Trends in prescribing of non-steroidal anti-inflammatory drugs in patients with cardiovascular disease: influence of national guidelines in UK primary care

Running head: NSAIDs use in CVD patients

Article category: Epidemiology

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Key messages

1. Despite guidelines, infrequent COX-2 inhibitors were still used in CVD patients

2. NSAIDs use was potentially restricted by MHRA guidelines in patients without CVD

3. Further advice appears to be needed regarding the correct prescribing of NSAIDs

Abstract

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, but have potential side-effects in patients with cardiovascular disease (CVD).

Objectives

To determine trends in NSAIDs prescribing between 2002-2010 in patients with CVD, and ascertain if prescribing patterns changed following publication of major national (the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health and Clinical Excellence (NICE)) guidance to GPs.

Methods

This was an observational database study of adult patients in 11 practices (Staffordshire, England). NSAIDs were categorised into basic, COX-2 and topical. Study duration was divided on a quarterly basis from 2002-quarter-1 to 2010q4. CVD patients were identified using pre-defined Read Codes recorded in the two years prior to each quarter. Quarterly prevalence was determined. Times of significant changes in prescribing trends were determined using Joinpoint Regression, and compared to dates of the five major guidelines (in 2004q4, 2005q1, 2005q3, 2006q4, 2008q1).

Results

In CVD patients, the prescription of basic NSAIDs showed a decreasing trend throughout the study period, from 774 (95%CI, 691-863) per 10,000 patients in 2002q1 to 245 (204-291) in 2010q4. COX-2 prescribing increased from 232/10,000 (187–286) in 2002q1 to 403/10,000 (348-464) in 2004q3. Prescribing then fell sharply to 102/10,000 (76-134) in 2005q2 before stabilising around 55/10,000. Topical NSAIDs prescribing showed a steady increase, starting at 115/10,000 (108-123) in 2002q1 and ending at 270/10,000 (258-281) in 2010q4. Similar trends were observed in patients without CVD, particularly a sharp drop in COX-2 prescribing also occurred from 2004q4 when initial MHRA guidance was issued.

Conclusion

Despite guidelines and a trend toward decreased prescribing, the use of potentially harmful NSAIDs continued in CVD patients. The MHRA directives potentially might have affected patients without CVD who may have inappropriately restricted their use of COX-2.

Keywords: NSAID, cardiovascular diseases, drug prescribing, primary care, practice guideline, electronic health records

Introduction:

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for musculoskeletal conditions such as rheumatoid arthritis or osteoarthritis as they help reduce inflammatory pain and swelling.[1] However there has been increasing concern about their use within the last 15 years. From 2004 - 2006, a series of directives relating to the use of NSAIDs in patients with comorbid cardiovascular disease (CVD) were issued by the Medicines and Healthcare products Regulatory Agency (MHRA). This advice indicated that NSAIDs, in particular the COX-2 inhibitors, should not be used as they increased the chances of such patients suffering a further cardiovascular event such as a stroke or myocardial infarction (MHRA, 2004[2], 2005a[3], 2005b[4], 2006[5], see Table 1). A meta-analysis of randomised controlled trials indicated that use of a COX-2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events, compared with placebo.[6] CVD is a relatively common problem amongst the population. CVD prevalence amongst the whole of the UK population in 2010 was estimated at 3.4% (1.5 million people).[7] Since CVD is more prevalent amongst the elderly, a group also with increased risk of debilitating chronic painful conditions,[8] there exists the potential for the inappropriate prescribing of NSAIDs in light of the guidance issued by the MHRA. Additionally, the National Institute for Health and Clinical Excellence (NICE) revised its advice regarding managing osteoarthritis in 2008, advocating a step wise use of painkillers, initially using simple analgesics such as paracetamol or topical NSAIDs, followed by adding oral NSAIDs and finally opioid medications such as codeine (NICE 2008[9], see Table 1). This guidance, however, does stipulate that NSAIDs should be tailored to the patient such that where a patient may be perceived to be at higher risk, such patients do not receive them, but this is not necessarily an absolute condition of their use.

Previous studies have identified the limited benefit of guidelines[10], whilst others have shown that guidance with multifaceted aspects, incorporating social influence and management support can be substantially more effective in primary care[11,12]. In continental Europe, several guidelines and consensuses have recommended avoiding the prescription of NSAIDs in general in patients at high cardiovascular risk.[13,14] However, a study from the Netherlands showed that, although patients with a high cardiovascular risk were less likely to be prescribed an NSAID for musculoskeletal consultations compared to patients with a low cardiovascular risk, 1 in 5 high cardiovascular risk patients still

received an NSAID.[15] In the UK, the MHRA and NICE have advised GPs about their appropriate use, but presently it is unknown if they have implemented such advice or continue to prescribe in these conditions. Previously we showed that MHRA advice to not use COX-2 inhibitors in patients with ischaemic heart disease led to a general reduction in their levels of incident prescribing.[16] However, what is not known is whether this reduction was predominantly in the patients targeted by the directive (those with heart disease), or whether prescribing in patients without a higher risk of adverse events and potentially benefitting from NSAID prescriptions, also fell.

The first objective of the current study was to determine trends in NSAIDs prescribing between 2002 and 2010 in patients with CVD, and ascertain if prescribing patterns changed following the major national MHRA/NICE guidelines. The second objective was to ascertain whether any observed changes were also apparent in patients without CVD.

Methods:

Database

The study was carried out in the Consultations in Primary Care Archive (CiPCA) which contains all recorded primary care data from a subset of general practices in North Staffordshire, UK. The registered populations in the participating practices ranged from 4,653 to 12,390, with a median size of 8,570 (December 2010). The practices are from a mix of urban and rural areas, and whilst North Staffordshire is more deprived than England as a whole, the practices are based in both deprived and more affluent areas. The practices have a research agreement with Keele (Research Institute for Primary Care & Health Sciences) and code clinical activity to a high standard having followed the Keele consultation data audit, training and validation programme.[17] The quality of the data is comparable to that of larger national general practice databases.[18] Consultation, prescription and demographic data from the 11 practices that have contributed to CiPCA continuously from 2000 – 2010 were analysed for people aged 18 and over.

NSAIDs grouping

All NSAIDs from British National Formulary[1] chapters 4.7.1, 4.7.2, 10.1.1 and 10.3.2 were included and grouped into three major categories for analysis. Excluded medications include aspirin 75mg (but not ≥ 300mg). The first group was basic NSAIDs including drugs such as ibuprofen; the second group was COX-2 NSAIDs such as celecoxib; and the third group was topical NSAIDs, for example ibuprofen gel 5%. A list of all drugs and their allocated groups are available at www.keele.ac.uk/mrr.

Quarterly prescription prevalence

Each year from 2002 to 2010 was divided into quarterly time periods. The quarters were defined on a seasonal basis from the first quarter of 2002 (comprising January, February and March) to the last quarter of 2010 (October, November and December).

In UK primary care, problems, including disease labels, are generally recorded using the "Read" system of codes.[19] Patients recorded with at least one CVD Read code in the two years prior to each time period were identified from the consultation database using pre-defined Read codes for CVD. For example, when identifying existing CVD patients for the 3rd quarter of 2002 (July, August and September), consultations with a recorded CVD Read code between with 1st July 2000and 30th June 2002 were identified. The CVD codes were agreed through a consensus exercise between JB and RH (available at www.keele.ac.uk/mrr). They covered generalised cardiovascular disease (including heart failure), ischaemic heart disease, myocardial infarction, cerebrovascular disease, and abnormal heart rhythm (including atrial fibrillation). The numerators for calculating quarterly prescription prevalence were the number of identified CVD patients receiving at least one prescription within a NSAIDs group within each quarterly time period. Repeat or multiple prescriptions in the same NSAID group following the first prescription for a medication in that group within each quarter were ignored. The registration status for each patient in the studied practices was checked on a half-year basis (1st July and 31st December). Patients included in the denominator were those with confirmation of registration at both flanking check points. Stratified analysis by age group (< 65, ≥ 65 & < 75, ≥ 75 years old) and gender was also carried out.

Quarterly prescription prevalence of NSAIDs was also calculated in all registered patients (aged 18 and over) without a CVD record in the previous two years.

Major national guidance

During the assessment period (2002 - 2010), four national guidelines regarding the use of NSAIDs in patients with CVD (or with a high risk profile), and one national guideline with regard to a stepwise use of painkillers in patients with OA were issued. The date, content and issuing body of these interventions are briefly listed in Table 1. Advice issued by the MHRA is sent on an individualized basis using personal letters to all prescribing doctors ensuring that all GPs are aware of the changes suggested in analgesic use. NICE also disseminated their guideline in 2008 to specific groups including all GPs.

Changes in GP prescribing behaviour (changes in trends of prescribed NSAIDs) in relation to the five major pieces of national guidance were assessed. If significant changes in trend are identified at the time of guidance being announced, it cannot be assumed to be a causal link, but the fact that both the intervention and change occur within the same time frame suggests strongly that there is some association between the advice and related change in behaviour.

Statistical analysis

Joinpoint regression was used to identify quarters where a statistically significant change over time in the linear slope of the trend occurred.[20,21] Permutation tests using Monte Carlo methods were used to determine the minimum number of joinpoints required to provide an adequate fit to the data. The analysis started with zero joinpoints and tested whether one or more joinpoints improved the model (based on a 5% significance level and up to five joinpoints). Quarterly percentage change in prescribing prevalence was estimated for each time period separated by the identified joinpoints. Joinpoint analyses were performed using the joinpoint regression program (version 4.1.1, Statistical Research and Applications Branch, National Cancer Institute, 2014). The time point for the start of each identified change in the underlying prescribing trend (the joinpoint) was then compared with the dates of the interventions.

Results

Population characteristics

From 2002 to 2010, the total registered population aged 18 and above of the practices ranged from 71,713 (2005) to 77,056 (2010). The age and gender distributions changed little across all years, with the median ages being 48-49 years old with 51-52% being female (Supplementary Table S1). Therefore, it was not felt necessary to standardize the prevalence figures.

Prevalence of CVD

The number of patients with CVD identified for each quarter ranged from 3,787 (2002 quarter 1) to 5,250 (2008 quarter 4). The prevalence of patients with CVD recorded in the previous 2 years increased from 523 (95% CI, 507 - 540) per 10,000 registered population aged 18 and over in 2002 quarter 1 to 722 (95% CI, 704 - 742) per 10,000 in 2006 quarter 2 before decreasing slightly to 663 (95% CI, 645 - 681) per 10,000 in 2010 quarter 4. Males had higher prevalent rates, and both genders displayed similar trends (Supplementary Figure S1). The median age of those patients was from 71 in 2002 quarter 1 rising to 73 in 2010 quarter 4 (Supplementary Table S2).

NSAIDs prescription in patients with CVD

In patients with CVD, initially there was a generally increasing trend in the prescription of COX-2 inhibitors from 232 (95% CI, 187 - 286) per 10,000 in 2002 quarter 1 to 403 (95% CI, 348 - 464) per 10,000 in 2004 quarter 3. Prescribing then fell sharply to 102 (95% CI, 76 - 134) per 10,000 in 2005 quarter 2 before stabilising around 55 per 10,000 (Figure 1). The use of basic NSAIDs overall showed a decreasing trend throughout the study period, starting from 774 (95% CI, 691 - 863) per 10,000 in 2002 quarter 1 and ended at 245 (95% CI, 204 - 291) per 10,000 in 2010 quarter 4. Particularly noticeable was a short-term increase in basic NSAIDs at the same time of the sharp decline in COX-2 inhibitor prescribing (Figure 1). The use of topical NSAIDs showed a steady increase through the study period, with quarterly prevalence starting at 115 (95% CI, 108 - 123) per 10,000 in 2002 quarter 1 and ending at 270 (95% CI, 258 - 281) per 10,000 in 2010 quarter 4 (Figure 1).

The time points of advisory interventions on NSAIDs (national guidance) and the NSAIDs' prescribing trends are shown in Figure 1. The joinpoint regression analysis for any significant change in the trend

in prescription of NSAIDs (basic oral NSAIDs, COX-2 inhibitor, topical NSAIDs, and basic oral and COX-2 inhibitor NSAIDs combined) in patients with CVD is shown in Table 2. For example, the quarterly percentage change for COX-2 inhibitors during 2004 quarter 3 – 2005 quarter 2 was -39 (95% CI, -50, -26) (i.e. a decrease of 39% in each quarter during the period).

In general the trend in prescribing was similar by age group. However, higher prevalence of basic NSAIDs prescribed in younger patients with CVD and topical NSAIDs in older patients was observed (Figure 2). No difference in COX-2 inhibitor prescribing was seen among the age groups (Figure 2).

The prescribing patterns were largely similar between males and females. However, higher prevalence of COX-2 inhibitors and topical NSAIDs was seen among females (Supplementary Figure S2), although this may be due to more females in older age groups.

NSAIDs prescription in patients without CVD

Figure 3 shows the NSAIDs prescribing in all registered population (aged 18 and above) without CVD from 2002 to 2010. A sharp drop in COX-2 inhibitor prescribing starting from 2002 quarter 4 also occurred, similar to those with CVD. The joinpoint regression analysis for non-CVD patients is summarized in Supplementary Table S3.

Discussion

Main findings

This is the first study in UK primary care to investigate trends in the prevalence of NSAIDs prescribing in patients with CVD and particularly to assess the association with major national guidance issued during the study period 2002 – 2010. We have shown there was a shift in use between oral (basic and COX-2 inhibitors) and topical NSAIDs. 10% of patients with CVD received oral (basic or COX-2 inhibitors) and 4% topical NSAIDs per quarter in 2002, while such rates changed to 3% for oral and 8% for topical NSAIDs in 2010. The overall reduction in use of oral NSAIDs can be attributed to both basic and COX-2 inhibitor drugs. Particularly, following the MHRA 2004-2005 interventions, COX-2 inhibitor prescribing showed a sharp reduction within 6 months, with the rates dropping from 4% to

1%, suggesting a marked effectiveness of the guidance. During the same period, a short-term increase in basic NASIDs prescribing was seen, which may reflect basic NASIDs as one of the major alternatives to COX-2 inhibitors. In the following years, the trends were more stable therefore no obvious association of later guidance with prescribing change was determined. Overall, during 2002 – 2010 there was a reduction in use of NSAIDs. Our results are in line with Koffeman *et al*[15] and a USA study which indicated that there was still a large proportion of CVD patients using NSAIDs despite a decline after a Food and Drug Administration warning in 2005.[22]

We have shown that a significant drop in COX-2 inhibitor prescribing also occurred in the population without pre-existing CVD when MHRA published the guidance during later 2004 and early 2005. This is surprising as the guidance was directed at patients with cardiovascular problems. To some extent, this implied that the guidance may be over looked as the GPs tended to not prescribe COX-2 inhibitor drugs to any patients. It also suggested that GPs might have been under treating patients who may benefit from COX-2 when there was no reason not to give it to them. Indeed, some patients being given basic NSAIDs perhaps should have had COX-2 as this is less risky for them in terms of gastrointestinal adverse events such as peptic ulceration. It is unknown whether such a decision was made based on more careful review of patients' cardiovascular risk, or it was just easier to do for the GPs to use a blanket approach to NSAIDs due to the perceived risks and worry that litigation from patients who might not have CVD could occur.

On the other hand, after several national guidances issued during 2004 – 2008 there were still some CVD patients receiving COX-2 inhibitors with a quarterly prevalence at approximately 50 per 10,000. Whether or not these prescriptions were appropriate is unknown. Further research will be needed to look at the demographic, lifestyle and co-morbid characteristics of these patients and to assess the reason behind these COX-2 inhibitor prescriptions.

We have also shown that in patients with CVD, NSAIDs prescribing trends were similar in different age and gender groups. However, patients with younger age tended to receive basic oral NSAIDs instead of topical NSAIDs perhaps because they were perceived to be less likely to suffer complications from the oral drugs compared to the older patients. However, other age-related factors, which may influence drug prescription such as severity of pain, disability level or patient preference, has yet to be investigated.

Limitations

Our study has several limitations. First, although the demographic structure of the population from our study was comparable to the general population of UK, this population was from more deprived areas compared to England as a whole. Here, we have shown that the average prevalence of CVD in our population was approximately 6% which was higher than the national figure (3.5%)[7], although the method of identifying patients was different. Second, we were unable to identify the use of over-the-counter (OTC) NSAIDs, and GPs may advise purchase of OTC NSAIDs rather than prescribe them. This might potentially lead to under reporting of NSAIDs use in the studied population. However, since 90% of English prescriptions are issued free to patients, the amount of missing data on NSAIDs use should not have had a large impact on our results. Third, the data used in this study were derived from the years 2002 – 2010 and trends in prescribing may have changed more recently.

Impact of the study

Despite guidelines and a trend toward decreased prescribing, the use of potentially harmful NSAIDs continued in patients with CVD. The MHRA directives had similar effects on both patient groups such that COX-2 prescribing became very infrequent, and basic NSAIDs decreased, based on our data up to 2010. Further advice appears to be needed regarding the correct use of NSAIDs since CVD patients might still be using them inappropriately, and non-CVD patients, who might benefit, have had their use inappropriately restricted.

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Ethical approval

Ethical approval for download and research using these databases was originally gained from the North Staffordshire Research Ethics Committee.

Conflict of interest

None of the authors has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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Table 1 Issuance of national guidance with regard to the use of NSAIDs during the study period

Intervention	Date	Content	Issue body
1	21 Dec. 2004	Advice to stop using Cox-2 drugs in patients with IHD; Use lowest dose of NSAIDs.	MHRA
2	17 Feb. 2005	Advice to not use Cox-2 drugs in patients with heart disease.	MHRA
3	02 Aug. 2005	Advice to tailor the dose of basic NSAIDs to the individual patient's risk profile.	MHRA
4	01 Oct. 2006	Advice that basic NSAIDs may be associated with increased thrombotic risk.	MHRA
5	Feb. 2008	NICE OA management guidelines: advice a step wise use of painkillers, initially using simple analgesics such as paracetamol or topical NSAIDs, followed by adding oral NSAIDs and finally opioid type medications such as codeine.	NICE

MHRA, the Medicines and Healthcare products Regulatory Agency; NICE, the National Institute for Health and Clinical Excellence.

Table 2 Joinpoint regression analysis of quarterly prevalence of NSAIDs (basic NSAIDs, Cox-2, topical NSAIDs, and basic and Cox-2 NSAIDs) prescribing in patients with CVD (aged 18 and over)

	Average QPC 2002 - 2010	Trend 1		Trend 2		Trend 3		Trend 4	
		Period 1	QPC	Period 2	QPC	Period 3	QPC	Period 4	QPC
In patients with CVD									
Basic	-3.0† (-4.3, -1.6)	02Q1 – 04Q3	-3.8† (-5.0, -2.5)	04Q3 – 05Q2	4.9 (-11.2, 24.0)	05Q2 – 10Q4	-3.6† (-4.0, -3.2)	-	-
Cox-2	-3.9† (-5.7, -2.0)	02Q1 – 04Q3	5.6† (4.3, 7.0)	04Q3 – 05Q2	-39.2† (-50.2, -25.7)	05Q2 – 09Q1	-4.5† (-5.9, -2.9)	09Q1 – 10Q4	2.6 (-1.6, 6.9)
Topical	2.7† (2.3, 3.0)	02Q1 – 07Q1	1.7† (1.2, 2.2)	07Q1 – 10Q4	3.9† (3.3, 4.5)	-	-	-	-
Basic and Cox-2	-3.2† (-4.2, -2.2)	02Q1 – 04Q2	-0.4 (-1.5, 0.7)	04Q2 – 05Q1	-8.6 (-19.0, 3.2)	05Q1 – 10Q4	-3.5† (-3.9, -3.2)	-	-

NSAIDs, non-steroidal anti-inflammatory drugs; Cox-2, cyclooxygenase-2 inhibitor; CVD, cardiovascular disease; QPC, quarterly percentage change indicates the percentage change in prescribing prevalence per quarter over the stated time period. A positive percentage indicates an increase in prevalence; † QPC significantly different from 0 (0 indicating no change in prevalence, significant cut-off point p = 0.05); End quarter of each period signifies a joinpoint.

Figure 1

Caption

Figure 1 Quarterly prevalence of NSAIDs prescribing (basic oral NSAIDs, Cox-2, topical NSAIDs, and basic and Cox-2 NSAIDs combined) in patients (aged 18 and above) with CVD

Legend

Vertical axis, quarterly prevalence (per 10,000); horizontal axis, quarters from 2002 to 2010; vertical lines, time of issue of national guidance (intervention); 95% CI, 95% confidence interval; CVD, cardiovascular disease; NSAIDs, non-steroidal anti-inflammatory drugs; Cox-2, cyclooxygenase-2 inhibitor.

Figure 2

Caption

Figure 2 Quarterly prevalence of NSAIDs prescribing (basic oral NSAIDs, Cox-2, topical NSAIDs, and basic and Cox-2 NSAIDs combined) in CVD patients stratified by age-group

Legend

Age group, ≥18 & <65 yrs in Black, ≥65 & <75 yrs in Blue, ≥75 yrs in Red; Dash line, 95% confidence interval; Vertical axis, quarterly prevalence (per 10,000); horizontal axis, quarters from 2002 to 2010; CVD, cardiovascular disease; NSAIDs, non-steroidal anti-inflammatory drugs; Cox-2, cyclooxygenase-2 inhibitor.

Figure 3

Caption

Figure 3 Quarterly prevalence of NSAIDs prescribing (basic oral NSAIDs, Cox-2, topical NSAIDs, and basic and Cox-2 NSAIDs combined) in patients (aged 18 and above) without CVD

Legend

Vertical axis, quarterly prevalence (per 10,000); horizontal axis, quarters from 2002 to 2010; vertical lines, time of issue of national guidance (intervention); 95% CI, 95% confidence interval; CVD, cardiovascular disease; NSAIDs, non-steroidal anti-inflammatory drugs; Cox-2, cyclooxygenase-2 inhibitor.