Population impact of regulatory activity restricting prescribing of COX-2 inhibitors: ecological study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Cyclooxygenase-2 (COX-2) inhibitors are selective nonsteroidal anti-inflammatory drugs (NSAIDs), purported to demonstrate lower gastrointestinal toxicity than nonselective NSAIDs.
- Prescriptions of selective COX-2 inhibitors declined internationally after 2004 following voluntary withdrawal and regulatory intervention because of possible cardiovascular side-effects.
- A study in Canada indicated that rates of gastrointestinal haemorrhage actually increased during the period of increasing COX-2 inhibitor prescriptions, due to the increased number of people receiving NSAIDs.

WHAT THIS STUDY ADDS

- The reduction in availability of COX-2 inhibitors in the UK was temporally associated with a favourable reversal of the trend in emergency hospital admissions for acute myocardial infarction among people aged ≥ 65 years, but there were no related changes in myocardial infarction mortality trends.
- There was some indication that hospital admissions for gastrointestinal haemorrhage among people aged 55–64 years started to increase following a previously declining trend, but this change predated withdrawal/regulation of COX-2 inhibitors by up to 2 years.
- The withdrawal/regulation of coxibs did not appear to have any adverse impact on population health and may have been beneficial.

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Keywords

cyclooxygenase-2 inhibitors, drug regulations, gastrointestinal haemorrhage, myocardial infarction, rofecoxib

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AIMS

To investigate impacts of withdrawal and regulatory advice regarding cyclooxygenase-2 (COX-2) inhibitors on UK population rates of gastrointestinal haemorrhage and acute myocardial infarction (MI).

METHODS

Ecological time series study of prescribing, mortality and hospital admission trends in people aged ≥ 55 years.

RESULTS

Withdrawal and regulatory advice limiting COX-2 inhibitor availability from 2004 were temporally associated with reversal of previously unfavourable trends in emergency MI admissions among people aged ≥ 65 years. Annual admission rate trends changed from +4.6% to –3.1% ($P < 0.001$) among women and from +2.1% to –3.8% ($P = 0.003$) among men. Absolute changes in average annual trend in the number of individuals aged ≥ 65 years admitted following MI were from +981 (1999–2004) to –819 (2004–2006) per year for women and from +713 to –995 for men. No change in trend was apparent among people aged 55–64 years, or in MI mortality trends. There was some suggestion of an unfavourable change in admission trends for gastrointestinal haemorrhage among 55–64-year-olds, although this appeared to occur prior to COX-2 inhibitor withdrawal/regulation by up to 2 years. These trends were not apparent in older people, or in gastrointestinal haemorrhage mortality rates.

CONCLUSIONS

Withdrawal/regulation of COX-2 inhibitors was temporally associated with a favourable reversal of population-level hospital admission trends in MI among people aged ≥ 65 years. Unfavourable reversal of previous declines in gastrointestinal haemorrhage admissions probably occurred before changes in COX-2 inhibitor availability. Withdrawal/regulation of COX-2 inhibitors did not appear to have any adverse impact on population health and may have been beneficial.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are consumed by at least 15% of people aged >60 years, largely for musculoskeletal pain [1]. It has been variously estimated, however, that each year there are between 5000 and 16 500 deaths in the USA [1, 2] and 400–2000 deaths in the UK [1, 3] as a direct result of NSAID-associated gastrointestinal haemorrhage and ulceration. The search for safer drugs led to the development in the 1990s of NSAIDs that selectively inhibit cyclooxygenase-2 (COX-2) activity [1]. Based on a combination of theoretical considerations [1] and trial evidence [4], these drugs were heavily marketed as being less gastrototoxic than nonselective NSAIDs [5, 6], resulting in a rapid increase in the number of people exposed to NSAIDs [7, 8].

Yet soon after selective COX-2 inhibitors were first marketed in 1999, concerns were raised about potential cardiotoxicity [9, 10]. A 2001 review by the US Food and Drug Administration indicated that any gastrointestinal benefits of rofecoxib were 'paralleled by the increased risk of developing cardiovascular thrombotic events' [11]. In September 2004, rofecoxib was voluntarily withdrawn after the publication of a placebo-controlled randomized trial showed a twofold increased risk of cardiovascular events associated with its use [12]. Increased risks of cardiovascular outcomes associated with other selective COX-2 inhibitors, celecoxib [13] and valdecoxib [14], raised the possibility of a class effect, as well as concerns about the cardiovascular safety of other NSAIDs [15]. In December 2004, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that patients with ischaemic heart disease or cerebrovascular disease should not be prescribed selective COX-2 inhibitors [16].

There has been vigorous debate about the balance of risks and benefits, at an individual level, of the restrictions on COX-2 inhibitor prescribing [4, 17–19]. A more recent study using the UK General Practice Research Database indicated that the risks of cardiovascular harm probably outweighed the gastrointestinal benefits of COX-2 inhibitors [20].

However, there has been little research on the population-level impact of the withdrawal of rofecoxib and subsequent regulatory guidance limiting selective COX-2 inhibitor use. Ecological data from Ontario, Canada indicated that increases in selective COX-2 inhibitor prescribing between 2000 and 2002 were associated with a 10% rise in hospitalization rates for upper gastrointestinal haemorrhage [21], illustrating that paradoxical adverse impacts at the population level can occur when newer drugs, associated with a lower risk of side-effects to the individual, are prescribed to very large numbers of people. However, that study was too early to investigate the population impact of the recent regulatory limitations applied to COX-2 inhibitor prescribing on levels of fatal and

nonfatal upper gastrointestinal haemorrhage or acute myocardial infarction (MI).

We have investigated the impact of withdrawal and regulation of COX-2 inhibitors on levels of fatal and nonfatal upper gastrointestinal haemorrhage and acute MI. We hypothesized that if COX-2 inhibitors doubled the risk of MI, then regulatory activity limiting their prescribing may have reduced hospital admissions for, and/or deaths from, MI, but may have adversely impacted on hospitalization or death rates from gastrointestinal haemorrhage (if COX-2 inhibitors reduced gastric ulceration risk compared with other NSAIDs).

Methods

This investigation used methods similar to those described in a previous paper based on the population impacts of pharmaceutical regulation [22]. We assembled three time series datasets from 1999–2006 using relevant prescribing and morbidity/mortality figures.

Prescribing trends

Quarterly prescribing data for 1999–2006 were obtained from the IMS Health Medical Data Index (described elsewhere [23]), detailing numbers of prescriptions of selective COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib) and other NSAIDs (aceclofenac, acemetacin, azapropazone, benorilate, dexibuprofen, diclofenac, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, lornoxicam, mefenamic acid, meloxicam, misoprostol, nabumetone, naproxen, piroxicam, piroxicam betadex, sulindac, tenoxicam and tiaprofenic acid) to men and women aged ≥55 years in the UK. We also collected data from the same source on other drugs that may potentially influence the incidence of gastrointestinal haemorrhage or acute MI; for gastrointestinal haemorrhage these drugs were: antiulcerants (proton pump inhibitors and H₂-receptor antagonists; note: these drug classes could not be distinguished in our dataset) and selective serotonin reuptake inhibitor (SSRI) antidepressants [24]; and, for cardiovascular outcomes: anticoagulants (vitamin K antagonists, heparins), antiplatelet drugs (cyclooxygenase inhibitors, adenosine diphosphate receptor antagonists, platelet cAMP enhancing platelet aggregation inhibitors) and statins. Prescription data for aspirin were not available in the same format due to changes over time in the aggregation of data; however, total annual prescribing rates for aspirin were available from the Department of Health Prescription Cost Analysis [25].

Mortality and hospital admission trends

The annual number of deaths from 1999 to 2006 due to acute MI and gastrointestinal haemorrhage were obtained from the Office for National Statistics (ONS). We used an

extract from the Department of Health's Hospital Episode Statistics [26] to calculate quarterly admission rates for acute MI (emergency admissions) and gastrointestinal haemorrhage from 1999 to 2006. The International Classification of Diseases (ICD) codes used to identify admissions/deaths due to acute MI were ICD-9: 410; ICD-10: I21, I22. Those for gastrointestinal haemorrhage were ICD-9: 531–534, 578.0, 578.1, 578.9; ICD-10: K25–K28, K92.0–K92.2. For sensitivity to more subtle cardiovascular outcomes, we also investigated trends in unstable angina admissions (ICD-10 I20.0).

Analysis

We calculated admission, mortality and prescribing rates using annual mid-year population estimates [27], interpolated/extrapolated to quarterly estimates where necessary. The study was restricted to people aged ≥ 55 years to exclude the younger population with a relatively low incidence of the outcomes of interest and limited prescribing of the drugs concerned. Analyses were stratified by sex and by age group (prescribing data allowed only two broad age groups, 55–64 years and ≥ 65 years) to allow for any differential prescribing patterns, particularly those relating to different cardiovascular risk groups. Secular trends in prescribing rates were graphed with admission and mortality rates in order to compare changes over time. Additionally, we used joinpoint regression (<http://srab.cancer.gov/joinpoint>, Version 3 of the software) to investigate trends in the annual percentage change (APC) in prescribing, hospital admission and mortality rates and to highlight time periods when a marked change in trend occurred ('joinpoints') [28]. Joinpoint regression models were fitted with a maximum of three joinpoints, and we used sequential hypothesis testing to find the number and selection of joinpoints best fitting the data. The overall significance level for selection of the optimum joinpoint regression model for each data series was set at 0.05. For each trend segment, the APC and its 95% confidence interval (CI) were estimated. In addition, the joinpoint software tested whether there was any statistical evidence that the slope of each trend segment differed from the segment immediately preceding it.

Statistical power

Given the use of national population datasets, the analyses involved very large numbers of outcome events. Our *a priori* power calculations presented below turned out to be conservative when we actually obtained the data used in the present analysis. Assuming a total of 8500 hospital admissions with ulcer bleeding in England per year in those aged ≥ 60 years [29], that $>40\%$ ($n = 3500$) of these episodes were causally related to NSAIDs [29], and if use of COX-2 inhibitors prevented 20% (=700) of possible NSAID-associated gastrointestinal haemorrhage [6], then we would have $>95\%$ power (5% significance criterion) to

detect an 8% (i.e. 20% of 40%) relative increase in hospital admissions with ulcer bleeding from 8500 to 9200 subsequent to regulatory advice to limit COX-2 prescribing (given ONS mid-2005 population estimates of 10.6 million aged >60 years). Power is 80% to detect a 4% relative increase in admissions.

Assuming 25 000 hospital admissions for MI per year in England [30], that 5% of the population take COX-2 inhibitors [18] and a risk ratio for COX-2 inhibitors associated with MI of 2.3 [31] suggests a population attributable risk of 6%. We would have $>95\%$ power to detect a 6% relative reduction in hospital admissions for MI from 25 000 to 23 500 (assuming a class effect [32]).

Results

COX-2 inhibitors and other NSAIDs

Figure 1 illustrates trends in prescribing rates of selective COX-2 inhibitors, other NSAIDs, and all NSAIDs combined (see Table 1 for total prescriptions, admissions and deaths). These show similar patterns across age groups and by sex, although prescribing rates are generally higher among women and the older age group. Joinpoint regression indicates that overall COX-2 inhibitor prescribing rates to all people aged ≥ 55 years increased rapidly from market launch in early 1999 to the end of 2001, with an APC of 154.4% (95% CI 95.5, 231.0). This very high APC partly reflects very low numbers of prescriptions at market launch, but does indicate a very rapid uptake of prescribing this new class of drugs. Excluding the first two quarters of data (where prescriptions are zero) makes no difference to the joinpoint regression results, which reflect trends rather than comparison with a baseline figure. Following 2001, growth slowed to an APC of 33.4% (22.9, 44.8) and rates peaked in the third quarter of 2004, when COX-2 inhibitors accounted for 28% of all NSAID prescribing to this age group. Following rofecoxib withdrawal and regulatory advice against all selective COX-2 inhibitors, total COX-2 inhibitor prescribing rates declined dramatically from a peak of 85 prescriptions per thousand people aged ≥ 55 years in the third quarter of 2004 to 15 prescriptions per thousand in the second quarter of 2005. COX-2 inhibitor prescribing subsequently levelled out at around 10–15 prescriptions per thousand population per quarter, with an APC of -19.7% (95% CI -45.2 , 17.8). Prescribing rates of other NSAIDs declined steadily as use of COX-2 inhibitors increased (APC 1999 quarter 1 to 2004 quarter 2 = -5.5% ; 95% CI -6.2 , -4.8), and following regulatory advice/withdrawal increased from mid 2004 to mid 2005 (APC = 27.2% ; 95% CI 10.8, 46.0), before declining from mid 2005 to the end of 2006 (APC = -10.6% ; 95% CI -14.7 , -6.4). Total (all ages ≥ 55 /male and female) NSAID (selective COX-2 inhibitors plus all other NSAIDs) prescribing rates reflect these combined trends, with an indication of a

Figure 1

Trends in prescribing rates of selective cyclooxygenase (COX)-2 inhibitors and other nonsteroidal anti-inflammatory drugs (NSAIDs). COX-2 inhibitors (—■—); other NSAIDs (---○---); total NSAIDs (·····▲·····). Notes: UK, 1999–2006. Vertical line marks date of rofecoxib withdrawal. Data source: IMS Health

Table 1

Annual prescription and outcome totals, people aged ≥55 years

Year	Total COX-2 prescriptions	Total other NSAID prescriptions	Gastrointestinal haemorrhage individuals admitted to hospital	Deaths	Acute myocardial infarction individuals admitted to hospital (emergency admissions)	Deaths
1999	29 000	15063 000	81 870	5113	70 856	52,797
2000	810 000	13883 000	83 354	5226	70 245	48,667
2001	1831 000	13334 000	81 676	5153	72 456	44,327
2002	3203 000	13359 000	81 908	5116	76 761	43,386
2003	4556 000	12412 000	82 671	5127	78 054	41,305
2004	4996 475	12719 966	83 048	4842	78 415	37,396
2005	1066 465	15034 950	83 968	4520	76 536	34,649
2006	791 099	13859 325	85 849	4432	74 504	31,485

Note: Totals for UK (prescriptions), England and Wales (deaths), England (admissions).

slight decline from 1999 to the end of 2000 (APC = −2.4%; 95% CI −5.5, 0.8). This was followed by an increase from 2001 to mid 2004 (APC = 3.7%; 95% CI 2.6, 4.8), and lastly a decline to the end of 2006 (APC = −11.5%; 95% CI −13.4, −9.6, *P*-value for difference in rates <0.001).

Cardiovascular outcomes

Among people aged 55–64 years, emergency admissions for MI decreased steadily from 1999 to 2006 (Figure 2), with joinpoint regression indicating annual percentage

Figure 2

Trends in acute myocardial infarction outcomes with joinpoint regression lines. Quarterly emergency admissions for acute myocardial infarction (MI); individuals per 100 000 population (●); Annual acute MI mortality rate per 100 000 (■). Notes: Vertical line marks date of rofecoxib withdrawal. Data sources: Office of National Statistics (mortality) and Department of Health (hospital admissions)

changes of -4.4% (95% CI $-5.2, -3.7$) for women and -3.4% (95% CI $-3.9, -2.9$) for men in this age group. However, among people aged ≥ 65 years, there is evidence of a change in admission rates in the hypothesized direction during the relevant time period. The graphs in Figure 2 indicate a slight upward trend in emergency MI admissions from 1999 to 2004 (APC = 4.6% ; 95% CI 3.2, 6.0 for women and APC = 2.1% ; 95% CI 0.4, 3.9 for men). Joinpoint regression indicated that changes in these trends occurred at 2004 quarter (Q) 1 (95% CI 2003 Q1 to 2005 Q2, P for change in trend <0.001) for women and at 2003 Q4 (95% CI 2002 Q1 to 2005 Q2, P for change in trend = 0.003) for men. Trends in admission rates following these joinpoints, i.e. from 2004 to 2006, were (APC) -3.1% (95% CI $-6.2, 0.2$) for women and -3.8% (95% CI $-7.0, -0.5$) for men. The mean absolute annual trend in the number of women aged ≥ 65 years admitted changed from +981 per year (1999–2004)

to -819 per year (2004–2006). The mean annual change in the number of men aged ≥ 65 years admitted reversed from +713 per year (1999–2004) to -995 per year (2004–2006). In sensitivity analyses, trends in admissions of people aged ≥ 65 years for unstable angina demonstrated a similar favourable change during the same period, with 2004 quarter 3 well inside joinpoint 95% CIs.

Acute MI mortality rates demonstrated steady decreases between 1999 and 2006 for both age groups, and joinpoint regression found no evidence for any change in the mortality rate trend during the study period (Figure 2). The annual percentage change in the mortality rate for 55–64-year-olds was -11.0% (95% CI $-11.9, -10.0$) for women and -9.2% (95% CI $-10.0, -8.4$) for men. The APC in the ≥ 65 -year-old age group was -7.0% (95% CI $-8.0, -5.9$) for women and -7.6% (95% CI $-8.3, -6.9$) for men.

Gastrointestinal outcomes

Trends in hospital admissions for gastrointestinal haemorrhage shown in Figure 3 appear to demonstrate patterns that would be consistent with our hypothesis, although changes in rates occurred earlier than expected given the timing of changes in COX-2 prescribing rates (2004 Q3). Admission rates declined during the period that COX-2 inhibitor prescribing increased, and then, particularly in the 55–64 year age group, appear to flatten in men [APC prior to joinpoint -5.7% ($-7.5, -3.8$) and subsequently -0.4% ($-1.6, 0.8$)] and increase in women [change in APC from -4.7% ($-6.1, -3.2$) to 1.6% ($-0.02, 3.3$)]. The joinpoint models estimated the joinpoint for men aged 55–64 years to be at 2002 Q2 (95% CI 2001 Q2 to 2004 Q3) (P -value for difference in rates <0.001). For women in this age group, the joinpoint was estimated at 2003 Q1 (95% CI 2001 Q4 to 2004 Q1) (P -value for difference in rates <0.001). The mean

absolute annual change in the number of people admitted for gastrointestinal haemorrhage for women aged 55–64 years changed from -128 per year 1999–2002 to $+208$ per year 2002–2006. Equivalent figures for men aged 55–64 years were from -230 per year 1999–2002 to $+155$ per year 2002–2006. That the absolute admission numbers appear to demonstrate a more marked reversal of trend than the rates may be partly explained by an increase in the rate of estimated population growth in this age group from 2001 to 2002/3 (Figure 4).

Trends in mortality due to gastrointestinal haemorrhage (Figure 3) appear not to be associated with the changing trends in NSAID prescribing patterns. Joinpoint regression only finds one marked change in trend, among women aged ≥ 65 years, although statistical evidence for this change is weak. The joinpoint is estimated to occur at the year 2003 (95% CI 2000–2005), with an APC

Figure 3

Trends in gastrointestinal (GI) haemorrhage outcomes with joinpoint regression lines. Quarterly emergency admissions for GI haemorrhage; individuals per 100 000 population (●); Annual GI haemorrhage mortality rate per 100 000 (■). Notes: Vertical line marks date of rofecoxib withdrawal. Data sources: Office of National Statistics (mortality) and Department of Health (hospital admissions)

Figure 4

Estimated quarterly population, England, 1999–2006. Men (—■—); Women (---▲---). Note: Interpolated/extrapolated from Office of National Statistics annual population estimates 1998–2006 (<http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=601>)

Table 2

Joinpoint regression results: potentially confounding prescribing patterns, all people aged ≥ 55 years

	Segment	Segment start	Segment end	APC	APC 95% LCL	APC 95% UCL	Joinpoint	Joinpoint 95% LCL	Joinpoint 95% UCL	P-value for change in trend
Prescribing potentially confounding associations between COX-2 inhibitors and gastrointestinal haemorrhage										
Anti-ulcerants	0	1999 Q1	2004 Q1	5.6	5.0	6.3				
	1	2004 Q1	2005 Q1	16.9	6.7	28.2	2004 Q1	2003 Q3	2004 Q3	0.032
	2	2005 Q1	2006 Q4	8.2	5.8	10.6	2005 Q1	2004 Q3	2005 Q4	0.10
SSRIs	0	1999 Q1	2001 Q4	16.5	14.7	18.3				
	1	2001 Q4	2005 Q2	3.9	2.8	4.9	2001 Q4	2001 Q1	2002 Q2	<0.001
	2	2005 Q2	2006 Q4	12.3	9.0	15.7	2005 Q2	2004 Q1	2005 Q4	<0.001
Prescribing potentially confounding associations between COX-2 inhibitors and acute myocardial infarction										
Anti-coagulants	0	1999 Q1	2004 Q1	5.0	4.0	6.0				
	1	2004 Q1	2004 Q4	21.3	–9.7	63.0	2004 Q1	2003 Q2	2004 Q3	0.32
	2	2004 Q4	2006 Q4	5.2	2.1	8.4	2004 Q4	2004 Q2	2005 Q4	0.33
Antiplatelets (excl. aspirin)	0	1999 Q1	2002 Q4	30.5	26.4	34.7				
	1	2002 Q4	2006 Q4	13.9	11.7	16.0	2002 Q4	2002 Q2	2003 Q3	<0.001
Statins	0	1999 Q1	2004 Q1	24.5	23.7	25.2				
	1	2004 Q1	2004 Q4	34.1	14.5	56.9	2004 Q1	2002 Q4	2004 Q3	0.34
	2	2004 Q4	2006 Q4	15.6	13.9	17.3	2004 Q4	2004 Q3	2005 Q2	0.065
Aspirin (annual data, all ages)	0	1999	2004	9.4	9.1	9.6				
	1	2004	2006	7.4	6.4	8.4	2004	2002	2005	0.008

Segments are periods of constant trend as determined by the joinpoint model. The annual percentage change refers to the trend during that segment. The joinpoint is the estimated quarter during which a change in trend occurred, with 95% confidence limits. APC, annual percentage change; LCL, lower confidence limit; UCL, upper confidence limit; Q, quarter.

between 1999 and 2003 of 0.2% (–3.7, 4.1) and from 2003 to 2006 of –6.8% (–12.7, –0.5) (P -value for difference in rates = 0.056); the APC for the model with no joinpoints was –2.6% (–4.5, –0.7). Gastrointestinal haemorrhage mortality also declined between 1999 and 2006 for women aged 55–64 years (APC –5.1%; –7.1, –3.1) and men aged 55–64 years (APC –1.1%; –3.0, 0.9) and ≥ 65 years (APC –3.5%; –4.4, –2.6).

Potentially confounding prescribing

Table 2 presents the results of joinpoint analysis of trends in prescribing of drugs with the potential to confound

associations between the timing of changes in COX-2 prescribing and trends in gastrointestinal haemorrhage/MI rates (see Figures 5 and 6 for graphs). These results indicate some changes that could confound associations of interest. With regard to gastrointestinal haemorrhage, at 2004 Q1 (95% CI 2003 Q3 to 2004 Q3) the overall annual percentage change (for men and women aged ≥ 55 years combined) in the prescribing rate of antiulcerants increased from 5.6% (95% CI 5.0, 6.3) to 16.9% (95% CI 6.7, 28.2). This increased prescribing of gastroprotective agents could have countered increases in gastrointestinal haemorrhage risk due to changes in NSAID prescribing to some

Figure 5

Trends in prescribing rates of potentially confounding drugs, UK, 1999–2006. Anti-ulcerants (—●—); Anticoagulants (—○—); Antiplatelets (excluding aspirin) (—■—); Statins (—▲—); Selective serotonin reuptake inhibitors (—△—). Notes: Vertical line marks date of rofecoxib withdrawal. Data source: IMS Health

Figure 6

Annual trend in prescribing rate of aspirin (all ages), England, 1999–2006. Aspirin prescribing rate (antiplatelet) (—■—); Aspirin prescribing rate (analgesic) (—▲—); Aspirin prescribing rate (total) (—●—). Data source: Department of Health Prescription Cost Analysis (via <http://www.ic.nhs.uk/>)

extent. There was a slow-down in the growth of SSRI prescribing to this age group between around 2001 and 2004, after which the growth in prescribing rates increased again. This increase in annual growth of SSRI prescribing is estimated to have occurred at 2005 Q2 (95% CI 2004 Q1 to 2005 Q4), a time approximately coinciding with changes in COX-2 prescribing, and potentially also influencing the gastrointestinal haemorrhage incidence rate.

With the exception of temporary (approximately 1 year) increases in prescribing rates of anticoagulants and

statins in 2004, there were steady trends in prescribing of cardioprotective agents and the existence of any changes were subject to statistical uncertainty. Thus it seems unlikely that changes in prescribing of these agents explain the reduction in admissions for MI seen after 2004 among ≥ 65 -year-olds. Results of the full joinpoint analysis of prescribing trends for these groups of drugs disaggregated by sex and age group are presented in Table 3.

Discussion

Main findings

This ecological time series study indicates that population trends in hospital admissions and mortality due to gastrointestinal haemorrhage have not, in general, demonstrated appreciable associations with the marked changes in COX-2 inhibitor prescribing patterns following their introduction and subsequent withdrawal/regulatory advice. There was some suggestion of a reversal of previously favourable trends in hospital admissions for gastrointestinal haemorrhage among people aged 55–64 years, although statistical models placed the timing of this reversal up to 2 years earlier than regulatory advice was given and rofecoxib was withdrawn. As regards MI, there was no evidence for an association between pharmaceutical withdrawal/regulatory activity and mortality, but there was evidence for a favourable change in hospital admis-

Table 3
Joinpoint regression results: potentially confounding prescriptions, by age and sex

	Sex	Age group (years)	Segment	Segment start	Segment end	APC	APC 95% LCL	APC 95% UCL	Joinpoint	Joinpoint 95% LCL	Joinpoint 95% UCL	P-value for change in trend
Prescribing potentially confounding associations between COX-2 inhibitors and gastrointestinal haemorrhage												
Anti-ulcerants	Female	55–64	0	1999 Q1	2003 Q1	5.9	4.7	7.2	2003 Q1	2000 Q1	2004 Q4	0.001
			1	2003 Q1	2006 Q4	9.0	7.8	10.2				
			0	1999 Q1	2004 Q1	6.3	5.7	6.9				
		65+	0	1999 Q1	2005 Q1	21.1	10.0	33.5	2004 Q1	2003 Q4	2004 Q3	0.01
			2	2005 Q1	2006 Q4	8.3	5.8	10.9	2005 Q1	2004 Q3	2005 Q4	0.029
	Male	55–64	0	1999 Q1	2004 Q1	4.0	3.2	4.9	2004 Q1	2003 Q1	2004 Q3	<0.001
			1	2004 Q1	2006 Q4	10.1	8.3	12.0				
			0	1999 Q1	2004 Q2	6.5	5.9	7.0				
		65+	1	2004 Q2	2005 Q1	19.1	–0.9	43.1	2004 Q2	2003 Q3	2004 Q4	0.221
			2	2005 Q1	2006 Q4	8.3	5.9	10.8	2005 Q1	2004 Q3	2006 Q1	0.302
SSRIs	Female	55–64	0	1999 Q1	2002 Q1	18.0	16.0	20.0	2002 Q1	2001 Q4	2002 Q3	<0.001
			1	2002 Q1	2005 Q2	3.1	1.7	4.5	2005 Q2	2004 Q4	2005 Q4	<0.001
			2	2005 Q2	2006 Q4	13.1	9.2	17.1				
		65+	0	1999 Q1	2000 Q2	25.4	17.8	33.6	2000 Q2	1999 Q3	2001 Q2	0.001
			1	2000 Q2	2002 Q4	10.8	8.4	13.3	2002 Q4	2001 Q4	2003 Q2	0.003
	Male	55–64	2	2002 Q4	2004 Q1	–2.0	–8.9	5.5	2004 Q1	2003 Q2	2005 Q3	0.003
			3	2004 Q1	2006 Q4	10.7	9.1	12.3	2004 Q1	2003 Q2		
			0	1999 Q1	2002 Q1	13.5	10.3	16.8	2002 Q1	2001 Q1	2002 Q4	<0.001
		65+	1	2002 Q1	2006 Q4	4.7	3.5	5.9				
			0	1999 Q1	2001 Q2	17.8	14.7	21.1	2001 Q2	2000 Q4	2001 Q4	<0.001
Prescribing potentially confounding associations between COX-2 inhibitors and acute myocardial infarction	Female	55–64	2	2001 Q2	2005 Q4	4.8	3.9	5.7	2005 Q4	2002 Q3	2006 Q2	0.034
			0	1999 Q1	2001 Q1	–8.2	–15.2	–0.7				
			1	2001 Q1	2001 Q4	29.2	–36.6	163.1	2001 Q1	1999 Q3	2001 Q3	0.334
		65+	2	2001 Q4	2006 Q4	1.6	–0.1	3.4	2001 Q4	2000 Q4	2006 Q2	0.493
			0	1999 Q1	2001 Q1	10.6	6.1	15.3	2001 Q1	1999 Q3	2004 Q2	0.003
	Male	55–64	1	2001 Q1	2003 Q2	0.7	–3.2	4.7	2003 Q2	2000 Q2	2005 Q1	0.002
			2	2003 Q2	2004 Q4	16.1	7.7	25.1	2004 Q4	2002 Q4	2006 Q2	0.109
			3	2004 Q4	2006 Q4	8.7	5.2	12.3				
		65+	0	1999 Q1	2006 Q4	4.8	3.8	5.8	2006 Q4	2002 Q4		
			0	1999 Q1	2001 Q1	11.0	7.7	14.5	2001 Q1	1999 Q3	2003 Q1	0.003
Antiplatelets (excl. aspirin)	Female	55–64	1	2001 Q1	2004 Q1	4.9	3.2	6.7	2004 Q1	2003 Q1	2004 Q3	0.008
			2	2004 Q1	2005 Q1	23.5	10.3	38.3	2005 Q1	2004 Q3	2005 Q4	0.003
			3	2005 Q1	2006 Q4	2.4	–0.4	5.4				
		65+	0	1999 Q1	1999 Q3	168.7	–27.1	891.2	1999 Q3	1999 Q3	2002 Q2	0.089
			1	1999 Q3	2000 Q2	–39.6	–80.9	90.9	2000 Q2	2000 Q2	2003 Q4	0.153
	Male	55–64	2	2000 Q2	2002 Q4	37.7	25.4	51.1	2002 Q4	2002 Q1	2006 Q2	<0.001
			3	2002 Q4	2006 Q4	9.6	6.5	12.7				
			0	1999 Q1	2002 Q4	33.5	29.4	37.7	2002 Q4	2002 Q2	2003 Q3	<0.001
		65+	1	2002 Q4	2005 Q1	15.2	13.1	17.3	2005 Q1	2004 Q2	2005 Q4	0.002
			0	1999 Q1	2006 Q4	24.9	22.5	27.3				
Statins	Female	55–64	1	2005 Q1	2006 Q4	8.7	0.6	17.6	2006 Q4	2004 Q2	2005 Q4	0.125
			0	1999 Q1	1999 Q4	54.0	9.8	116.1	1999 Q4	1999 Q3	2001 Q2	0.088
			1	1999 Q4	2000 Q3	–9.7	–50.9	65.9	2000 Q3	2000 Q2	2002 Q3	<0.001
		65+	2	2000 Q3	2002 Q1	53.9	36.7	73.3	2002 Q1	2001 Q3	2006 Q2	
			3	2002 Q1	2006 Q4	13.5	12.2	14.7				
	Male	55–64	0	1999 Q1	2006 Q4	16.6	15.9	17.3	2006 Q4	2002 Q4	2004 Q3	0.216
			0	1999 Q1	2004 Q1	29.4	28.6	30.2	2004 Q1	2002 Q4	2005 Q2	<0.001
			1	2004 Q1	2005 Q1	35.3	25.9	45.5	2005 Q1	2004 Q3	2005 Q2	
		65+	2	2005 Q1	2006 Q4	16.1	14.2	18.0				
			0	1999 Q1	2006 Q4	16.8	16.2	17.3	2006 Q4	2004 Q4	2005 Q2	<0.001

Prescriptions of aspirin were not available disaggregated by sex and age group. Data source: IMS-Health. APC, annual percentage change; LCL, lower confidence limit; UCL, upper confidence limit; Q, quarter.

sions in the expected direction at the appropriate time among people aged ≥ 65 years.

Cardiovascular outcomes

Trends in emergency hospital admissions for acute MI for men and women aged ≥ 65 years are consistent with the hypothesized effects of the withdrawal of rofecoxib and associated regulatory advice on other COX-2 inhibitors. An increase in the rate of admissions from 1999 to approximately 2004 reversed to become a decrease, with joinpoint regression estimating changes in trend to have occurred at a time consistent with the key withdrawal/regulation timing, with 2004 Q3 well within confidence limits for the joinpoints. If the change in availability of COX-2 inhibitors was indeed causally linked with this reversal of trend, the benefits were considerable, given an average annual absolute trend of +1694 individuals (men and women combined) aged ≥ 65 years admitted per year from 1999 to 2004, and an average annual trend of -1814 individuals aged ≥ 65 years admitted per year from 2004 to 2006. The marked seasonality of admission rates in this age group is consistent with expectations [33], with rates highest during the winter months (Q4 and Q1). Although there were seasonal effects, the length of our data series should allow longer term trends to be distinguished from short-term seasonal variations.

Although it is clear that prescribing of nonselective NSAIDs increased as COX-2 inhibitor prescribing fell, this study does not add any evidence to the debate regarding cardiovascular risks of nonselective NSAIDs. Total NSAID prescribing declined following rofecoxib withdrawal, meaning that, even in the presence of increased cardiovascular risk associated with some nonselective NSAIDs at the individual level, we could still have witnessed the observed population trends in acute MI admissions. Additionally, our *a priori* hypothesis regarded COX-2 inhibitors specifically, and any cardiovascular risks of nonselective NSAIDs are likely to be mixed [15], and not detectable when considered as a group.

The trend among 55–64-year-olds was different from that for people aged >64 years, with a steady decline in admission rates from 1999 to 2006 and no indication of a change in trend during that period. This difference between the age groups could be a real interaction, with a higher prevalence of risk factors for cardiovascular disease among the older population leading to greater sensitivity to any COX-2 inhibitor-related risks. Alternatively, the difference may be due to the lower rate of COX-2 inhibitor prescribing in the younger age group (see Figure 1), leading to less total population exposure. Furthermore, the absolute number of individuals admitted from this age group (approximately 15 000 per year) was approximately a quarter of that admitted from the older age group (approximately 60 000 per year). The pre-existing declining trend in admissions, driven by other factors, may have also been insensitive to any small reduction in population risk

associated with the decreased availability of COX-2 inhibitors in the 55- to 64-year-old group.

Trends in prescribing of cardioprotective drugs do not appear to provide alternative explanations for the trends in MI emergency admissions witnessed here. Growth in prescribing of both statins and anticoagulants appeared to increase temporarily during 2004, but declined thereafter to pre-2004 rates or less. Other changes over time in the wide range of risk factors affecting population risk of MI can also not be ruled out as causing some or all of the reversal in trend in admission rates in the older age group. Nevertheless, an association between regulation to limit prescribing of COX-2 inhibitors and population reductions in acute MI admissions, to the extent observed in our study, is plausible. First, increased risks of MI emerge within the first month of selective COX-2 inhibitor use [34, 35], so our follow-up period is likely to have been sufficient. Second, the decline in numbers of acute MI admissions of around 1800 in 2005 (post regulation) compared with 2004 is consistent with the attributable risk of MI associated with COX-2 inhibitors. About 5% of the population took COX-2 inhibitors prior to COX-2 regulation [18]; assuming a risk ratio for COX-2 inhibitors associated with MI of 2.3 [31] suggests a population attributable risk of 6%. Given at least 64 000 hospital admissions for MI in the year prior to COX-2 regulation (observed for those aged ≥ 65 years), withdrawing COX-2s would be expected to reduce MI admissions by 4000 to around 60 000 (assuming a class effect of COX-2s [32]). If any effect on MI incidence was limited to rofecoxib (which accounts for 50% of all COX-2 prescribing, i.e. a 3% population attributable risk), we would have expected a fall of 2000–62 000. The magnitude of this fall is close to what we observed.

Trends in mortality due to acute MI appear to be unaffected by changes in COX-2 inhibitor prescribing rates. It is possible that these trends in population mortality rates are so strongly influenced by other risk factors that any population-level cardiovascular effects of the changing availability of COX-2 inhibitors may not be detectable. Reductions in the case-fatality rate for MI over time [36, 37] may also explain to some extent the discordance between admission rate and mortality trends among the older age group.

Gastrointestinal outcomes

The slowing/reversal in previously declining trends in hospital admissions for gastrointestinal haemorrhage in the younger age group (55–64 years) are consistent with the expected population impact of the withdrawal of rofecoxib and the regulatory guidance regarding other COX-2 inhibitors. However, these changes in trend occur prior to the clear changes in prescribing patterns following 2004 Q3. The joinpoint for gastrointestinal haemorrhage admissions for men is estimated to occur at 2002 Q2, although the 95% CI does include the quarter in which rofecoxib was withdrawn (2004 Q3). The joinpoint for women in this age

group is estimated at 2003 Q1, but with 95% CIs extending only to 2004 Q1. One explanation for this disparity between prescribing and hospital admission trends could be that the mismatch is an artefact of the quite considerable random fluctuation in admission rates from quarter to quarter. Although those indicated here are the most likely given the data, alternative joinpoint models rejected in favour of those illustrated in Figure 3 do place joinpoints consistent with the hypothesized effects at around the end of 2004/beginning of 2005. Similar unfavourable changes in gastrointestinal haemorrhage admissions in Canada were associated with upward trends in total NSAID prescribing [21], but that does not seem to be the case in the UK (see Figure 1). Furthermore, trends observed in gastrointestinal haemorrhage admissions are likely to have been influenced by changing underlying patterns of NSAID-related gastrointestinal conditions during the study period. For example, a cohort study in the USA and Canada found that NSAID-related gastropathy increased during the 1980s and early 1990s, but then declined from 1992 to 2000, long before the introduction of COX-2 inhibitors [38]. This decline was found to result largely from the prescribing of lower doses and changes towards less gastrotoxic nonselective (traditional) NSAIDs. These changes suggest that the unfavourable reversal of gastrointestinal haemorrhage admission trends observed here, prior to COX-2 inhibitor withdrawal/regulation, could well have been related to other changes in prescribing patterns of NSAIDs.

The changes in admission rate trend are not reflected in gastrointestinal haemorrhage mortality figures. The only change in trend identified for fatal gastrointestinal haemorrhage is that for women aged ≥ 65 years, indicating a mortality decline following a joinpoint at 2003. Since this analysis indicates a decline in mortality rates following the joinpoint, as opposed to an increase (which might be expected with the decline in prescriptions of COX-2 inhibitors and coincident uptake of other NSAIDs), and given that this is observed only among one age/sex sub-group with a *P*-value consistent with chance (*P* = 0.06), it is not likely to be associated with the prescribing trends of interest. It could, however, be associated with a slight upturn in the prescribing of antiulcer drugs that occurred at around this time (Table 3), or with the decline in total prescribing of all NSAIDs in the ≥ 65 years age group in women (see Figure 1).

The contradictory results for admissions compared with mortality could indicate that COX-2 inhibitors had the predicted effect on population gastrointestinal haemorrhage rates, but that gastrointestinal haemorrhage mortality is too rare (relatively) to be noticeably affected by what is a quite subtle change in incidence (e.g. there were 4842 deaths, but 83 057 admissions among >55 -year-olds in 2004). Alternatively, it may be that NSAIDs cause less severe, nonfatal gastrointestinal haemorrhage in the younger age group, or that this age group are more likely to notice symptoms and/or be admitted early on, so an

influence of the rapid fall in COX-2 inhibitor use on mortality would not be observed, in contrast to admissions among 55–64-year-olds. Additionally, the change in gastrointestinal haemorrhage admission rate trend at the time of COX-2 regulatory action is not apparent in the older age group (≥ 65 years). One possible explanation for this differential finding is that older people were considered to be at greater risk of haemorrhage, and were more likely to be prescribed gastroprotective antiulcer drugs than people in the younger age group. The increase in the growth of antiulcerant prescribing rates in 2004 (Table 2) may well have countered, to some extent, any increase in population gastrointestinal haemorrhage risk associated with the changing profile of NSAID prescribing.

Our findings differ from those for Ontario, Canada, which suggested that admission rates for gastrointestinal haemorrhage increased following the introduction of COX-2 inhibitors. These trends were thought to be due to increases in the use of COX-2 inhibitors as first-line NSAIDs rather than switching from other NSAIDs to COX-2 inhibitors [21]. Conversely, for England, we observed declining admission (and, generally, mortality) rates in temporal association with increasing prescribing of COX-2 inhibitors from 1999 to 2004. In common with Ontario, the UK also saw increasing total NSAID prescribing during this time. One possible explanation for the difference is that the mix of nonselective and selective NSAIDs prescribed in the two countries differed; Mamdani *et al.* [21] report only total NSAID prescribing, so it is not possible to verify whether or not this is the case.

Strengths and limitations

An ecological study is the most appropriate for our specific research question as it has the benefit of considering the whole population, and so is suited to our aim of detecting population level impacts of regulatory activity, rather than cause–effect relationships at the individual level. However, our findings should be viewed in the context of a number of methodological and data-related limitations. First, the study is subject to the ecological fallacy, as we are unable to assess whether or not individuals exposed to particular pharmaceuticals experienced the health outcomes of interest. However, as stated above, the emphasis of this study is on the population level impact of regulation, rather than specific aetiological relationships.

This study design is also limited in its ability to control for the effects of any factors confounding or modifying the temporal association between regulation and public health. Although we have examined trends in prescribing of other drugs that may have influenced the associations of interest, this provides only partial control. Furthermore, wider factors not considered here may have influenced trends in gastrointestinal haemorrhage and acute MI. For example, we are unable to account for any changes over time in the accuracy of diagnostic coding of hospital admissions or deaths. In particular, it is possible that admis-

sions coding has become more accurate over time due to changes in the financial structuring of the National Health Service, with the change to 'payment by results' [39].

The three datasets being compared here are produced for different geographical areas: hospital admissions for England, mortality for England and Wales, and prescribing for the entire UK. This lack of co-terminosity should have relatively little effect on any findings, as trends will be dominated by those for England, which accounted for 84% of the UK population in 2006 [27]. Additionally, regulatory action taken by the MHRA affects the whole of the UK simultaneously, and there is no reason to suspect differential application in the different constituent countries.

Conclusion

The voluntary withdrawal of rofecoxib and subsequent regulatory action to restrict the use of COX-2 inhibitors, because of fears about their cardiovascular safety profile, was temporally associated with favourable reversal of previously rising trends in emergency hospital admissions for acute MI among people aged >64 years. No such association was evident with trends in MI admissions to people aged 55–64 years, or for MI mortality trends among either age group. The reversal of a previously favourable trend in admissions for gastrointestinal haemorrhage among 55–64-year-olds appeared to predate relevant changes in COX-2 inhibitor availability by up to 2 years.

Competing interests

D.G. is a member of the MHRA's Pharmacovigilance Expert Advisory Group. He acts as an independent advisor, receiving travel expenses and a small fee for meeting attendance and reading materials in preparation for the meeting. P.S. is employed by IMS HEALTH. IMS has received funds for a variety of research projects and data from both the pharmaceutical manufacturers and regulatory authorities. B.W.W., R.M.M. and C.M. declare no competing interests.

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