of Nonsurgical Treatments-A Systematic Review. *Archives of Physical Medicine and Rehabilitation* 2010;91:981-1004.
32. Jordan J, Konstantinou K, O'Dowd J. Herniated lumbar disc. *Clin Evid (Online)* 2009;pii1118.
33. Laine L, White WB, Rostom A, Hochberg M. COX-2 selective inhibitors in the treatment of osteoarthritis. *Semin Arthritis Rheum* 2008;38:165-87.
34. McIntosh G, Hall H. Low back pain (acute). *Clin Evid (Online)* 2011;pii11102.
35. Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. *Curr Med Res Opin* 2011;27:11-33.
36. Moulin DE, Smith B, Gribbin M. Systemic drug treatment for chronic musculoskeletal pain. *Clinical Journal of Pain* 2001;17:S86-S93.

37. Murphy RJ, Carr AJ. Shoulder pain. *Clin Evid (Online)* 2010;pii1107.
38. Profit L, Chrisp P. Lumiracoxib: the evidence of its clinical impact on the treatment of osteoarthritis. *Core Evid* 2007;2:131-50.
39. Reid MC, Shengelia R, Parker SJ. Pharmacologic Management of Osteoarthritis-Related Pain in Older Adults: A Review Shows that Many Drug Therapies Provide Small-to-Modest Pain Relief. *Hss J* 2012;8:159-64.
40. Schellingerhout JM, Thomas S, Verhagen AP. Aspecific shoulder complaints: Literature review to assess the efficacy of current interventions. *Ned Tijdschr Geneeskd* 2007;151:2892-97.
41. Scott D. Osteoarthritis of the hip. *Clin Evid (Online)* 2006;pii1122.
42. Scott D, Kowalczyk A. Osteoarthritis of the knee. *Clin Evid (Online)* 2007;pii1121.
43. Smith D, McMurray N, Disler P. Early intervention for acute back injury: can we finally develop an evidence-based approach? *Clin Rehabil* 2002;16:1-11.
44. White AP, Arnold PM, Norvell DC, Ecker E, Fehlings MG. Pharmacologic management of chronic low back pain: synthesis of the evidence. *Spine (Phila Pa 1976)* 2011;36:S131-43.
45. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010;18:476-99.
46. Towheed TE, Hochberg MC, Shea BJ, Wells G. WITHDRAWN: Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. *Cochrane Database Syst Rev* 2006:CD000517.
47. Green S, Buchbinder R, Glazier R, Forbes A. WITHDRAWN: Interventions for shoulder pain. *Cochrane Database Syst Rev* 2006:CD001156.
48. Binder AI. Neck pain. *Clin Evid (Online)* 2008;pii1103.
49. Hurwitz EL, Carragee EJ, van der Velde G, Carroll LJ, Nordin M, Guzman J, et al. Treatment of neck pain: noninvasive interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine (Phila Pa 1976)* 2008;33:S123-52.
50. Peloso P, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie S, et al. Medicinal and injection therapies for mechanical neck disorders. *Cochrane Database Syst Rev* 2007:CD000319.
51. Luijsterburg PA, Verhagen AP, Ostelo RW, van Os TA, Peul WC, Koes BW. Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review. *Eur Spine J* 2007;16:881-99.
52. Faber E, Kuiper JI, Burdorf A, Miedema HS, Verhaar JA. Treatment of impingement syndrome: a systematic review of the effects on functional limitations and return to work. *J Occup Rehabil* 2006;16:7-25.
53. Hamamoto Filho PT, Leite FV, Ruiz T, Resende LA. A Systematic Review of Anti-inflammatories for Mild to Moderate Carpal Tunnel Syndrome. *Journal of Clinical Neuromuscular Disease* 2009;11:22-30.
54. Johansson K, Oberg B, Adolfsson L, Foldevi M. A combination of systematic review and clinicians' beliefs in interventions for subacromial pain. *Br J Gen Pract* 2002;52:145-52.
55. Konijnenberg HS, de Wilde NS, Gerritsen AA, van Tulder MW, de Vet HC. Conservative treatment for repetitive strain injury. *Scand J Work Environ Health* 2001;27:299-310.
56. Rinkel WD, Schreuders TA, Koes BW, Huisstede BM. Current evidence for effectiveness of interventions for cubital tunnel syndrome, radial tunnel syndrome, instability, or bursitis of the elbow: a systematic review. *Clin J Pain* 2013;29:1087-96.

57. van der Sande R, Rinkel WD, Gebremariam L, Hay EM, Koes BW, Huisstede BM. Subacromial impingement syndrome: effectiveness of pharmaceutical interventions-nonsteroidal anti-inflammatory drugs, corticosteroid, or other injections: a systematic review. *Arch Phys Med Rehabil* 2013;94:961-76.
58. Ellis R, Hing W, Reid D. Iliotibial band friction syndrome—a systematic review. *Man Ther* 2007;12(3):200-8.
59. McLauchlan GJ, Handoll HH. Interventions for treating acute and chronic Achilles tendinitis. *Cochrane Database Syst Rev* 2001:CD000232.
60. Jones P, Lamdin R. Oral cyclo-oxygenase 2 inhibitors versus other oral analgesics for acute soft tissue injury: systematic review and meta-analysis. *Clin Drug Investig* 2010;30:419-37.
61. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004;292:2388-95.
62. Marcus DA. Fibromyalgia: diagnosis and treatment options. *Gend Med* 2009;6:139-51.
63. Moore RA, Derry S, McQuay HJ. Discontinuation rates in clinical trials in musculoskeletal pain: meta-analysis from etoricoxib clinical trial reports. *Arthritis Res Ther* 2008;10:R53.
64. Januzzi E, Nasri-Heir C, Grossmann E, Leite FM, Heir GM, Melnik T. Combined palliative and anti-inflammatory medications as treatment of temporomandibular joint disc displacement without reduction: a systematic review. *Cranio* 2013;31:211-25.
65. Abeles M, Solitar BM, Pillinger MH, Abeles AM. Update on fibromyalgia therapy. *Am J Med* 2008;121:555-61.
66. Adatia A, Rainsford KD, Kean WF. Osteoarthritis of the knee and hip. Part II: therapy with ibuprofen and a review of clinical trials. *J Pharm Pharmacol* 2012;64:626-36.
67. Altman RD. Pharmacological therapies for osteoarthritis of the hand: a review of the evidence. *Drugs Aging* 2010;27:729-45.
68. Argoff CE. Recent developments in the treatment of osteoarthritis with NSAIDs. *Curr Med Res Opin* 2011;27:1315-27.
69. Bjordal JM, Klovning A, Ljunggren AE, Slordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. *Eur J Pain* 2007;11:125-38.
70. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *Bmj* 2004;329:1317.
71. Chavez ML, DeKorte CJ. Valdecoxib: a review. *Clin Ther* 2003;25:817-51.
72. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *Bmj* 2002;325:619.
73. Delafuente JC. Emerging controversies in the treatment of osteoarthritis in older individuals. *Consult Pharm* 2004;19:135-42.
74. Edwards JE, McQuay HJ, Moore RA. Efficacy and safety of valdecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *Pain* 2004;111:286-96.
75. Garner SE, Fidan DD, Frankish R, Maxwell L. Rofecoxib for osteoarthritis. *Cochrane Database Syst Rev* 2005:CD005115.
76. Gerritsen AA, de Krom MC, Struijs MA, Scholten RJ, de Vet HC, Bouter LM. Conservative treatment options for carpal tunnel syndrome: a systematic review of randomised controlled trials. *J Neurol* 2002;249:272-80.

77. Goodyear-Smith F, Arroll B. What can family physicians offer patients with carpal tunnel syndrome other than surgery? A systematic review of nonsurgical management. *Ann Fam Med* 2004;2:267-73.
78. Heintjes E, Berger MY, Bierma-Zeinstra SM, Bernsen RM, Verhaar JA, Koes BW. Pharmacotherapy for patellofemoral pain syndrome. *Cochrane Database Syst Rev* 2004:CD003470.
79. Keller A, Hayden J, Bombardier C, van Tulder M. Effect sizes of non-surgical treatments of non-specific low-back pain. *Eur Spine J* 2007;16:1776-88.
80. Kuijpers T, van Middelkoop M, Rubinstein SM, Ostelo R, Verhagen A, Koes BW, et al. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J* 2011;20:40-50.
81. Lee C, Hunsche E, Balshaw R, Kong SX, Schnitzer TJ. Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis. *Arthritis Rheum* 2005;53:510-8.
82. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 2004;51:746-54.
83. Lewis R, Williams N, Matar H, Din N, Fitzsimmons D, Phillips C, et al. The clinical effectiveness and cost-effectiveness of management strategies for sciatica: Systematic review and economic model. *Health Technology Assessment* 2011;15:iii-303.
84. List T, Axelsson S, Leijon G. Pharmacologic interventions in the treatment of temporomandibular disorders, atypical facial pain, and burning mouth syndrome. A qualitative systematic review. *J Orofac Pain* 2003;17:301-10.
85. Machado LA, Kamper SJ, Herbert RD, Maher CG, McAuley JH. Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. *Rheumatology (Oxford)* 2009;48:520-7.
86. Mahendira D, Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: an update. *Osteoarthritis Cartilage* 2009;17:1263-8.
87. McCarberg BH. Acute back pain: benefits and risks of current treatments. *Curr Med Res Opin* 2010;26:179-90.
88. McCormack PL. Celecoxib: a review of its use for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. *Drugs* 2011;71:2457-89.
89. Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. *Cochrane Database Syst Rev* 2010:CD004715.
90. O'Connor D, Marshall S, Massy-Westropp N. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2003:CD003219.
91. Pattanittum P, Turner T, Green S, Buchbinder R. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database Syst Rev* 2013;5:CD003686.
92. Pavelka K. A comparison of the therapeutic efficacy of diclofenac in osteoarthritis: a systematic review of randomised controlled trials. *Curr Med Res Opin* 2012;28:163-78.
93. Piazzini DB, Aprile I, Ferrara PE, Bertolini C, Tonali P, Maggi L, et al. A systematic review of conservative treatment of carpal tunnel syndrome. *Clin Rehabil* 2007;21:299-314.
94. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. *Bmj* 2012;344:e497.
95. Reurink G, Goudswaard GJ, Tol JL, Verhaar JA, Weir A, Moen MH. Therapeutic interventions for acute hamstring injuries: a systematic review. *Br J Sports Med* 2012;46:103-9.

96. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2008:CD000396.
97. Schnitzer TJ, Ferraro A, Hunsche E, Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. *J Pain Symptom Manage* 2004;28:72-95.
98. Snijders E, Thomas S, Verhagen A. Assessment of the effectiveness of conservative treatment of acute ankle sprain. A review of the literature. *Huisarts Wet* 2008;51:17-23.
99. Stam W, Jansen J, Taylor S. Efficacy of etoricoxib, celecoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. *Open Rheumatol J* 2012;6:6-20.
100. Trijau S, Avouac J, Escalas C, Gossec L, Dougados M. Influence of flare design on symptomatic efficacy of non-steroidal anti-inflammatory drugs in osteoarthritis: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2010;18:1012-8.
101. Verkleij SP, Luijsterburg PA, Bohnen AM, Koes BW, Bierma-Zeinstra SM. NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. *Osteoarthritis Cartilage* 2011;19:921-9.
102. Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: a systematic review. *J Spinal Disord* 2000;13:463-9.
103. Wegman A, van der Windt D, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *J Rheumatol* 2004;31:344-54.
104. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105-21.
105. Babej-Dolle R, Freytag S, Eckmeyer J, Zerle G, Schinzel S, Schmeider G, et al. Parenteral dipyrone versus diclofenac and placebo in patients with acute lumbago or sciatic pain: randomized observer-blind multicenter study. *Int J Clin Pharmacol Ther* 1994;32:204-9.
106. Szpalski M, Hayez JP. Objective functional assessment of the efficacy of tenoxicam in the treatment of acute low back pain. A double-blind placebo-controlled study. *Br J Rheumatol* 1994;33:74-8.
107. Dreiser RL, Marty M, Ionescu E, Gold M, Liu JH. Relief of acute low back pain with diclofenac-K 12.5 mg tablets: a flexible dose, ibuprofen 200 mg and placebo-controlled clinical trial. *Int J Clin Pharmacol Ther* 2003;41:375-85.
108. Coats TL, Borenstein DG, Nangia NK, Brown MT. Effects of valdecoxib in the treatment of chronic low back pain: results of a randomized, placebo-controlled trial. *Clin Ther* 2004;26:1249-60.
109. Katz N, Ju WD, Krupa DA, Sperling RS, Bozalis Rodgers D, Gertz BJ, et al. Efficacy and safety of rofecoxib in patients with chronic low back pain: results from two 4-week, randomized, placebo-controlled, parallel-group, double-blind trials. *Spine (Phila Pa 1976)* 2003;28:851-8.
110. Pallay RM, Seger W, Adler JL, Ettlinger RE, Quaidoo EA, Lipetz R, et al. Etoricoxib reduced pain and disability and improved quality of life in patients with chronic low back pain: a 3 month, randomized, controlled trial. *Scand J Rheumatol* 2004;33:257-66.
111. Berry H, Bloom B, Hamilton EB, Swinson DR. Naproxen sodium, diflunisal, and placebo in the treatment of chronic back pain. *Ann Rheum Dis* 1982;41:129-32.
112. Birbara CA, Puopolo AD, Munoz DR, Sheldon EA, Mangione A, Bohidar NR, et al. Treatment of chronic low back pain with etoricoxib, a new cyclo-oxygenase-2 selective inhibitor:

improvement in pain and disability—a randomized, placebo-controlled, 3-month trial. *J Pain* 2003;4:307-15.
113. Dreiser RL, Le Parc JM, Velicitat P, Lleu PL. Oral meloxicam is effective in acute sciatica: two randomised, double-blind trials versus placebo or diclofenac. *Inflamm Res* 2001;50:S17-23.
114. Herrmann WA, Geertsen MS. Efficacy and safety of lornoxicam compared with placebo and diclofenac in acute sciatica/lumbo-sciatica: an analysis from a randomised, double-blind, multicentre, parallel-group study. *Int J Clin Pract* 2009;63:1613-21.
115. Goldie I. A clinical trial with indomethacin (indomee(R)) in low back pain and sciatica. *Acta Orthop Scand* 1968;39:117-28.
116. Amlie E, Weber H, Holme I. Treatment of acute low-back pain with piroxicam: results of a double-blind placebo-controlled trial. *Spine (Phila Pa 1976)* 1987;12:473-6.
117. Hancock MJ, Maher CG, Latimer J, McLachlan AJ, Cooper CW, Day RO, et al. Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial. *Lancet* 2007;370:1638-43.
118. Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. *Spine (Phila Pa 1976)* 1993;18:1433-8.
119. Basmajian JV. Acute back pain and spasm. A controlled multicenter trial of combined analgesic and antispasm agents. *Spine (Phila Pa 1976)* 1989;14:438-9.
120. Jacobs JH, Grayson MF. Trial of an anti-inflammatory agent (indomethacin) in low back pain with and without radicular involvement. *Br Med J* 1968;3:158-60.
121. Weber H, Aasand G. The effect of phenylbutazone on patients with acute lumbago-sciatica. A double blind trial. *J Oslo City Hosp* 1980;30:69-72.
122. Chang MH, Chiang HT, Lee SS, Ger LP, Lo YK. Oral drug of choice in carpal tunnel syndrome. *Neurology* 1998;51:390-3.
123. Davis PT, Hulbert JR, Kassak KM, Meyer JJ. Comparative efficacy of conservative medical and chiropractic treatments for carpal tunnel syndrome: a randomized clinical trail. *J Manipulative Physiol Ther* 1998;21:317-26.
124. Labelle H, Guibert R. Efficacy of diclofenac in lateral epicondylitis of the elbow also treated with immobilization. The University of Montreal Orthopaedic Research Group. *Arch Fam Med* 1997;6:257-62.
125. Hay EM, Paterson SM, Lewis M, Hosie G, Croft P. Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care. *Bmj* 1999;319:964-8.
126. Suter E, Herzog W, Bray RC. Quadriceps inhibition following arthroscopy in patients with anterior knee pain. *Clin Biomech (Bristol, Avon)* 1998;13:314-19.
127. Bentley G, Leslie IJ, Fischer D. Effect of aspirin treatment on chondromalacia patellae. *Ann Rheum Dis* 1981;40:37-41.
128. Reynolds JF, Noakes TD, Schwellnus MP, Windt A, Bowerbank P. Non-steroidal anti-inflammatory drugs fail to enhance healing of acute hamstring injuries treated with physiotherapy. *S Afr Med J* 1995;85:517-22.
129. Moran M. Double-blind comparison of diclofenac potassium, ibuprofen and placebo in the treatment of ankle sprains. *J Int Med Res* 1991;19:121-30.
130. Ekman EF, Fiechtner JJ, Levy S, Fort JG. Efficacy of celecoxib versus ibuprofen in the treatment of acute pain: a multicenter, double-blind, randomized controlled trial in acute ankle sprain. *Am J Orthop (Belle Mead NJ)* 2002;31:445-51.

131. Bahamonde LA, Saavedra H. Comparison of the analgesic and anti-inflammatory effects of diclofenac potassium versus piroxicam versus placebo in ankle sprain patients. *J Int Med Res* 1990;18):104-11.
132. Moran M. An observer-blind comparison of diclofenac potassium, piroxicam and placebo in the treatment of ankle sprains. *Curr Med Res Opin* 1990;12:268-74.
133. Lacey PH, Dodd GD, Shannon DJ. A double blind, placebo controlled study of piroxicam in the management of acute musculoskeletal disorders. *Eur J Rheumatol Inflamm* 1984;7:95-104.
134. De Nies F LW, Patka P. The effect of flurbiprofen in acute ankle sprains [Het effect van flurbiprofen bij acute enkeldistorsies]. *Nederlands tijdschrift voor geneeskunde* 1989;133:449-51.
135. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum* 1986;29:1371-7.
136. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial. *J Rheumatol* 1989;16:527-32.
137. Singer E, Dionne R. A controlled evaluation of ibuprofen and diazepam for chronic orofacial muscle pain. *J Orofac Pain* 1997;11:139-46.
138. Ta LE, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen. *Pain* 2004;111:13-21.
139. Schiff M, Minic M. Comparison of the analgesic efficacy and safety of nonprescription doses of naproxen sodium and Ibuprofen in the treatment of osteoarthritis of the knee. *J Rheumatol* 2004;31:1373-83.
140. Puopolo A, Boice JA, Fidelholtz JL, Littlejohn TW, Miranda P, Berrocal A, et al. A randomized placebo-controlled trial comparing the efficacy of etoricoxib 30 mg and ibuprofen 2400 mg for the treatment of patients with osteoarthritis. *Osteoarthritis Cartilage* 2007;15:1348-56.
141. Wiesenhutter CW, Boice JA, Ko A, Sheldon EA, Murphy FT, Wittmer BA, et al. Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005;80:470-9.
142. Day R, Morrison B, Luza A, Castaneda O, Strusberg A, Nahir M, et al. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Rofecoxib/Ibuprofen Comparator Study Group. *Arch Intern Med* 2000;160:1781-7.
143. Grifka JK, Zacher J, Brown JP, Seriolo B, Lee A, Moore A, et al. Efficacy and tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand. *Clin Exp Rheumatol* 2004;22:589-96.
144. Seiler V. Meclofenamate sodium in the treatment of degenerative joint disease of the hand (Heberden nodes). *Arzneimittelforschung* 1983;33:656-9.
145. Dreiser RL, Gersberg M, Thomas F, Courcier S. Ibuprofen 800 mg in the treatment of arthrosis of the fingers or rhizarthrosis [L'ibuprofene 800 mg dans le traitement de l'arthrose des doigts ou de la rhizarthrose]. *Rev Rhum Ed Fr* 1993;60:836-41.
146. Lund B, Distel M, Bluhmki E. A double-blind, randomized, placebo-controlled study of efficacy and tolerance of meloxicam treatment in patients with osteoarthritis of the knee. *Scand J Rheumatol* 1998;27:32-7.
147. Bensen WG, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999;74:1095-105.

148. Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169-78.
149. Dore R, Ballard I, Constantine G, McDonald P. Efficacy and safety of etodolac and naproxen in patients with osteoarthritis of the knee: a double-blind, placebo-controlled study. *Clin Ther* 1995;17:656-66.
150. Ehrich EW, Bolognese JA, Watson DJ, Kong SX. Effect of rofecoxib therapy on measures of health-related quality of life in patients with osteoarthritis. *Am J Manag Care* 2001;7:609-16.
151. Fleischmann RM, Flint K, Constantine G, Kolecki B. A double-masked comparison of Naprelan and nabumetone in osteoarthritis of the knee. Naprelan Study Group. *Clin Ther* 1997;19:642-55.
152. Gibofsky A, Williams GW, McKenna F, Fort JG. Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design considerations and results of a randomized, placebo-controlled trial. *Arthritis Rheum* 2003;48:3102-11.
153. Gottesdiener K, Schnitzer T, Fisher C, Bockow B, Markenson J, Ko A, et al. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. *Rheumatology (Oxford)* 2002;41:1052-61.
154. Kivitz A, Eisen G, Zhao WW, Bevirt T, Recker DP. Randomized placebo-controlled trial comparing efficacy and safety of valdecoxib with naproxen in patients with osteoarthritis. *J Fam Pract* 2002;51:530-7.
155. Lee P, Davis P, Prat A. The efficacy of diflunisal in osteoarthritis of the knee. A Canadian Multicenter Study. *J Rheumatol* 1985;12:544-8.
156. Makarowski W, Weaver A, Rubin B, Caldwell J, McMahon FG, Noveck RJ, et al. The efficacy, tolerability, and safety of 1200 mg/d of oxaprozin and 1500 mg/d of nabumetone in the treatment of patients with osteoarthritis of the knee. *Clin Ther* 1996;18:114-24.
157. McKenna F, Borenstein D, Wendt H, Wallemark C, Lefkowith JB, Geis GS. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. *Scand J Rheumatol* 2001;30:11-8.
158. Schnitzer TJ, Ballard IM, Constantine G, McDonald P. Double-blind, placebo-controlled comparison of the safety and efficacy of orally administered etodolac and nabumetone in patients with active osteoarthritis of the knee. *Clin Ther* 1995;17:602-12.
159. Scott DL, Berry H, Capell H, Coppock J, Daymond T, Doyle DV, et al. The long-term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee: a randomized placebo-controlled trial. *Rheumatology (Oxford)* 2000;39:1095-101.
160. Simon LS, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. *Arthritis Rheum* 1998;41:1591-602.
161. Tannenbaum H, Berenbaum F, Reginster JY, Zacher J, Robinson J, Poor G, et al. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13 week, randomised, double blind study versus placebo and celecoxib. *Ann Rheum Dis* 2004;63:1419-26.
162. Uzun H, Tuzun S, Ozaras N, Aydin S, Ozaras R, Dondurmaci S, et al. The effect of flurbiprofen and tiaprofenic acid on serum cytokine levels of patients with osteoarthrosis. *Acta Orthop Scand* 2001;72:499-502.
163. Weaver A, Rubin B, Caldwell J, McMahon FG, Lee D, Makarowski W, et al. Comparison of the efficacy and safety of oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the knee. *Clin Ther* 1995;17:735-45.

164. Williams PI, Hosie J, Scott DL. Etodolac therapy for osteoarthritis: a double-blind, placebo-controlled trial. *Curr Med Res Opin* 1989;11:463-70.
165. Williams GW, Hubbard RC, Yu SS, Zhao W, Geis GS. Comparison of once-daily and twice-daily administration of celecoxib for the treatment of osteoarthritis of the knee. *Clin Ther* 2001;23:213-27.
166. Zhao SZ, McMillen JI, Markenson JA, Dedhiya SD, Zhao WW, Osterhaus JT, et al. Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. *Pharmacotherapy* 1999;19:1269-78.
167. Detrembleur C, De Nayer J, van den Hecke A. Celecoxib improves the efficiency of the locomotor mechanism in patients with knee osteoarthritis. A randomised, placebo, double-blind and cross-over trial. *Osteoarthritis Cartilage* 2005;13:206-10.
168. Kivitz AJ, Greenwald MW, Cohen SB, Polis AB, Najarian DK, Dixon ME, et al. Efficacy and safety of rofecoxib 12.5 mg versus nabumetone 1,000 mg in patients with osteoarthritis of the knee: a randomized controlled trial. *J Am Geriatr Soc* 2004;52:666-74.
169. Lehmann R, Brzosko M, Kopsa P, Nischik R, Kreisse A, Thurston H, et al. Efficacy and tolerability of lumiracoxib 100 mg once daily in knee osteoarthritis: a 13-week, randomized, double-blind study vs. placebo and celecoxib. *Curr Med Res Opin* 2005;21:517-26.
170. McKenna F, Weaver A, Fiechtner JJ, Bello AE, Fort JG. COX-2 specific inhibitors in the management of osteoarthritis of the knee: a placebo-controlled, randomized, double-blind study. *J Clin Rheumatol* 2001;7:151-9.
171. Sheldon E, Beaulieu A, Paster Z, Dutta D, Yu S, Sloan VS. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005;27:64-77.
172. Fiechtner JJ, Seikes D, Recker D, et al. A double-blind, placebo-controlled dose ranging study to evaluate the efficacy of valdecoxib, a novel COX-2 specific inhibitor, in treating signs and symptoms of osteoarthritis of the knee. *Presented at: European Congress of Rheumatology* 2001;Abstract 0048.
173. Makarowski W, Zhao WW, Bevirt T, Recker DP. Efficacy and safety of the COX-2 specific inhibitor valdecoxib in the management of osteoarthritis of the hip: a randomized, double-blind, placebo-controlled comparison with naproxen. *Osteoarthritis Cartilage* 2002;10:290-6.
174. Study 054. Integrated clinical and statistical report for a double-blind placebo controlled, randomised comparison study of the efficacy and safety of SC-58635 50mg, 100mg and 200mg BID and naproxen 500mg BID in treating the signs and symptoms of osteoarthritis of the hip. *Pharmacia: Data on file* 1997.
175. Truitt KE, Sperling RS, Ettinger WH, Jr., Greenwald M, DeTora L, Zeng Q, et al. A multicenter, randomized, controlled trial to evaluate the safety profile, tolerability, and efficacy of rofecoxib in advanced elderly patients with osteoarthritis. *Aging (Milano)* 2001;13:112-21.
176. Ehrich EW, Schnitzer TJ, McIlwain H, Levy R, Wolfe F, Weisman M, et al. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. *J Rheumatol* 1999;26:2438-47.
177. Geba GP, Polis AB, Najarian DK, et al. Onset of efficacy and patient assessment of clinical response in osteoarthritis (OA): comparison of rofecoxib to nabumetone. *American Geriatric Society* 2001.
178. Saag K, van der Heijde D, Fisher C, Samara A, DeTora L, Bolognese J, et al. Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-

inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. Osteoarthritis Studies Group. *Arch Fam Med* 2000;9:1124-34.

179. Kivitz AJ, Moskowitz RW, Woods E, Hubbard RC, Verburg KM, Lefkowith JB, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J Int Med Res* 2001;29:467-79.
180. Lisse J, Espinoza L, Zhao SZ, Dedhiya SD, Osterhaus JT. Functional status and health-related quality of life of elderly osteoarthritic patients treated with celecoxib. *J Gerontol A Biol Sci Med Sci* 2001;56:M167-75.
181. Leung AT, Malmstrom K, Gallacher AE, Sarembock B, Poor G, Beaulieu A, et al. Efficacy and tolerability profile of etoricoxib in patients with osteoarthritis: A randomized, double-blind, placebo and active-comparator controlled 12-week efficacy trial. *Curr Med Res Opin* 2002;18:49-58.
182. Fisher CA, Curtis S, Resnick H, Ripley P, Leung AT, Ko AT, et al. Treatment with etoricoxib, a COX-2 selective inhibitor, resulted in clinical improvement in knee and hip osteoarthritis (OA) over 52 weeks. *Arthritis Rheum* 2001;44:S135.
183. Birbara C, Ruoff G, Sheldon E, Valenzuela C, Rodgers A, Petruschke RA, et al. Efficacy and safety of rofecoxib 12.5 mg and celecoxib 200 mg in two similarly designed osteoarthritis studies. *Curr Med Res Opin* 2006;22:199-210.
184. Smugar SS, Schnitzer TJ, Weaver AL, Rubin BR, Polis AB, Tershakovec AM. Rofecoxib 12.5 mg, rofecoxib 25 mg, and celecoxib 200 mg in the treatment of symptomatic osteoarthritis: results of two similarly designed studies. *Curr Med Res Opin* 2006;22:1353-67.
185. Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. *Ann Rheum Dis* 2007;66:1178-83.
186. Bingham CO, Sebba AI, Rubin BR, Ruoff GE, Kremer J, Bird S, et al. Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology (Oxford)* 2007;46:496-507.
187. Fleischmann R, Sheldon E, Maldonado-Cocco J, Dutta D, Yu S, Sloan VS. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. *Clin Rheumatol* 2006;25:42-53.
188. Geba GP WA, Polis AB, Najarian DK, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002;287:64-71.
189. Schnitzer TJ, Beier J, Geusens P, Hasler P, Patel SK, Senftleber I, et al. Efficacy and safety of four doses of lumiracoxib versus diclofenac in patients with knee or hip primary osteoarthritis: a phase II, four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004;51:549-57.
190. Williams GW ER, Ruderman EM, et al. Treatment of osteoarthritis with a once-daily dosing regimen of celecoxib. *J Clin Rheumatol* 2000;6:65-74.
191. Schnitzer TJ, Weaver AL, Polis AB, Petruschke RA, Geba GP, Vact, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee. A combined analysis of the VACT studies. *J Rheumatol* 2005;32:1093-105.
192. Hawel R, Klein G, Singer F, Mayrhofer F, Kahler ST. Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip. *Int J Clin Pharmacol Ther* 2003;41:153-64.

193. Zacher J FD, Gerli R, Scott D, Hou SM, Uebelhart D, Rodger IW, Ozturk ZE. A comparison of the therapeutic efficacy and tolerability of etoricoxib and diclofenac in patients with osteoarthritis. *Curr Med Res Opin* 2003;19:725-36.
194. Wittenberg RH, Schell E, Krehan G, Maeumbaed R, Runge H, Schluter P, et al. First-dose analgesic effect of the cyclo-oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled comparison with celecoxib [NCT00267215]. *Arthritis Res Ther* 2006;8:R35.
195. Schnitzer TJ, Kivitz AJ, Lipetz RS, Sanders N, Hee A. Comparison of the COX-inhibiting nitric oxide donator AZD3582 and rofecoxib in treating the signs and symptoms of Osteoarthritis of the knee. *Arthritis Rheum* 2005;53:827-37.
196. Svensson O, Malmenas M, Fajutrao L, Roos EM, Lohmander LS. Greater reduction of knee than hip pain in osteoarthritis treated with naproxen, as evaluated by WOMAC and SF-36. *Ann Rheum Dis* 2006;65:781-4.
197. Lohmander LS, McKeith D, Svensson O, Malmenas M, Bolin L, Kalla A, et al. A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. *Ann Rheum Dis* 2005;64:449-56.
198. Davies GM, Watson DJ, Bellamy N. Comparison of the responsiveness and relative effect size of the western Ontario and McMaster Universities Osteoarthritis Index and the short-form Medical Outcomes Study Survey in a randomized, clinical trial of osteoarthritis patients. *Arthritis Care Res* 1999;12:172-9.
199. Bocanegra TS, Weaver AL, Tindall EA, Sikes DH, Ball JA, Wallemark CB, et al. Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. Arthrotec Osteoarthritis Study Group. *J Rheumatol* 1998;25:1602-11.
200. Bourgeois P, Dreiser RL, Lequesne MG, Macciocchi A, Monti T. Multi-centre double-blind study to define the most favourable dose of nimesulide in terms of efficacy/safety ratio in the treatment of osteoarthritis. *Eur J Rheumatol Inflamm* 1994;14:39-50.
201. Nguyen M, Dougados M, Berdah L, Amor B. Diacerhein in the treatment of osteoarthritis of the hip. *Arthritis Rheum* 1994;37:529-36.
202. Evans DP, Burke MS, Newcombe RG. Medicines of choice in low back pain. *Curr Med Res Opin* 1980;6:540-7.
203. Nadler SF, Steiner DJ, Erasala GN, Hengehold DA, Hinkle RT, Beth Goodale M, et al. Continuous low-level heat wrap therapy provides more efficacy than Ibuprofen and acetaminophen for acute low back pain. *Spine (Phila Pa 1976)* 2002;27:1012-7.
204. Wiesel SW, Cuckler JM, Deluca F, Jones F, Zeide MS, Rothman RH. Acute low-back pain. An objective analysis of conservative therapy. *Spine (Phila Pa 1976)* 1980;5:324-30.
205. Hickey RF. Chronic low back pain: a comparison of diflunisal with paracetamol. *N Z Med J* 1982;95:312-4.
206. Milgrom C, Finestone A, Lev B, Wiener M, Floman Y. Overexertional lumbar and thoracic back pain among recruits: a prospective study of risk factors and treatment regimens. *J Spinal Disord* 1993;6:187-93.
207. Muckle DS. Flurbiprofen for the treatment of soft tissue trauma. *Am J Med* 1986;80:76-80.
208. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *New England Journal of Medicine* 1991;325:87-91.

209. Williams HJ, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum* 1993;36:1196-206.
210. Pincus T, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;44:1587-98.
211. Lequesne M, Fannius J, Reginster JY, Verdickt W, du Laurier MV. Floctafenin versus acetaminophen for pain control in patients with osteoarthritis in the lower limbs. Franco-Belgian Task Force. *Revue du Rhumatisme (English Edition)* 1997;64:327-33.
212. Erturk H CR, Aydin M, Ugur O. Comparison of efficacy and tolerability of acemetacin and acetaminophen in the treatment of knee osteoarthritis. *J Rheum Med Rehab* 1998;9:157-61.
213. Miceli-Richard C LBM, Schmidely N, Dougados M. Paracetamol in osteoarthritis of the knee. *Ann Rheum Dis* 2004;63:923-30.
214. Batlle-Gualda E, Roman Ivorra J, Martin-Mola E, Carbonell Abello J, Linares Ferrando LF, Tornero Molina J, et al. Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial. *Osteoarthritis Cartilage* 2007;15:900-8.
215. Boureau F, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis* 2004;63:1028-34.
216. Golden HE, Moskowitz RW, Minic M. Analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee. *American Journal of Therapeutics* 2004;11:85-94.
217. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004;63:931-9.
218. Schnitzer TJ, Tesser JR, Cooper KM, Altman RD. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1-7.
219. Shen H, Sprott H, Aeschlimann A, Gay RE, Michel BA, Gay S, et al. Analgesic action of acetaminophen in symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)* 2006;45:765-70.
220. Temple AR, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6-12 months) safety of acetaminophen in adult patients with osteoarthritis. *Clin Ther* 2006;28:222-35.

APPENDICES

Appendix I - Search terms

(cervical pain*[tw] OR neck pain*[tw] OR back pain*[tw] OR lumbal pain*[tw] OR lumbar pain*[tw] OR lumbosacral pain*[tw] OR lumbo-sacral pain*[tw] OR sacral pain*[tw] OR costal pain*[tw] OR rib pain*[tw] OR chest pain*[tw] OR shoulder pain*[tw] OR arm pain*[tw] OR elbow pain*[tw] OR wrist pain*[tw] OR hand pain*[tw] OR finger pain*[tw] OR hip pain*[tw] OR leg pain*[tw] OR knee pain*[tw] OR ankle pain*[tw] OR foot pain*[tw] OR toe pain*[tw] OR jaw*[tw] OR tempomandibul*[tw] OR temporomandibul*[tw] OR whiplash*[tw] OR whip-lash*[tw] OR neck disorder*[tw] OR nerve root*[tw] OR radiculit*[tw] OR radiculopath*[tw] OR ischialg*[tw] OR sciatic*[tw] OR tietze*[tw] OR rotator cuff*[tw] OR shoulder impingement*[tw] OR frozen shoulder*[tw] OR acrom*[tw] OR subacrom*[tw] OR epicondylalgi*[tw] OR epicondyliti*[tw] OR tennis elbow*[tw] OR carpal tunnel syndrome*[tw] OR quervain*[tw] OR dupuytren*[tw] OR hand disease*[tw] OR hand disorder*[tw] OR palmar fasciit*[tw] OR trigger finger*[tw] OR mallet*[tw] OR iliotibial band syndrome*[tw] OR femoropatellar pain*[tw] OR femoro-patellar pain*[tw] OR patellofemoral pain*[tw] OR patello-femoral pain*[tw] OR cruciate ligament*[tw] OR meniscus*[tw] OR jumper's knee*[tw] OR jumpers knee*[tw] OR collateral ligament*[tw] OR coup de fouet*[tw] OR tennis leg*[tw] OR posterior tibial tendon dysfunct*[tw] OR foot disease*[tw] OR foot disorder*[tw] OR heel spur*[tw] OR metatarsalgi*[tw] OR meta-tarsalgi*[tw] OR plantar fasciit*[tw] OR osteoarthrit*[tw] OR degenerative arthriti*[tw] OR arthrosis*[tw] OR arthrot*[tw] OR arthralgi*[tw] OR arthropath*[tw] OR joint pain*[tw] OR muscle cramp*[tw] OR muscle pain*[tw] OR muscular cramp*[tw] OR muscular pain*[tw] OR myopath*[tw] OR tendinopath*[tw] OR tendon entrap*[tw] OR tendonit*[tw] OR tenosynoviti*[tw] OR bursiti*[tw] OR capsulit*[tw] OR chondromalaci*[tw] OR chondropath*[tw] OR ((wide spread pain*[tw] OR widespread pain*[tw]) AND pain syndrome*[tw]) OR fibromyalgi*[tw] OR musculoskeletal system/injuries[mesh] OR ankle distor*[tw] OR ankle inversion*[tw] OR (strain*[tw] NOT medline[sb]) OR rib contus*[tw] OR sprain*[tw] OR sprains and strains[mesh] OR soft tissue injur*[tw] OR knee distor*[tw] OR ligament rupture*[tw] OR cumulative trauma disorder*[tw] OR overuse injur*[tw] OR overuse syndrome*[tw] OR repetitive motion disorder*[tw] OR repetition strain injur*[tw] OR repetitive strain injur*[tw])
AND
(Anti-Inflammatory Agents, Non-Steroidal[mesh] OR nsaid[tw] OR nsaids[tw] OR ((non-steroidal[tw] OR nonsteroidal[tw]) AND (anti-inflammatory[tw] OR antiinflammatory[tw])) OR cyclooxygenase*[tw])
AND
(review*[tw] OR evidence*[tw] OR ebm[tw] OR meta-anal*[tw] OR metaanal*[tw])
AND
2000:2014[dp] NOT (animals[mesh] NOT humans[mesh]

Appendix II. Summary of characteristics and results of systematic reviews of RCTs for efficacy of NSAIDs versus placebo

Systematic review	Diagnosis	Relevant RCTs† (subjects)	MA	Dose PDD/ DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
DISORDERS OF THE BACK								
Keller, 2007[79]	Acute LBP	3 RCTs[105-107] (705)	Yes	Not reported	Pain (100mm VAS); Short-term FU: Pooled ES 0.51 (0.16, 0.86)	7/11	Moderate	4
	Chronic LBP	3 RCTs[108-110] (1079)	Yes	Not reported	Pain (100mm VAS); Short-term FU: Pooled ES 0.61 (0.50, 0.74)	9/11	Moderate	
Kuijpers, 2011[80]	Chronic LBP	4 RCTs[108 109 111 112] (1020)	Yes	Not reported	Pain (100 mm VAS); Long-term FU: WMD -12.40 (-15.53, -9.26)	7/11	Moderate	7
Lewis, 2011[83]	Sciatica	2 RCTs[113 114] (703)	No	0.5	Pain (100mm VAS); Immediate FU: Mean difference -6.00 (-11.54, -0.46) for meloxicam, -9.70 (-18.24, -1.16) for lornoxicam	3/5	Small	8
		1 RCT[114] (171)	No	0.7	Pain (100mm VAS); Immediate FU: Mean difference -6.60 (-15.14, 1.94)	4/5	Small	
		1 RCT[113] (532)	No	1.0	Pain (100mm VAS); Immediate FU: Mean difference -5.00 (-10.54, 0.54)	2/5	Small	
		2 RCTs[113 114] (703)	No	0.5	Proportion improved; Immediate FU: OR 1.71 (1.07, 2.72) for meloxicam, 2.19 (0.99, 4.81) for lornoxicam	3/5	NNT=6-9	
		1 RCT[114] (171)	No	0.7	Proportion improved; Immediate FU: OR 1.56 (0.73, 3.34)	4/5	NNT=10	
		1 RCT[115] (50)	No	0.8	Proportion improved; Immediate FU: OR 0.72 (-0,23, 2.23)	3/5	No significant difference	
		1 RCT[113] (532)	No	1.0	Proportion improved; Immediate FU: OR 1.73 (1.09, 2.74)	2/5	NNT=9	
Machado 2009[85]	Acute LBP	3 RCTs[105-107] (427)	Yes	Not reported	Pain (100-point scale); Short-term FU: Pooled mean difference -6 (-1, -11)	Not assessable	Small	3
	Chronic LBP	4 RCTs[108-110 112] (922)	Yes	Not reported	Pain (100-point scale); Short-term FU: Pooled mean difference -10 (-3, -17)	Not assessable	Moderate	

Systematic review	Diagnosis	Relevant RCTs† (subjects)	MA	Dose PDD/ DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
McCarbergh, 2010[87]	Acute LBP	4 RCTs[106 107 116 117] (963)	No	Not reported	Pain (measure not reported): Immediate FU: 3 RCTs found a significant effect on at least one timepoint, 1 RCT no difference	Not reported	Not assessable	1
Pinto, 2012[94]	Acute sciatica	3 RCTs[113 114 118] (658)	Yes	0.5-2	Pain (100-point scale); Immediate FU: Pooled mean difference -4.9 (-10.2, 0.4)	7/10	Negligible	7
Roelofs, 2008[96]	Acute LBP without sciatica	3 RCTs[106 107 116] (577)	Yes	0.5-2	Pain (100mm VAS); Short-term FU: Pooled mean difference -7.69 (-12.08, -3.3)	7/11	Small	8
	Acute LBP with sciatica	2 RCTs[113 118] (565)	Yes	0.5-2	Pain (100mm VAS); Short-term FU: Pooled mean difference -0.16 (-11.92, 11.59)	7/11	No significant difference	
	Acute LBP mixed population	7 RCTs[106 107 113 115 119-121] (945)	Yes	0.5-4	Proportion improved; Short-term FU: RR 1.19 (1.07, 1.33)	7/11	NNT=10	
	Chronic LBP	4 RCTs[108 109 111 112] (1020)	Yes	1-4	Pain (100mm VAS); Long-term FU: Pooled mean difference -12.40 (-15.53, 9.26)	7/11	Moderate	
Schnitzer, 2004[97]	Acute LBP	1 RCT[116] (282)	No	1-2	Pain (100mm VAS); Immediate FU: Significant effect	72/100	Not assessable	3
	Chronic LBP	1 RCT[111] (37)	No	1-1.3	Pain (100mm VAS); Immediate FU: Significant effect	47/100	Not assessable	
Vroomen, 2000[102]	Sciatica	3 RCTs[115 118 121] (321)	Yes	0.75-4	Proportion improved; Immediate FU: Pooled OR 0.99 (0.6, 1.7)	60/100	No significant difference	4
DISORDERS OF THE UPPER EXTREMITY								
Gerritsen, 2002[76]	CTS	1 RCT[122] (45)	No	1	Proportion improved; Short-term FU: No significant difference	9/11	No significant difference	6
Goodyear-Smith, 2004[77]	CTS	2 RCTs[122 123] (not reported)	No	Not reported	Proportion improved; FU not reported: No significant difference	6.5/10	No significant difference	4

Systematic review	Diagnosis	Relevant RCTs† (subjects)	MA	Dose PDD/ DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
O'Connor, 2003[90]	CTS	1 RCT[122] (44)	No	1	Proportion improved; Short-term FU: No significant effect	Not assessable	No significant difference	8
Pattanittum, 2013[91]	Lateral elbow pain	1 RCT[124] (128)	No	1.5	Pain (100mm VAS); Short-term FU: Mean difference -13.90 (-23.20, -4.60)	2/6	Moderate	9
		1 RCT[125] (111)	No	1	Proportion improved; Short-term FU: RR 1.17 (0.82, 1.67)	3/6	No significant difference	
Piazzini, 2007[93]	CTS	1 RCT[122] (73)	No	1	Proportion improved; Short-term FU: Significant effect	9/11	Not assessable	5
DISORDERS OF THE LOWER EXTREMITY								
Heintjes, 2004[78]	PFPS	1 RCT[126] (42)	No	1	Pain (100mm VAS): Short-term FU: SMD -0.78 (-1.46, -0.10)	20/32	Moderate	9
		1 RCT[127] (30)	No	Not reported	Proportion improved; Long-term FU: RR 1.22 (0.43, 3.42)	24/32	No significant difference	
Reurink, 2011[95]	Acute hamstring injury	1 RCT[128] (44)	No	Not reported	Pain (100mm VAS); Immediate FU: No significant difference (pain score 7.9±6.6 for meclofenamate, 8.8±7.7 for diclofenac and 3.9±3.3 for placebo group)	7/10	No significant difference	7
Snijders, 2008[98]	Acute ankle sprain	6 RCTs[129-134] (not reported)	No	Not reported	Pain (measure not reported); FU not reported: 5 RCTs found a significant effect (of which 1 found an effect ≥ 20%), 1 RCT found no significant difference	Not reported	Not assessable	1
GENERALIZED DISORDERS								
Abeles, 2008[65]	Fibromyalgia	2 RCTs[135 136] (not reported)	No	Not reported	Proportion improved; FU not reported: No significant difference	Not reported	No significant difference	0
TEMPEROMANDIBULAR DISORDERS								
List, 2003[84]	TMD	1 RCT[137] (not reported)	No	2	Pain (measure not reported); FU not reported: No significant difference	Not reported	No significant difference	6

Systematic review	Diagnosis	Relevant RCTs† (subjects)	MA	Dose PDD/ DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
Mujakperuo, 2010[89]	TMD	1 RCT[138] (68)	No	1	Pain (100mm VAS); Short-term FU – nsNSAID: Mean difference -1.70 (-2.14, -1.25) for nsNSAID, 0.03 (-0.40, 0.45) for coxib	5/6	Negligible	9
OSTEOARTHRITIS								
Adatia 2012[66]	Hip and knee OA	1 RCT[139] (298)	No	1	Pain (various scales); Short-term FU: Significant effect for pain in motion but not for pain in rest	Not reported	Not assessable	1
		3 RCTs[140-142] (1399)	No	Not reported	Pain (various scales); Long-term FU: Significant effect	Not reported	Not assessable	
Altman 2010[67]	Hand OA	3 RCTs[143-145] (695)	No	0.66 - 4	Pain (various scales); Short-term FU: Significant effect	Not reported	Not assessable	0
Argoff 2011[68]	OA	1 RCT[146] (513)	No	0.5 - 1	Pain on movement/past 24h; Short-term FU: Significant effect	Not reported	Not assessable	0
Bjordal 2004[70]	Knee OA	23 RCTs[146-166] (10845)	Yes	Not reported	Pain (various scales converted to 100mm VAS): Short- and long-term FU: Pooled ES 0.32 (0.24-0.39)	4/5	Small	7
Bjordal 2007[69]	Knee OA	25 RCTs[146-155 157-171] (9964)	Yes	Not reported	Pain (100mmVAS); Short-term FU: Pooled mean difference 10.2 (8.8-11.6)	4/5	Moderate	6
Chavez 2003[71]	OA	3 RCTs[154 172 173] (1923)	No	0.1	Proportion improved; Long-term FU: No significant effect	Not reported	Not assessable	1
				0.4-2	Proportion improved; Long-term FU: Significant effect			
Deeks 2002[72]	OA	3 RCTs [147 166 174] (1946)	Yes	1-4	Pain (WOMAC); Long-term FU: SMD -0.34 (-0.43, -0.25)	5/5	Small	6
Edwards 2004[74]	OA	2 RCTs[154 173] (1162)	Yes	1	Pain (WOMAC); Long-term FU: WMD -0.8 (-0.1, -1.5)	5/5	Not assessable	7
		1 RCT[154] (815)	No	2	Pain (WOMAC); Long-term FU: WMD -0.9 (-0.02, -1.8)	5/5	Not assessable	

Systematic review	Diagnosis	Relevant RCTs† (subjects)	MA	Dose PDD/ DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
Garner 2005[75]	OA	2 RCTs[142 175] (424)	Yes	0.5	Pain (WOMAC); Long-term FU: SMD 0.50 (0.30, 0.71)	5/5	Moderate	9
		4 RCTs[142 152 175 176] (855)	Yes	1	Pain (WOMAC); Long-term FU: SMD 0.62 (0.47, 0.77)	5/5	Small	
		1 RCT[176] (145)	Yes	5	Pain (WOMAC); Long-term FU: SMD 1.08 (0.73, 1.43)	5/5	Large	
		3 RCTs[168 177 178] (2316)	Yes	0.5	Proportion improved; Long-term FU: Pooled RR 1.85 (1.59, 2.16)	5/5	NNT=4	
		2 RCTs[152 178] (582)	Yes	1	Proportion improved; Long-term FU: Pooled RR 1.75 (1.35, 2.26)	5/5	NNT=4	
Lee 2005[81]	OA	15 RCTs[142 147 150 152-154 157 165 170 173 178-182] (10172)	Yes	0.5-2	Pain (WOMAC); Long-term FU: Pooled ES 0.37 (0.26, 0.49) for nsNSAIDs, 0.44 (0.33, 0.55) for coxibs	Not reported	Small	4
Mahendira 2009[86]	Hand OA	3 RCTs[143-145] (1330)	No	Not reported	Proportion improved; Short-term FU: Significant effect	Not assessable	Not assessable	5
McCormack 2011[88]	OA	9 RCTs[152 161 169 171 183-187] (not reported)	No	Not reported	Pain (WOMAC); FU not reported: Significant effect	Not reported	Not assessable	2
		2 RCTs[152 170] (not reported)	No	Not reported	Pain on walking (100mm VAS); FU not reported: Significant effect	Not reported	Not assessable	

Systematic review	Diagnosis	Relevant RCTs† (subjects)	MA	Dose PDD/ DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
Stam 2012[99]	OA	26 RCTs[140 141 147 148 152 153 157 161 169 171 179-181 183 184 186-193] (21941)	Yes	0.5	Pain (WOMAC); Long-term FU: Pooled ES -0.11 (-0.31, -0.10) for celecoxib, -0.66 (-0.83, -0.49) for etoricoxib	Not reported	Negligible to moderate	5
				1	Pain (WOMAC); Long-term FU: Pooled ES -0.34 (-0.41, -0.27) for celecoxib, -0.30 (-0.46, -0.14) for lumiracoxib, -0.62 (-0.78, -0.45) for etoricoxib	Not reported	Small to moderate	
				1.5	Pain (WOMAC); Long-term FU: Pooled ES -0.49 (-0.67, -0.31)	Not reported	Moderate	
				2	Pain (WOMAC); Long-term FU: Pooled ES -0.39 (-0.53, -0.26) for naproxen, -0.41 (-0.63, -0.18) for ibuprofen, -0.27 (-0.45, -0.10) for celecoxib, -0.27 (-0.44, -0.13) for lumiracoxib	Not reported	Small	
				4	Pain (WOMAC); Long-term FU: Pooled ES -0.29 (-0.46, -0.13)	Not reported	Small	
Trijau 2010[100]	OA	33 RCTs[141-143 145 146 148 153 155 157 161 162 165 166 168 169 171 173 176 179-181 183 186 187 189 194-201] (20915)	Yes	Not reported	Pain (100-point scale); Short- and long-term FU: Pooled ES -0.66 (-0.71, -0.61) for 27 RCTs with flare design and -0.45 (-0.54, -0.36) for 6 RCTs without flare design	4/5	Small to moderate	3

CTS: carpal tunnel syndrome; DDD: defined daily dosage; ES: effect size; FU: follow-up; MA: meta-analysis; NNT: number needed to treat; NSAID: non-steroidal anti-inflammatory drug; LBP: low back pain; OR: odds ratio; PDD: prescribed daily dosage; PFPS: patellofemoral pain syndrome; RCT: randomized controlled trial; RR: risk ratio; SMD: standardised mean difference; TMD: temperomandibular disorders; VAS: visual analogue scale; WMD: weighted mean difference; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

† considered relevant if meeting our inclusion criteria for population, intervention, control and outcome.

‡ as assessed and reported by the authors of each systematic review

Appendix III. Summary of characteristics and results of systematic reviews of RCTs for efficacy of NSAIDs versus paracetamol

Review	Diagnosis	Relevant studies† (subjects)	MA	Dose NSAID PDD/DDD	Dose PCM PDD/DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
DISORDERS OF THE BACK									
Roelofs, 2008[96]	Acute LBP	3 RCTs[202-204] (309)	Yes	0.8-1.6	Not reported	Pain (various scales); Short-term FU: SMD -0.21 (-0.43, 0.02)	4/11	No significant difference	8
		3 RCTs[205-207] (128)	Yes	1.3-2	1-1.3	Proportion improved; Short-term FU: Pooled RR 1.23 (0.88, 1.73)	4/11	NNT=9	
	Chronic LBP	1 RCT[205] (30)	No	1.3	1.3	Proportion improved; Short-term FU: Significant effect	7/11	Not assessable	
Schnitzer, 2004[97]	Acute LBP	1 RCT[202] (60)	No	1-1.6	1.3	Pain (measure not specified); Short-term FU: Significant effect	36/100	Not assessable	3
	Chronic LBP	1 RCT[205] (30)	No	1.3	1.3	Proportion improved; Short-term FU: Significant effect	61/100	Not assessable	
OSTEOARTHRITIS									
Delafuente, 2004[73]	OA	1 RCT[208] (204)	No	0.5-1	1.3	Pain (measure not specified); Short-term FU: No significant difference	Not reported	Not assessable	1
		1 RCT[209] (174)	No	1.5	0.9	Pain (measure not specified); Long-term FU: No significant difference	Not reported	Not assessable	
		1 RCT[210] (227)	No	1.5	1.3	Pain (measure not specified); Long-term FU: Significant effect	Not reported	Not assessable	
		1 RCT[188] (382)	No	2-5	1.3	Pain (measure not specified); Long-term FU: Significant effect	Not reported	Not assessable	
Garner, 2005[75]	OA	1 RCT[188] (186)	No	1	1.3	Pain (WOMAC); Long-term FU: SMD 0.14 (-0.15, 0.43)	5/5	No significant difference	9
				1	1.3	Proportion improved; Long-term FU: RR 1.33 (1.06, 1.97)	5/5	NNT=6	
				2	1.3	Pain (WOMAC); Long-term FU: SMD 0.46 (0.17, 0.75)	5/5	Small	
				2	1.3	Proportion improved; Long-term FU: RR 1.54 (1.14, 2.08)	5/5	NNT=5	

Review	Diagnosis	Relevant studies† (subjects)	MA	Dose NSAID PDD/DDD	Dose PCM PDD/DDD	Results Outcome measure, duration of FU, results (95% CI)	Mean quality score of RCTs according to SR‡	Magnitude of group difference / NNT	AMSTAR score
Lee, 2004[82]	OA	6 RCTs[148 188 208-211] (1208)	Yes	0.5-2	0.9-1.3	Pain at rest (100mm VAS); Short- to long-term FU: WMD -6.33 (-9.24, -3.41)	4/5	Small	8
		6 RCTs[148 188 208-210 212] (1051)	Yes	0.5-2	0.7-1.3	Pain on movement (100mm VAS): Short to long-term FU: WMD -5.76 (-8.99, -2.52)	4/5	Small	
Pavelka, 2012[92]	OA	1 RCT[148] (54)	No	1.5	1.3	Pain (WOMAC); Long-term FU: Group difference not assessable	Not reported	Not assessable	0
Stam, 2012[99]	OA	9 RCTs[140 141 181 186 188 191 193 213] (6535)	No	0.5	1.3	Pain (WOMAC); Long-term FU: Pooled ES -0.57 (-0.80, -0.34)	Not reported	Moderate	5
Verkleij, 2011[101]	Knee and hip OA	14 RCTs[148 188 191 208-211 214-220] (4552)	Yes	0.5-2	0.4-1.3	Pain (various scales); Immediate, short and long-term FU: SMD -0.29 (-0.35, -0.22)	8.9/12	Small	8
Wegman, 2004[103]	Hip and knee OA	3 RCTs[208-210] (589)	Yes	0.5-2	0.3-1.3	Pain (general or at rest, various scales); Short- and long-term FU: SMD 0.33 (0.15, 0.50)	6.5/11	Small	4

DDD: defined daily dosage; ES: effect size; FU: follow-up; MA: meta-analysis; NNT: number needed to treat; NSAID: non-steroidal anti-inflammatory drug; LBP: low back pain; OR: odds ratio; PDD: prescribed daily dosage; RCT: randomized controlled trial; RR: risk ratio; SMD: standardised mean difference; VAS: visual analogue scale; WMD: weighted mean difference; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

† considered relevant if meeting our inclusion criteria for population, intervention, control and outcome.

‡ as assessed and reported by the authors of each systematic review

Chapter 3
Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints

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ABSTRACT

Objective

To determine the influence of ischaemic cardiovascular (CV) risk on prescription of non-steroidal anti-inflammatory drugs (NSAIDs) by general practitioners (GPs) in patients with musculoskeletal (MSK) complaints.

Design

Cohort study.

Setting

A healthcare database containing the electronic GP medical records of over one million patients throughout the Netherlands.

Patients

474,201 adults consulting their GP with a new MSK complaint between 2000 and 2010. Patients were considered at high CV risk if they had a history of myocardial infarction, angina pectoris, stroke, transient ischaemic attack or peripheral arterial disease, and at low CV risk if they had no CV risk factors.

Main Outcome Measures

Frequency of prescription of non-selective (ns)NSAIDs and selective cyclooxygenase-2 inhibitors (coxibs).

Results

Overall, 24.4% of patients were prescribed an nsNSAID and 1.4% a coxib. Of the 41,483 patients with a high CV risk, 19.9% received an nsNSAID and 2.2% a coxib. These patients were more likely to be prescribed a coxib than patients with a low CV risk (OR 1.9, 95% CI 1.8-2.0). Prescription of nsNSAIDs decreased over time in all risk groups and was lower in patients with a high CV risk than in patients with a low CV risk (OR 0.8, 95% CI 0.7-0.8).

Conclusion

Overall, patients with a high CV risk were less likely to be prescribed an NSAID than patients with a low CV risk. Nevertheless, one in five high CV risk patients received an NSAID, indicating that there is still room for improvement.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of musculoskeletal (MSK) complaints because of their analgesic and anti-inflammatory properties. International and national guidelines on various MSK complaints, such as back pain, shoulder pain and osteoarthritis, recommend prescribing NSAIDs, either as a first choice analgesic or as a second choice if paracetamol fails to provide sufficient pain relief.[1-6] The use of NSAIDs is known to be associated with peptic ulcer disease and its complications, most notably upper gastrointestinal (UGI) bleeding, obstruction and perforation.[7 8] The need to limit these UGI complications led to the development of selective cyclooxygenase-2 inhibitors (coxibs), which are associated with a significantly lower incidence of UGI complications when compared to traditional, non-selective NSAIDs (nsNSAIDs).[9-12]

However, shortly after the introduction of coxibs, concerns were raised regarding their cardiovascular (CV) safety profile. In September 2004, rofecoxib was withdrawn from world markets after a randomized controlled trial showed the incidence of stroke, myocardial infarction, or sudden cardiac death in patients taking rofecoxib was two times that of patients taking placebo.[13] An increased risk of ischaemic CV events was also observed in studies of other coxibs, leading the European Medicines Agency to contraindicate the use of any coxib in patients with established ischaemic heart disease, stroke or peripheral arterial disease in 2005.[14] Since then, there is increasing evidence that the risk of ischaemic CV events is increased not only by the use of coxibs but also by the use of nsNSAIDs, with the possible exception of naproxen.[15-18] Recent guidelines and consensus therefore recommend avoiding the prescription of NSAIDs in general in patients at high CV risk.[19-21]

In this population-based cohort study, we aimed to examine the association between ischaemic CV risk and the prescription of NSAIDs in patients with MSK complaints. In addition, we aimed to determine the influence of demographic factors, prior NSAID prescription, the type of MSK complaint presented and the presence of UGI risk factors and renal insufficiency on NSAID prescription in this group of patients.

MATERIALS AND METHODS

Setting

A cohort study was conducted in the Integrated Primary Care Information (IPCI) database. This primary health care database contains the electronic patient records of over one million patients registered with GPs throughout the Netherlands. In the Netherlands, all 16.8 million citizens are registered with a GP, who forms the first point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The electronic medical record of each patient can therefore be assumed to contain all relevant medical

information, including medical findings and diagnoses from secondary care. Further details of the database have been described elsewhere.[22 23]

Study cohort

The study population comprised all patients ≥ 18 years of age newly diagnosed with a MSK complaint between 1st January 2000 and 31st December 2010. Diagnoses were considered new if the patient had not been diagnosed with the same MSK complaint in the six months prior to consultation. Only patients with at least 12 months of valid database history prior to study entry were included. Diagnoses of MSK complaints were identified based on International Classification for Primary Care (ICPC)-coding.[24] If the patient consulted their GP again with the same complaint within six months of initial diagnosis, this consultation was considered part of the same MSK complaint episode. For each patient, only the first newly diagnosed complaint episode was included. The date of first consultation was considered the index date.

Cardiovascular risk, upper gastrointestinal risk and renal insufficiency

In defining CV risk, UGI risk and renal insufficiency we aimed to conform to Dutch prescription guidelines as much as possible. For cardiovascular risk, no Dutch guideline is currently available, but a national consensus report was published in 2009 containing prescription recommendations.[21] In line with this report, patients were considered at high CV risk if they had a history of myocardial infarction, angina pectoris, stroke, transient ischaemic attack, or peripheral arterial disease prior to the index date. They were considered at moderate CV risk if they did not have one of the risk factors described above but did have a history of diabetes, hypertension or hyperlipidaemia. Patients without any of these CV risk factors were considered at low CV risk. In addition, risk factors for the occurrence of UGI complications were identified. Based on the most recent Dutch guideline on the prescription of NSAIDs,[25] patients were considered at high UGI risk if they had a history of upper gastrointestinal bleeding or ulceration, were aged over 70 years or had two or more of the following risk factors: age 60-70 years, history of heart failure, diabetes or severe rheumatoid arthritis, use of antithrombotics, corticosteroids, or selective serotonin reuptake inhibitors. They were considered at moderate UGI risk if only one of the latter risk factors was present. In the absence of any of these risk factors patients were considered to have a low UGI risk. Finally, we identified each patient's most recent available laboratory measurement of glomerular filtration rate (GFR) prior to the index date. If this GFR was <30mL/min, patients were considered to have significant renal insufficiency.[26]

The history of the diseases and conditions described above were assessed based on ICPC-coding and free text search strings. In the case of diabetes and hyperlipidaemia, the use of respectively antidiabetic and lipid modifying drugs, identified based on ATC classification code,[27] was taken into account in addition to ICPC coding as proxy . If patients had a his-

tory of rheumatoid arthritis based on an ICPC-code L88, this was defined as being severe if they also had a prescription in the year prior to the index date of specific antirheumatic agents, immunosuppressants, hydroxychloroquine, sulfasalazine or cyclophosphamide.

NSAID prescription

For all included patients, the first NSAID prescription issued during the complaint episode was identified based on ATC-classification code.[27] Only NSAID prescriptions issued on the day of a consultation for the MSK complaint were included. It has been suggested that the use of naproxen is less likely to increase cardiovascular risk than the use of other nsNSAIDs, and that the prescription of naproxen may be warranted in patients at a high CV risk.[19 20 28] In addition, there are indications the risk of CV disease increased with NSAID use in a dose-dependent manner.[29] To examine whether GPs take these possibilities into account, a sensitivity analysis was conducted excluding naproxen and excluding all low-dosed nsNSAID and low-dosed coxib prescriptions, which was defined as a prescribed daily dosage (PDD) smaller than half the defined daily dosage (DDD).

Statistics

Baseline characteristics of the moderate and high CV risk groups were compared to those of the low CV risk group using a χ^2-test for dichotomous variables and independent t-test for age as a continuous variables. Univariate analyses of potential predictors of NSAID prescription such as age, gender, CV risk and UGI risk were conducted and unadjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by performing logistic regression analyses. For the predictor CV risk group, the same univariate logistic regression analyses were performed stratified per UGI risk group. For this stratified analysis, we also conducted multivariate analyses to present ORs adjusted for other predictors of nsNSAID and coxib prescription. Finally, the influence of CV risk on coxib and nsNSAID prescription was studied stratified per time period, and ORs adjusted for the year of the MSK complaint episode within each time period were calculated, again using multivariate logistic regressions analysis. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL).

Study approval

The study was approved by the Board of Directors of the IPCI database.

RESULTS

Study cohort

Between 2000 and 2010, 804,261 adult patients aged over 18 years contributed data to the IPCI database. These patients were comparable to the general population of the Netherlands with regards to age and gender (mean age 40 years, 52% female versus 41 years, 51% female in the Dutch general population).[30] Of these, 474,201 patients (59%) presented with a new MSK complaint and were included in the cohort. Baseline characteristics of all included patients are described in table 1. This table also shows the baseline characteristics per CV risk group. When comparing patients with a moderate or high CV risk to those with a low CV risk group, statistically significant differences were found for almost all characteristics with the exception of two symptomatic diagnoses of the MSK system.

Predictors of nsNSAID and coxib prescription

In total, 115,713 (24.7%) of all MSK complaint episodes were treated with an nsNSAID and 6,456 (1.4%) were treated with a coxib (table 2). The most frequently prescribed nsNSAIDs were diclofenac, naproxen and ibuprofen (respectively 58%, 13% and 12% of all nsNSAIDs prescribed) and the most frequently prescribed coxibs were rofecoxib and etoricoxib (49% and 33% of all coxibs prescribed, results not shown in table).

Age, gender and NSAID prescription in the 6 months prior to the index date were all predictive of nsNSAID and coxib prescription. The frequency of nsNSAID and coxib prescription also varied depending on the type of MSK complaint diagnosed. The prescription of coxibs was particularly high in patients suffering from arthritis. When corrected for age and gender, the odds of receiving a coxib were still tenfold in patients with arthritis when compared to those with complaints after trauma (adjusted OR 9.8; 95% CI 8.4-11.5, not shown in table). The individual CV risk factors were all associated with a higher chance of coxib prescription and a lower chance of nsNSAID prescription. Similarly, patients in the moderate and high CV risk group were significantly more likely to receive a coxib than patients in the low CV risk group. The pattern for prescription of nsNSAIDs was less clear, as they were prescribed somewhat more frequently to patients with a moderate CV risk when compared to those with a low CV risk, but less frequently to those with a high CV risk than those with a low CV risk. UGI risk was also a strong predictor of coxib prescription, whereas a high UGI risk was associated with a lower chance of nsNSAID prescription. Patients with renal insufficiency were less likely to be prescribed an nsNSAID and more likely to be prescribed a coxib than patients without renal insufficiency.

Table 1. Baseline characteristics in the study population.

	Total	Per CV risk group		
	(n=474 201) n (%)	Low CV risk (n=365 534) n (%)	Moderate CV risk (n=67 184) n (%)	High CV risk (n=41 483) n (%)
Age (mean ± SD)	46.6 ± 17.4	42.2 ± 15.5	58.9 ± 14.7	65.3 ± 14.5
Age category				
18-35 years	144 797 (30.5)	138 809 (38.0)	4 532 (6.7)	1 456 (3.5)
36-50 years	147 497 (31.1)	127 403 (34.9)	14 773 (22.0)	5 321 (12.8)
51-65 years	108 132 (22.8)	69 526 (19.0)	25 735 (38.3)	12 871 (31.0)
>65 years	73 775 (15.6)	29 796 (8.2)	22 144 (33.0)	21 835 (52.6)
Female	256 015 (54.0)	196 550 (53.8)	38 906 (57.9)	20 559 (49.6)
NSAID prescription in 6 months prior to diagnosis	37 637 (7.9)	26 472 (7.2)	6 831 (10.2)	4 334 (10.4)
MSK complaint episode				
Symptomatic diagnosis				
Back/neck	108 213 (22.8)	86 957 (24.1)	12 641 (18.8)	7 615 (18.4)
Upper extremity	82 026 (17.3)	63 366 (17.3)	11 810 (17.6)^{NS}*	6 850 (16.5)
Lower extremity	66 107 (13.9)	49 802 (13.6)	10 003 (14.9)	6 302 (15.2)
Generalized/other	59 986 (12.6)	46 572 (12.7)	8 035 (12.0)	5 379 (13.0)^{NS}**
Arthritis	21 529 (4.5)	11 548 (3.2)	5 739 (8.5)	4 242 (10.2)
Inflammatory arthritis	4 676 (1.0)	2 874 (0.8)	1 045 (1.6)	757 (1.8)
Osteoarthritis	11 211 (2.4)	5 944 (1.6)	3 056 (4.5)	2 211 (5.3)
Gout	5 642 (1.2)	2 730 (0.7)	1 638 (2.4)	1 274 (3.1)
Radiculopathy	25 409 (5.4)	19 180 (5.2)	3 822 (5.7)	2 407 (5.8)
Trauma	55 211 (11.6)	45 586 (12.5)	6 064 (9.0)	3 561 (8.6)
Other	55 720 (11.8)	41 523 (11.4)	9 070 (13.5)	5 127 (12.4)
Individual CV risk factors†				
Diabetes	28 597 (6.0)	-	20 847 (31.0)	7 750 (18.7)
Hypertension	63 841 (13.5)	-	46 077 (68.6)	17 764 (42.8)
Hyperlipidaemia	30 600 (6.5)	-	18 129 (27.0)	12 471 (30.1)
MI/AP	27 118 (5.7)	-	-	27 118 (65.4)
Stroke/TIA	14 118 (3.0)	-	-	14 118 (34.0)
PAD	5 715 (1.2)	-	-	5 715 (13.8)
UGI risk group				
Low UGI risk	335 556 (70.8)	305 168 (83.5)	22 003 (32.8)	8 385 (20.2)
Moderate UGI risk	63 843 (13.5)	34 692 (9.5)	21 058 (31.3)	8 093 (19.5)
High UGI risk	74 802 (15.8)	25 674 (7.0)	24 123 (35.9)	25 005 (60.3)
Renal insufficiency	285 (0.1)	27 (0.01)	118 (0.2)	140 (0.3)

CV: cardiovascular; NSAID: non-steroidal anti-inflammatory drug; NS: non-significant; MSK: musculoskeletal; MI: myocardial infarction; AP: angina pectoris; TIA: transient ischaemic attack; PAD: peripheral arterial disease; UGI: upper gastrointestinal.

Comparisons were made for the moderate versus the low CV risk group and for the high versus the low CV risk group. All comparisons between moderate or high CV risk patients and low CV risk patients were statistically significant (P-value<0.05), unless otherwise stated with the letters 'NS': non-significant.

*Comparison with low CV risk patients not statistically significant, P-value 0.13

**Comparison with low CV risk patients not statistically significant, P-value 0.19.

† Risk factors used to define low, moderate and high CV risk groups.

Table 2. Predictors of prescription of nsNSAIDs and coxibs.

	No NSAID prescribed (n=352 032) n (%*)	nsNSAID prescribed (n=115 713) n (%*)	Coxib prescribed (n=6 456) n (%*)	OR (95% CI)	
				nsNSAID vs. no NSAID	coxib vs. no NSAID
Age category					
18-35 years	114 077 (78.8)	29 948 (20.7)	772 (0.5)	1 (ref.)	1 (ref.)
36-50 years	105 154 (71.3)	40 815 (27.7)	1 528 (1.0)	1.5 (1.5-1.5)	2.2 (2.0-2.3)
51-65 years	76 359 (70.6)	29 688 (27.5)	2 085 (1.9)	1.5 (1.5-1.5)	4.0 (3.7-4.4)
>65 years	56 442 (76.5)	15 262 (20.7)	2 071 (2.8)	1.0 (1.0-1.1)	5.4 (5.0-5.9)
Gender					
Male	159 766 (73.2)	55 909 (25.6)	2 511 (1.2)	1 (ref.)	1 (ref.)
Female	192 266 (75.1)	59 804 (23.4)	3 945 (1.5)	0.9 (0.9-0.9)	1.3 (1.2-1.4)
NSAID prescription in 6 months prior	24 860 (66.1)	11 688 (31.1)	1 089 (2.9)	1.5 (1.4-1.5)	2.7 (2.5-2.9)
MSK complaint					
Trauma	49 345 (89.4)	5 605 (10.2)	261 (0.5)	1 (ref.)	1 (ref.)
Symptomatic diagnosis					
Back/neck	70 464 (65.1)	36 477 (33.7)	1 272 (1.2)	4.6 (4.4-4.7)	3.4 (3.0-3.9)
Upper extremity	56 150 (68.5)	24 558 (29.9)	1 318 (1.6)	3.9 (3.7-4.0)	4.4 (3.9-5.1)
Lower extremity	54 211 (82.0)	11 109 (16.8)	787 (1.2)	1.8 (1.7-1.9)	2.8 (2.4-3.2)
Generalized/other	46 926 (78.2)	12 308 (20.5)	752 (1.3)	2.3 (2.2-2.4)	3.0 (2.6-3.5)
Arthritis	13 943 (64.8)	6 545 (30.4)	1 041 (4.8)	4.1 (4.0-4.3)	14.1 (12.3-16.2)
Inflammatory arthritis	3 027 (64.7)	1 386 (29.6)	263 (5.6)	4.0 (3.8-4.3)	16.4 (13.8-19.6)
Osteoarthritis	8 239 (73.5)	2 349 (21.0)	623 (5.6)	2.5 (2.4-2.6)	14.3 (12.3-16.6)
Gout	2 677 (47.4)	2 810 (49.8)	155 (2.7)	9.2 (8.7-9.8)	10.9 (8.9-13.4)
Radiculopathy	16 699 (65.7)	8 269 (32.5)	441 (1.7)	4.4 (4.2-4.5)	5.0 (4.3-5.8)
Other	44 294 (79.5)	10 842 (19.5)	584 (1.0)	2.2 (2.1-2.2)	2.5 (2.2-2.9)
Individual CV risk factors					
No CV risk factors	270 758 (74.1)	90 615 (24.8)	4 161 (1.1)	1 (ref.)	1 (ref.)
Diabetes	21 113 (73.8)	6 864 (24.0)	620 (2.2)	1.0 (1.0-1.0)	1.9 (1.8-2.1)
Hypertension	48 168 (75.6)	14 261 (22.4)	1 312 (2.0)	0.9 (0.9-0.9)	1.8 (1.7-1.9)
Hyperlipidaemia	23 118 (75.5)	6 853 (22.4)	629 (2.1)	0.9 (0.9-0.9)	1.8 (1.6-1.9)
MI/AP	21 113 (77.9)	5 356 (19.8)	649 (2.4)	0.8 (0.7-0.8)	2.0 (1.8-2.2)
Stroke/TIA	11 209 (79.4)	2 626 (18.6)	283 (2.0)	0.7 (0.7-0.7)	1.6 (1.5-1.9)
PAD	4 484 (78.5)	1 117 (19.5)	114 (2.0)	0.7 (0.7-0.8)	1.7 (1.4-2.0)
CV risk group					
Low CV risk	270 758 (74.1)	90 615 (24.8)	4 161 (1.1)	1 (ref.)	1 (ref.)
Moderate CV risk	48 970 (72.9)	16 852 (25.1)	1 362 (2.0)	1.0 (1.0-1.1)	1.8 (1.7-1.9)
High CV risk	32 304 (77.9)	8 246 (19.9)	933 (2.2)	0.8 (0.7-0.8)	1.9 (1.8-2.0)
UGI risk group					
Low UGI risk	248 705 (74.1)	83 753 (25.0)	3 098 (0.9)	1 (ref.)	1 (ref.)
Moderate UGI risk	45 724 (71.6)	16 792 (26.3)	1 327 (2.1)	1.1 (1.1-1.1)	2.3 (2.2-2.5)
High UGI risk	57 603 (77.0)	15 168 (20.3)	2 031 (2.7)	0.8 (0.8-0.8)	2.8 (2.7-3.0)
Renal insufficiency					
No renal insufficiency	351 801 (74.2)	115 666 (24.4)	6 449 (1.4)	1 (ref.)	1 (ref.)
Renal insufficiency	231 (81.1)	47 (16.5)	7 (2.5)	0.6 (0.5-0.8)	1.7 (0.8-3.5)

nsNSAID: non-selective non-steroidal anti-inflammatory drug; NSAID: non-steroidal anti-inflammatory drug; MSK: musculoskeletal; CV: cardiovascular; MI: myocardial infarction; AP: angina pectoris; TIA: transient ischaemic attack; PAD: peripheral arterial disease; UGI: upper gastrointestinal.

*Row percentage.

Table 3. Prescription of coxibs and nsNSAIDs versus no NSAID in moderate and high CV risk patients versus low CV risk patients per GI risk group.

UGI risk group	CV risk group	Number of patients	No NSAID n (%*)	nsNSAID n (%*)	Coxib n (%*)	OR (95% CI)		adj. OR (95% CI)†	
						nsNSAID vs. no NSAID	coxib vs. no NSAID	nsNSAID vs. no NSAID	coxib vs. no NSAID
Low	Low	305 168	226 617 (74.3)	75 915 (24.9)	2 636 (0.9)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Moderate	22 003	15 842 (72.0)	5 836 (26.5)	325 (1.5)	1.1 (1.1-1.1)	1.7 (1.5-1.9)	0.9 (0.9-0.9)	1.1 (1.0-1.2)
	High	8 385	6 246 (74.5)	2 002 (23.9)	137 (1.6)	1.0 (0.9-1.0)	1.9 (1.6-2.3)	0.8 (0.8-0.8)	1.3 (1.1-1.5)
Moderate	Low	34 692	24 776 (71.4)	9 164 (26.4)	752 (2.2)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Moderate	21 058	14 945 (71.0)	5 708 (27.1)	405 (1.9)	1.0 (1.0-1.1)	0.9 (0.8-1.0)	1.0 (1.0-1.1)	0.9 (0.8-1.2)
	High	8 093	6 003 (74.2)	1 920 (23.7)	170 (2.1)	0.9 (0.8-0.9)	1.0 (0.8-1.1)	0.8 (0.8-0.9)	1.0 (0.8-1.2)
High	Low	25 674	19 365 (75.4)	5 536 (21.6)	773 (3.0)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Moderate	24 123	18 183 (75.4)	5 308 (22.0)	632 (2.6)	1.0 (1.0-1.1)	0.9 (0.8-1.0)	1.0 (1.0-1.1)	0.9 (0.8-1.0)
	High	25 005	20 055 (80.2)	4 324 (17.3)	626 (2.5)	0.8 (0.7-0.8)	0.8 (0.7-0.9)	0.8 (0.7-0.8)	0.8 (0.7-0.9)

nsNSAID: non-selective non-steroidal anti-inflammatory drug; NSAID: non-steroidal anti-inflammatory drug; CV: cardiovascular; GI: gastrointestinal.
*Row percentage.
† Adjusted for age, gender, prescription of NSAIDs in 6 months prior, type of MSK complaint, and presence of renal insufficiency.

Influence of UGI risk

Table 3 shows the odds of coxib and nsNSAID prescription versus no NSAID prescription in patients with a high or moderate CV risk versus patients with a low CV risk, stratified per UGI risk group. Within each UGI risk group, differences in prescription of nsNSAIDs and coxibs were found when comparing patients with a high or moderate CV risk with patients with a low CV risk. Notably for coxib prescription the direction of this difference varied depending on the UGI risk group. When adjusted for age, gender, previous NSAID prescription, the type of MSK complaint diagnosed and the presence of renal insufficiency, these differences diminished in magnitude but the same pattern still remained.

Prescription of nsNSAIDs and coxibs over time

Figure 1 shows the prescription of nsNSAIDs and coxibs over time. The prescription of coxibs initially increased over time in both high and low CV risk patients, until 2004, after which a sharp decrease is observed. During the peak year of 2004, the odds of prescription of coxibs in high CV risk patients was around 3 times higher than in 2000 and in 2005 (OR 2.9, 95% CI 2.2-3.7 and OR 3.4, 95% CI 2.5-4.6 for 2004 versus respectively 2000 and 2005, not shown in table).

The odds of coxib prescription significantly higher in patients at high CV risk than in patients at low CV risk (table 4), not only between 2000 and 2004 but also between 2005 and 2010. The odds of nsNSAID prescription remained significantly lower in patients at high CV risk than in patients at low CV risk in both time periods. In a sensitivity analysis

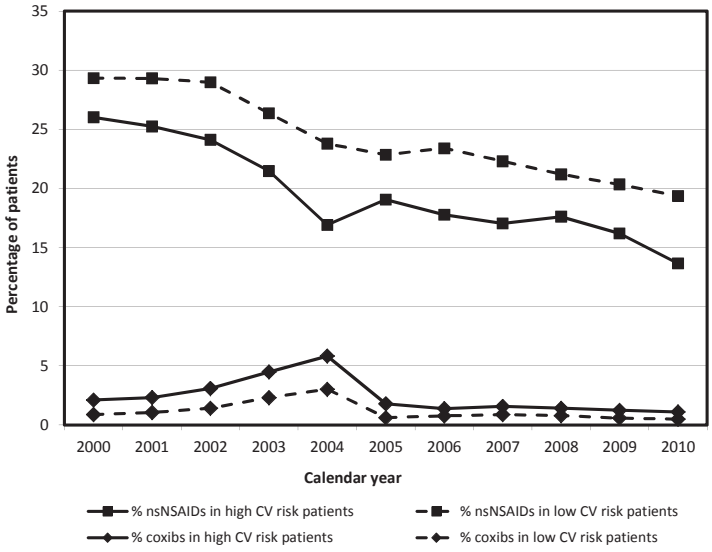

Figure 1. Percentage of patients with a high CV risk and with a low CV risk prescribed an nsNSAID or a coxib per year.

Table 4. Prescription of coxibs and nsNSAIDs versus no NSAID in moderate and high CV risk patients versus low CV risk patients per time period.

Time period	CV risk group	Number of patients	No NSAID n (%*)	nsNSAID n (%*)	Coxib n (%*)	adj. OR (95% CI)†	
						nsNSAID vs. no NSAID	coxib vs. no NSAID
2000-2004	Low	181 443	127 912 (70.5)	50 670 (27.9)	2 861 (1.6)	1 (ref.)	1 (ref.)
	Moderate	27 421	18 939 (69.1)	7 703 (28.1)	779 (2.8)	1.0 (1.0-1.1)	1.9 (1.7-2.1)
	High	18 574	13 619 (73.3)	4 349 (23.4)	606 (3.3)	0.8 (0.8-0.8)	2.0 (1.8-2.2)
2005-2010	Low	184 091	142 846 (77.6)	39 945 (21.7)	1 300 (0.7)	1 (ref.)	1 (ref.)
	Moderate	39 763	30 031 (75.5)	9 149 (23.0)	583 (1.5)	1.1 (1.1-1.1)	2.3 (1.9-2.4)
	High	22 909	18 685 (81.6)	3 897 (17.0)	327 (1.4)	0.8 (0.7-0.8)	1.9 (1.7-2.2)

CV: cardiovascular; NSAID: non-steroidal anti-inflammatory drug; nsNSAID: non-selective non-steroidal anti-inflammatory drug.
*Row percentage.
†Adjusted for year of MSK complaint episode within the time period.

in which prescriptions of naproxen and prescriptions with a PDD smaller than half the DDD were excluded, the odds of prescription of an nsNSAID or coxib versus no NSAID, in patients with a high CV risk versus patients with a low CV risk, were almost the same as that of all nsNSAIDs or coxibs versus no NSAIDs in both time periods (OR 0.8, 95% CI 0.8-0.8 and OR 0.7, 95% CI 0.7-0.8, for nsNSAID versus no NSAID in 2000-2004 and 2005-2010 respectively; OR 2.0, 95% CI 1.8-2.2 and OR 1.9, 95% 1.7-2.2 for coxib versus no NSAID in 2000-2004 and 2005-2010 respectively, not shown in table).

DISCUSSION

Statement of principal findings

In this study, we examined the prescription of NSAIDs in the treatment of MSK complaints by GPs over the course of the last decade, in which evidence emerged regarding the CV risks of these drugs. We found that one quarter of all patients presenting with a MSK complaint were treated with an NSAID. Prescription varied widely depending on the type of MSK complaint diagnosed. Coxibs gained in popularity during the first five years of marketing in the Netherlands, with prescription among high CV risk patients in 2004 almost three times higher than in 2000. After rofecoxib was removed from the market, a decrease in coxib prescription was observed. The decrease in coxib prescription observed after 2004 occurred not only in patients with a high CV risk, but equally in patients with a low CV risk, even after their use was contraindicated in these patients by the European Medicines Agency in 2005.[14] Conversely, nsNSAIDS were prescribed less frequently in patients with a high CV risk than in patients with a low CV risk throughout the study period. These observed differences in prescription between CV risk groups can be partly

explained by the overlap between CV risk and UGI risk. When stratified for UGI risk, the odds of both nsNSAID and coxib prescription decreased with increasing CV risk in patients at moderate or high UGI risk. Interestingly, however, for coxibs the opposite pattern was observed for patients with a low UGI risk. When corrected for other predictors, within the low UGI group coxibs were still prescribed more frequently in those with a high CV risk than in those with a low CV risk, suggesting that other factors play a role in GPs' decision to prescribe these drugs.

Strengths and weaknesses of the study

The strength of this study is that it was conducted in a database containing a large number of patients reflecting the Dutch general population. Nonetheless, some limitations should be considered when reviewing the results. First, only patients presenting with an ICPC coded MSK complaint were included in the cohort. As some GPs may apply the ICPC coding more diligently than others, this may have led to an underestimation or overestimation of NSAID treatment, if the prescribing behaviour of GPs is in any way related to their tendency to apply the ICPC coding. Secondly, we did not have any information on over-the-counter (OTC) use of analgesics. Although coxibs are not available without prescription in the Netherlands, nsNSAIDs are freely available. While this is important, our objective in this study was to determine the association between the cardiovascular risk profile of a patient and NSAID prescription by the GP.

Strengths and weaknesses in relation to other studies

Various studies examining changes in NSAID prescription in primary care over the past decade have been published.[31-34] However, few large-scale studies have focused specifically on the influence of CV risk on the prescription of NSAIDs by GPs, which was the aim of the present study. One prior study did investigate this in the primary care population as we did, but it only reported on the years 2000 to 2004, before evidence emerged of the CV risk of NSAIDs.[35] Other studies which have reported on CV risk and the use of NSAIDs both before and after rofecoxib withdrawal in 2004 were not population-based.[36 37] In addition, in these studies the CV risk profile of the patients was determined based on surrogate pharmacy markers. The strength of our population-based study lies in the fact that we were able to identify all relevant risk factors by conducting free text searches, assessing ICPC-codes and prescriptions of medication, using GP medical records which form a complete record of each patient's medical data.

Meaning of the study

Although international guidelines have provided recommendations on NSAID prescription in patients with CV risk factors,[19 20] as of yet no national Dutch guideline has been published specifically on this topic. The most recent Dutch guideline specifically on NSAID

prescription was published in 2003,[25] at which point in time little was known about the CV risks associated with NSAID use. Over time, prescription of NSAIDs has decreased in all risk groups which might relate to awareness of GPs on risks associated with NSAIDs. Nonetheless, overall one in five patients with a high CV risk presenting with a new MSK complaint received an NSAID. It appears that GPs do not fully consider the CV risks associated with NSAID use when prescribing NSAIDs in these patients, indicating that there is still room for improvement.

REFERENCES

1. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15:S192-300.
2. Chavannes AW, Mens JMA, Koes BW, Lubbers WJ, Ostelo R, Spinnewijn WEM, et al. NHG guideline non-specific low back pain [NHG-standaard aspecifieke lagerugpijn]. *Huisarts Wet* 2005;48:113-23.
3. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014 Jan 24 [Epub ahead of print].
4. Van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J* 2006;15:S169-91.
5. Winters JC, Van der Windt DAWM, Spinnewijn WEM, De Jongh AC, Van der Heijden GJMG, Buis PAJ, et al. NHG guideline shoulder complaints [NHG-standaard schouderklachten]. *Huisarts Wet* 2008;51:555-65.
6. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
7. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
8. Hernandez-Diaz S, Rodriguez LA. Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-99.
9. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-28.
10. Rostom A, Muir K, Dube C, Jolicoeur E, Boucher M, Joyce J, et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. *Clin Gastroenterol Hepatol* 2007;5:818-28.
11. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004;364:665-74.
12. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284: 1247-55.
13. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-1102.

14. European Medicines Agency. Press release: European Medicines Agency concludes action on COX-2 inhibitors. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/01/WC500059088.pdf.
15. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.
16. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and non-selective inhibitors of cyclooxygenase 2. JAMA. 2006;296:1633-44.
17. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
18. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiol Drug Saf* 2011;20:1225-36.
19. Chan FK, Abraham NS, Scheiman JM, Laine L. Management of patients on non-steroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Non-steroidal Anti-inflammatory Drugs and Anti-platelet Agents. *Am J Gastroenterol* 2008;103:2908-18.
20. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:728-38.
21. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PMLA, De Smet PAGM. Targeting outpatient drug safety: Recommendations of the Dutch Harm-Wrestling Task Force. *Drug Saf* 2012;35:245-59.
22. van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993; 119:1036-41.
23. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med* 1999;38:339-44.
24. Lamberts H WM, Hofmans-Okkens IM. International primary care classifications: the effect of fifteen years of evolution. *Fam Pract* 1992;9:330-39.
25. Guideline NSAID use and prevention of gastric damage [Richtlijn NSAID-gebruik en preventive van maagschade]. Utrecht: The Dutch Institute for Health Care improvement CBO; 2003.
26. De Grauw WJC, Kaasjager HAH, Bilo HJG, Faber EF, Flikweer S, Gaillard CAJM, et al. National transmural consensus chronic kidney disease [Landelijke transmurale afspraak chronische nierschade]. *Huisarts Wet* 2009;52:586-97.
27. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. Available at: http://www.whocc.no/.
28. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011;8:e1001098.
29. Singh BK, Haque SE, Pillai KK. Assessment of nonsteroidal anti-inflammatory drug-induced cardiotoxicity. *Expert Opin Drug Metab Toxicol* 2014;10:143-56.
30. Population; key statistics [Bevolking; kerncijfers]. Central Bureau of Statistics; 2012. Available at: http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=37296ned&D1=a&D2=0,10,20,30,40,50,(l-1)-l&HD=130215-1329&HDR=G1&STB=T.

31. Brattwall M, Turan I, Jakobsson J. Musculoskeletal pain: prescription of NSAID and weak opioid by primary health care physicians in Sweden 2004-2008 - a retrospective patient record review. *J Pain Res* 2010;3:131-5.
32. Bedson J, Belcher J, Martino OI, Ndlovu M, Rathod T, Walters K, et al. The effectiveness of national guidance in changing analgesic prescribing in primary care from 2002 to 2009: an observational database study. *Eur J Pain* 2013;17:434-43.
33. Alacqua M, Trifiro G, Cavagna L, Caporali R, Montecucco CM, Moretti S, et al. Prescribing pattern of drugs in the treatment of osteoarthritis in Italian general practice: the effect of rofecoxib withdrawal. *Arthritis Rheum* 2008;59:568-74.
34. Valkhoff VE, van Soest EM, Masclee GM, de Bie S, Mazzaglia G, Molokhia M, et al. Prescription of nonselective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal - a 617 400-patient study. *Aliment Pharmacol Ther* 2012;36:790-9.
35. Mosis G, Stijnen T, Castellsague J, Dieleman JP, van der Lei J, Stricker BH, et al. Channeling and prevalence of cardiovascular contraindications in users of cyclooxygenase 2 selective non-steroidal antiinflammatory drugs. *Arthritis Rheum* 2006;55:537-42.
36. Usher C, Bennett K, Teeling M, Feely J. Characterizing new users of NSAIDs before and after rofecoxib withdrawal. *Br J Clin Pharmacol* 2006;63:494-97.
37. Theibaud P, Patel BV, Nichol MB. Impact of Rofecoxib Withdrawal on Cyclooxygenase-2 Utilization among Patients with and without Cardiovascular Risk. *Value Health* 2006;9:361-8.

Chapter 4
Adverse drug reactions in a primary care population prescribed non-steroidal anti-inflammatory drugs

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(under review)

ABSTRACT

Objective

To determine how often patients with musculoskeletal (MSK) complaints prescribed a non-steroidal anti-inflammatory drug (NSAID), subsequently consult their general practitioner (GP) with a non-serious adverse drug reaction (ADR).

Design

Cohort study.

Setting

A healthcare database containing the electronic GP medical records of over 1.5 million patients throughout the Netherlands.
Patients: 16,626 adult patients with MSK complaints prescribed an NSAID.

Main Outcome Measures

The patients' medical records were manually assessed for the duration of NSAID use with a maximum of two months, and consultations for complaints predefined as adverse events were identified. Subsequently, causality assessment was performed and these adverse events were categorised as probable, possible or unlikely ADRs.

Results

In total, 961 patients (6%) consulted their GP with 1,227 non-serious adverse events. 174 patients (1%) presented at least one probable ADR, and a further 408 (2.5%) at least one possible ADR. Dyspepsia was the most frequent probable ADR, followed by diarrhoea and dyspnea (respectively 34%, 8% and 8% of all probable ADRs).

Conclusion

Of the patients with MSK complaints prescribed an NSAID, almost one in 30 patients reconsulted their GP with a complaint probably or possibly caused by this drug. The burden of such consultations for non-serious ADRs should be taken into account by GPs when deciding whether treatment with an NSAID is appropriate.

INTRODUCTION

Musculoskeletal (MSK) complaints are the most commonly presented complaints in the primary care population.[1] In around one quarter of consultations for these MSK complaints, the general practitioner (GP) prescribes a non-steroidal anti-inflammatory drug (NSAID).[2] The use of these is known to be associated with the occurrence of adverse drug reactions (ADRs), ranging from mild complaints to serious complications, particularly of the gastrointestinal (GI), cardiovascular and renal tract.[3-8] Over the past few decades, many studies have focussed on the occurrence of serious ADRs due to NSAIDs, and on related hospitalizations and death.[3-9] However, less is known about the incidence of non-serious ADRs due to NSAIDs in the primary care population and in resulting health care utilization in the form of GP consultations. One previous study which did focus specifically on primary care patients, found that 40% of chronic NSAID users suffering from gastrointestinal complaints consulted their GP for these complaints.[10] Whether other types of adverse events also lead to consultation and how frequently such consultations occur in short term NSAID users is not known. In this cohort study, we aim to determine how often patients with a MSK complaint newly treated with an NSAID by their GP, subsequently consult their GP because of an adverse drug reaction.

MATERIALS AND METHODS

Setting

This study was conducted in the Integrated Primary Care Information (IPCI) database. This Dutch primary health care database contains the electronic patient records of more than 1.5 million patients. In the Netherlands, all citizens are registered with one GP, who forms the first point of care for all medical complaints. The electronic medical records contain all journal entries written by the GPs, and coded and anonymous data on patient demographics, diagnoses using the International Classification for Primary Care (ICPC),[11] referrals, laboratory findings and drug prescriptions. Further details of the database have been described elsewhere.[12,13]

Patients

The study population comprised all patients ≥ 18 years newly prescribed an NSAID because of a MSK complaint between 1st January 2010 and 1st July 2010, with at least a 12-month valid database history prior to the date of study entry. Excluded were patients who had been prescribed an NSAID in the 6 months prior to study entry and patients without sufficient follow-up time in the IPCI database. Diagnoses of MSK complaints were identified based on ICPC-coding and were considered new if the patient had not been diagnosed with the

same MSK complaint in the six months prior to consultation. Only patients who received an NSAID prescription, identified by Anatomical Therapeutic Chemical (ATC) code,[14] on the day of a consultation for the MSK complaint were included.

Consultations for adverse events

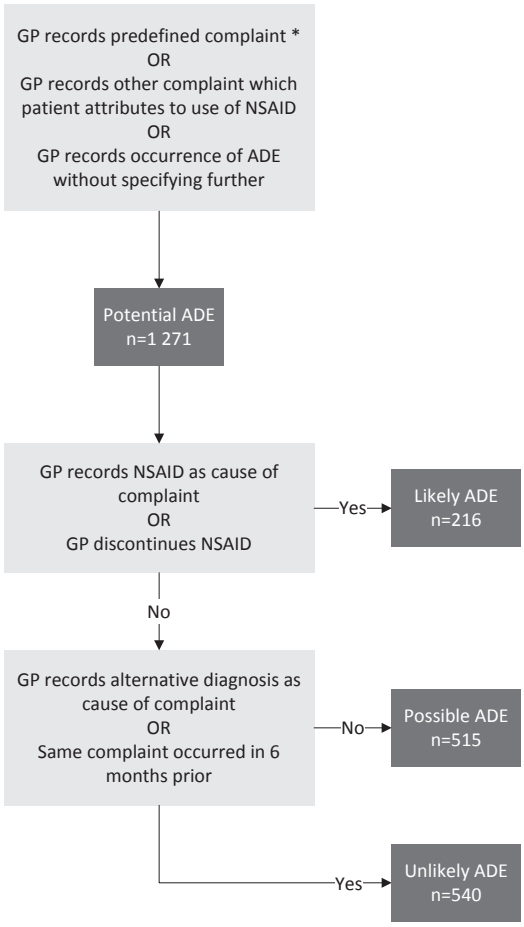
The electronic medical record of all included patients was manually assessed for the duration of continuous NSAID use with a maximum of two months, to determine whether the patient consulted their GP with an adverse event. Continuous use was defined as use of NSAIDs with treatment gaps of no more than 10% of the previous prescription duration. Adverse events were predefined based on listed common NSAID-related adverse drug reactions. All clinical complaints listed as common ADRs for at least two types of NSAID were included.[15] In addition to these, angio-oedema and signs of gastrointestinal bleeding were also included on clinical grounds. As a result, the following thirteen complaints were predefined as adverse events: skin reactions, dyspepsia, diarrhoea, constipation, peripheral oedema, dyspnea (including wheezing), headache, dizziness, drowsiness, angio-oedema, hematemesis, black stool and rectal bleeding. If a patient consulted their GP with a complaint which was not predefined as an adverse event but which the patient attributed to the use of NSAIDs, this was also recorded. If the GP recorded the occurrence of an ADR, without specifying the type of complaint presented, these unspecified ADRs were also recorded.

Causality assessment

In order to estimate the likelihood that an adverse events which led to GP consultation was causally related to the use of the NSAID, we read the GP's journal entry and recorded whether: (1) the GP explicitly recorded the NSAID as the cause of the adverse event; (2) the GP explicitly discontinued the NSAID; (3) the GP recorded an alternative diagnosis as the cause of the adverse event; and (4) the patient had consulted their GP for the same complaint as the adverse event in the 6 months prior to study entry. Based on these four criteria, adverse events were subsequently categorised as probable, possible or unlikely ADR according to the algorithm shown in figure 1.

Predictors of consultation for a probable ADR

To compare patients who consulted their GP because of a probable ADR to those without a consultation, concomitant prescription of a gastroprotective agent (GPA) was determined. This was defined as concomitant use of a proton pump inhibitor (PPI), double-dosed histamine-2 receptor antagonist (H2RA) or misoprostol, on the day of first NSAID-prescription. In addition, the NSAID prescribed was classified as a non-selective NSAID (nsNSAID) or a selective cox-2 inhibitor (coxib) based on ATC-coding.



GP: general practitioner; NSAID: non-steroidal anti-inflammatory drug; ADR: adverse drug reaction.
* skin reaction, angio-oedema, dyspepsia, diarrhoea, constipation, peripheral oedema, dyspnea, chest pain, headache, dizziness,

Figure 1. Causality algorithm.

Statistical analyses

Univariate analyses of potential predictors of a probable ADR such as age, gender and type of NSAID were conducted and odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by performing logistic regression analyses. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL).

RESULTS

Patients

In total, 16,626 adults were newly prescribed an NSAID for a MSK complaint and were included in this study (table 1). Symptomatic diagnoses of the back or neck were the most common indication for NSAID treatment. The most commonly prescribed NSAIDs were diclofenac (65%), ibuprofen (11%) and naproxen (8%). Coxibs were prescribed in 4%

Table 1. Baseline characteristics of the study population.

	Number of patients n=16 626
Age in years, mean (±SD)	50.9 (±15.7)
Age category, n(%)	
18-35	2 918 (17.6)
36-50	5 670 (34.1)
51-65	5 108 (30.7)
>65	2 930 (17.6)
Female, n(%)	8 950 (53.8)
Musculoskeletal complaint diagnosed, n(%)	
Symptomatic diagnosis	11 397 (68.5)
Back or neck	4 155 (25.0)
Upper extremity	3 540 (21.3)
Lower extremity	2 107 (12.7)
Generalized/other	1 595 (9.6)
Arthritis	1 283 (7.7)
Inflammatory arthritis	201 (1.2)
Osteoarthritis	442 (2.7)
Gout	640 (3.8)
Radiculopathy	1 165 (7.0)
Trauma	765 (4.6)
Other	2 016 (12.1)
Type of NSAID prescribed, n(%)	
Non-selective NSAID	16 041 (96.5)
Diclofenac	10 799 (65.0)
Ibuprofen	1 800 (10.8)
Naproxen	1 382 (8.3)
Other	2 060 (12.4)
Coxib	585 (3.5)
Celecoxib	170 (1.0)
Etoricoxib	415 (2.5)
Duration of NSAID prescription in days, median (IQR)	11.0 (7.0)
Concomitant GPA prescribed, n(%)	6 032 (36.3)

NSAID: non-steroidal anti-inflammatory drug; coxib: selective cox-2 inhibitor; IQR: interquartile range; GPA: gastroprotective agent.

of patients. In total, 36% of patients were prescribed a concomitant GPA or were already using a GPA on the date of NSAID prescription.

Consultation for an adverse event and likelihood of an ADR

In total, 961 patients (6%) consulted the GP for at least one adverse event (table 2). As 224 patients consulted their GP for more than one adverse event, a total of 1,227 adverse events were reported by these 961 patients. The median duration between the start of the NSAID and GP consultation for an adverse event was 7 days. The incidence rate was 4 consultations for an adverse event per 1000 person-days of NSAID prescription.

Table 2. Consultation for an adverse event

	Number of patients n=16 626
At least one consultation for adverse event, n(%)	961 (5.8)
Duration since start NSAID in days, median (IQR)	7.0 (8.0)
Number of adverse events reported per patient, n (%)	
1	743 (4.5)
2	184 (1.1)
3	34 (0.2)
4	4 (0.02)
5	2 (0.01)

NSAID: non-steroidal anti-inflammatory drug; IQR: interquartile range.

Table 3 shows the type of adverse events presented in more detail. The most frequently presented adverse events were dyspepsia (32%), dyspnea (13%) and skin reactions (12%). The causality criteria, as previously described and shown in figure 1, were applied in order to classify the presented adverse events as probable, possible or unlikely ADRs. The GP recorded the NSAID use as the cause of the adverse events in 146 cases, and discontinued the NSAID in 121 cases. Some overlap was present between these two causality criteria, leading to 216 adverse events (18%) to be categorized as probable. This corresponds with an incidence rate of 1 probable ADR presented per 1000 person-days of NSAID prescription. In 452 cases, the GP recorded an alternative diagnosis as the cause of the adverse event and in 248 cases the patient had presented the same complaint as the adverse event in the 6 months prior, resulting in 504 unlikely ADRs (again, overlap between causality criteria was present). The remaining 507 adverse events presented (41%) were categorized as possible ADRs. The incidence rate of probable and possible ADRs combined was 3 per 1000 person-days of NSAID prescription.

Table 3. Types of adverse events presented to GP and likelihood of an ADR

Adverse event			Causality criteria†			Likelihood ADR‡		
Type	Number	GP records NSAID as cause	GP discontinues NSAID	GP records alternate diagnosis	Same complaint in 6 months prior	Probable ADR	Possible ADR	Unlikely ADR
	n=1 227 n (%)	n=146 n (%)	n=121 n (%)	n=452 n (%)	n=248 n (%)	n=216 n (%)	n=507 n (%)	n=504 n (%)
Not specified	39 (3.2)	39 (26.7)	6 (5.0)	0 (0)	0 (0)	39 (18.1)	0 (0)	0 (0)
Not predefined	38 (3.1)	5 (3.4)	7 (5.8)	7 (1.5)	4 (1.6)	9 (4.2)	21 (4.1)	8 (1.6)
Skin reaction	142 (11.6)	10 (6.8)	6 (5.0)	100 (22.1)	31 (12.5)	13 (6.0)	26 (5.1)	103 (20.4)
Angio-oedema	28 (2.3)	8 (5.5)	7 (5.8)	12 (2.7)	6 (2.4)	10 (4.6)	5 (1.0)	13 (2.6)
Dyspepsia	398 (32.4)	39 (26.7)	51 (42.1)	83 (18.4)	78 (31.5)	73 (33.8)	208 (41.0)	117 (23.2)
Diarrhoea	104 (8.5)	13 (8.9)	10 (8.3)	22 (4.9)	14 (5.6)	17 (7.9)	60 (11.8)	27 (5.4)
Constipation	53 (4.3)	1 (0.7)	0 (0)	12 (2.7)	13 (5.2)	1 (0.5)	32 (6.3)	20 (4.0)
GI blood loss*	37 (3.0)	9 (6.2)	8 (6.6)	13 (2.9)	4 (1.6)	14 (6.5)	10 (2.0)	13 (2.6)
Oedema	57 (4.6)	5 (3.4)	8 (6.6)	16 (3.5)	15 (6.0)	10 (4.6)	26 (5.1)	21 (4.2)
Dyspnea	153 (12.5)	12 (8.2)	6 (5.0)	90 (19.9)	49 (19.8)	17 (7.9)	32 (6.3)	106 (21.0)
Headache	57 (4.6)	1 (0.7)	2 (1.7)	34 (7.5)	14 (5.6)	3 (1.4)	19 (3.7)	35 (6.9)
Dizziness	82 (6.7)	2 (1.4)	7 (5.8)	29 (6.4)	20 (8.1)	9 (4.2)	36 (7.1)	37 (7.3)
Drowsiness	39 (3.2)	2 (1.4)	3 (2.5)	5 (1.1)	0 (0)	3 (1.4)	32 (6.3)	4 (0.8)

ADR: adverse drug event; GP: general practitioner; NSAID: non-steroidal anti-inflammatory drug; GI: gastrointestinal.

* Hematemesis, melena or rectal bleeding.

† Criteria can overlap.

‡ According to causality algorithm.

Predictors of consultation for a probable ADR

In total, 174 patients, or 1% of the total cohort, consulted the GP for at least one probable ADR (table 4). Of those patients in whom no probable ADR occurred, 408 patients (2.5%) presented at least one possible ADR. When compared to patients who did not reconsult the GP for an adverse event, GP consultation for a probable ADR was more frequent in elderly patients, in women, and in those prescribed a coxib or concomitant GPA.

DISCUSSION

Statement of principal findings

In this study, we aimed to provide an insight into the incidence of GP consultation for non-serious ADRs, among primary care patients prescribed an NSAID by their GP because of MSK complaints. We found that almost one in 30 patients treated with NSAIDs for a median duration of 11 days, consulted their GP with a complaint that was probably or possibly an ADR. The incidence rate of consultations for such probable and possible ADRs

Table 4. Predictors of consultation for a probable ADR

	Consultation			No consultation	OR (95% CI) Probable ADR vs. no consultation	Adj.OR† (95% CI) Probable ADR vs. no consultation
	At least one probable ADR n=174 n (%)	At least one possible ADR* n=408 n (%)	At least one unlikely ADR** n=379 n (%)	n=15 665 n (%)		
Age category						
18-35	37 (21.3)	53 (13.0)	54 (14.2)	2 774 (17.7)	1 (ref.)	-
36-50	49 (28.2)	137 (33.6)	110 (29.0)	5 374 (34.3)	0.7 (0.4-1.1)	-
51-65	36 (20.7)	108 (26.5)	110 (29.0)	4 854 (31.0)	0.6 (0.4-0.9)	-
>65	52 (29.9)	110 (27.0)	105 (27.7)	2 663 (17.0)	1.5 (1.0-2.2)	-
Gender						
Male	59 (33.9)	131 (32.1)	137 (36.1)	7 349 (46.9)	1 (ref.)	-
Female	115 (66.1)	277 (67.9)	242 (63.9)	8 316 (53.1)	1.7 (1.3-2.4)	-
Type NSAID						
Non-selective NSAID	162 (93.1)	392 (96.1)	355 (93.7)	15 132 (96.6)	1 (ref.)	1 (ref.)
Coxib	12 (6.9)	16 (3.9)	24 (6.3)	533 (3.4)	2.1 (1.2-3.8)	1.9 (1.1-3.5)
Concomitant GPA prescribed						
None	82 (47.1)	227 (55.6)	214 (56.5)	10 071 (64.3)	1 (ref.)	1 (ref.)
PPI	67 (38.5)	142 (34.8)	135 (35.6)	4 231 (27.0)	1.9 (1.4-2.7)	1.8 (1.3-2.6)
H2RA in double dosage	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)	-	-
Misoprostol	25 (14.4)	39 (9.6)	30 (7.9)	1 350 (8.7)	2.3 (1.4-3.5)	2.2 (1.4-3.5)

ADR: adverse drug reaction; NSAID: non-steroidal anti-inflammatory drug; coxib: selective cox-2 inhibitor; GPA: gastroprotective agent; PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist.
* and no probable ADR.
** and no probable or possible ADR.
† adjusted for age and gender.

combined was 3 per 1000 person-days of NSAID prescription. Elderly and female patients were more likely to consult their GP because of a probable ADR, which may reflect the fact that such patients are generally more likely to consult their GP.[1] Patients prescribed coxibs or an nsNSAID with concomitant GPA were also most likely to present a probable ADR, which is likely due to confounding by indication. These results do indicate, however, that such gastroprotective strategies do not fully protect against the occurrence of non-serious ADRs in patients prescribed NSAIDs.

Strengths and weaknesses of the study

When interpreting the results, there are some limitations to be taken into account. Firstly, as the data were obtained from the medical journals, some information relevant to this study, such as verbal advice given to the patient regarding a complaint, may have been missed. This would result in an underestimation of the occurrence of adverse events reported

to the GP. In addition, we were unable to apply existing causality assessment methods, such as the algorithms by Kramer or Naranjo, or the WHO-UMC causality assessment system.[16-18] Our assessment of a probable ADR was based on the opinion of the treating GP as documented in the medical journal, or, if no information was recorded, on the GP's active discontinuation of the NSAID as a proxy. Again, the true number of ADRs is likely to be higher, as GPs may fail to take the use of the NSAID into account when assessing the cause of a complaint, or refrain from recording their considerations. Secondly, we had no information on the use of over-the-counter NSAIDs. Included patients were prescribed an NSAID by their GP, those patients not prescribed an NSAID but using NSAIDs over-the-counter were therefore not included in this study.

Strengths and weaknesses in relation to other studies

One previous study focusing on gastrointestinal complaints in primary care patients, found that of 1014 included chronic NSAID users, 185 had consulted their GP because of a gastrointestinal complaint in the past year (incidence rate 0.5 per 1000 person-days).[10] As this study only included chronic NSAID users who had used NSAIDs for at least 9 months, patients particularly prone to gastrointestinal symptoms while taking NSAIDs would have been 'selected out' and not formed part of the study population. The strength of our study is that we included and followed-up all new NSAID users, which may explain the higher consultation rate for gastrointestinal and other adverse events found. Another study performed in Italy included 1842 patients who were treated by their GP with ibuprofen.[19] During the follow-up of 30 days, ADRs were found to occur in 14% of patients (incidence rate 4.7 per 1000 person-days). Although these results are of interest, the generalizibility to the total primary care population remains unclear, as the methods for recruiting patients and the inclusion criteria were not reported.

Meaning of the study

The majority of patients in our study were treated with NSAIDs for symptomatic complaints of the musculoskeletal system, which are often self-limiting in nature. Indeed, the median duration of NSAID prescription in these patients was only 11 days and almost 60% of patients only consulted their GP once for their musculoskeletal complaint. In light of this, we feel that GPs should address not only the risk of serious ADRs when discussing treatment options for MSK complaints with their patients, but also our finding of reconsultation for non-serious ADRs. Although these non-serious ADRs are less harmful to the patient, they lead to an increase in primary health care utilization and may outweigh the benefits of NSAID treatment for many patients.

REFERENCES

1. Van der Linden MW, Westert GP, De Bakker DH, Schellevis FG. Second national survey of general practice. Morbidity in the population and in general practice. [Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk]. Utrecht/Bilthoven: NIVEL/RIVM; 2004. Available at: http://www.nivel.nl/sites/default/files/bestanden/ns2_r1_h02.pdf.
2. Cardol M, Van Dijk L, De Jong JD, De Bakker DH, Westert GP. Second Dutch national survey of general practice. GP care: what does the gatekeeper do? [Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: wat doet de poortwachter?] Utrecht/Bilthoven: NIVEL/RIVM; 2004. Available at: http://www.nivel.nl/sites/default/files/bestanden/ns2_rapport2.pdf.
3. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
4. Hernandez-Diaz S, Rodriguez LA. Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-99.
5. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and non-selective inhibitors of cyclooxygenase 2. *JAMA* 2006;296:1633-44.
6. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf. 2011;20:1225-36.
7. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
8. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis* 2005;45:531-9.
9. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PMLA, De Smet PAGM. Targeting outpatient drug safety: Recommendations of the Dutch Harm-Wrestling Task Force. *Drug Saf* 2012;35:245-59.
10. Jones RH, Tait CL. Gastrointestinal side-effects of NSAIDs in the community. *BJCP* 1995;49:67-70.
11. Lamberts H WM, Hofmans-Okkens IM. International primary care classifications: the effect of fifteen years of evolution. *Fam Pract* 1992;9:330-39.
12. van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993; 119:1036-41.
13. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med* 1999;38:339-44.
14. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. Available at: http://www.whocc.no/.
15. Dutch college for health insurances. Pharmacotherapeutic compass. 2013. Available at: http://www.farmacotherapeutischkompas.nl/.

16. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA* 1979:242;623-32.
17. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981:30;239-45.
18. World Health Organisation – Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. Available at: http://who-umc.org/Graphics/24734.pdf .
19. Benvenuti C, Beretta A, Longoni A, Pickvance N. A multi-centre general practice study evaluating the efficacy and tolerance of ibuprofen in common painful conditions. *Pharmatherapeutica* 1984:4:9-12.

Chapter 5

Time-trends in the prescribing of gastroprotective agents to primary care patients initiating low-dose aspirin or non-steroidal anti-inflammatory drugs: a population based cohort study

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ABSTRACT

Background

Low-dose aspirin (LDA) and non-steroidal-anti-inflammatory drugs (NSAIDs) both increase the risk of upper gastrointestinal events (UGIEs). In the Netherlands recommendations regarding the prescription of gastroprotective agents (GPA) in LDA users were first issued in 2009 in the HARM-Wrestling consensus. National guidelines on gastroprotective strategies in NSAID users were already issued in the first part of the decade.

Aims

To examine time-trends in gastroprotective strategies in patients initiating LDA and patients initiating NSAIDs between 2000 and 2012.

Method

Within a large electronic primary health care database, two cohorts were selected: (i) patients newly prescribed LDA and (ii) patients newly prescribed NSAIDs between 2000 and 2012. Excluded were patients who had been prescribed a GPA in the six months prior. For both cohorts, patients' risk of a UGIE was classified as low, moderate or high, based on the HARM-Wrestling consensus, and the presence of an adequate gastroprotective strategy was determined.

Results

37 578 patients were included in the LDA cohort, 365 793 patients in the NSAID cohort. In both cohorts, an increase of gastroprotective strategies was observed over time, but prescription of GPA was lower in the LDA cohort. By 2012, an adequate gastroprotective strategy was present in 31.8% of high-risk LDA initiators, versus 47.6% of high-risk NSAID initiators.

Conclusion

Despite a comparable risk of UGIEs, gastroprotective strategies are prescribed less in high-risk LDA initiators than in high-risk NSAID initiators. For both groups of patients, there is still room for improvement in guideline adherence.

INTRODUCTION

Low-dose aspirin (LDA) and non-steroidal anti-inflammatory drugs (NSAIDs) are both widely used in primary care.[1 2] They are associated with an increased risk of serious upper gastrointestinal events (UGIEs), such as ulceration, bleedings and perforation.[3-7] The risk of the occurrence of a UGIE is influenced by various factors, including age, comorbidity and concomitant use of other ulcerogenic medications.[3 4 8 9] The risk can be reduced by concomitant prescription of a gastroprotective agent (GPA).[10-12] For NSAIDs, prescription of a cox-2-selective NSAID (coxib) rather than a non-selective (ns)NSAID also helps lower the risk of a UGIE.[11]

In the last decade several national and international guidelines have been developed aimed at reducing the number of NSAID-related UGIEs.[11 13 14] In the Netherlands, a multidisciplinary guideline for prevention of UGIEs in NSAID users was first issued in 2003.[13] For prevention of UGIEs in LDA users, however, no national recommendations were issued until 2009, when the HARM-Wrestling report was published (initially in Dutch, definitive version in English).[15 16] This consensus report was issued by a multidisciplinary task force, and contained revised recommendations on the prescription of GPA in high-risk NSAID users and new recommendations on the prescription of GPA in high-risk LDA users. As LDA is less ulcerogenic than NSAIDs, risk groups for LDA users were defined separately, to equate the risk of a UGIE in high-risk LDA users and high-risk NSAID users. The risk of UGIEs is thus comparable in high-risk LDA users and high-risk NSAID users, and both high-risk groups have an equally strong indication for prescription of a GPA.[16]

The implementation of gastroprotective strategies (GPS) in high-risk NSAID users has been previously studied and was found to be around 40-60% in the years following publication of the first guideline on this topic in 2003.[17 18] However, much less is known about the prescription of GPA in high-risk LDA users. As the HARM-Wrestling consensus defined high-risk users of LDA in such a way that their risk corresponded as closely as possible to the risk of high-risk NSAID users, one might expect prescription patterns of GPA to be similar in both populations.

Many factors are known to play a role in the level of adherence to guidelines. Firstly, factors relating to healthcare professionals, such as awareness of a guideline and familiarity with its content, are known to play a role.[19] As guidelines for LDA users are relatively new, adherence may therefore currently be lower than for NSAID users.

Secondly, environmental factors such as electronic decision systems, economic and policy related factors have also been demonstrated to affect adherence to guidelines.[20 21] With regards to LDA and NSAID users, various environmental factors may have influenced the prescription of GPA over the last decade: (i) medication surveillance for drug-drug interactions, which were introduced at various time points depending on the electronic prescribing systems used; (ii) introduction of two inspectorate summative indicators for

community pharmacists: one in 2008, measuring the percentage of NSAID users aged over 70 years receiving a GPS, and one in 2011, measuring the percentage of high-risk LDA users receiving a GPA; (iii) availability of cheaper generic proton pump inhibitors (PPIs) since March 2002;[22] (iv) introduction of a policy in July 2008 which allowed health insurance companies to only reimburse a specific selection of medications, including PPIs, of their choosing;[23] and (v) an alteration in national reimbursement policy for PPIs in January 2012: incidental prescriptions of PPIs were no longer reimbursed, chronic use was still reimbursed with the exception of the first prescription issued.[24] Concerns regarding the cardiovascular safety of coxibs and regarding a possible negative effect of PPIs on the efficacy of clopidogrel may also have affected the prescription of these medications.[16 17 25]

The objective of this study is to examine time-trends in gastroprotective strategies in both LDA users and NSAID users, by performing a population based cohort study among incident LDA users and incident NSAID users between 2000 and 2012. We will also explore temporal relationships with various environmental factors that may have played a role.

METHOD

Study design

A cohort study was conducted among incident LDA users and incident NSAID users. Only incident users were included as prescribers tend to adhere to pharmacotherapeutic guidelines more stringently in new users than in prevalent users.[26]

Setting

Data for this study were retrieved from the Integrated Primary Care Information (IPCI) database. This longitudinal primary health care database contains the electronic patient records of over 1.5 million patients registered with general practitioners (GPs) throughout the Netherlands. In the Netherlands, GPs form the first point of care and act as a gatekeeper to secondary care. The medical records can be therefore assumed to contain all relevant medical information. It contains all journal entries by the GP, coded diagnoses using the International Classification for Primary Care (ICPC),[27] and referrals, clinical findings by specialists, laboratory findings and hospitalizations. In addition, there is a complete record of all drug prescriptions, their dosage regimen and the Anatomical Therapeutic Chemical (ATC) classification code.[28] More extensive details on the database have been reported elsewhere.[29 30]

Study cohorts

The source population comprised all patients contributing data to the IPCI database between 2000 and 2012, with at least 12 months of valid database history before the date

of study entry. From this source population, two cohorts of patients were identified and included in this study. The first cohort consisted of all patients newly prescribed LDA (defined as acetylsalicylic acid (ASA) ≤ 80mg/day or carbasalate calcium ≤ 100mg/day). New prescription was defined as no use in the six months prior. Only the first LDA prescription of each patient was included and the date of LDA prescription was defined as the index date. In this LDA cohort patients were excluded if they were using an NSAID on the index date, because recommendations on gastroprotection are more stringent for patients using NSAIDs.[16] The second cohort consisted of all patients newly prescribed a non-selective (ns) NSAID, coxib or high dose aspirin (defined as ASA > 80mg/day or carbasalate calcium > 100mg/day). Again, only the first NSAID prescription of each patient was included and the date of NSAID prescription was defined as the index date. In both cohorts, patients who had received a GPA in the six months prior to the index date were excluded, to avoid overestimation of adherence, as these patients may have other indications for use of GPA. As the same source population was used for each cohort, patients could be included in both. All prescriptions were identified based on ATC code (for specification see appendix I).

Upper gastrointestinal risk

In order to determine if patients were at an increased risk of developing a UGIE, each patient's age, medical history and use of co-medication were recorded. Concomitant use of medication was defined as overlapping duration of use on the index date. Definitions of upper gastrointestinal (UGI) risk were based on the HARM-Wrestling consensus for both cohorts and are described in Box 1.[16] The HARM-Wrestling consensus also defined concomitant use of therapeutic doses of low-molecular-weight-heparin (LMWH) as a risk factor. This risk factor was not included in our definition of UGI risk, as LMWH is mostly used for bridging while starting anticoagulants and including LMWH as a risk factor would therefore have led to false-positive high-risk cases.

The history of the diseases and conditions described in Box I were assessed based on ICPC coding and free text search strings (see appendix I for specifications). In the case of diabetes and severe rheumatoid arthritis, the use of specific types of medication, identified based on ATC classification code, was also taken into account in addition to ICPC coding as proxy for the identification of these comorbidities (see appendix I for specifications).

Gastroprotective strategy

For all included patients we subsequently assessed whether a GPS was implemented. In line with the definitive HARM-Wrestling consensus,[16] GPS was defined as follows:

- For the LDA cohort: concomitant prescription of a PPI or double dose H_2RA.
- For the NSAID cohort: (i) prescription of an nsNSAID or coxib with concomitant prescription of a PPI or double dose H_2RA or (ii) prescription of a coxib alone, provided there was no concomitant use of LDA.

Box 1. Definition of low, moderate and high UGI risk in each cohort.

UGI risk group	Definition in LDA cohort	Definition in NSAID cohort
High risk	At least one of the following high risk factors:	At least one of the following high risk factors:
	History of UGIE	History of UGIE
	Age ≥ 80	Age ≥ 70
	Age 70-79 and ≥ one other moderate risk factor	≥ Two moderate risk factors
	Age 60-69 and ≥ two moderate risk factors	
Moderate risk	No high risk and at least one of the following moderate risk factors:	No high risk and at least one of the following moderate risk factors:
	Age 70-79	Age 60-69 years
	Use of VKA	History of DM
	Use of clopidogrel	History of HF
	Use of corticosteroid	History of severe RA
	Use of SSRI	Use of VKA
	Use of spironolactone	Use of LDA
		Use of clopidogrel
		Use of corticosteroid
		Use of SSRI
		Use of spironolactone
		High-dose NSAID
Low risk	No moderate or high risk	No moderate or high risk

DM: diabetes mellitus; GI: gastrointestinal; HF: heart failure; NSAID: non-steroidal anti-inflammatory drug; LDA: low-dose aspirin; RA: rheumatoid arthritis; SSRI: serotonin-reuptake inhibitor; UGIE: upper gastrointestinal event; VKA: vitamin K antagonist.

According to the HARM-Wrestling consensus,[16] such a GPS should only be implemented in high-risk users. We also determined whether a GPS was prescribed in other risk groups, to examine whether GPs take this into account. Double dose H_2RA was defined as H_2RA in a prescribed daily dosage (PDD) of at least twice the defined daily dosage (DDD). Concomitant prescription was defined as overlapping duration of use on the index date or within two days after the index date. In line with the HARM-Wrestling consensus, we did not consider diclofenac-misoprostol to be an adequate GPS,[15] but we did determine the frequency of prescription of this combination, as misoprostol has been suggested as gastroprotection in previous literature and guidelines.[11 13]

Statistical analysis

For each cohort, prescription of a GPS in high- and moderate UGI risk patients was compared to those with a low UGI risk and odds ratios (ORs) and their 95% confidence interval (CI) were determined using univariate logistic regression. Univariate logistic regression was also used to compare the odds of GPS in high-risk LDA users to high-risk NSAID users. For the year 2012, potential predictors of high GI risk patients receiving a GPS were

examined, to evaluate which risk factors influence the GPs decision to implement a GPS. Crude ORs and their 95% CIs were calculated by performing univariate logistic regression analyses. In addition, multivariate logistic regression was performed to calculate adjusted ORs (OR_{adj}) adjusted for age. We chose not to adjust for other UGI risk factors, because of the potential interactions between these factors. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL).

RESULTS

Baseline characteristics

In total, 37 578 patients were newly prescribed LDA between 2000 and 2012 and were included in the LDA cohort (table 1). The mean age upon prescription was 66.2 (±14.1) and 55.2% of the cohort was male. In this cohort, 24.8% of patients were found to have a high UGI risk and 28.5% a moderate UGI risk. Overall, 14.1% of patients in this cohort received a GPS.

In the NSAID cohort, 365 793 patients were included (table 1). The mean age upon prescription was 45.8 (±17.9) years and 44.0% of the cohort was male. In this cohort, 24.7% of patients had a high UGI risk and 42.2% had a moderate UGI risk. Overall, 19.9% of the cohort received a GPS.

Gastroprotective strategy per UGI risk group

In both cohorts, over the entire time period, patients were more likely to receive an adequate GPS if they had a moderate or high UGI risk (table 2). In the LDA cohort, a GPS was prescribed in 7.7% of low risk patients, 16.4% of moderate-risk patients and 23.7% of high-risk patients (OR 2.3 [2.2-2.5] and 3.7 [3.5-4.0] for respectively moderate vs. low risk patients and high vs. low risk patients). In the NSAID cohort, these percentages were 10.0% for low risk, 15.4% for moderate-risk and 40.7% for high-risk patients (OR 1.6 [1.6-1.7] and 6.2 [6.0-6.3] for respectively moderate vs. low risk and high vs. low risk patients). This means that within all high-risk patients, the odds of LDA users receiving a GPS were half that of NSAID users (OR 0.5 [0.4-0.5] for high-risk LDA users versus high-risk NSAID users).

Gastroprotective strategy per UGI risk group over time

Figure 1 shows the percentage of incident users prescribed an adequate GPS over time per UGI risk group for each cohort.

In the LDA cohort (figure 1a), prescription of a GPS was fairly stable in all risk groups in the first part of the decade. In the second part of the decade, an increase is observed in all risk groups, with the strongest increase occurring in the high UGI risk group. By 2012,

Table 1. Baseline characteristics of the two study cohorts.

	Cohort	
	LDA	NSAID
	n= 37 578 n (%)	n=365 793 n (%)
Age (mean±sd)	66.2 (±14.1)	45.8 (±17.9)
Gender (% male)	20 758 (55.2)	161 093 (44.0)
Type of index-prescription		
NsNSAID	NA	325 947 (89.1)
Diclofenac-misoprostol	NA	25 288 (6.9)
Coxib	NA	14 558 (4.0)
Individual UGI risk factors		
Age 60-69	10 163(27.0)	45 994 (12.6)
Age 70-79	9 107 (24.2)	25 387 (6.9)
Age ≥ 80	6 529 (17.4)	10 916 (3.0)
History of UGIE	1 757 (4.7)	7 951 (2.2)
History of DM	7 575 (20.2)	25 886 (7.1)
History of HF	7 763 (20.7)	22 143 (6.1)
History of severe RA	134 (0.4)	932 (0.3)
Use of VKA	1 361 (3.6)	3 142 (0.9)
Use of clopidogrel	2 815 (7.5)	565 (0.2)
Use of corticosteroids	558 (1.5)	1 350 (0.4)
Use of SSRI	1 220 (3.2)	9 663 (2.6)
Use of spironolactone	802 (2.1)	709 (0.2)
Use of LDA	NA	15 365 (4.2)
High-dose NSAID	NA	192 606 (52.7)
UGI risk group[a]		
Low risk	17 565 (46.7)	121 053 (33.1)
Moderate risk	10 709 (28.5)	154 272 (42.2)
High risk	9 304 (24.8)	90 468 (24.7)
Gastroprotective agent		
PPI	5 309 (14.1)	62 102 (17.0)
H_2RA double dose	7 (0.0)	28 (0.0)
Gastroprotective strategy[b]	5 316 (14.1)	72 611 (19.9)

DM: diabetes mellitus; UGI: upper gastrointestinal; HF: heart failure; H2RA: histamine-2 receptor antagonist; LDA: low-dose aspirin; NA: not applicable; NSAID: non-steroidal anti-inflammatory drug; nsNSAID: non-selective NSAID; PPI: proton pump inhibitor; RA: rheumatoid arthritis; SSRI: selective serotonin-reuptake inhibitor; UGIE: upper gastrointestinal event; VKA: vitamin K antagonist.

[a] As defined separately for each cohort.

[b] Gastroprotective strategy: Concomitant PPI or double-dose H2RA; in NSAID cohort also coxib (provided concomitant LDA was not prescribed).

Table 2. Gastroprotective strategy in each cohort per GI risk group.

UGI risk group[a]	Gastroprotective strategy[b]		OR (95% CI)	P-value
	No n (%[c])	Yes n (%[c])		
LDA cohort	n=32 262	n=5 316		
Low risk	16 210 (92.3)	1 355 (7.7)	1 (ref)	
Moderate risk	8 954 (83.6)	1 755 (16.4)	2.3 (2.2-2.5)	<0.001
High risk	7 098 (76.3)	2 206 (23.7)	3.7 (3.5-4.0)	<0.001
NSAID cohort	n=293 182	n=72 611		
Low risk	108 943 (90.0)	12 110 (10.0)	1 (ref)	
Moderate risk	130 573 (84.6)	23 699 (15.4)	1.6 (1.6-1.7)	<0.001
High risk	53 666 (59.3)	36 802 (40.7)	6.2 (6.0-6.3)	<0.001

UGI: upper gastrointestinal; H_2RA: histamine-2 receptor antagonist; LDA: low-dose aspirin; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor.

[a] As defined separately for each cohort.

[b] Gastroprotective strategy: Concomitant PPI or double-dose H_2RA; in NSAID cohort also coxib (if no concomitant LDA).

[c] Row percentage.

a GPS was present in 31.8%, 24.2% and 11.8% of high-, moderate- and low UGI risk patients respectively.

In the NSAID cohort (figure 1b), a slight increase in gastroprotection in high UGI risk patients is already observed before publication of the first national guideline on this topic in 2003. A temporary decrease is observed in 2005, from 2006 onwards a further increase over time is observed in all GI risk groups. In 2012, a GPS was prescribed in 47.6% of incident users with high GI risk, 19.3% of those with moderate GI risk and 12.0% of those with low GI risk.

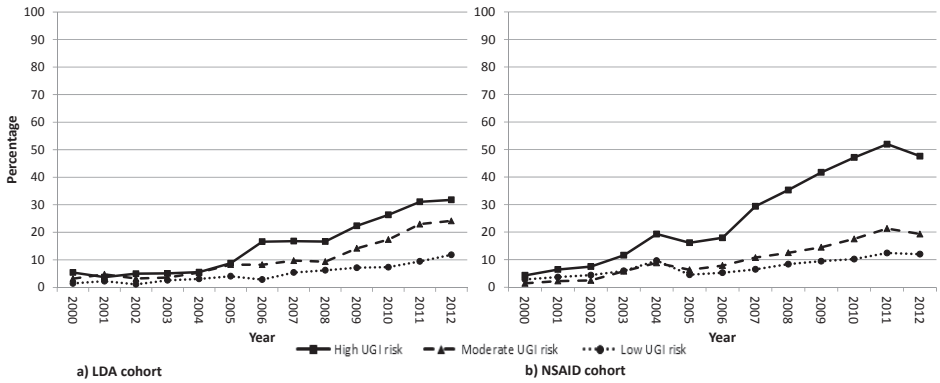

Figure 1. Percentage of patients prescribed a gastroprotective strategy per year for each GI risk group (as defined separately for each cohort).

Types of gastroprotective strategies

Figure 2 shows the types of GPS over time in high-risk patients in each cohort. In both cohorts, double dose H_2RA is rarely prescribed. An increase in PPI prescription is present in the second part of the decade in both cohorts, but this trend is not continued into the year 2012, with a decrease occurring particularly in the NSAID cohort. In the NSAID cohort, a sudden drop in coxib prescription is seen in 2005. The combination of diclofenac-misoprostol, which was recommended in early guidelines but not in the HARM-Wrestling consensus in 2009, is still prescribed in 9.6% of high-risk NSAID patients in 2012.

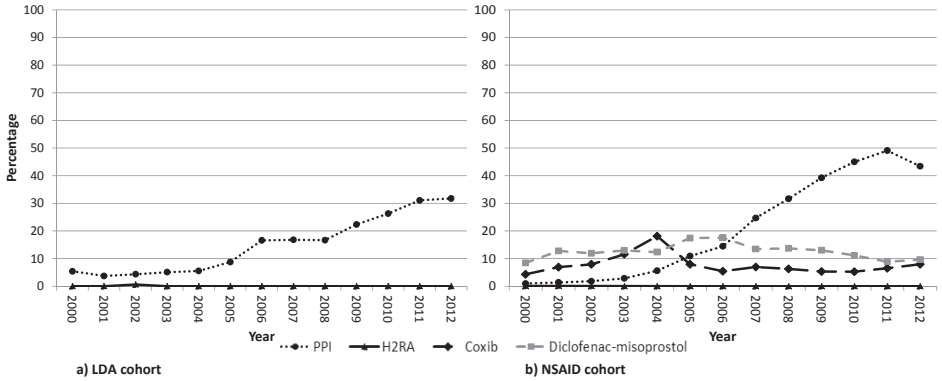

Figure 2. Type of gastroprotective strategy in high-risk patients per year.

Predictors of adequate gastroprotective strategy in high GI risk patients in 2012

Table 3 shows the predictors of prescription of a GPS in high GI risk patients within each cohort in 2012. In the LDA cohort, a history of UGIE was not significantly associated with GPS prescription (OR_{adj} 1.2 [95% CI 0.9-1.5], P-value 0.237). When compared to patients aged < 60 years, those aged 70-79 with at least one moderate risk factors were significantly more likely to receive a GPS (OR_{adj} 2.5 [95% CI 1.5-3.0], P-value <0.001), as were those aged 60-69 with at least two other moderate risk factors (OR_{adj} 2.6 [95% CI 1.1-6.4], P-value 0.032), but for those aged ≥ 80 years no statistically significant association was found (OR_{adj} 1.3 [95% CI 0.8-2.1], P-value 0.216). Of the moderate risk factors, concomitant use of an SSRI and corticosteroids were the strongest predictors of a GPS (respectively OR_{adj} 4.2 [95% CI 2.9-6.1], P-value < 0.001 and 3.4 [95% CI 2.2-5.3] P-value < 0.001).

In the NSAID cohort, all individual high risk factors were associated with increased odds of prescription of a GPS. For the high risk factor '≥ 2 moderate risk factors', the odds of a GPS varied depending on the combination of risk factors present (table 3). Of the moderate risk factors, most were significantly associated with the presence of a GPS, with the exception of a history of severe RA (OR_{adj} 1.1 [95% CI 0.8-1.6], P-value 0.439) and

Table 3. Predictors of prescription of gastroprotective strategy in high GI risk patients in 2012 per cohort

	Gastroprotective strategy[a]		OR crude (95% CI)	OR adjusted[b] (95% CI)	P- value
	No n (%[c])	Yes n (%[c])			
LDA cohort	1 479	689			
Gender					
Male	689 (69.3)	305 (30.7)	1 (ref)	1 (ref)	
Female	790 (67.3)	384 (32.7)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	0.428
High risk factors					
History of UGIE	322 (67.8)	153 (32.2)	1.0 (0.8-1.3)	1.2 (0.9-1.5)	0.237
Age ≥ 80	1 031 (69.9)	445 (30.1)	0.8 (0.7-1.0)	1.3 (0.8-2.1)[d]	0.216
Age 70-79 and ≥ 1 other MRF	175 (55.6)	140 (44.4)	1.9 (1.5-2.4)	2.5 (1.5-4.0)[d]	<0.001
Age 60-69 and ≥ 2 other MRF	14 (53.8)	12 (46.2)	1.9 (0.9-4.0)	2.6 (1.1-6.4)[d]	0.032
Moderate risk factors					
Age 60-69	107 (67.3)	52 (32.7)	1.0 (0.7-1.5)	1.5 (0.9-2.6)[d]	0.150
Age 70-79	258 (61.0)	165 (39.0)	1.5 (1.2-1.9)	2.0 (1.2-3.2)[d]	0.005
Use of VKA	119 (68.4)	55 (31.6)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	0.963
Use of clopidogrel	110 (49.3)	113 (50.7)	2.4 (1.8-3.2)	2.6 (1.9-3.4)	<0.001
Use of corticosteroid	34 (40.0)	51 (60.0)	3.4 (2.2-5.3)	3.4 (2.2-5.3)	<0.001
Use of SSRI	49 (36.6)	85 (63.4)	4.1 (2.9-5.9)	4.2 (2.9-6.1)	<0.001
Use of spironolactone	73 (54.9)	60 (45.1)	1.8 (1.3-2.6)	1.9 (1.3-2.7)	0.001
NSAID cohort	n=9 999	n=9 082			
Gender					
Male	4 772 (55.1)	3 889 (44.9)	1 (ref)	1 (ref)	
Female	5 227 (50.2)	5 193 (49.8)	1.2 (1.2-1.3)	1.2 (1.1-1.3)	<0.001
High risk factors					
History of UGIE	1 046 (56.5)	804 (43.5)	0.8 (0.8-0.9)	1.2 (1.1-1.3)	0.002
≥ 70	2 882 (40.0)	4 331 (60.0)	2.3 (2.1-2.4)	2.7 (2.5-3.0)[d]	<0.001
≥ 2 moderate risk factors	7 488 (55.3)	6 061 (44.7)	0.7 (0.6-0.7)	1.5 (1.3-1.7)[d]	<0.001
Age 60-69 + risk medication	640 (43.3)	838 (56.7)	1.5 (1.3-1.7)	2.4 (2.1-2.7)[d]	<0.001
Age 60-69 + HF/DM/RA	1 586 (55.5)	1 273 (44.5)	0.9 (0.8-0.9)	1.5 (1.3-1.6)[d]	<0.001
Age 60-69 + high-dose NSAID	2 893 (57.0)	2 180 (43.0)	0.8 (0.7-0.8)	1.4 (1.3-1.5)[d]	<0.001
Moderate risk factors					
Age 60-69	3 985 (56.8)	3 031 (43.2)	0.8 (0.7-0.8)	1.4 (1.3-1.5)[d]	<0.001
History of DM	3 091 (56.7)	2 361 (43.3)	0.8 (0.7-0.8)	0.8 (0.8-0.9)	<0.001
History of HF	3 368 (55.1)	2 742 (44.9)	0.9 (0.8-0.9)	0.9 (0.8-0.9)	<0.001
History of severe RA	77 (51.3)	73 (48.7)	1.0 (0.8-1.4)	1.1 (0.8-1.6)	0.439
Use of VKA	233 (35.6)	422 (64.4)	2.0 (1.7-2.4)	1.7 (1.5-2.0)	<0.001
Use of clopidogrel	54 (41.9)	75 (58.1)	1.5 (1.1-2.2)	1.4 (1.0-2.0)	0.051
Use of corticosteroid	98 (37.0)	167 (63.0)	1.9 (1.5-2.4)	2.1 (1.6-2.7)	<0.001
Use of SSRI	603 (42.2)	827 (57.8)	1.6 (1.4-1.7)	2.6 (2.3-2.9)	<0.001
Use of spironolactone	49 (38.9)	77 (61.1)	1.7 (1.2-2.5)	1.5 (1.0-2.1)	0.047
Use of LDA	1 174 (42.4)	1 593 (57.6)	1.6 (1.5-1.7)	1.4 (1.3-1.5)	<0.001
High-dose NSAID	6 475 (53.8)	5 570 (46.2)	0.9 (0.8-0.9)	1.1 (1.0-1.1)	0.072

DM: diabetes mellitus; GI: gastrointestinal; HF: heart failure; H2RA: histamine-2 receptor antagonist; LDA: low-dose aspirin; MRF: moderate risk factor; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; SSRI: selective serotonin-reuptake inhibitor; UGIE: upper gastrointestinal event; VKA: vitamin K antagonist.

[a] Gastroprotective strategy: Concomitant PPI or double-dose H2RA; in NSAID cohort also coxib (if no concomitant LDA)

[b] Adjusted for age.

[c] Row percentage.

[d] Reference group is age < 60.

prescription of a high-dose NSAID (OR_{adj} 1.1 [95% CI 1.0-1.1], P-value 0.072). For a history of diabetes mellitus and heart failure, negative associations were found (respectively OR_{adj} 0.8 [95% CI 0.8-0.9], P-value <0.001 for diabetes and OR_{adj} 0.9 [95% CI 0.8-0.9], P-value < 0.001 for heart failure).

DISCUSSION

This study shows that the prescription of GPA is lower in high-risk LDA users than in high-risk NSAID users, despite a comparable risk of UGIEs in these high-risk groups. Although adherence to recommendations regarding gastroprotection improved over time in both cohorts, adequate gastroprotective strategy was present in only 31.8% of high-risk LDA initiators in 2012, compared to 47.6% of NSAID initiators. Less familiarity with the recommendations for LDA users, which were not issued until 2009, may have played a role. However, environmental factors also appear to affect adherence.

Environmental factors potentially influencing prescribing behavior

After the alteration in national reimbursement policy for PPIs in January 2012, a sudden decrease of PPI prescription is seen in high-risk NSAID initiators (figure 2). In the LDA cohort, no decrease is observed, but the prior increase in PPI prescriptions appears to stabilize, despite the introduction in 2011 of an inspectorate indicator measuring adherence to LDA recommendations. The effect of the new reimbursement policy may be less strong in this cohort, because in contrast to NSAIDs, LDA tends to be prescribed chronically. In this case, patients only have to pay for the first PPI prescription.

Medication surveillance for drug-drug interactions may also play a role, as concomitant use of most types of ulcerogenic medication is predictive of a GPS in both cohorts (table 3). Whilst this may of course also be explained by general practitioners' knowledge of the literature and guidelines, it is notable that factors such as a history of diabetes, heart failure and severe rheumatoid arthritis, which do not lead to warnings within these surveillance systems, were not associated with increased prescription of a GPS.

In the NSAID cohort, a decrease in coxib prescription is observed in 2005. This decrease has also been found in previous studies and appears to be in response to the removal of rofecoxib from the market in 2004, after evidence emerged that its use was associated with an increased incidence of ischemic cardiovascular events.[2 25 31] Other environmental factors such as the availability of cheaper generic PPIs since 2002 do not appear to have played a strong role in prescribing behavior. A relatively strong increase in PPI prescriptions is seen in the LDA cohort in 2006. It remains unclear which factors caused this temporary additional increase, which is not seen in the NSAID cohort.

Comparison with existing literature

Recently, a Dutch cohort study was published regarding predictors of PPI prescription in LDA users in the years 2008-2010.[32] In this study, 46% of high-risk patients prescribed LDA were found to receive regular concomitant PPI prescriptions. In our cohort, concomitant prescription of a PPI was found to be much lower in this time period (23%). This difference may be explained in part by differences in cohort definition, as the cohort described in the previous study consisted of all regular LDA users, rather than only LDA initiators, and patients who had used GPA prior to cohort entry were not excluded. In addition, LDA users with concomitant use of NSAIDs were not excluded. As the HARM-Wrestling recommendations for NSAID users are more stringent than those for LDA users, this may have increased the percentage of LDA users with concomitant PPI found. Indeed, concomitant NSAID use was found to be one of the strongest predictors of PPI prescription in this previous cohort of LDA users. The fact that we excluded patients with concomitant NSAID use from our LDA cohort allows for a better estimate of adherence to the HARM-Wrestling recommendations for LDA users.

Strengths and limitations

Strengths of this study include the fact that it was conducted in a database containing a large number of patients, reflecting the Dutch general population. By using consistent methods to include cohorts of LDA and NSAID initiators from this population, our study allows for a comparison between adherence to guidelines in these two patient groups. There are, however, several limitations that should be considered when reviewing the results. First of all, the HARM-Wrestling recommendations do not only contain measures which should be taken to decrease the risk of UGIE if LDA or NSAIDs are prescribed, but also state that physicians should carefully weigh the risks and benefits of prescribing these medications in patients at risk.[33] In this study, we did not examine the indications for NSAID and LDA prescriptions and we were therefore unable to assess whether GPs have become more cautious in prescribing these drugs in high-risk patients. Secondly, we only had access to prescriptions issued by GPs. Prescriptions issued by specialists in secondary care and medications used over-the-counter, are not captured in this database. This may have led to some underestimation of high UGI risk patients.

Conclusion

Overall, our study shows that gastroprotective strategies are implemented less in high-risk LDA users than in NSAID users, despite a comparable risk of upper gastrointestinal events. For both groups of patients, there is still room for improvement in guideline adherence. Of the various environmental factors that could have played a role in the level of adherence achieved, the change in reimbursement policy of PPIs had the clearest visible effect.

REFERENCES

1. Cardol M, van Dijk L, de Jong JD, de Bakker DH, Westert GP. The second Dutch National Survey of General Practice. GP care: what does the gatekeeper do? [Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter?]. NIVEL/RIVM: Utrecht/Bilthoven, 2004. Available at: http://www.nivel.nl/sites/default/files/bestanden/ns2_rapport2.pdf.
2. Koffeman AR, Valkhoff VE, Jong GW, et al. Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints. *Scand J Prim Health Care* 2014;32:90-8.
3. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
4. Yeomans ND, Lanas AI, Talley NJ, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharm Therap* 2005;22:795-801.
5. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther* 2013;15:S3.
6. Valkhoff VE, Sturkenboom MC, Hill C, Veldhuyzen van Zanten S, Kuipers EJ. Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: a meta-analysis of randomized clinical trials and observational studies. *Can J Gastroenterol* 2013;27:159-67.
7. Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011;9:762-68 e6.
8. Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal Antiinflammatory Drug-Associated Gastropathy - Incidence and Risk Factor Models. *Am J Med* 1991;91:213-22.
9. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006;119:624-38.
10. Hsiao FY, Tsai YW, Huang WF, et al. A Comparison of Aspirin and Clopidogrel With or Without Proton Pump Inhibitors for the Secondary Prevention of Cardiovascular Events in Patients at High Risk for Gastrointestinal Bleeding. *Clin Ther* 2009;31:2038-47.
11. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:728-38.
12. Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). *Heart* 2011;97:797-802.
13. The Dutch Institute for Health Care improvement CBO. Guideline NSAID use and prevention of gastric damage. [Richtlijn NSAID-gebruik en preventie van maagschade]. The Dutch Institute for Health Care improvement CBO: Utrecht, 2003. Available at: http://www.mdl.nl/uploads/240/117/NSAID-gebruik_en_preventie_van_maagschade_-_CBO_2003.pdf.
14. National Institute for Health and Care Excellence. NSAIDs - prescribing issues. 2013. Available at: http://cks.nice.org.uk/nsaids-prescribing-issues#!scenariorecommendation:3.
15. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PM, De Smet PA. Targeting outpatient drug safety: recommendations of the Dutch Harm-Wrestling Task Force. [HARM-WRESTLING: een voorstel van de Expergroep Medicatieveiligheid m.b.t. concrete interventies die de extramurale medicatieveiligheid op korte termijn kunnen verbeteren]. Ministry

of Health, Welfare and Sport: Den Haag, 2009. Available at: http://www.knmp.nl/downloads/medicijnen-zorgverlening/medicatieveiligheid/harmwrestlingrapportdefnov2009.pdf.
16. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PM, De Smet PA. Targeting outpatient drug safety: recommendations of the Dutch Harm-Wrestling Task Force. Royal Dutch Pharmacists Association: Den Haag, 2010. Available at: http://www.knmp.nl/downloads/medicijnen-zorgverlening/medicatieveiligheid/rapport-harm-wrestling-english.pdf .
17. Valkhoff VE, van Soest EM, Sturkenboom MC, Kuipers EJ. Time-trends in gastroprotection with nonsteroidal anti-inflammatory drugs (NSAIDs). *Aliment Pharmacol Ther* 2010;31:1218-28.
18. Helsper CW, Smeets HM, Numans ME, Knol MJ, Hoes AW, de Wit NJ. Trends and determinants of adequate gastroprotection in patients chronically using NSAIDs. *Pharmacoepidemiol Drug Saf* 2009;18:800-06.
19. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Medical Informatics & Decision Making* 2008;8:38.
20. Kooij FO, Klok T, Hollmann MW, Kal JE. Decision support increases guideline adherence for prescribing postoperative nausea and vomiting prophylaxis. *Anesthesia & Analgesia* 2008;106:893-8.
21. Lavis JN, Rottingen JA, Bosch-Capblanch X, et al. Guidance for evidence-informed policies about health systems: linking guidance development to policy development. *PLoS medicine* 2012;9:e1001186.
22. Foundation for Pharmaceutical Statistics. Facts and Figures 2004. 2004. Available at: http://www.sfk.nl/english/Factsandfigures2004.pdf.
23. Foundation for Pharmaceutical Statistics. Facts and Figures 2010. 2010. Available at: http://www.sfk.nl/english/2010fandf.pdf.
24. Foundation for Pharmaceutical Statistics. Decrease in gastroprotection in NSAID users. [Minder maagbescherming bij gebruik NSAID]. 2012. Available at: http://www.sfk.nl/nieuws-publicaties/PW/2012/minder-maagbescherming-bij-gebruik-nsaid.
25. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.
26. Geijer RM, Rikken SA. Decrease in the number of prescriptions for third-generation contraceptive pills. [Afname van het aantal voorschriften van 3e-generatie-anticonceptiepillen]. *Ned Tijdschr Geneeskd* 2000;144:2069-70.
27. Lamberts H, Wood M, Hofmans-Okkens IM. International primary care classifications: the effect of fifteen years of evolution. *Fam Pract* 1992;9:330-9.
28. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. Oslo, 2013. Available at http://www.whocc.no/filearchive/publications/2014_guidelines.pdf.
29. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993;119:1036-41.
30. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med* 1999;38:339-44.
31. Valkhoff VE, van Soest EM, Masclee GM, et al. Prescription of nonselective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal - a 617 400-patient study. *Aliment Pharmacol Ther* 2012;36:790-9.

32. de Jong HJ, Korevaar JC, van Dijk L, Voogd E, van Dijk CE, van Oijen MG. Suboptimal prescribing of proton-pump inhibitors in low-dose aspirin users: a cohort study in primary care. *Bmj Open* 2013;3.
33. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PM, De Smet PA. Targeting outpatient drug safety: Recommendations of the Dutch Harm-Wrestling Task Force. *Drug Saf* 2012;35:245-59.

Appendix I. Specification of medications and comorbidities

Medication	Specification
Clopidogrel	ATC-code B01AC04 (clopidogrel), B01AC22 (prasugrel), or B01AC30 (platelet aggregation inhibitors, combinations)
Corticosteroid	ATC-code H02AB (glucocorticoids), with the exception of topical or local application
Coxib	ATC-code M01AH (coxibs)
Diclofenac-misoprostol	ATC-code M01AB55 (arthrotec)
H2RA	ATC-code A02BA (H2RA)
High-dose NSAID	Prescribed daily dosage ≥ the recommended daily maximum.
Low-dose aspirin	ATC-code B01AC06 (acetylsalicylic acid) , B01AC08 (carbasalate calcium), B01AC30 (platelet aggregation inhibitors, combinations), N02BA01 (acetylsalicylic acid) in dosage ≤ 80mg, or N02BA15 (carbasalate calcium) in dosage ≤ 100mg.
NSAID	One of the following: 1) ATC-code M01A, with the exception of M01AX05 (glucosamine), M01AX12 (glucosaminoglycan polysulfate), M01AX21 (diacerein), M01AX24 (oxaceprol), M01AX25 (chondroitin sulfate) and M01AX26 (avocado and soyabean oil) 2) ATC-code N02BA01 (acetylsalicylic acid) in dosage > 80mg, N02BA15 (carbasalate calcium) in dosage > 100mg, N02BA11 (diflunisal), N02BA51 (acetylsalicylic acid, combinations), or N02BA65 (carbasalate calcium, combinations).
NsNSAID	One of the following: 1) ATC-code M01A with the exception of M01AH (coxibs), M01AX05 (glucosamine), M01AX12 (glucosaminoglycan polysulfate), M01AX21 (diacerein), M01AX24 (oxaceprol), M01AX25 (chondroitin sulfate) and M01AX26 (avocado and soyabean oil) 2) ATC-code N02BA01 (acetylsalicylic acid) in dosage > 80mg, N02BA15 (carbasalate calcium) in dosage > 100mg, N02BA11 (diflunisal), N02BA51 (acetylsalicylic acid, combinations), or N02BA65 (carbasalate calcium, combinations)
PPI	ATC-code A02BC (PPI) or M01AE52 (naproxen and esomeprazole)
Spironolactone	ATC-code C03DA01 (spironolactone)
SSRI	ATC-code N06AB (SSRI), N06AX21 (duloxetine) or N06AX16 (venlafaxine)
VKA	ATC-code B01AA (vitamin K antagonists)
Comorbidity	Specification
History of UGIE	One of the following: 1) History of UGIE according to journal text (search algorithm) 2) ICPC-code D85 (duodenic ulcer) or D86 (other peptic ulcer)
History of DM	One of the following: 1) History of DM according to journal text (search algorithm); 2) ICPC-code T90 (DM) 3) ATC-code A10 (drugs used in diabetes)
History of HF	One of the following: 1) History of HF according to journal text (search algorithm) 2) ICPC-code K77 (HF)
History of severe RA	Both of the following: 1) ICPC-code L88 (RA) 2) prescription of at least one of the following in the year prior to index date: ATC-code A07EC01, L01AA01, L04AA13, L04AA27, L04AB01, L04AB02, L04AB04, L04AB05, L04AB06, L04AC03, L04AC07, L04AD01, L04AX01, L04AX03, L01XC02, M01CB01, M01CC01, P01BA01 or P01BA02 (drugs used in severe RA)

ATC: Anatomical Therapeutic Chemical; DM: diabetes mellitus; HF: heart failure; H2RA: histamine-2 receptor antagonist; ICPC: International Classification for Primary Care; LDA: low-dose aspirin; NSAID: non-steroidal anti-inflammatory drug; nsNSAID: non-selective NSAID; PPI: proton pump inhibitor; RA: rheumatoid arthritis; SSRI: selective serotonin-reuptake inhibitor; UGIE: upper gastrointestinal event; VKA: vitamin K antagonist.

Chapter 6
High-risk use of over-the-counter non-steroidal anti-inflammatory drugs: population based cross-sectional study

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ABSTRACT

Background

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with serious adverse drug events (ADEs).

Aim

To determine the prevalence of over-the-counter (OTC) NSAID use in the general population and in patients with a high risk of developing a serious NSAID-related ADE.

Design and setting

Cross-sectional study in four general practices in The Netherlands.

Method

Two patient samples were selected: (i) random sample of adults (general population sample); (ii) adult patients with a high risk of developing a serious ADE in case of NSAID use (high-risk sample). All included patients were sent a questionnaire regarding their use of OTC NSAIDs in the four weeks prior to participation.

Results

In the general population sample, 118 of 456 (26%) invited patients completed the questionnaire. Of these, 35 (30%) had used an OTC NSAID. In the high-risk sample, 264 of 713 (37%) invited patients completed the questionnaire, and of these high-risk patients 33 (13%) had used an OTC NSAID. Over 20% of OTC NSAID users in the general population sample and over 30% in the high-risk sample had used the OTC NSAID for more than seven days. OTC NSAIDs were used in a dosage exceeding the recommended daily maximum by 9% and 3% of OTC NSAID users in respectively the general population and the high-risk sample.

Conclusion

OTC NSAIDs are used by almost one third of the general population. In the high-risk patients we selected, one in eight patients used an OTC NSAID. Continued efforts by health authorities and healthcare professionals to inform patients of the risks of these drugs are warranted.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed because of their analgesic and anti-inflammatory properties. Their use is associated with the occurrence of serious adverse drug events (ADEs), particularly of the gastrointestinal, cardiovascular and renal tract.[1-6] To limit the occurrence of such ADEs, guidelines have been developed and recommend avoiding the prescription of these drugs in patients with known risk factors for development of ADEs, such as old age, comorbidity or concurrent use of interacting medication.[7-12]

In many countries NSAIDs are freely available over-the-counter (OTC). Use of OTC NSAIDs and other OTC analgesics appears to be widespread.[13,14] In general, short-term use of NSAIDs is considered relatively safe, provided it is used in OTC-doses by adults without contraindications or interacting medications.[15] However, in previous studies performed in the UK and Australia, around one quarter of all OTC analgesic users were found to do so at a dosage exceeding the maximum dose and one third of OTC NSAID users had a warning or contraindication for use of these drugs, or used concurrent interacting medication.[14,16]

We conducted a cross-sectional population-based study to determine the current prevalence of OTC NSAID use in the general Dutch population and in patients at a high risk of developing a serious gastrointestinal, cardiovascular, or renal NSAID-related ADE. In addition, we aimed to examine the duration and dosage of use, the reasons for use and the place of purchase and information provision upon purchase.

METHOD

Setting

We conducted a cross-sectional study in April 2012 within four general practitioner (GP) practices in the Rotterdam region, recruited from an academic network of practices associated with the Erasmus University Medical Center. In the Netherlands, all citizens are registered with one GP, who forms the first point of care for all medical complaints. The 33,593 patients registered with the four participating practices are comparable to the general population of the Netherlands with regards to age and gender (mean age 41 years, 51% female in the Dutch general population versus 40 years, 51% female in the participating practices).[17] All four GP practices contribute data to the Integrated Primary Care Information (IPCI) database. This longitudinal GP electronic health record database contains the anonymized patient records of patients registered with GPs throughout the Netherlands, containing data on patient demographics, diagnoses using the International Classification for Primary Care (ICPC)[18] and journal entries, referrals, laboratory results and hospitalizations. In addition, details of drug prescriptions using the Anatomical Therapeu-

tic Chemical (ATC) code[19] and their dosage regimens are available. Further details of the database have been described elsewhere.[20-21]

Study population

Within the participating practices, two samples of patients were selected, using the medical records contained in the IPCI database. The first was a random sample of all adult patients aged ≥ 18 years (general population sample). In the second sample we specifically selected adult patients who, according to Dutch clinical prescription guidelines,[7,10-12] had at least one risk factor leading to a high risk of developing a serious NSAID-related ADE (high-risk sample). We aimed to select at least the following number of patients from each of the following risk groups: 1) 150 patients with a history of peptic ulcer or ulcer complication; 2) 200 patients aged over 70; 3) 300 patients with two or more of the following minor risk factors: use of anticoagulant, use of aspirin, use of corticosteroid, use of selective serotonin reuptake inhibitor, age 60-70 years, history of severe rheumatoid arthritis, diabetes mellitus or heart failure; 4) 50 patients with a history of myocardial infarction; 5) 50 patients with a history of stroke; 5) 100 patients with a history of heart failure; or 6) 50 patients with a glomerular filtration rate (GFR) < 30mL/min. As these risk factors often overlap, patients could be selected more than once, thereby contributing to the numbers in each risk group. The diagnoses of diseases and conditions mentioned were identified based on ICPC-coding. The prescriptions of interacting medication were identified based on ATC-coding and patients were assumed to use such medication if the prescription had been issued in the three months prior to selection. Kidney function was determined based on the most recent laboratory measurement of GFR, performed in the five years prior to selection.

As the data contained within the IPCI database are anonymous, selected patients could not be approached directly. All patients have a unique identity code within the database which can only be decrypted by their GPs. The identity codes of selected patients were therefore sent to their respective GPs, who were asked to decrypt the patients' codes and to send them an information pack, thereby inviting them to participate in the study. GPs were allowed to exclude any patients they did not deem appropriate for participation.

Consent form and questionnaire

All invited patients received a consent form and a questionnaire regarding their use of OTC NSAIDs. Only participants who completed the consent form were included. The questionnaires were returned directly to us and contained a study code, so that we could link them back to the participant's medical record in the IPCI database. They were developed using Teleform® (Autonomy Cardiff, Vista, CA, USA), an optical character recognition system which allows the completed questionnaires to be optically read directly into a database. All questionnaires were manually checked after scanning to correct for any reading errors.

In the questionnaire, participants were asked whether they had used OTC NSAIDs in the four weeks prior to completion of the questionnaire. To aid them, an information leaflet containing the names and logos of all brands of available OTC NSAIDs in the Netherlands was provided. Those patients who had used OTC NSAIDs were asked to also answer questions regarding: 1) the type(s) of OTC NSAIDs used; 2) the number of days of use; 3) the average number of tablets used per day; 4) the dosage per tablet used; 5) the reason(s) for use; 6) the place of purchase; and 7) the provision of information upon purchase. If participants had used more than two NSAIDs, they were asked to complete these follow-up questions for the two most frequently used only. To determine whether any participants had used an OTC NSAID in a dosage exceeding the daily maximum, the average daily dosage used was calculated per NSAID by multiplying the average number of tablets used per day by the dosage per tablet used.

Characteristics of participants

To compare participants who had used an OTC NSAID to those who had not, some additional characteristics were determined from their medical records. GP prescriptions of an NSAID or proton pump inhibitor (PPI) in the six months prior to selection were identified based on ATC-coding. Diagnoses of musculoskeletal complaints, headache or menstrual pain in the six months prior to selection were identified based on ICPC-coding.

Statistical analyses

Characteristics were compared between participants and non-participants and between those who had used an OTC NSAIDs and those who had not using a Chi-squared test for dichotomous variables and independent t-test for age as a continuous variable. Information provision upon purchase was compared per place of purchase using a Chi-squared test or Fisher's exact test. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL, USA).

RESULTS

Response and patient characteristics

We initially selected 500 patients from the general population. In the high-risk sample, sampling from each risk group as described in the methods section led to a selection of 819 high-risk patients. Table 1 shows the individual risk factors within this high-risk sample and within high-risk patients in the source population. The participating GPs excluded a total of 44 patients from the general population sample and 106 high-risk patients (figure 1). The most common reasons for exclusion given were language barriers, cognitive impairment and severe comorbidity. When compared to included patients, excluded

Table 1. Individual risk factors within high-risk patients in the source population and in the high-risk sample.

Risk factor*	Number of high-risk patients	
	Source population n=5550 n (%)	High-risk sample n=819 n (%)
History of peptic ulcer/UGI complication	428 (8)	184 (22)
Age > 70 years	3662 (66)	390 (48)
Two or more minor UGI risk factors**	1711 (31)	410 (50)
History of myocardial infarction	686 (12)	152 (19)
History of stroke	504 (9)	108 (13)
Heart failure	214 (4)	156 (19)
Chronic renal insufficiency (GFR < 30 mL/min)	69 (1)	60 (7)

UGI: upper gastrointestinal; GFR: glomerular filtration rate.
* Risk factors can overlap.
** Two or more of the following minor risk factors: use of anticoagulant, use of aspirin, use of corticosteroid, use of selective serotonin reuptake inhibitor, age 60-70 years, history of severe rheumatoid arthritis, diabetes mellitus or heart failure.

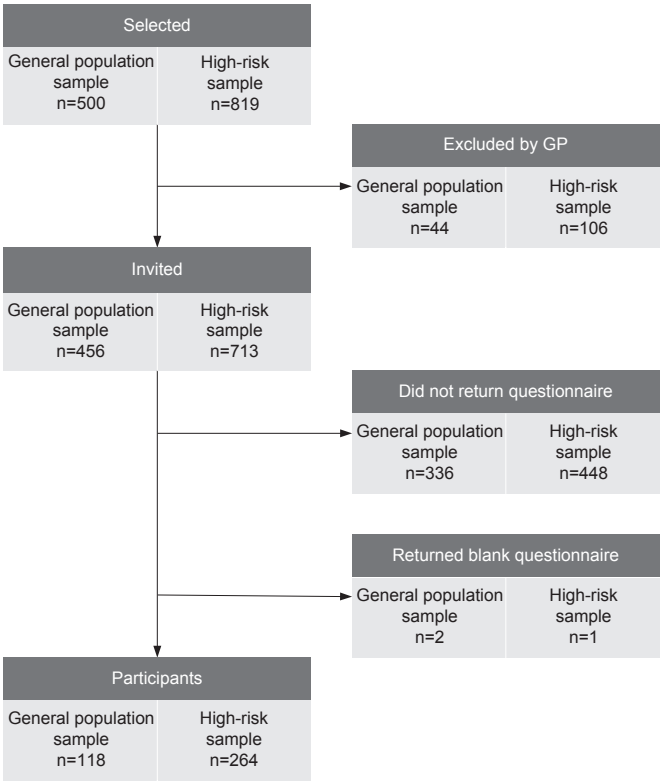

Figure 1. Flow chart of participants.

patients in the general population sample were significantly older (mean age 59 versus 49 years, P-value=0.004) and significantly more likely to have a high gastrointestinal risk (46% versus 19% of patients, P-value <0.001) or high cardiovascular risk (14% versus 4% of patients, P-value=0.016). In the high-risk sample, no statistically significant differences between excluded and included patients were found for gastrointestinal risk, but excluded patients were older (mean age 78 versus 68 years, P-value<0.001), more likely to be female (65% versus 48% of patients, P-value 0.002) and more likely to have a high cardiovascular risk (58 versus 43% of patients, P-value 0.004) or high renal risk (22% versus 5%, P-value<0.001) when compared to included patients.

Table 2. Characteristics of participants and non-participants in the two study samples.

	General population sample			High-risk sample		
	Non-participants (n=338) n (%)	Participants (n=118) n (%)	P-value*	Non-participants (n=449) n (%)	Participants (n=264) n (%)	P-value*
Age (mean ± SD)	47.1 (±17.2)	55.3 (±15.5)	<0.001	67.3 (±14.2)	68.8 (±10.5)	0.11
Age category						
18-40 years	138 (40.8)	23 (19.5)	<0.001	24 (5.3)	3 (1.1)	0.004
41-60 years	122 (36.1)	45 (38.1)	0.69	98 (21.8)	44 (16.7)	0.10
61-80 years	72 (21.3)	48 (40.7)	<0.001	250 (55.7)	178 (67.4)	0.002
> 80 years	6 (1.8)	2 (1.7)	0.95	77 (17.1)	39 (14.8)	0.41
Female	176 (52.1)	71 (60.2)	0.02	215 (47.9)	128 (48.5)	0.88
High gastrointestinal risk	55 (16.3)	31 (26.3)	0.02	413 (92.0)	249 (94.3)	0.24
History of peptic ulcer/UGI complication	4 (1.2)	3 (2.5)	0.30	117 (26.1)	46 (17.4)	0.008
Age > 70 years	42 (12.4)	22 (18.6)	0.09	199 (44.3)	110 (41.7)	0.49
Two or more minor risk factors**	14 (4.1)	9 (7.6)	0.14	212 (47.2)	149 (56.4)	0.017
High cardiovascular risk	14 (4.1)	5 (4.2)	0.96	190 (42.3)	115 (43.6)	0.75
History of myocardial infarction	10 (3.0)	3 (2.5)	0.82	83 (18.5)	48 (18.2)	0.92
History of stroke	5 (1.5)	1 (0.8)	0.60	51 (11.4)	38 (14.4)	0.24
Heart failure	2 (0.6)	1 (0.8)	0.77	80 (17.8)	37 (14.0)	0.19
High renal risk: chronic renal insufficiency	0 (0)	0 (0)	NA	29 (6.5)	8 (3.0)	0.046

UGI: upper gastrointestinal.

* participants versus non-participants, Chi-squared test for dichotomous variables and independent t-test for age as a continuous variable.

** two or more of the following minor risk factors: use of anticoagulant, use of aspirin, use of corticosteroid, use of selective serotonin reuptake inhibitor, age 60-70 years, history of severe rheumatoid arthritis, diabetes mellitus or heart failure.

In the general population sample 118 of the 456 invited patients (26%) completed the questionnaire and in the high-risk sample 264 of the 713 invited patients (37%). Two patients in the general population sample and one patient in the high-risk sample did complete a consent form but did not answer any of the questions in the questionnaire. These patients were considered non-participants. The mean duration between selection of the patient and completion of the questionnaire was 30 days.

Table 2 shows the characteristics of participants and non-participants in each study population. In the general population sample, participants were significantly older than non-participants and were significantly more likely to be female. In the high-risk sample the mean age and gender of participants did not differ significantly from non-participants.

Use of OTC NSAIDs

In the general population sample, 35 of the 118 participants (30%) reported use of an OTC NSAID in the four weeks prior to completion of the questionnaire (table 3). Of these 35 OTC NSAID users, 11 (31%) had used two or more NSAIDs and 8 (23%) had used the NSAID for more than seven days. Nine percent of the OTC NSAID users in the general

Table 3. Use of OTC NSAIDs in the two study samples.

	General population sample (n=118)	High-risk sample (n=264)
OTC NSAID used*		
Yes	35 (29.7)	33 (12.5)
No	83 (70.3)	231 (87.5)
Number of OTC NSAIDs used**		
One	24 (68.6)	27 (81.8)
Two	7 (20.0)	5 (15.2)
More than two	4 (11.4)	1 (3.0)
Duration of OTC NSAID use**		
1-7 days	27 (77.1)	19 (57.6)
8-14 days	5 (14.3)	7 (21.2)
15-21 days	1 (2.9)	2 (6.1)
22-28 days	2 (5.7)	2 (6.1)
Missing	0 (0)	3 (3.0)
Daily dosage**		
Within daily maximum	31 (88.6)	32 (97.0)
Exceeding daily maximum	3 (8.6)	1 (3.0)
Missing	1 (2.9)	0 (0)

OTC: over-the-counter; NSAID: non-steroidal anti-inflammatory drug.
* n (% of total population).
** n (% of OTC NSAID users).

population sample were found to have used the NSAID in a daily dosage exceeding the recommended daily maximum.

In the high-risk sample, 33 of the 264 participants (13%) reported having used an OTC NSAID. Of those, 6 (18%) reported having used two or more NSAIDs and 11 (33%) had used the OTC NSAID for more than seven days. In this population, only 1 of the OTC NSAID users (3%) had used the NSAID in a high dose. Table 4 shows the percentage of OTC NSAID use per risk group within the high-risk sample. As most participants had more than one risk factor, these risk groups overlap.

Table 4. Use of OTC NSAIDs per risk group within the high-risk sample.

	Total invited (n)	Total participants n (% of invited)	OTC NSAID used n (% of participants)
Total number of patients*	713	264 (37.0)	33 (12.5)
High gastrointestinal risk	662	249 (37.6)	31** (12.4)
History of peptic ulcer/UGI complication	163	46 (28.2)	7 (15.2)
Age > 70 years	309	110 (35.6)	8 (7.3)
Two or more minor risk factors	361	149 (41.3)	18 (12.1)
Use of anticoagulant	72	31 (43.1)	1 (3.2)
Use of aspirin	288	118 (41.0)	11 (9.3)
Use of corticosteroid	57	21 (36.8)	3 (14.3)
Use of SSRI	49	13 (26.5)	1 (7.7)
Age 60-70 years	254	117 (46.1)	16 (13.7)
Severe rheumatoid arthritis	14	5 (35.7)	0 (0)
Heart failure	117	37 (31.6)	6 (16.2)
Diabetes mellitus	122	45 (36.9)	8 (17.8)
High cardiovascular risk	305	115 (37.7)	14 (12.2)
History of myocardial infarction	131	48 (36.6)	5 (10.4)
History of stroke	89	38 (42.7)	5 (13.2)
Heart failure	117	37 (31.6)	6 (16.2)
High renal risk: chronic renal insufficiency	37	8 (21.6)	2 (25.0)

OTC: over-the-counter; NSAID: non-steroidal anti-inflammatory drug; UGI: upper gastrointestinal; SSRI: selective serotonin reuptake inhibitor.

* each patient can potentially have more than one risk factor.

** of which 5 (16.1%) had been prescribed a proton pump inhibitor in 3 months prior to selection.

Types of NSAIDs used, reasons for use and place of purchase

In the general population sample, ibuprofen was the most commonly used NSAID, followed by high-dosed acetylsalicylic acid, naproxen and diclofenac (respectively 54%, 28%, 9% and 9% of all OTC NSAIDs used). The most common reasons for use in this population were headache, musculoskeletal complaints and menstrual pain (respectively 42%, 31% and 16% of all given reasons for use). In the high-risk sample, musculoskeletal complaints

and headache formed the most common reasons for use (respectively 51% and 38% of all given reasons for use). In this population, high-dosed acetylsalicylic acid was the most popular, followed by ibuprofen, diclofenac and naproxen (respectively 53%, 29%, 11% and 8% of all OTC NSAIDs used in this group).

In both the general population and the high-risk sample, participants were most likely to purchase the NSAID at drugstores (respectively 58% and 62% of all OTC NSAIDs), followed by pharmacies (respectively 23% and 21%) and supermarkets (15% in both populations). High-risk OTC NSAID users were more likely to receive information upon purchase at a pharmacy than at a drugstore or supermarket (88% versus 50% and 33% respectively). In the general population sample, this trend was not observed, as OTC NSAID users were most likely to receive information at the drugstore, followed by the pharmacy and supermarket (47%, 33% and 25% respectively).

Table 5. Characteristics of OTC NSAID users versus non-users.

	General population sample			High-risk sample		
	OTC NSAID used		P-value*	OTC NSAID used		P-value*
	No (n=83) n(%)	Yes (n=35) n(%)		No (n=231) n(%)	Yes (n=33) n(%)	
Age (mean ± SD)	58.0 (± 15.0)	49.0 (± 14.8)	0.004	69.4 (± 10.2)	64.9 (± 11.6)	0.022
Female	48 (57.8)	23 (65.7)	0.42	109 (47.2)	19 (57.6)	0.26
NSAID prescribed in 6 months prior	14 (16.9)	9 (25.7)	0.27	24 (10.4)	6 (18.2)	0.24
PPI prescribed in 6 months prior	18 (21.7)	4 (11.4)	0.19	110 (47.6)	10 (30.3)	0.06
GP diagnosis in 6 months prior of:						
musculoskeletal complaint	33 (39.8)	14 (40.0)	0.98	79 (34.2)	19 (57.6)	0.009
headache	3 (3.6)	0 (0)	0.55	4 (1.7)	3 (9.1)	0.014
menstrual pain	0 (0)	1 (2.9)	0.30	1 (0.4)	0 (0)	1.00

OTC: over-the-counter; NSAID: non-steroidal anti-inflammatory drug; GP: general practitioner; PPI: proton pump inhibitor.

* OTC NSAID users versus non-users, Chi-squared test or Fisher's exact test

Characteristics of OTC NSAID users versus non-users

In both the general population and the high-risk sample, OTC NSAID users were younger than non-users (table 5). In the high-risk sample, 58% of OTC NSAID users had been diagnosed with a musculoskeletal complaint by their GP in the six months prior to consultation, versus only 34% of non-users (P-value <0.05). OTC NSAID users in this population were also more likely than non-users to have consulted their GP because of headache (9% of OTC NSAID users versus 2% of non-users, P-value <0.05).

DISCUSSION

Summary

In this cross-sectional study, we found that one in eight patients selected because of their high gastrointestinal, cardiovascular or renal risk used OTC NSAIDs. We found the percentage of use to be at least 10% in the majority of the separate risk groups we investigated. In addition, almost one third of the general population sample were found to use OTC NSAIDs. Although most people in this general population have no contraindications for use, there is still potential for inappropriate use. Almost one third of OTC NSAID users in this population had used more than one NSAID and two users had used NSAIDs on a daily basis over the previous four weeks. In addition, 9% of OTC NSAID users in this population were found to do so in a dosage exceeding the daily maximum. Considering the widespread use of OTC NSAIDs in particularly the general population, this would result in at least 333,000 Dutch adults using OTC NSAIDs in a dosage exceeding the maximum at any given time.

Strengths and limitations

The strength of this study is that we had access to participants' electronic medical records and were therefore able to accurately identify patients at a high risk of developing an ADE in case of NSAID use. There are, however, several limitations that should be considered when reviewing the results. Firstly, the fact that we oversampled patients from specific risk groups in the high-risk sample, means that our overall result in this sample cannot be extrapolated directly to the total population of high-risk patients in the Netherlands. However, the results per individual risk group are representative, and we found the percentage of use to be at least 10% in the majority of the risk groups investigated. Secondly, the participating GPs excluded patients who they deemed inappropriate for participation, which limits to some degree the generalizability of our results and may have led to a slight overestimation of actual OTC NSAID use, as excluded patients were older and more likely to have a high risk than included patients. Thirdly, the response rate was low in both groups, which may have led to an under- or overestimation of OTC NSAID use. However, even in the unlikely event that none of the non-participants used an OTC NSAID, OTC NSAID use in the high-risk sample would still be at least 5%. Finally, it has been suggested that more than 60% of people cannot identify the active ingredient in their brand of analgesic.[22] If this is the case, the use of OTC NSAID may have been underreported by participants in this study. The risk of participants under- or overreporting the use of OTC NSAIDs was minimized, by supplying an overview of all brands of NSAIDs available OTC in the Netherlands, including pictures of the brand logo's, and by asking them to tick the box by the OTC NSAID they had used.

Comparison with existing literature

The prevalence of use of OTC NSAIDs in patients with a contraindication for use has been examined in one previous Dutch study in 2005.[23] This previous study did not examine OTC NSAID use in the general population and did not include ischaemic cardiovascular disease as a contraindication for NSAID use. Nonetheless, at 14% the prevalence of OTC NSAID use among high-risk patients found in this previous study is similar to our current finding of 13%. NSAIDs are available OTC in many other countries, including the US, UK and Australia. A US survey conducted in 1997, found that 12% of adults had used OTC NSAIDs on at least two occasions in the past 12 months for at least 5 consecutive days at a time.[24] In a later survey performed in the same country in 2002, 83% of individuals interviewed reported OTC analgesic use in the last year, and 37% of those interviewed reported using them daily or several times a week.[24] In our study, we only examined the use of OTC NSAIDs in the past month, which makes it difficult to compare our findings among the general population with those in the US. A UK study did investigate the same time period and found that 68% of individuals interviewed had used an OTC NSAID in the past month.[14] This high prevalence may be explained by the fact that the study was performed among University students instead of the general population, but may also reflect differences between countries. In Australia, for instance, the use of OTC NSAIDs was found to be much lower than in our study. In two surveys performed there in 2001 and 2009, respectively 7.5% and 14% of adults reported regular NSAID use (at least once a month). The authors suggest that the increase found may be due to the fact that ibuprofen received a general sales status in 2004, making it more widely available.[16]

Implications for health authorities and health care authorities

In the Netherlands, high-dose NSAIDs and large package sizes can only be purchased in pharmacies, while lower doses in smaller package sizes are freely available in drugstores and, in the case of ibuprofen 200mg, in supermarkets.[25] The majority of OTC NSAID users in this study purchased their NSAID at a drugstore. It has been suggested that changing the legal status of all NSAIDs to 'Pharmacy Only' may reduce the use of OTC NSAIDs by high-risk patients, as pharmacists can often identify such patients.[12] In this study, high-risk patients did appear to receive information upon purchase more frequently at a pharmacy than at a drugstore or supermarket. The question remains whether the information they received was sufficient, as they did proceed to purchase the NSAID. In addition, this study provides no information on the number of high-risk patients who intended to purchase OTC NSAIDs, but refrained from purchasing them after being warned against such use. Further studies are needed to assess whether changing the legal status of all NSAIDs (including low doses) to 'Pharmacy Only' will improve safe use of OTC NSAIDs.

GPs can also play an important role in improving safe use of OTC NSAIDs, by informing patients of the risks of these drugs, for instance when a new diagnosis is made or

medication is prescribed that alters the patient's risk profile. Compared to non-users, OTC NSAID users in the high-risk sample were far more likely to have been diagnosed with a musculoskeletal complaint or headache by their GP in the six months prior to participation. At least 58% of OTC NSAID users in this population had consulted their GP because of one or both of these complaints. The true percentage is likely to be even higher, as we only examined ICPC-coded diagnoses and GPs do not always apply this coding. These consultations therefore provide an additional opportunity to inform patients of their risk of developing ADEs in case of NSAID use. It is possible that GPs also play a role in the high percentage of OTC NSAID use found in the general population. In the Netherlands, for many patients the use of OTC NSAIDs may be cheaper than using NSAIDs on prescription. It is possible that GPs recommend OTC NSAID use in such patients. If this is the case, it is important that sufficient warnings are given regarding the dosage and duration of use.

Within the high-risk sample, the use of OTC NSAIDs was particularly low in patients using anticoagulants. This may be explained by the fact that these patients are monitored at anticoagulant clinics, where they are frequently seen and receive extensive advice regarding interacting medication. This suggests that providing more structural advice regarding NSAIDs for patients using aspirin, corticosteroids or SSRIs, may improve safe use in these risk groups. Larger scale studies are needed to further explore these findings and to investigate interventions aimed at improved informing of specific groups of high-risk patients.

In conclusion, the use of OTC NSAIDs is widespread, not only in the general population but also in patients in whom such use may lead to a high risk of developing serious ADEs. Future studies should focus on specific risk groups and interventions aimed at improving safe use of OTC NSAIDs. Continued efforts by health authorities and healthcare professionals to inform patients of the risks of these drugs are warranted.

REFERENCES

1. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
2. Hernandez-Diaz S, Rodriguez LA. Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-99.
3. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011;8):e1001098.
4. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiol Drug Saf* 2011;20:1225-36.
5. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
6. Huerta C, Castellsague J, Varas-Lorenzo C, et al. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis* 2005; 45(3): 531-539.
7. The Dutch Institute for Health Care Improvement CBO. Guideline NSAID use and prevention of gastric damage [Richtlijn NSAID gebruik en preventie van maagschade]. Utrecht: The Dutch Institute for Health Care Improvement CBO; 2003. Available at: http://www.cbo.nl/Downloads/259/richtlijnnsaid.pdf.
8. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:728-38.
9. Chan FK, Abraham NS, Scheiman JM, et al. Management of patients on non-steroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Non-steroidal Anti-inflammatory Drugs and Anti-platelet Agents. *Am J Gastroenterol* 2008;103:2908-18.
10. Hoes AW, Walma EP, Rutten FH, et al. Multidisciplinary guideline heart failure [Multidisciplinaire richtlijn hartfalen]. The Dutch College of General Practice, the Dutch Society for Cardiology and the Dutch College of Internal Medicine; 2010. Available at: http://www.cbo.nl/Downloads/1081/rl_hartfalen_2010.pdf.
11. De Grauw WJC, Kaasjager HAH, Bilo HJG, et al. National Transmural Consensus Chronic Renal Insufficiency [Landelijke transmurale afspraak chronische nierschade]. *Huisarts Wet* 2009;52:586-697.
12. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, et al. Targeting outpatient drug safety: Recommendations of the Dutch Harm-Wrestling Task Force. *Drug Saf* 2012;35:245-59.
13. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int* 2012;32:1491-1502.
14. French DP, James DH. Reasons for the use of mild analgesics among English students. *Pharm World Sci* 2008;30:79-85.
15. Moore N, Van Ganse E, Le Parc JM, et al. The PAIN Study: Paracetamol, Aspirin and Ibuprofen New Tolerability Study. A large scale randomised clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. *Clin Drug Invest* 1999;18:89-98.
16. Stosic R, Dunagan F, Palmer H, et al. Responsible self-medication: perceived risks and benefits of over-the-counter analgesic use. *Int J Pharm Pract* 2011;19:236-45.

17. Population; key statistics [Bevolking; kerncijfers]. Central Bureau of Statistics; 2012. Available at: http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=37296ned&D1=a&D2=0,10,20,30,40,50,(l-1)-l&HD=130215-1329&HDR=G1&STB=T.
18. Lamberts H, Wood M, Hofmans-Okkens IM. International primary care classifications: the effect of fifteen years of evolution. *Fam Pract* 1992;9:330-39.
19. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. Available at: http://www.whocc.no/.
20. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993;119:1036-41.
21. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med* 1999;38:339-44.
22. Roumie CL, Griffin MR. Over-the-counter analgesics in older adults: a call for improved labeling and consumer education. *Drugs Aging* 2004;21:485-98.
23. Jeucken YM, van Minnen YPM, van der Werf GTh. Use of over-the-counter NSAIDs by patients with contra-indications [Vrij verkrijgbare NSAID's gebruikt door patiënten met contra-indicaties]. *Huisarts Wet* 2005;8:388-91.
24. Wilcox CM, Cryer B, Triadafilopoulos G. Patterns of use and public perception of over-the-counter pain relievers: focus on non-steroidal anti-inflammatory drugs. *J Rheumatol* 2005;32:2218-24.
25. Motivation for classification system of legal status of supply for anti-inflammatories (NSAIDs) and acetylsalicylic acid, defined by the MEB on 2 July 2009. The Hague, The Netherlands: Medicines Evaluation Board; 2010. Available at: http://www.cbg-meb.nl/NR/rdonlyres/D97C7481-5C4E-4488-851C-A3D3DE371DCB/0/UKMotiveringNSAIDs20090820.pdf.

Chapter 7
General discussion

Musculoskeletal complaints are highly prevalent in the general population and are the most common reason for general practitioner (GP) consultation.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are often recommended in the treatment of such complaints.[2-8] As their use is associated with adverse drug reactions, these medications should be used with caution.[9] Careful weighing of the benefits and harms is required. This thesis aimed to provide an insight into various efficacy and safety aspects of NSAIDs in primary care patients with musculoskeletal complaints. In this chapter, the key findings of this thesis are reviewed in the context of current knowledge and evidence, and methodological issues are addressed. In addition, the implications of these findings for clinical practice are discussed and directions for future research provided.

Key findings and methodological issues

Efficacy of NSAIDs in musculoskeletal complaints

Chapter 2 provided a comprehensive overview of the available evidence on the efficacy of NSAIDs versus placebo or paracetamol in musculoskeletal complaints common in primary care, by summarizing the evidence from systematic reviews of RCTs. A strong overlap in RCTs between the systematic reviews was found and results for the efficacy of NSAIDs varied, but for most conditions only small effects of NSAIDs compared to placebo or paracetamol were found.

The vast majority of included reviews focused on osteoarthritis, far less evidence was available for many other highly prevalent musculoskeletal conditions frequently treated with NSAIDs in primary care. For instance, neck pain is the second musculoskeletal complaint in primary care, with an incidence of 15.4 per 1000 per year and a prevalence of 23.3 per 1000 per year,[1] yet none of the systematic reviews on neck pain meeting our inclusion criteria found any relevant RCTs.[10-12] Evidence from RCTs was also found to be lacking in systematic reviews of other common conditions of the musculoskeletal system, such as subacromial impingement syndrome and repetitive motion injury.[13-16] Considering the high prevalence of these musculoskeletal disorders in primary care, more focus on these conditions is needed. This is especially true for the efficacy of NSAIDs compared to paracetamol, for which far fewer studies were found than for NSAIDs versus placebo, even though paracetamol is generally recommended as a first choice analgesic in musculoskeletal disorders because of its more favourable safety profile.[2-8] As is noted in chapter 2, in this regard, a comparison between the efficacy of oral NSAIDs and topical NSAIDs would also have been of interest, as topical NSAIDs have also been shown to be safer than oral NSAIDs, and may thus form a suitable treatment alternative in musculoskeletal complaints.[17 18]

An important finding of chapter 2 which deserves more in-depth discussion here, is the fact that most of the systematic reviews found reported only on mean differences in pain

reduction, and did not conduct responder analyses. It is important to recognize that even if a small group difference in mean pain reduction is found for NSAIDs versus the comparator group, there may still be a sizable percentage of individuals within the NSAID group who experienced a clinically important change. Responder analyses, in which the percentage of patients who have a clinically important change in the treatment groups are compared, are needed to determine whether this is the case.[19 20] The majority of included studies did not report on the percentage of patients showing a clinically important change.

The few reviews which did report on this outcome, were further limited by the fact that they could not use a standardized definition of a clinically important change. Recommendations regarding such responder criteria have been previously published for some disorders, such as chronic pain and osteoarthritis,[19 20] but are not yet available for all types of musculoskeletal disorders. The included studies instead used various definitions of treatment response, such as 'relief from pain: complete (vs fair or none)' and 'treatment success (complete recovery or improved)'. In our review, we grouped these outcomes under proportion improved, but the variability of definitions used make it difficult to interpret and compare the results found for this outcome.

Responder analyses are also important because they may help identify specific subgroups of patients most likely to respond to NSAID treatment. For instance, for osteoarthritis there are strong indications that such subgroups exist, especially with regard to pain mechanisms.[21] Pain in osteoarthritis consists of nociceptive pain in the joint itself, peripheral sensitized pain from locally generated inflammatory factors, and centrally sensitized pain.[22] Patients with centrally sensitized pain probably respond particularly poorly to NSAIDs, as these do not have a centrally acting effect. In this regard, the question is whether the efficacy of NSAIDs should always be determined separately for all individual disorders of the musculoskeletal system. In disorders in which the underlying pain mechanism is similar, one would not expect large differences in efficacy. If this is found to be the case, pragmatic trials examining the effectiveness of NSAIDs in specific patient populations within primary care may be of greater interest than further efficacy trials.

Prescription of NSAIDs by GPs in patients suffering from musculoskeletal complaints

In chapter 3, we showed that GPs prescribe an NSAID in 25% of patients who consult them because of a new musculoskeletal complaint. This percentage decreased over time, but in 2010 NSAIDs were still prescribed in 20% of such consultations. Considering the findings on efficacy described in chapter 2, this percentage seems relatively high. For instance, of the patients presenting with neck complaints, for which no evidence on efficacy is available, 28% were treated with an NSAID.

The percentage of consultations in which an NSAID was prescribed also seems high, when one considers the fact that only first consultations for new musculoskeletal complaints were included. As most guidelines on musculoskeletal disorders recommend a

stepped approach with paracetamol as a first step,[2-8] one might expect a lower percentage of NSAID prescription on initial consultation. However, an important limitation of the study presented in chapter 3, is that we were unable to asses prior use of paracetamol. Paracetamol is available over-the-counter in the Netherlands. It is therefore possible that patients newly presenting a complaint to the GP, had already used paracetamol over-the-counter prior to consultation, and had found its effect insufficient.

Another limitation related to this, is the fact that we did not assess the prescription of paracetamol by the GP on initial consultation. The problem with examining such paracetamol prescriptions as an outcome is the fact that most paracetamol prescriptions, unlike NSAID prescriptions, are not reimbursed in the Netherlands. As a result, it is much cheaper for patients to purchase paracetamol themselves, to avoid prescription costs. The exception to this is Panadol 1000mg, which is reimbursed. Some GPs choose to prescribed Panadol for this reason, but it is still common practice for GPs to advise patients to purchase paracetamol over-the-counter, rather than issuing a prescription. The same applies to prescriptions of topical NSAIDs, which are also not reimbursed at present and are available over-the-counter. Dutch guidelines on musculoskeletal disorders do not yet recommend the use of topical NSAIDs, but some international guidelines have incorporated topical NSAIDs, either as adjunctive treatment or as an alternative to oral analgesics.[8 23 24]

Despite these reimbursement issues, it would have been of interest to assess prescriptions of paracetamol, topical NSAIDs and other types of analgesics in chapter 3. A previous study performed in the UK, which examined the influence of national guidelines on GP's analgesic prescribing, found that a temporary decrease in NSAID prescription which occurred in 2004, was accompanied by an increase in prescriptions of other analgesics (figure

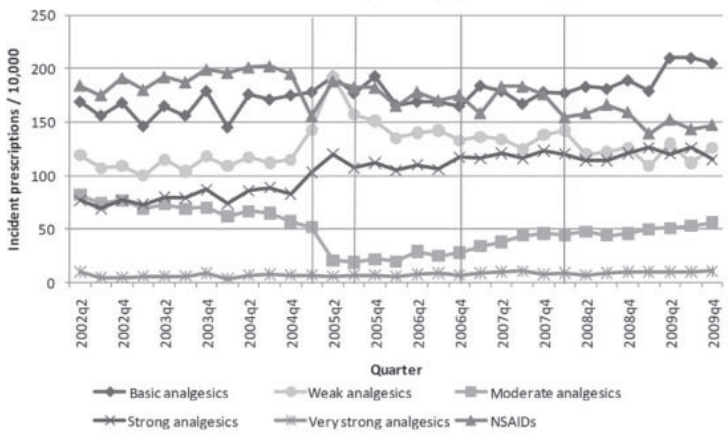

Figure 1. Incident number of patients per 10,000 registered population prescribed analgesics per quarter in the UK.[25]

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1).[25] These included strong analgesics such as tramadol. It is thus possible that the gradual decrease in NSAID prescription for musculoskeletal conditions in the Netherlands shown in chapter 3, was accompanied by an increase in other analgesics for these complaints, with their own safety issues. In this respect, it should be noted that the relative safety of paracetamol is currently under scrutiny. In addition to the risk of hepatotoxicity,[26] there is evidence to suggest that paracetamol is associated with cardiovascular and gastrointestinal adverse reactions.[27-33] Though the associations found in observational studies may in part be explained by confounding by indication, some evidence from randomized controlled trials is also available.[34 35]

Adherence to guidelines on gastroprotection

The fact that the use of NSAIDs is associated with an increased risk of gastrointestinal (GI) events has been known for a long time; the first study demonstrating gastric damage due to aspirin was published as early as 1938.[36] This risk can be lowered by concomitant use of a gastroprotective agent (GPA) such as a proton pump inhibitor (PPI), or by using a coxib instead of a non-selective (ns)NSAID. Guidelines have been developed nationally and internationally, defining patients who are most at risk and should receive a gastroprotective strategy in the form of concomitant GPA or a coxib.[9 37 38] Several previous studies have already examined adherence to these guidelines, and showed it to be far from optimal.[39 40] In order to improve guideline adherence, it is important to know more about the factors that play a role in adherence.

In chapter 5 we therefore examined time-trends in adherence to recommendations regarding gastroprotective strategies in patients prescribed NSAIDs and in patients prescribed low-dose aspirin (LDA), and explored temporal relationships with various environmental factors that may have played a role. We found that prescription of gastroprotective strategies was higher in patients initiating NSAID therapy than in those initiating LDA, which may be related to the fact that guidelines for NSAID users have been available for longer and GPs may therefore be more familiar with them.[37] Importantly, however, environmental factors such as changes in reimbursement policies also appeared to have a strong influence on guidelines adherence. The national reimbursement policy for PPIs was altered on 1st January 2012. Under the new policy, incidental prescriptions of PPIs were no longer reimbursed. In case of chronic use, prescriptions were still reimbursed, with the exception of the first prescription issued.[41] As is shown in chapter 5, this change in policy appears to have had a negative effect on guideline adherence, as the percentage of NSAID initiators with a high risk of GI events prescribed a PPI, which showed a steady increase until 2011, suddenly decreased from 49% in 2011 to 43% in 2012.

Ours is not the first study to demonstrate this influence of the change in reimbursement policy of PPIs. In 2013, a report was published examining the number of high risk NSAID users to whom pharmacies issued a PPI in 2011 and 2012.[42] In this report, a decrease

of 4% was found in 2012, compared to 2011, breaking the upward trend seen in the years prior. As this study used data on the issuing of PPIs by pharmacies, it was not clear whether this decrease was caused by a decrease in prescription of PPIs, or a decrease in the number of patients who collect their prescribed PPI from their pharmacy. In chapter 5, we demonstrate that a decrease in prescriptions by GPs is indeed present. The fact that we found an even stronger decrease of 6%, may be related to the fact that we focused only on new NSAID prescriptions by the GP, whereas the previous report included all NSAID users, regardless of duration of use or place of prescription.[42]

These findings suggest that the reimbursement policy for PPIs should be reconsidered. It has been estimated that the decrease in PPIs issued by pharmacies has led to around 360 extra patients with gastrointestinal bleedings in 2012.[42] In addition to the harm caused to patients, such extra bleedings lead to additional health care costs, as around a quarter of patients suffering from these bleedings are estimated to require hospital admittance.[42] The question remains whether these costs to the health care system are compensated by the savings created by the lack of reimbursement under the new policy.

Ischaemic cardiovascular risk

In chapter 5, we showed that adherence to guidelines on gastroprotection is limited, as only 48% of high risk NSAID initiators were given an adequate gastroprotective strategy in 2012. In contrast to gastrointestinal risk, no national guidelines have been developed as of yet regarding ischaemic cardiovascular (CV) risk. Evidence that the risk of ischaemic CV events is increased by both coxibs and nsNSAIDs only emerged over the course of the last decade.[43-46] In chapter 3, we wished to examine whether GPs are aware of this new evidence regarding ischaemic cardiovascular risk.

We therefore examined the association between ischaemic CV risk and the prescription of NSAIDs by GPs, in patients with MSK complaints. A decrease of coxib prescription was observed in 2004, after rofecoxib was removed from world markets because of its association with stroke, myocardial infarction and sudden cardiac death.[47] This sudden decrease suggests that GPs were indeed aware of this new information. However, an important finding in this chapter is the fact that the sudden decrease in coxib prescription found was not limited to high CV risk patients. In fact coxibs continued to be prescribed more frequently in high CV risk patients than in low CV risk patients. If the decrease in coxib prescription was caused by an increased awareness by GPs of the cardiovascular risks of these drugs, one would expect to find the opposite pattern. As is discussed in chapter 3, one reason for the high frequency of coxib prescription in high CI risk patients appears to be the correlation between ischaemic CV risk and upper gastrointestinal risk. However, based on the stratified analysis shown, other factors also appear to play a role.

It is possible that these results reflect differences in prescribing behaviour between GPs. An important limitation of our study in chapter 3, is that we only determined the percent-

age of prescriptions within the total patient population. Differences in prescribing between GPs were not examined. A report published in 2012, in which quality indicators for primary care were developed, determined the percentage of prescription of various types of risk medication per GP practice.[48] Large differences in prescribing behaviour between GP practices were found. For example, the percentage of non-selective NSAID users who had a prior history of stroke or ischaemic heart disease, was shown to be 13.8% in a median GP practice in 2010, but the 5th and 95th percentile were 7.5% and 23.5% respectively (figure 2).[48] To gain more insight into GPs awareness of the cardiovascular risk of NSAIDs, it would therefore have been of interest to examine differences in prescribing patterns between GPs.

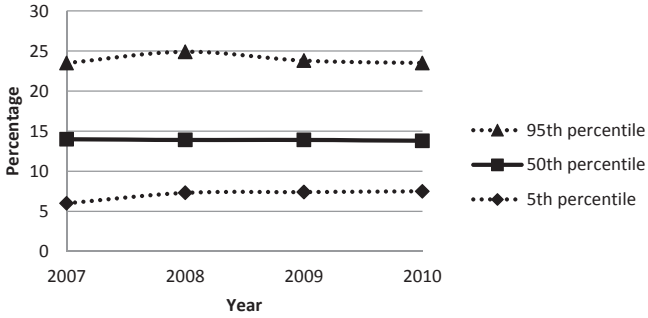

Figure 2. Percentage of non-selective NSAID users with a history of ischaemic heart disease or stroke per GP practice per year in the Netherlands (adapted from source).[48]

A second limitation of the study described in chapter 3, is that we did not take the duration of prescription of the NSAID into account. This duration may be important, because on an individual patient level, the absolute risk of an ischaemic CV event is relatively low in the short-term. Thus, in short-term NSAID prescription, the increased relative risk of ischaemic CV events may be less relevant to individual patients and prescribers. Although the duration of NSAID prescription was not determined for the cohort described in chapter 3, we did determine the duration of continuous prescription in a subcohort of this total cohort, which is described in chapter 4. The median duration of NSAID prescription was found to be only 11 days, with an interquartile range of 7 days. It is possible that this short duration of exposure plays a role in GPs' decision to prescribe NSAIDs in individual patients with a high cardiovascular risk.

Non-serious adverse drug reactions

Although much research has been performed into the occurrence of serious NSAID-related adverse drug reactions (ADRs), far fewer studies are available on the occurrence of non-

serious ADRs, especially in the primary care population. Considering the small effect sizes of NSAIDs found for many musculoskeletal conditions in chapter 2, the incidence of such non-serious ADRs is relevant when weighing the benefits and harms of treatment. In chapter 4, we showed that almost one in 30 patients treated with NSAIDs for a median duration of 11 days, consulted their GP with a complaint that was probably or possibly a non-serious NSAID-related ADR. The incidence rate of consultations for such probable and possible ADRs combined was 3 per 1000 person-days of NSAID prescription.

As is already discussed in chapter 4, it is important to note that the actual incidence of non-serious ADRs is likely to be much higher, as we only used data from an electronic GP health care database, and not all patients will consult their GP if an ADR occurs. This Integrated Primary Care Information (IPCI) database, which was used both for this study and for the studies described in chapters 3, 5 and 6, provides a wealth of valuable data, as it includes the full GP records of over 1 million patients throughout the Netherlands, including free journal text. However, working with such a database comes with its own limitations, as is described in detail in the general discussion of a thesis by Valkhoff in 2012.[49] One of the main limitations in relation to this current thesis and particularly to chapter 4, is the fact that free text is entered into the medical journals in an unstructured way by the GPs. Not only does this limit the use of automated searches, it also means that any information not recorded by the GP is missed. A second important limitation with respect to the studies described in chapter 3, 4 and 5, is the fact that the use of over-the-counter (OTC) NSAIDs could not be determined. NSAIDs are available without prescription in the Netherlands, but use of such OTC NSAIDs is not captured in the IPCI database.

Use of over-the-counter NSAIDs

In chapter 6 we therefore studied the use of OTC NSAIDs by sending questionnaires to patients, who were selected using information from their medical records contained within the IPCI database. In the general population, one in three participants were found to have used an OTC NSAID in the four weeks prior to participation, in patients with a high risk of adverse drug reactions they were used by one in eight. Musculoskeletal complaints formed the most common reason for use in such high-risk patients.

As discussed in chapter 6, the frequent use of OTC NSAIDs by high-risk patients raises the question whether such patients are sufficiently aware of the risks of OTC NSAIDs. We did not explore this within our study, as we were concerned that including questions on this issue in our questionnaire may influence the way participants answered the other questions concerning OTC NSAID use. It is important to gain more insight into high-risk OTC NSAID users' knowledge of the risks of these medications and their considerations in using OTC NSAIDs, in order to develop interventions aimed at improving safe use of OTC NSAIDs.

From a public health perspective, the high prevalence of NSAID use in the general population is also relevant. Although the absolute risk of ADRs is much lower in healthy individuals than in patients with contraindications, the widespread use of OTC NSAIDs is still likely to have consequences for the number of adverse drug events occurring on a population level, especially as OTC NSAIDs were often used in high dosages and for longer periods of time. Previous studies examining medication-related hospital admissions only took prescription NSAIDs into account.[9] The contribution of OTC NSAID use to hospital admissions is not known, but based on our findings in chapter 6 this is likely to be considerable and certainly warrants further investigation.

Implications for clinical practice

The findings of this thesis suggest that a smaller role for NSAIDs in the treatment of musculoskeletal complaints by GPs would be more appropriate. The efficacy of NSAIDs compared to placebo and to paracetamol is relatively small and adverse drug events requiring reconsulation frequently occur. A greater awareness and adherence to prescribing guidelines by GPs is also needed, as the implementation of gastroprotective measures is still far from optimal. Importantly, GPs should be aware that NSAIDs are frequently used OTC. They should enquire after such OTC NSAID use when prescribing medications which lead to an increased risk of gastrointestinal events. In addition, patients in whom conditions such as diabetes, heart failure, severe rheumatoid arthritis or renal insufficiency are diagnosed, should receive information on the risks of NSAID use upon diagnosis. As such patients are often also seen by nurse practitioners on a regular basis, especially those with diabetes, the quality of information provision could be further improved by incorporating counseling on NSAIDs into these standard consultations. Finally, many of the OTC NSAID users with musculoskeletal pain were found to have previously consulted their GP for these complaints. This forms an additional point of contact in which GPs can provide information to encourage safer use of OTC NSAIDs.

Pharmacists can also play a valuable role in improving safe use of OTC NSAIDs. When newly issuing prescription medications such as anticoagulants, aspirin, corticosteroids, or SSRIs, they should provide targeted information to inform patients of the risks of using OTC NSAIDs whilst on these medications. Pharmacies, drugstores and supermarkets should also be encouraged to provide adequate information upon purchase of OTC NSAIDs. The question remains whether drugstores and supermarkets are sufficiently qualified to provide such information, and a 'Pharmacy Only' status for NSAIDs should therefore be considered.

Future directions for research

The discussion in this chapter leads to the following recommendations for future research. Firstly, there should be more focus on identifying specific subgroups of patients with musculoskeletal complaints who respond most strongly to NSAID treatment. As many RCTs

on the efficacy of NSAIDs have already been performed, it may not always be necessary to set up new trials to study specific predictors of response, instead meta-analyses using individual patient data from previous RCTs could be performed. The OA Trial Bank, for instance, is an initiative in which researchers cooperate in a consortium and enter individual patient data from their osteoarthritis trials in a central pooled database, from which subgroup meta-analyses can subsequently be performed.[50] Future initiatives to set up similar consortia for other disorders should be encouraged, to fully exploit the potential of data gathered in previous RCTs.

More pragmatic clinical trials within a primary care setting are also needed, to determine the effectiveness of NSAIDs versus other treatment options in musculoskeletal complaints within this population. Prevalent disorders such as shoulder and neck complaints are of particular interest, and reporting of relevant outcomes should include responder analyses using standardized definitions. Within such pragmatic trials, the occurrence of both serious and non-serious ADRs and discontinuation of treatment within this population should also be incorporated. One method which could be employed to achieve this, is a randomized database study. In a randomized database study, electronic patient records are used to identify possible candidates, to randomize treatments, and to collect data on the natural course of the treatment and outcomes. A previous study conducted within the IPCI database, showed that this method certainly has potential, but also highlighted specific obstacles which need to be addressed in future studies to improve the feasibility and increase the performance of this method.[51]

Qualitative studies are also required to explore GPs' knowledge and considerations in prescribing NSAIDs as treatment in musculoskeletal complaints. Greater knowledge of the factors that currently play a role, can assist in developing tools to aid GPs in achieving balanced prescribing decisions. On the one hand this may concern knowledge based tools, such as guidelines and decision guiding aids. Such guidelines should incorporate all safety aspects of NSAIDs, as there is a strong overlap between risk factors such as upper gastrointestinal risk, cardiovascular risk and renal insufficiency. On the other hand, if other factors such as time constraints, a lack of alternative treatment options, or expectations of patients' wishes play a role, other tools may be required. In this light, qualitative studies exploring patients' expectations and satisfaction with NSAID treatment are also of interest.

The question remains whether guidelines and practical tools for GPs are the most effective way of reducing NSAID-related ADRs and hospital admissions on a national level. Policy measures such as reimbursement of gastroprotective agents are also important. Future studies should examine the effect of recent changes in reimbursement of PPIs on the number of upper gastrointestinal events occurring, including outcomes on the cost-effectiveness of these measures. In addition, OTC NSAID use should form a priority for future studies. Not only should we examine whether OTC NSAID users are aware of the risks of these medications, more data on the incidence of serious ADRs in OTC NSAID

users and on the impact of potential measures aimed at safer use of OTC NSAIDs is also of great importance. Health authorities should consider this issue a priority, as from a public health perspective there may well be more to be gained here than in measures aimed at GP prescription of NSAIDs.

REFERENCES

1. Van der Linden MW, Westert GP, De Bakker DH, Schellevis FG. Second national survey of general practice. Morbidity in the population and in general practice. [Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk]. Utrecht/Bilthoven: NIVEL/RIVM; 2004. Available at: http://www.nivel.nl/sites/default/files/bestanden/ns2_r1_h02.pdf.
2. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15:S192-300.
3. Chavannes AW, Mens JMA, Koes BW, Lubbers WJ, Ostelo R, Spinnewijn WEM, et al. NHG guideline non-specific low back pain. [NHG-standaard aspecifieke lagerugpijn]. *Huisarts Wet* 2005;48:113-23.
4. Conaghan PG, Dickson J, Grant RL, Guideline Development G. Care and management of osteoarthritis in adults: summary of NICE guidance. *BMJ* 2008;336:502-3.
5. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014 Jan 24 [Epub ahead of print].
6. Van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J* 2006;15:S169-91.
7. Winters JC, Van der Windt DAWM, Spinnewijn WEM, De Jongh AC, Van der Heijden GJMG, Buis PAJ, et al. NHG guideline shoulder complaints [NHG-standaard schouderklachten]. *Huisarts Wet* 2008;51:555-65.
8. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
9. Warlé-Van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PM, De Smet PA. Targeting outpatient drug safety: recommendations of the Dutch Harm-Wrestling Task Force. [HARM-WRESTLING: een voorstel van de Expergroep Medicatieveiligheid m.b.t. concrete interventies die de extramurale medicatieveiligheid op korte termijn kunnen verbeteren]. Ministry of Health, Welfare and Sport: Den Haag, 2009. Available at: http://www.knmp.nl/downloads/medicijnen-zorgverlening/medicatieveiligheid/harmwrestlingrapportdefnov2009.pdf.
10. Binder AI. Neck pain. *Clin Evid (Online)* 2008;pii1103.
11. Hurwitz EL, Carragee EJ, Van Der Velde G, Carroll LJ, Nordin M, Guzman J, et al. Treatment of neck pain: noninvasive interventions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and its Associated Disorders. *Spine* 2008;33:S123-S52.
12. Peloso P, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie S, et al. Medicinal and injection therapies for mechanical neck disorders. *Cochrane Database Syst Rev* 2007:CD000319.
13. Faber E, Kuiper JI, Burdorf A, Miedema HS, Verhaar JA. Treatment of impingement syndrome: a systematic review of the effects on functional limitations and return to work. *J Occup Rehabil* 2006;16:7-25.
14. Johansson K, Oberg B, Adolfsson L, Foldevi M. A combination of systematic review and clinicians' beliefs in interventions for subacromial pain. *Br J Gen Pract* 2002;52:145-52.

15. van der Sande R, Rinkel WD, Gebremariam L, Hay EM, Koes BW, Huisstede BM. Subacromial impingement syndrome: effectiveness of pharmaceutical interventions-nonsteroidal anti-inflammatory drugs, corticosteroid, or other injections: a systematic review. *Arch Phys Med Rehabil* 2013;94:961-76.
16. Konijnenberg HS, de Wilde NS, Gerritsen AA, van Tulder MW, de Vet HC. Conservative treatment for repetitive strain injury. *Scand J Work Environ Health* 2001;27:299-310.
17. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2012;9:CD007400.
18. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Rockville: Agency for Healthcare Research and Quality; 2011.
19. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105-21.
20. Pham T, Van Der Heijde D, Lassere M, Altman RD, Anderson JJ, Bellamy N, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. *J Rheumatol* 2003;30:1648-54.
21. Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1236-42.
22. Schaible HG. Mechanisms of chronic pain in osteoarthritis. *Current rheumatology reports* 2012;14:549-56.
23. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137-62.
24. National Institute for Health and Clinical Excellence. Osteoarthritis: The Care and Management of Osteoarthritis in Adults. NICE Clinical Guideline 59. London: National Institute for Health and Clinical Excellence; 2008.
25. Bedson J, Belcher J, Martino OI, Ndlovu M, Rathod T, Walters K, et al. The effectiveness of national guidance in changing analgesic prescribing in primary care from 2002 to 2009: an observational database study. *Eur J Pain* 2013;17:434-43.
26. Ferner RE, Dear JW, Bateman DN. Management of paracetamol poisoning. BMJ. 2011;342:d2218.
27. Dedier J, Stampfer MJ, Hankinson SE, Willett WC, Speizer FE, Curhan GC. Nonnarcotic analgesic use and the risk of hypertension in US women. *Hypertension* 2002;40:604-8.
28. Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. *Arch Intern Med* 2002;162:2204-8.
29. Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007;167:394-9.
30. Forman JP, Stampfer MJ, Curhan GC. Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension* 2005;46:500-7.
31. Chan AT, Manson JE, Albert CM, Chae CU, Rexrode KM, Curhan GC, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation* 2006;113:1578-87.

32. Garcia Rodriguez LA H-DS. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis Res* 2001;3:98-101.
33. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol* 2008;103:872-82.
34. Sudano I, Flammer AJ, Periat D, Enseleit F, Hermann M, Wolfrum M, et al. Acetaminophen increases blood pressure in patients with coronary artery disease. *Circulation* 2010;122:1789-96.
35. Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, et al. A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. *Ann Rheum Dis* 2011;70:1534-41.
36. Hawkey CJ. COX-2 chronology. *Gut* 2005;54:1509-14.
37. The Dutch Institute for Health Care Improvement CBO. Guideline NSAID use and prevention of gastric damage [Richtlijn NSAID gebruik en preventie van maagschade]. Utrecht: The Dutch Institute for Health Care Improvement CBO; 2003. Available at: http://www.cbo.nl/Downloads/259/richtlijnnsaid.pdf.
38. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:728-38.
39. Helsper CW, Smeets HM, Numans ME, Knol MJ, Hoes AW, de Wit NJ. Trends and determinants of adequate gastroprotection in patients chronically using NSAIDs. *Pharmacoepidemiol Drug Saf* 2009;18:800-06.
40. Valkhoff VE, van Soest EM, Sturkenboom MC, Kuipers EJ. Time-trends in gastroprotection with nonsteroidal anti-inflammatory drugs (NSAIDs). *Aliment Pharmacol Ther* 2010;31:1218-28.
41. Foundation for Pharmaceutical Statistics. Decrease in gastroprotection in NSAID users. [Minder maagbescherming bij gebruik NSAID]. 2012. Available at: http://www.sfk.nl/nieuws-publicaties/PW/2012/minder-maagbescherming-bij-gebruik-nsaid.
42. Meulepas M, Lambooij A. Use of gastroprotection with NSAIDs and ASA [Maagzuurremmergebruik als protectie bij NSAID en ASA]. Utrecht: Instituut voor Verantwoord Medicijngebruik; 2013. Available at: http://www.medicijngebruik.nl/product/detail/493.
43. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.
44. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS medicine* 2011;8:e1001098.
45. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
46. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiol Drug Saf* 2011;20:1225-36.
47. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.
48. De Smet PAGM, Sturkenboom MCJM, Herings R, Warlé-Van Herwaarden MF, Valkhoff VE, Koffeman AR, et al. Acute hospital admitance possibly related to medication [Acute zieken-

huisopnamen die mogelijk zijn gerelateerd aan geneesmiddelbijwerkingen]. 2012. Available at: http://www.rijksoverheid.nl/documenten-en-publicaties/rapporten/2013/02/12/acute-ziekenhuisopnamen-die-mogelijk-zijn-gerelateerd-aan-geneesmiddelbijwerkingen.html.

49. Valkhoff VE. Use and Safety of NSAIDs and Aspirin. Chapter 14 Summary and General Discussion. Doctoral thesis, Erasmus MC University Medical Center, Rotterdam, 2012. Available at: http://repub.eur.nl/pub/37862/121109_Valkhoff,%20Vera%20Esther.pdf.
50. van Middelkoop M, Dziedzic KS, Doherty M, Zhang W, Bijlsma JW, McAlindon TE, et al. Individual patient data meta-analysis of trials investigating the effectiveness of intra-articular glucocorticoid injections in patients with knee or hip osteoarthritis: an OA Trial Bank protocol for a systematic review. *Systematic reviews* 2013;2:54.
51. Mosis G, Dieleman JP, Stricker BC, van der Lei J, Sturkenboom MCJM. A randomized database study in general practice yielded quality data but patient recruitment in routine consultation was not practical. *J Clin Epidemiol* 2006;59:497-502.

Summary

Introduction

Musculoskeletal complaints form a common problem in the general population and are the most common reason for consulting the general practitioner (GP) in the Netherlands. The types and severity of musculoskeletal disorders presented vary greatly, but one common feature these disorders share is that their most burdensome component is pain. In many cases, the GP will therefore wish to prescribe an analgesic. Treatment guidelines recommend a stepped approach to such analgesic therapy. Paracetamol is recommended as a first step, as it is effective in many painful conditions and is considered relatively safe. When paracetamol fails, GPs can prescribe non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are a group medicines with analgesic, anti-inflammatory and anti-pyretic properties. They inhibit the action of the cyclooxygenase (COX), which is a central enzyme in the synthesis of prostaglandins. The use of NSAIDs is known to be associated with various unintended adverse drug reactions (ADRs). The most important and well known of these is the occurrence of peptic ulcer disease and its complications, most notably upper gastrointestinal bleeding, obstruction and perforation. In order to reduce the risk of gastrointestinal complications in patients prescribed NSAIDs, guidelines have been developed with recommendations regarding the prescription of these drugs and preventive measures which can be taken to reduce the risk, such as concomitant prescription of a gastroprotective agent or prescription of a selective COX-2 inhibitors (coxib) rather than a traditional, non-selective (ns)NSAID. Over the course of the last decade, it was discovered that use of NSAIDs is also associated with ischaemic cardiovascular events. As of yet, no national guideline has been published specifically on this topic, but a consensus report published in definitive form in 2009 warned against this risk of ischaemic adverse events and recommended avoiding NSAIDs in patients with a prior ischaemic cardiovascular history. Other adverse events known to be associated with NSAID use include a deterioration of renal function and heart failure. The use of NSAIDs is therefore contraindicated in patients with severe chronic renal insufficiency and in those with heart failure.

The efficacy of non-steroidal anti-inflammatory drugs in musculoskeletal disorders common in primary care

Much research has been performed into the efficacy of NSAIDs in specific musculoskeletal disorders, but an overview of the evidence was lacking. In **chapter 2**, we therefore conducted a systematic review to summarize and review the available evidence on the efficacy of oral NSAIDs, in the treatment of musculoskeletal disorders commonly presented in primary care. We included systematic reviews of RCTs assessing the efficacy of oral NSAIDs versus placebo or paracetamol. Outcomes of interest were pain and proportion improved.

For pain the magnitude of group differences was classified as negligible, small, moderate, or large, for improvement the number needed to treat (NNT) was calculated where possible. Our search yielded 5370 studies, 58 systematic reviews met our inclusion criteria. 19 reviews, including studies highly prevalent disorders such as neck pain and shoulder disorders, did not find any RCTs. Of the remaining 39 reviews, 22 reported sufficient data to assess magnitudes of effect. These often overlapped in terms of included RCTs. For instance, four reviews were found on chronic low back pain, but combined these reported on only five RCTs and overlap was present. The majority of included reviews focused on NSAIDs versus placebo. Results for pain varied greatly, a moderate group difference was found in some reviews, but the majority found a small difference or no significant difference versus placebo. NNT for improvement ranged from 4 to 10 for NSAIDs compared to placebo. For paracetamol as a comparison, far fewer studies were found, the majority of these found a small group difference for pain in favour of NSAIDs. NNT for improvement ranged from 5 to 9 for NSAIDs versus paracetamol. The results of this review draw into question the current strong emphasis on and frequent use of NSAIDs in the treatment of musculoskeletal pain in general practice. For some prevalent conditions, little evidence on efficacy is available to support such treatment. For many non-arthritic conditions for which systematic reviews were found, no significant difference or only small effects relative to placebo or paracetamol were reported. Even for conditions which have been studied extensively, such as osteoarthritis, large effects were rarely found, especially when compared to paracetamol.

Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints

In chapter 3, we aimed to determine the influence of ischaemic cardiovascular (CV) risk on prescription of NSAIDs by GPs in patients with musculoskeletal complaints. We performed a cohort study in the Integrated Primary Care Information database, an electronic health care database which contains the electronic GP medical records of over one million patients throughout the Netherlands. Our cohort consisted of 474,201 adults consulting their GP with a new musculoskeletal complaint between 2000 and 2010. Patients were considered at high CV risk if they had a history of myocardial infarction, angina pectoris, stroke, transient ischemic attack or peripheral arterial disease. Those with a history of hypertension, hyperlipidemia or diabetes were considered at moderate CV risk and those without CV risk factors at low CV risk. For each patient presenting with a new musculoskeletal complaint, we determined whether the GP prescribed an nsNSAID or coxib upon consultation. Overall, 24.4% of patients were prescribed an nsNSAID and 1.4% a coxib. Of the 41,483 patients with a high CV risk, 19.9% received an nsNSAID and 2.2% a coxib. These patients were more likely to be prescribed a coxib than patients with a low CV risk (OR 1.9, 95% CI 1.8-2.0). Prescription of nsNSAIDs decreased over time in all risk groups and was lower in

patients with a high CV risk than in patients with a low CV risk (OR 0.8, 95% CI 0.7-0.8). Nonetheless, overall one in five high CV risk patients received either a coxib or an nsNSAID, indicating that there is room for improvement.

Adverse drug reactions in a primary care population prescribed non-steroidal anti-inflammatory drugs

Over the past few decades, many studies have focussed on the occurrence of serious ADRs due to NSAIDs, and on related hospitalizations and death. However, less research has been performed into the incidence of non-serious ADRs due to NSAIDs in the primary care population, and in resulting health care utilization in the form of GP consultations. In **chapter 4** we therefore aimed to determine how often patients with musculoskeletal complaints prescribed an NSAID subsequently consult their GP with a non-serious ADR. We included a subcohort of 16,626 adult patients from the cohort presented in chapter 3, only including those patients newly prescribed an NSAID upon consultation between 1st January 2010 and 1st July 2010. The patients' medical records were manually assessed for the duration of NSAID use with a maximum of two months, and consultations for complaints predefined as adverse events were identified. Subsequently, causality assessment was performed and these adverse events were categorised as probable, possible or unlikely ADRs. In total, 961 patients (6%) consulted their GP with 1,227 non-serious adverse events. 174 patients (1%) presented at least one probable ADR, and a further 408 (2.5%) at least one possible ADR. Dyspepsia was the most frequent probable ADR, followed by diarrhoea and dyspnea (respectively 34%, 8% and 8% of all probable ADRs). Overall, almost one in 30 patients treated with NSAIDs for a median duration of 11 days, consulted their GP with a complaint that was probably or possibly an ADR. The incidence rate of consultations for such probable and possible ADRs combined was 3 per 1000 person-days of NSAID prescription. The burden of such consultations for non-serious ADRs should be taken into account by GPs when deciding whether treatment with an NSAID is appropriate.

Time-trends in the prescribing of gastroprotective agents to primary care patients initiating non-steroidal anti-inflammatory drugs or low-dose aspirin

Guidelines have been developed nationally and internationally, defining patients who are most at risk of a UGIE in case of NSAID use, and who should therefore receive a gastroprotective strategy in the form of concomitant GPA or a coxib. Several previous studies have already examined adherence to these guidelines, and showed it to be far from optimal. In order to improve guideline adherence, it is important to know more about the factors that play a role in adherence. In **chapter 5** we therefore examined time-trends in adherence to recommendations regarding gastroprotective strategies in patients prescribed NSAIDs, and explored temporal relationships with various environmental factors that may have played a

role. A comparison was made with patients prescribed low-dose aspirin (LDA), which also leads to an increased risk of UGIE, but for which guidelines have only recently been issued. We again conducted a cohort study in the IPCI database, two cohorts were selected: (i) patients newly prescribed LDA and (ii) patients newly prescribed NSAIDs between 2000 and 2012. Excluded were patients who had been prescribed a gastroprotective agent in the six months prior. For both cohorts, patients' risk of a UGIE was classified as low, moderate or high, and the presence of an adequate gastroprotective strategy was determined. 37,578 patients were included in the LDA cohort, 365,793 patients in the NSAID cohort. In both cohorts, an increase of gastroprotective strategies was observed over time, but prescription of gastroprotective agents was lower in the LDA cohort. By 2012, an adequate gastroprotective strategy was present in 31.8% of high-risk LDA initiators, versus 47.6% of high-risk NSAID initiators. This difference may be related to the fact that guidelines for NSAID users have been available for longer, and GPs may therefore be more familiar with them. Importantly, however, environmental factors such as changes in reimbursement policies also appeared to have a strong influence on guidelines adherence. The percentage of NSAID initiators with a high risk of GI events prescribed a proton pump inhibitor (PPI), which showed a steady increase until 2011, suddenly decreased from 49% in 2011 to 43% in 2012, after the national reimbursement policy for PPIs was altered on 1st January 2012.

High-risk use of over-the-counter non-steroidal anti-inflammatory drugs

In many countries NSAIDs are freely available over-the-counter (OTC). In general, short-term use of NSAIDs is considered relatively safe, provided it is used in OTC-doses by adults without contraindications or interacting medications. However, in previous studies performed in the UK and Australia, OTC analgesic users were often found to have contra-indications for the use of these drugs, and they frequently used the OTC analgesics in a dosage exceeding the maximum dose. In **chapter 6**, we determined the prevalence of OTC NSAID use in the general population and in patients with a high risk of developing a serious NSAID-related ADE, by performing a cross-sectional study in four general practices in The Netherlands. Two patient samples were selected: (i) random sample of adults (general population sample); (ii) adult patients with a high risk of developing a serious ADR in case of NSAID use (high-risk sample). All included patients were sent a questionnaire regarding their use of OTC NSAIDs in the four weeks prior to participation. In the general population sample, 118 of 456 (26%) invited patients completed the questionnaire. Of these, 35 (30%) had used an OTC NSAID. In the high-risk sample, 264 of 713 (37%) invited patients completed the questionnaire, and of these high-risk patients 33 (13%) had used an OTC NSAID. Over 20% of OTC NSAID users in the general population sample and over 30% in the high-risk sample had used the OTC NSAID for more than seven days. OTC NSAIDs were used in a dosage exceeding the recommended daily maximum by 9% and 3% of OTC NSAID users in respectively the general population and the high-risk sample. Considering

this frequent high-risk use of OTC NSAIDs, continued efforts by health authorities and healthcare professionals to inform patients of the risks of these drugs are warranted.

Discussion

As is discussed in detail in **chapter 7**, the findings of this thesis suggest that a smaller role for NSAIDs in the treatment of musculoskeletal complaints by GPs would be more appropriate. The efficacy of NSAIDs compared to placebo and to paracetamol is relatively small and adverse drug events requiring reconsulation frequently occur. A greater awareness and adherence to prescribing guidelines by GPs is also needed, as the implementation of gastroprotective measures is still far from optimal. Importantly, GPs should be aware that NSAIDs are frequently used OTC. They should enquire after such OTC NSAID use when prescribing medications which lead to an increased risk of gastrointestinal events and provide information on the risks of OTC NSAID use to high-risk patients. Pharmacists can also play a valuable role in improving safe use of OTC NSAIDs, by providing targeted information when newly issuing ulcerogenic prescription medications.

Future research should focus on identifying specific subgroups of patients with musculoskeletal complaints who respond most strongly to NSAID treatment. It may not always be necessary to set up new trials to study specific predictors of response, instead meta-analyses using individual patient data from previous RCTs could be performed. More pragmatic clinical trials within a primary care setting are also needed, to determine the effectiveness and safety of NSAIDs versus other treatment options in musculoskeletal complaints within this population. Prevalent disorders such as shoulder and neck complaints are of particular interest, and reporting of relevant outcomes should include responder analyses using standardized definitions. Qualitative studies are also required to explore GPs' knowledge and considerations in prescribing NSAIDs as treatment in musculoskeletal complaints, and to explore patients' expectations and satisfaction with NSAID treatment.

The question remains whether guidelines and practical tools for GPs are the most effective way of reducing NSAID-related ADRs and hospital admissions on a national level. Policy measures such as reimbursement of gastroprotective agents are also important, and future studies should examine the effect of recent changes in reimbursement of PPIs on the number of upper gastrointestinal events occurring, including outcomes on the cost-effectiveness of these measures. In addition, OTC NSAID use should form a priority for future studies. Not only should we examine whether OTC NSAID users are aware of the risks of these medications, more data on the incidence of serious ADRs in OTC NSAID users and on the impact of potential measures, such as a 'pharmacy only' status for NSAIDs, is also of great importance. Health authorities should consider this issue a priority, as from a public health perspective there may well be more to be gained here than in measures aimed at GP prescription of NSAIDs.

Samenvatting

Introductie

Klachten van het bewegingsapparaat komen frequent voor in de algemene populatie en vormen in Nederland de meest voorkomende reden om een huisarts te raadplegen. Het type klachten en de ernst varieert sterk, maar in de regel gaat het om pijnklachten. Huisartsen zullen dan ook vaak een pijnstiller voorschrijven. Richtlijnen adviseren een stapsgewijze benadering bij het voorschrijven van pijnstillers. Als eerste stap wordt paracetamol geadviseerd, omdat het effectief is bij veel soorten pijn en relatief veilig is. Als paracetamol onvoldoende effect heeft kan de huisarts een non-steroidal anti-inflammatory drug (NSAID) voorschrijven. NSAIDs hebben een pijnstillende, anti-inflammatoire en koortsremmende werking. Ze inhiberen de werking van het enzym cyclooxygenase (COX), dat een centrale rol speelt in de synthese van prostaglandines.

Het gebruik van NSAIDs is geassocieerd met verschillende bijwerkingen. De meest bekende hiervan is het ontstaan van maagulcera en complicaties hiervan, met name hoge tractus digestivus bloedingen, -obstructie en -perforatie. Om het risico op gastrointestinale bijwerkingen te verlagen, zijn richtlijnen ontwikkeld met aanbevelingen betreffende het voorschrijven van NSAIDs en preventieve maatregelen, zoals het gelijktijdig voorschrijven van een maagbeschermer of het voorschrijven van een selectieve COX-2 inhibitor (coxib) in plaats van een traditioneel, non-selective (ns)NSAID. Het afgelopen decennium werd vastgesteld dat het gebruik van NSAIDs ook geassocieerd is met ischaemische cardiovasculaire bijwerkingen. Tot op heden is er geen landelijke richtlijn betreffende dit onderwerp, maar een consensus rapport dat in 2009 werd gepubliceerd bevatte een waarschuwing over het risico op ischaemische cardiovasculaire bijwerkingen en adviseerde het voorschrijven van NSAIDs te vermijden bij patiënten met een cardiovasculaire voorgeschiedenis. Andere bijwerkingen die kunnen optreden bij NSAID gebruik zijn onder andere achteruitgang van de nierfunctie en hartfalen. Het gebruik van NSAIDs is dan ook gecontraïndiceerd bij patiënten met ernstige nierfunctiestoornissen en bij patiënten met hartfalen.

De effectiviteit van non-steroidal anti-inflammatory drugs bij de behandeling van veel voorkomende klachten van het bewegingsapparaat

Er is veel onderzoek verricht naar de effectiviteit van NSAIDs bij specieke aandoeningen van het bewegingsapparaat, maar er bestond nog geen overzicht van de evidence. In **hoofdstuk 2** hebben we een systematische review verricht om alle beschikbaar evidence betreffende de effectiviteit van orale NSAIDs in kaart te brengen en te evalueren, bij de behandeling van aandoeningen van bewegingsapparaat die veel voorkomen in de eerste lijn. We includeerden systematische reviews van RCTs die de effectiviteit van orale NSAIDs vergeleken met placebo of paracetamol. Uitkomsten waren pijn en de proportie van pati-

enten die verbetering ervaarde. Voor de uitkomst pijn werd de grootte van het verschil in pijnreductie tussen de groepen geclassificeerd als verwaarloosbaar, klein, matig of groot, voor de proportie met verbetering werd waar mogelijk het number needed to treat (NNT) bepaald. Onze search leverde 5370 studies, 58 systematische reviews werden geïncludeerd. 19 reviews, waaronder studies naar aandoeningen met een zeer hoge prevalentie zoals nekpijn en schouderaandoeningen, vonden geen RCTs. Van de resterende 30 reviews, rapporteerden er 22 voldoende data om de grootte van het effect te kunnen beoordelen. Er bestond veel overlap met betrekking tot de geïncludeerde RCTs. Voor chronische rugpijn werden bijvoorbeeld vier reviews gevonden, maar gecombineerd rapporteerden deze vier reviews over slechts vijf RCTs. De meerderheid van de reviews richtte zich op NSAIDs versus placebo. Resultaten voor pijn varieerden sterk, sommige reviews vonden een matig verschil in pijnreductie, maar de meesten vonden een klein verschil of geen significant verschil versus placebo. NNT voor verbetering varieerde van vier tot 10 voor NSAIDs versus placebo. Veel minder studies onderzochten de effectiviteit van NSAIDs in vergelijking met paracetamol. De meerderheid hiervan vond een klein verschil in pijnreductie, waarbij NSAIDs iets effectiever waren. NNT voor verbetering varieerde van vijf tot negen voor NSAIDs versus placebo. De resultaten van deze review stellen het huidige frequente gebruik van NSAIDs in de behandeling van klachten van het bewegingsapparaat in de huisartspraktijk ter discussie. Voor een aantal prevalente aandoeningen is weinig evidence betreffende de effectiviteit van NSAIDs voorhanden. Voor veel aandoeningen waar wel systematische reviews over gevonden werden, werd geen significant effect of slecht een klein effect gevonden in vergelijking met placebo of paracetamol. Zelfs voor artrose, waarvoor de effectiviteit van NSAIDs uitgebreid onderzocht is, werd zelden een groot effect gevonden, vooral wanneer werd vergeleken met paracetamol.

Ischaemisch cardiovasculair risico en het voorschrijven van non-steroidal anti-inflammatory drugs bij klachten van het bewegingsapparaat

In **hoofdstuk 3** onderzochten we de invloed van het ischaemisch cardiovasculair (CV) risico van patiënten op het voorschrijven van NSAIDs door huisartsen bij klachten van het bewegingsapparaat. We verrichtten een cohort studie binnen de Integrated Primary Care Information (IPCI) database. Deze grote database bevat de electronische huisartsendossiers van ruim een miljoen patiënten verspreid over heel Nederland. Ons cohort bestond uit 474.201 volwassenen die tussen 2000 en 2010 hun huisarts consulteerde wegens een nieuwe klacht van het bewegingsapparaat. Patiënten met een myocardinfarct, angina pectoris, CVA, TIA of perifeer arterieel vaatlijden in de voorgeschiedenis, werden beschouwd als hoog CV risico patiënten. Patiënten met hypertensie, hypercholesterolemie of diabetes werden beschouwd als matig CV risico patiënten. Patiënten zonder cardiovasculaire risicofactoren werden beschouwd als laag CV risico patiënten. Voor elke patiënt die zich presenteerde met een nieuwe klacht van het bewegingsapparaat, bepaalden we of de

huisarts een nsNSAID of coxibs voorschreef tijdens het eerste consult. In totaal werd aan 24.4% van de patiënten een nsNSAID voorgeschreven en aan 1.4% van de patiënten een coxib. Van de 41.483 patiënten met een hoog CV risico, ontving 19.9% een nsNSAID en 2.2% een coxib. Aan deze patiënten werd vaker een coxib voorgeschreven dan aan patiënten met een laag CV risico (OR 1,9, 95% CI 1,8-2,0). Het voorschrijven van nsNSAIDs nam tussen 2000 en 2010 in alle risicogroepen af en was lager bij patiënten met een hoog CV risico dan bij patiënten met een laag CV risico (OR 1,9, 95% CI 1,8-2,0). Desondanks werd aan één op de vijf hoog CV risico patiënten een coxib of nsNSAID voorgeschreven, hetgeen aangeeft dat er nog ruimte is voor verbetering.

Bijwerkingen van NSAIDs in een eerstelijns populatie

Gedurende het afgelopen decennium zijn veel studies verricht naar het vóórkomen van ernstige bijwerkingen bij het gebruik van NSAIDs en naar gerelateerde ziekenhuisopnames en mortaliteit. Veel minder is bekend over de incidentie van milde bijwerkingen van NSAIDs in de eerstelijns populatie en over de resulterende zorgvraag in de vorm van huisartsconsultaties. Het doel van **hoofdstuk 4** was om te bepalen hoe vaak patiënten aan wie de huisarts een NSAID voorschrijft wegens een klacht van het bewegingsapparaat, de huisarts opnieuw consulteren wegens een milde bijwerking. We includeerden een subcohort van 16.626 volwassen patiënten vanuit het cohort dat in **hoofdstuk 3** werd beschreven. In dit subcohort includeerden we alleen de patiënten die zich tussen 1 januari 2010 en 1 juli 2010 presenteerde met een nieuwe klacht van het bewegingsapparaat en die bij presentatie een NSAID kregen van de huisarts. De electronische dossiers van geïncludeerde patiënten werden vervolgens handmatig beoordeeld, waarbij de journaals werden gelezen gedurende de duur van het NSAID voorschrift met een maximum van twee maanden, om consultaties te identificeren wegens klachten die van te voren werden gedefinieerd als potentiële bijwerkingen. Vervolgens werd een causaliteitsbeoordeling toegepast om deze klachten te classificeren als waarschijnlijke, mogelijke of onwaarschijnlijke NSAID-gerelateerde bijwerking. In totaal consulteerden 961 patiënten (6%) hun huisarts wegens 1.227 potentiële bijwerkingen. 174 patiënten (1%) presenteerde minimaal één waarschijnlijke bijwerking en 408 patiënten (2.5%) minimaal één mogelijke bijwerking. Dyspepsie was de meest voorkomende waarschijnlijke bijwerking, gevolgd door diarree en dyspnoe (respectievelijk 34%, 8% en 8% van alle waarschijnlijke bijwerkingen). Bijna 1 op de 30 patiënten die gedurende een mediaan van 11 dagen werden behandeld met een NSAID, consulteerde hun huisarts wegens een waarschijnlijke of mogelijke bijwerking. De incidentie van consulten wegens dergelijke waarschijnlijke of mogelijke bijwerkingen was 3 per 1000 persoonsjaren NSAID prescriptie. De belasting van dergelijke consultaties moet door huisartsen worden meegenomen bij de afweging of behandeling met een NSAID gewenst is.

Time-trends in het voorschrijven van maagbeschermers aan eerstelijns patiënten die starten met non-steroidal anti-inflammatory drugs of laag-gedoseerd aspirine

Landelijke en internationale richtlijnen bevatten aanbevelingen over welke patiënten een hoog risico hebben op maagschade bij gebruik van een NSAID en bij wie een maagbeschermende strategie is geïndiceerd in de vorm van een gelijktijdig voorgeschreven maagbeschermer of een coxib. Verschillende eerdere studies hebben aangetoond dat het opvolgen van deze richtlijnen verre van optimaal is. Om de adherentie aan richtlijnen te verbeteren, is het van belang om meer te weten over de factoren die hierbij een rol spelen. In **hoofdstuk 5** onderzochten we hoe het opvolgen van richtlijnen gedurende de tijd is veranderd bij patiënten die starten met NSAIDs en welke omgevingsfactoren hierbij mogelijk een rol spelen. Er werd een vergelijking gemaakt met patiënten die starten met laag-gedoseerd aspirine (LDA), omdat het gebruik hiervan ook een verhoogd risico geeft op maagschade, maar er slechts recent aanbevelingen betreffende maagbescherming zijn gepubliceerd. We voerden opnieuw een cohort studie uit in de IPCI database, waarbij twee cohorten werden geselecteerd: (i) patiënten die een nieuw LDA voorschrift ontvingen en (ii) patiënten die een nieuw NSAID voorschrift ontvingen tussen 2000 en 2012. Patiënten die in de 6 maanden voorafgaand aan inclusie een maagbeschermer hadden ontvangen werden geëxcludeerd. In beide cohorten werd het gastrointestinale risico van elke patiënt geclassificeerd als laag, matig of hoog, en werd onderzocht of een maagbeschermende strategie werd toegepast. Het LDA cohort bestond uit 37.578 patiënten en het NSAID cohort uit 365.793 patiënten. In beide cohorten werd gedurende de tijd steeds vaker een maagbeschermende strategie toegepast, maar het voorschrijven hiervan was in het LDA cohort lager. In 2012 werd een maagbeschermende strategie toegepast bij 31,8% van de hoogrisico LDA starters, versus 47,6% van de hoogrisico NSAID starters. Dit verschil is mogelijk gerelateerd aan het feit dat richtlijnen voor NSAID gebruikers veel eerder beschikbaar waren en dat huisartsen deze daardoor mogelijk beter kennen. Een belangrijke bevinding is echter dat omgevingsfactoren zoals wijzigingen in vergoedingsregelingen ook een grote invloed op het volgen van de richtlijnen leek te hebben. Het percentage NSAID starters met een hoog gastrointestinaal risico dat een proton pump inhibitor (PPI) kreeg, nam gestaag toe tot aan 2011, waarna het plots afnam van 49% in 2011 naar 43% in 2012, nadat de vergoedingsregeling voor PPIs op 1 januari 2012 werd gewijzigd.

Hoogrisico gebruik van vrij verkrijgbare non-steroidal anti-inflammatory drugs

In veel landen zijn NSAIDs vrij verkrijgbaar. Over het algemeen wordt het kortdurende gebruik van vrij verkrijgbare NSAIDs als relatief veilig beschouwd, zolang het in normale doseringen wordt gebruikt door volwassenen zonder contraïndicaties of interacterende geneesmiddelen. In eerdere Britse en Australische studies bleek echter dat vrij verkrijgbare

pijnstillers vaak werden gebruikt door mensen met een contraïndicatie hiervoor en dat de pijnstillers vaak werden gebruikt in een te hoge dosering. In **hoofdstuk 6** onderzochten we de prevalentie van gebruik van vrij verkrijgbare NSAIDs in de algemene populatie en onder patiënten met een hoog risico op een ernstige NSAID-gerelateerde bijwerking, middels een cross-sectionele studie in vier huisartspraktijken in Nederland. Er werden twee patiënten samples geselecteerd: (i) een random sample van volwassenen (algemene populatie sample); en (ii) volwassen patiënten met een hoog risico op een ernstige bijwerking in geval van gebruik van een NSAID (hoogrisico sample). Alle geïncludeerde patiënten ontvingen een vragenlijst over hun gebruik van een vrij verkrijgbaar NSAID in de vier weken voorafgaand aan deelname. In het algemene populatie sample retourneerden 118 van de 456 (26%) uitgenodigde patiënten de vragenlijst. Hiervan hadden 35 (30%) een vrij verkrijgbaar NSAID gebruikt. In het hoogrisico sample retourneerden 264 van 713 (37%) uitgenodigde patiënten de vragenlijst. Van deze hoogrisico patiënten hadden 33 patiënten (13%) een vrij verkrijgbaar NSAID gebruikt. Meer dan 20% van de NSAID gebruikers in de algemene populatie sample en meer dan 30% in de hoogrisico sample had het vrij verkrijgbare NSAID gedurende meer dan zeven dagen gebruikt. Vrij verkrijgbare NSAIDs werden gebruikt in een dosering hoger dan het aanbevolen dagelijkse maximum door 9% van de gebruikers in de algemene populatie sample en 3% van de gebruikers in de hoogrisico sample. Gezien dit frequente risicovolle gebruik van vrij verkrijgbare NSAIDs, is het van belang dat gezondheidsautoriteiten en professionals zich blijven inzetten om patiënten te informeren over de risico's van deze geneesmiddelen.

Discussie

Zoals in **hoofdstuk 7** wordt bediscussieerd, suggereren de bevindingen van dit proefschrift dat een kleinere rol voor NSAIDs in de behandeling van klachten van het bewegingsapparaat door de huisarts passend zou zijn. De effectiviteit van NSAIDs is vergeleken met placebo en paracetamol relatief klein en bijwerkingen leidend tot herconsultatie komen frequent voor. Daarnaast is verbetering in het opvolgen van richtlijnen door huisartsen noodzakelijk, aangezien het inzetten van maagbeschermende strategieën nog verre van optimaal is. Huisartsen moeten zich tevens bewust zijn van het feit dat NSAIDs vaak zonder recept worden gebruikt. Zij moeten navragen of deze middelen zonder recept gebruikt worden wanneer ze andere geneesmiddelen voorschrijven die tot een verhoogd risico op maagproblemen leiden en informatie verschaffen aan hoogrisico patiënten over de risico's van vrij verkrijgbare NSAIDs. Apothekers kunnen ook een belangrijke rol spelen in het verbeteren van veilig gebruik van NSAIDs, door informatie te verschaffen wanneer een nieuw medicijn wordt verstrekt.

Toekomstig onderzoek moet zich richten op het identificeren van specifieke subgroepen van patiënten met klachten van het bewegingsapparaat die het sterkst responderen op behandeling met NSAIDs. Om voorspellers van een goede response op NSAIDs te identifi-

ceren zal het niet altijd noodzakelijk zijn om nieuwe trials op te zetten. In plaats daarvan kunnen meta-analyses worden verricht met gebruik van individuele patiëntdata van eerdere RCTs. Meer pragmatische trials binnen de eerstelijns setting zijn ook van belang, om de effectiviteit en veiligheid van NSAIDs in vergelijking met andere behandelingsopties vast te stellen bij klachten van het bewegingsapparaat in deze populatie. Frequent voorkomende aandoeningen zoals nek- en schouderklachten verdienen hierbij met name aandacht en responder analyses met gebruik van gestandaardiseerde definities zijn van belang. Kwalitatieve studies zijn ook nodig om de kennis en overwegingen van huisartsen bij het voorschrijven van NSAIDs vast te stellen en om de verwachtingen en tevredenheid van patiënten rondom NSAID behandeling in kaart te brengen.

Het is de vraag of richtlijnen en praktische besluitvormingstools voor huisartsen de meeste effectieve methoden zijn om het aantal NSAID-gerelateerde bijwerkingen en ziekenhuisopnames op een landelijk niveau terug te dringen. Beleidsmaatregelen zoals de vergoeding van maagbeschermers zijn ook van belang. Toekomstige studies moeten uitwijzen welk effect de recente wijzigingen in vergoeding van PPIs heeft gehad op het aantal maagbloedingen, waarbij ook de kosteneffectiviteit van deze maatregel moet blijken. Daarnaast moet nader onderzoek naar het gebruik van vrij verkrijgbare NSAIDs een prioriteit vormen. We moeten onderzoeken in hoeverre gebruikers van vrij verkrijgbare NSAIDs zich bewust zijn van de risico's van deze geneesmiddelen. Tevens is meer inzicht nodig in de incidentie van ernstige bijwerkingen in gebruikers van vrij verkrijgbare NSAIDs en is meer informatie over het effect van maatregelen om de veiligheid te vergroten, zoals een 'uitsluitend apotheek' status voor NSAIDs, van groot belang. Gezondheidsautoriteiten moeten dit als een prioriteit beschouwen, aangezien hier mogelijk veel meer winst te behalen valt dan uit maatregelen gericht op het voorschrijven van NSAIDs door huisartsen.

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About the author

Aafke Koffeman was born on 10th December 1981 in Bernisse, the Netherlands. She passed her GCSEs in London in 1997 and graduated from the VWO in the Hague in 2000. She studied Medicine at the VU University in Amsterdam from 2000 to 2007. During this time, she lived in in Manchester for a year and completed an internship in Tropical Medicine in Nyangao, Tanzania. As part of her medical degree she performed research at the Alzheimer Center at the VU University Medical Center, under supervision of prof. dr. Philip Scheltens. After obtaining her medical degree in 2007, she worked as a resident in Internal Medicine for two years at the Albert Schweitzer hospital in Dordrecht, before commencing GP training at the Erasmus University Medical Center in Rotterdam in 2009. From 2010 onwards, she combined her GP training with the research described in this thesis, under supervision of prof.dr. Sita Bierma-Zeinstra and prof.dr. Miriam Sturkenboom. She also studied at the Netherlands Institute of Health Sciences of the Erasmus University Medical Center during this time and obtained her Master of Clinical Epidemiology in 2012. In 2013 she completed her GP training and started working as a GP, while completing the research described in this thesis.

PhD Portfolio

PhD training

Master of Science in Clinical Epidemiology
Netherlands Institute for Health Sciences, Erasmus MC, Rotterdam, 2010-2012, 60 ECTS

Vocational training

GP training (PhD completed as 'Arts in opleiding tot huisarts-onderzoeker')
Department of General Practice, Erasmus MC, Rotterdam, 2009-2013.

Oral presentations

Potentially harmful prescription of NSAIDs in a primary care population with musculoskeletal complaints

- EULAR Annual Congress, Berlin, 2012, 1 ECTS
- NAPCRG Annual Meeting, New Orleans, 2012, 1 ECTS

Use of over-the-counter NSAIDs in the general population and in patients with a high risk of adverse drug events

- EULAR Annual Congress, Madrid, 2013, 1 ECTS
- ICPE Annual Conference, Montreal, 2013, 1 ECTS

Adverse drug events in a primary care population with musculoskeletal complaints treated with NSAIDs

- NAPCRG Annual Meeting, Ottawa, 2013, 1 ECTS. Selected for inclusion as a PEARL in the "best of NAPCRG" presentation by the Community Clinician Advisory Group, 2014.

Poster presentations

Potentially harmful prescription of NSAIDs in a primary care population with musculoskeletal complaints

- NHG Wetenschapsdag, Nijmegen, 2012, 1 ECTS
- WEON Annual Conference, Rotterdam, 2012, 1 ECTS
- ICPE Annual Conference, Barcelona, 2012, 1 ECTS

Use of over-the-counter NSAIDs in the general population and in patients with a high risk of adverse drug events

- NHG Wetenschapsdag, Maastricht, 2013, 1 ECTS

Teaching activities

Tutoring medical students during the 'Kennismaking met de Beroepspraktijk' programme
Faculty of Medicine, Erasmus MC, Rotterdam, 2013, 8 hours

Supervising two Master's theses
Department of General Practice, Erasmus MC, 2012, 120 hours

List of publications

This thesis

Koffeman AR, Valkhoff VE,'t Jong GW, Warlé-van Herwaarden MF, Bindels PJE, Sturkenboom MJCM, Luijsterburg PAJ, Bierma-Zeinstra SMA. Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints. *Scandinavian Journal of Primary Health Care* 2014;32:90-9.

Koffeman AR, Valkhoff VE, Çelik S,'t Jong GW, Sturkenboom MCJM, Bindels PJE, van der Lei J, Luijsterburg PAJ, Bierma-Zeinstra SMA. High-risk use of over-the-counter non-steroidal anti-inflammatory drugs: population based cross-sectional study. *British Journal of General Practice 2014*; 64: e191-8.

Other publications

Warlé-van Herwaarden MF, Valkhoff VE, Teichert M, Koffeman AR, 't Jong GW, Sturkenboom MC, De Smet PA. Development and application of indicators for the reduction of potentially preventable hospital admissions related to medications. *Expert Opin Drug Saf 2014;13:157-65*.

Rigter ME, Koffeman AR. Revised guidelines for cardiovascular risk management. Comment on: Revised guidelines for cardiovascular risk management - time to stop medication? A practice-based intervention study. *Br J Gen Pract 2011;61:548*.

Report

De Smet PAGM, Sturkenboom MCJM, Herings R, Warlé-Van Herwaarden MF, Valkhoff VE, Koffeman AR, et al. Acute ziekenhuisopnamen die mogelijk zijn gerelateerd aan geneesmiddelbijwerkingen. Developed for the Ministry of Health, Welfare and Sport by the Erasmus MC, Radboud University Nijmegen, PHARMO insitute and Stichting Farmaceutische Kengetallen, 2012. Available at: http://www.rijksoverheid.nl/documenten-en-publicaties/rapporten/2013/02/12/acute-ziekenhuisopnamen-die-mogelijk-zijn-gerelateerd-aan-geneesmiddelbijwerkingen.html.

Musculoskeletal complaints are the most common reason for consulting the general practitioner in the Netherlands. Although the types and severity of complaints vary, the one common feature they share is that their most burdensome component is pain. NSAIDs, a group of medicines with analgesic and anti-inflammatory properties, are frequently used to combat the pain associated with these musculoskeletal complaints.

But how effective are NSAIDs in the treatment of such musculoskeletal pain? Do general practitioners take prescribing guidelines into account? And is the general public sufficiently aware of the adverse effects associated with these drugs?

This thesis aims to answer these and other questions surrounding the efficacy and safety of NSAIDs in primary care patients with musculoskeletal complaints.
It presents an overview of the evidence from literature, results from observational studies within a large electronic health care database and a cross-sectional study into over-the-counter use of NSAIDs. It thereby provides new insights to aid general practitioners and health care authorities in ensuring careful and balanced use of NSAIDs.