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Iatrogenic Effects of COX-2 Inhibitors in the US Population

Findings from the Medical Expenditure Panel Survey

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Abstract

Background: Selective cyclo-oxygenase 2 inhibitors ('coxibs') have been demonstrated to increase cardiovascular risk, but the cumulative burden of adverse effects in the US population is uncertain.

Objective: To quantify cardiovascular and gastrointestinal (GI) haemorrhage disease burden from coxibs and traditional 'non-selective' non-steroidal anti-inflammatory drugs (t-NSAIDs) in the US population.

Design, setting and participants: Adult respondents from the 1999–2003 Medical Expenditure Panel Survey, a representative sample of the US population which first became available in December 2006, were included. Respondents were followed for 2 years. Exposure was defined by two or more prescriptions of rofecoxib, celecoxib or a t-NSAID in the first year.

Main outcome measures: Acute myocardial infarction (AMI), stroke and/or GI haemorrhage in the year following exposure.

Results: Exposure to rofecoxib was associated with an adjusted odds ratio (OR) of 3.30 for AMI (95% CI 1.41, 7.68; $p = 0.01$) and 4.28 for GI haemorrhage (95% CI 1.33, 13.71; $p = 0.02$). Celecoxib was not associated with a statistically significant effect on AMI (OR 1.44; 95% CI 0.57, 3.69; $p = 0.44$), but there was an OR of 2.43 for stroke (95% CI 1.05, 5.58; $p = 0.04$) and 4.98 for GI haemorrhage (95% CI 2.22, 11.17; $p < 0.001$). The group of t-NSAIDs was not associated with a significant adverse effect on AMI (OR 1.47; 95% CI 0.76, 2.84; $p = 0.25$) or stroke (OR 1.26; 95% CI 0.42, 3.81; $p = 0.68$), and was associated with an OR of 2.38 for GI haemorrhage (CI 1.04, 5.46; $p = 0.04$). In the 1999–2004 period rofecoxib was associated with 46 783 AMIs and 31 188 GI haemorrhages; celecoxib with 21 832 strokes and 69 654 GI haemorrhages; resulting in an estimated 26 603 deaths from both coxibs. The t-NSAID group was associated with an excess of 87 327 GI haemorrhages and 9606 deaths in the same period.

Conclusions: Iatrogenic effects of coxibs in the US population were substantial, posing an important public health risk. Drugs that were rapidly accepted for assumed safety advantages proved instead to have caused substantial injury and death.

Background

The rapid introduction of selective cyclooxygenase-2 inhibitors ('coxibs') into clinical practice in the first half of this decade was intended to provide adequate anti-inflammatory action and analgesia with a reduction in the gastrointestinal (GI) adverse effects commonly experienced with traditional 'non-selective' non-steroidal anti-inflammatory drugs (t-NSAIDs). However, an unpredicted increase in cardiovascular events, predominantly with a focus on acute myocardial infarction (AMI), led to the withdrawal of rofecoxib and a 'black box' warning for celecoxib.[1]

Celecoxib continues to be taken, with over 3.7 million Americans having been exposed to this drug in 2005.[2] Furthermore, the resumption of direct-to-consumer advertising suggests that the celecoxib market is poised to expand.[3] It is therefore timely to consider the cumulative risks posed by coxibs as a whole in the US population, and to contrast these with the risks associated with t-NSAIDs. While anti-inflammatory medications have important benefits for treating arthritis – a source of considerable morbidity – these benefits must be balanced against the risks.

Previous studies have reported an increased risk of AMI and stroke associated with coxib use in a variety of patient populations.[4-8] There is agreement from the literature that coxibs increase the risk of cardiovascular events in the form of AMI and stroke.[9] However, since previous studies have not analysed a representative population, they have not established the cumulative burden of disease in the US population.

In this study we used the 1999–2004 Medical Expenditure Panel Survey, the largest US population-based health survey available, to examine the population effects of the selected coxibs and t-NSAIDs as a group on AMI, stroke and GI haemorrhage longitudinally, and to quantify the cost in terms of actual numbers of patients who have been harmed over that period as a result of exposure to these drugs.

Methods

We used publicly available data on adults aged 18 years or older from panels 4 to 8 of the Medical Expenditure Panel Survey (MEPS).[10] We combined the Household Component, Medical Conditions, Prescribed Medicines and Longitudinal Weights information using the unique individual identifier. MEPS is a nationally representative survey of the US civilian non-institutionalized population designed to collect data on healthcare utilization, expenditure and health status. It is structured as an overlapping panel.

A new panel of sample households is selected each year, and data for each panel are collected for 2 calendar years. The 2 years of data for each panel are collected in five rounds of interviews that take place over a 2.5-year period. This enabled us to construct a 2-year longitudinal panel. We utilized MEPS panels 4 through to 8. Data on panel 8 became available in December 2006. The overall response rate for the panels ranged between 68% and 78%; however, since MEPS provides longitudinal weights that allow users to adjust for non-response bias, this relatively low response rate does not undermine validity.

We classified individuals as having been exposed to rofecoxib, celecoxib or a t-NSAID if at any time in calendar year 1 they had obtained two or more prescriptions or refills of the particular coxib or t-NSAID, and had not received any prescription for either the other coxib or a t-NSAID, whichever the patient had not been exposed to in either the year of prescription (year 1) or the following year (year 2). Data on

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prescription usage are based on data gathered from the respondent's household pharmacy provider.

Events are ascertained in calendar year 2. A health condition is recorded as described *ad verbatim* by the patient, recorded by the survey taker and subsequently coded by professional coders. This improves the validity of event reporting in the MEPS data since respondents are not asked to provide an explicit diagnosis. A 3-digit International Classification of Diseases (9th edition) [ICD-9] code is generated but is not available to researchers. Instead, Clinical Classification Software is used to aggregate data into 263 mutually exclusive clinical categories, some of which map exactly to the 3-digit ICD-9 Clinical Modification (ICD-9-CM) codes. Based on these clinical classifications as well as on the ICD-9 2-digit code available from the MEPS data, we considered three conditions: AMI (ICD-9 CM codes 410), stroke (433–435) and GI haemorrhage (153; see table I for the ICD-9 codes for GI haemorrhage). In order to ensure that attribution was as accurate as possible within the confines of our data, we excluded from our analysis respondents who had any evidence of the event (AMI, stroke or GI haemorrhage) in year 1.

In summary, our sample is taken from all respondents who entered the MEPS data between 1999 and 2003. Each respondent is followed in MEPS for 2 years. Therefore, exposure is defined as exposure in the first year they enter MEPS ('year 1') and event is identified in their second year in MEPS ('year 2').

We constructed the sample in two steps. First, we excluded all respondents aged younger than 18 years or those who had any evidence of an event in year 1.

Next, to construct our sample for celecoxib we excluded all respondents who were exposed to one or more prescriptions of either a t-NSAID or rofecoxib in *either* year 1 or year 2. This yielded a sample size for celecoxib of 42 917. The samples for rofecoxib and t-NSAIDs as a group were constructed in a similar fashion, yielding sample sizes of 42 750 and 47 064, respectively.

We carried out multivariate regression results using the 'svy: logistic' command in Stata (version 9.2, Stata Corp., College Station, TX, USA), which estimates a logistic model in the presence of complex sampling. Adjusting for factors beyond simply age and sex is important in this study since celecoxib and rofecoxib were both new and expensive drugs that would have been prescribed to wealthier patients who were more likely to be insured, and who might therefore have different underlying risks. To allow for regional and temporal trends in exposure, which might have confounded the results, we adjusted for the following potential confounders: age using 5-year age effects, sex, family poverty level, insurance coverage, region, ethnicity and a year of observation variable. All reported results were weighted using the MEPS longitudinal weights to ensure that results were representative of the US population and standard errors were adjusted to account for the complex survey design.

When a statistically significant difference was found between the exposed and unexposed

Table I. International Classification of Diseases (9th edition) [ICD-9] codes for gastrointestinal (GI) haemorrhage (Clinical Classification Code 153)

ICD-9 code	Description
4560, 45620	Oesophageal varices and portal hypertension
5307	Mallory Weiss Syndrome
53082	Oesophageal haemorrhage
53100, 53101, 53120, 53121, 53140, 53141	Gastric ulcer haemorrhage
53200, 53201, 53220, 53221, 53240, 53241	Duodenal ulcer haemorrhage
53300, 53301, 53320, 53321, 53340, 53341	Peptic ulcer with haemorrhage
53400, 53401, 53420, 53421, 53440, 53441	Gastrojejunal ulcer with haemorrhage
5693	Haemorrhage of rectum and anus
5780, 5781, 5789	Other, GI haemorrhage

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Table II. Population demographics: exposed vs unexposed[a]

Drug group and demographics	Unexposed [mean (95% CI)]	Exposed [mean (95% CI)]
t-NSAIDs		
Age (y)	45.23 (44.88, 45.57)	52.37 (51.32, 53.41)
Males (%)	48.1 (47.7, 48.6)	44.1 (41.3, 46.9)
Covered by private insurance (%)	74.0 (73.0, 75.1)	67.0 (63.8, 70.2)
Uninsured (%)	12.8 (12.1, 13.5)	6.7 (5.2, 8.2)
Very poor (<100 FPL) [%]	10.1 (9.6, 10.7)	14.3 (12.2, 16.3)
Rich (>400 FPL) [%]	40.9 (39.7, 42.2)	37.2 (34.2, 40.3)
Rofecoxib		
Age (y)	45.58 (45.23, 45.93)	59.45 (57.80, 61.10)
Males (%)	48.6 (48.1, 49.1)	37.3 (32.3, 42.3)
Covered by private insurance (%)	73.9 (72.9, 75.0)	77.5 (73.5, 81.5)
Uninsured (%)	13.0 (12.3, 13.7)	3.4 (1.8, 5.0)
Very poor (<100 FPL) [%]	9.9 (9.4, 10.5)	9.8 (7.3, 12.4)
Rich (>400 FPL) [%]	41.1 (39.9, 42.4)	42.6 (37.3, 48.0)
Celecoxib		
Age (y)	45.66 (45.30, 46.01)	62.21 (60.56, 63.86)
Males (%)	48.6 (48.2, 49.1)	29.7 (25.6, 33.7)
Covered by private insurance (%)	73.9 (72.8, 74.9)	74.9 (70.4, 79.4)
Uninsured (%)	13.0 (12.3, 13.7)	3.6 (2.1, 5.1)
Very poor (<100 FPL) [%]	9.9 (9.4, 10.5)	11.6 (9.0, 14.3)
Rich (>400 FPL) [%]	41.1 (39.8, 42.3)	41.5 (36.3, 46.7)

a Weighted to reflect US population and standard errors adjusted for complex sampling. Exposed is defined as having two or more prescriptions in year 1.

FPL = Federal Poverty Level; **t-NSAIDs** = traditional 'non-selective' non-steroidal anti-inflammatory drugs.

populations, we estimated the cumulative burden of disease for the US population as a whole by utilizing the Stata post-estimation command 'adjust'. This command estimates the predicted probability of the event for the population using the estimated parameters of the logistic regression model and evaluated at the population mean of all variables (unless otherwise specified). The predicted probability evaluated at the mean for all variables was calculated. We then calculated the predicted probability after setting the exposure variable at zero (and maintaining all other variables at their mean value). The difference in probabilities is the excess event risk in the population due to exposure. This difference was then multiplied by the total person-years 18 years and older who were at risk, namely, the aggregate US adult population between 1999 and 2003 taken from the US Census of Population interim projections.

Results

Table II summarizes the characteristics of the exposed and unexposed populations. The sample exposed was significantly older and more likely to be female. Those exposed to a t-NSAID were less likely to be covered by private insurance, more likely to be uninsured and more likely to live in poorer families than those exposed to one of the coxibs. In the case of coxibs, only non-insurance was statistically significant with exposed groups being much more likely to be privately insured.

Table III presents the raw sample data with exposure and event counts. In the unexposed sample, the rate of AMI was 3 per 1000, which is very similar to the published figure of 2.8 per 1000 for AMI hospitalization for a first attack.[11]

With respect to the results of the logistic regression, exposure to two or more prescriptions of rofecoxib resulted in a 3-fold increase in AMI risk

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(odds ratio [OR] 3.30; 95% CI 1.41, 7.68; p = 0.01) and an OR of 4.28 for GI haemorrhage (95% CI 1.33, 13.71; p = 0.02; figure 1). There were no strokes in the exposed population, therefore the stroke effect could not be ascertained.

Celecoxib's effect on AMI was not statistically significant (OR 1.44; 95% CI 0.57, 3.69; p = 0.44), but the stroke risk was approximately doubled (OR 2.43; 95% CI 1.05, 5.58; p = 0.04) and was also associated with a 5-fold increase in GI haemorrhage risk (OR 4.98, 95% CI 2.22, 11.17; p < 0.001; figure 2).

t-NSAIDs as a group had no adverse effect on AMI (OR 1.47; 95% CI 0.76, 2.84; p = 0.25) or stroke (OR 1.26; 95% CI 0.42, 3.81; p = 0.68) but they were associated with a 2.38 adjusted OR for GI haemorrhage (95% CI 1.04, 5.46; p = 0.04; figure 3).

Table IV presents the predicted cumulative risk in the US adult population (190 million individuals). We estimated that coxibs were associated with 46 783 AMIs, 21 832 strokes and 100 842 excess GI haemorrhages in the US population between 1999 and 2004. t-NSAIDs were associated with an excess of 87 327 GI haemorrhages.

We can also calculate the total deaths associated with each of the events using conservative reported fatality rates. A case fatality rate of 21% at 365 days for AMI was used based on the 1993/95 Worcester data.[12] Reported stroke case fatality rates are more variable and range from 26.3%[13] to 49.3%.[14] We have used the most conservative estimate of 26.3% to calculate potential stroke mortality from coxibs. GI haemorrhage mortality was derived from a reported 11% 30-day mortality in a study of patients hospitalized for peptic ulcer bleeding.[15] Utilizing these rates, we calculated 26 603 excess deaths due to coxibs. t-NSAIDs were associated with 9606 deaths.

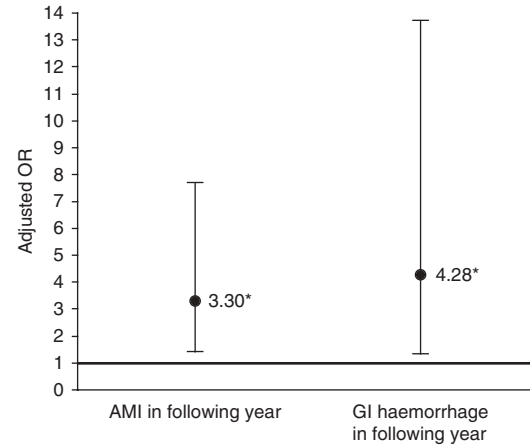

Fig. 1. Rofecoxib exposure (adjusted odds ratio [OR] and 95% confidence interval of event). Adjusted for age, sex, region, year, poverty and ethnicity. Weighted to reflect US population and adjusted for complex sampling. Insufficient stroke events for estimation. **AMI** = acute myocardial infarction; **GI** = gastrointestinal; * p < 0.05.

Table III. Event and exposure counts[a]

Drug groups and events	Exposed	Not exposed
t-NSAIDs		
AMI in following year	13/1769	149/45 295
Stroke in following year	5/1769	95/45 295
GI haemorrhage in following year	9/1769	110/45 295
Rofecoxib		
AMI in following year	8/515	131/42 215
Stroke in following year	0/515	86/42 215
GI haemorrhage in following year	5/515	105/42 215
Celecoxib		
AMI in following year	6/704	133/42 213
Stroke in following year	9/704	89/42 213
GI haemorrhage in following year	9/704	104/42 213

a Numbers are for unweighted raw counts of the sample.

AMI = acute myocardial infarction; **GI** = gastrointestinal; **t-NSAIDs** = traditional 'non-selective' non-steroidal anti-inflammatory drugs.

Discussion

In this study, we used population-level data and estimated that coxibs were associated with an excess of nearly 50 000 myocardial infarctions and 21 832 strokes. These figures included almost 30 000 deaths in the US over a 4-year period. We also found an association between coxibs and strokes, which has not been well documented in previous literature. In addition, although the coxibs were marketed as having a lower risk of GI adverse effects, the frequency of GI bleeding in the US population was high and these agents were in fact associated with more GI bleeding than were t-NSAIDs during this period (although physicians probably prescribed these drugs preferentially to patients at high risk).

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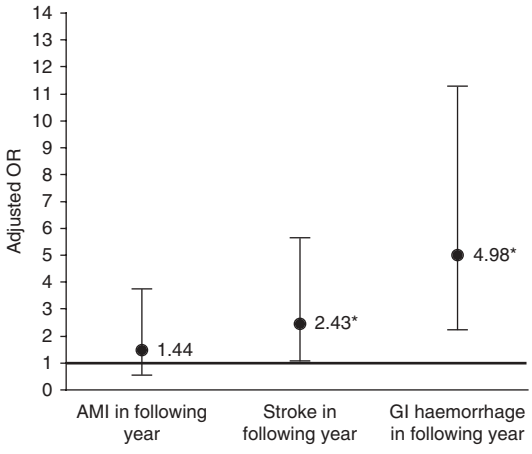

Fig. 2. Celecoxib exposure (adjusted odds ratio [OR] and 95% confidence interval of event). Adjusted for age, sex, region, year, poverty and ethnicity. Weighted to reflect US population and adjusted for complex sampling. **AMI** = acute myocardial infarction; **GI** = gastrointestinal; * $p < 0.05$.

We used MEPS data to verify currently accepted cardiovascular and GI risks attributed to coxibs and t-NSAIDs.[5,8,16,17] The methodology confirms the known odds ratio of AMI with rofecoxib,[1,5,7,8,16,17] the previous finding that rofecoxib AMI risk increases with time[7] and the well known GI haemorrhage risk from t-NSAIDs.[18-20] Furthermore, the MEPS data have allowed more analysis of risks in the US population outside of a clinical trial setting.

The finding of an increased GI haemorrhage potential with both celecoxib and rofecoxib suggests that in widespread clinical use there is a significant burden of disease. Of concern is a possible confounding due to concomitant low-dose aspirin (acetylsalicylic acid) exposure. To test for this, we re-estimated the odds ratio after excluding those respondents taking prescribed aspirin and found that the magnitude of GI haemorrhage potential remained similar. While the magnitude of the GI effect in our sample appears very large, this should be interpreted cautiously as the affected population are very likely to have been at high risk of GI adverse effects (often the reason for their being prescribed a coxib).[21]

A second important finding from the data is the large iatrogenic consequence of the prescription of coxibs over the 1999–2003 period. We estimate that annually rofecoxib was responsible for 9356 AMIs, which is equal to a 0.5% increase in annual AMI occurrences in the population.[22] This AMI figure is lower than the estimates of Graham et al.[7] who suggested a range of 88 000 to 140 000, which was based on the relative risks reported in clinical trials. For strokes we estimated a 4366 annual increase due to celecoxib, which also represents a 0.6% population-wide increase in stroke occurrence.[22] The number of GI bleeds annually due to rofecoxib is 31 188; for celecoxib it is 13 930 and for t-NSAIDs it is 21 832.

The third finding of clinical relevance is that we found no evidence that t-NSAID use increases the risk of AMI or stroke, although the GI haemorrhage risk remains significant. Clearly the small sample size reduces the power of the test and the failure to find significance needs to be interpreted in this context.

Our study has limitations. Because the data were taken from MEPS, we could not independently validate their accuracy. In addition, we were unable to fully assess the dosage of celecoxib, for which a higher dosage has been associated with cardiovascular risk.[23]

Our study design excludes patients exposed to one prescription. We also exclude the effects of concurrent exposure, as well as patients who obtain t-NSAIDs such as low-dose aspirin over the

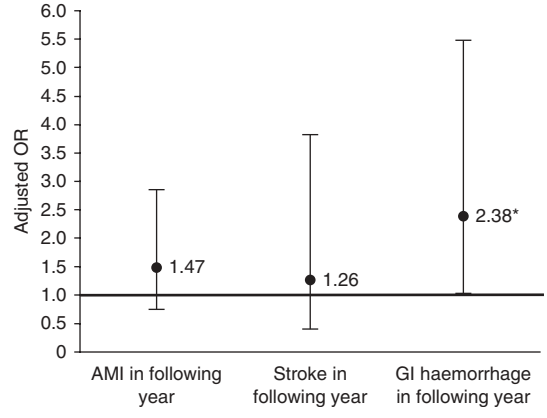

Fig. 3. t-NSAIDs exposure (adjusted odds ratio [OR] and 95% confidence interval of event). Adjusted for age, sex, region, year, poverty and ethnicity. Weighted to reflect US population and adjusted for complex sampling. **AMI** = acute myocardial infarction; **GI** = gastrointestinal; * $p < 0.05$.

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Table IV. Predicted cumulative risk for US population (1999–2004)[a]

Drug groups and events	Estimated events
t-NSAIDs	
AMI	NE[b]
Stroke	NE[b]
GI haemorrhage	87 327
Total deaths due to t-NSAIDs	9 606
Rofecoxib	
AMI	46 783
Stroke	NE[b]
GI haemorrhage	31 188
Total deaths due to rofecoxib	13 199
Celecoxib	
AMI	NE[b]
Stroke	21 832
GI haemorrhage	69 654
Total deaths due to celecoxib	13 404

a Predictions based on estimated model. Represents 951 800 000 person-years.

b Not estimated for events/exposure that did not yield statistically significant estimates at 5% confidence level.

AMI = acute myocardial infarction; **GI** = gastrointestinal; **t-NSAIDs** = traditional 'non-selective' non-steroidal anti-inflammatory drugs.

counter. This leads to an underestimate of the exposure levels in the population and consequently the overall disease burden. Therefore, our estimates of disease burdens are conservative.

Due to the limitation in the MEPS data we are unable to adjust for base-line risk of cardiovascular events or GI bleed. Regarding the GI risks, we cannot exclude the possibility that those who were exposed had higher underlying risks of GI bleeds. Therefore, our GI effects are likely to be overestimated. Overall, the small numbers of individuals who experienced events in the study imply that the study has limited power. This means that one needs to be cautious in interpreting insignificance t-ratios as meaning no effect.

Given the constraints of the MEPS data, we are unable to establish exactly when exposure occurred. Restricting attention to those who were at least exposed in year 1 ensures that exposure is not subsequent to event. It also ensures that delayed effects are estimated. However, to the extent that it reduces the link between exposure and event, it biases our method towards finding no statistically significant effect.

Given our study design, the results cannot be interpreted as a head-to-head comparison of celecoxib, rofecoxib and the group of t-NSAIDs. Therefore, even though our regression analysis shows the marginal effect of coxibs on GI risk is greater than that of t-NSAIDs, the difference is not necessarily statistically significant.

Despite these limitations, we believe that our study provides a novel way of using the MEPS data, which are freely accessible. Given that MEPS has been collected since 1996, it now provides a very large sample of the exposure of the US population to prescription medication. While our method is in no way a replacement for randomized control trials and postmarketing surveillance, it does provide a relatively inexpensive and quick method for researchers and agencies to monitor drug effects.

A strength of our statistical approach and reliance on a representative sample of the US population is that we are able to estimate the burden of disease caused by the adverse effects of exposure to drugs. The US FDA has monitored voluntarily reported adverse drug events since 1998. From that time to the present, outpatient drug prescriptions have steadily increased and reported serious adverse events increased four times faster. Rofecoxib was identified as the 14th most commonly implicated drug in causing death over the period 1998–2005, with 932 attributable deaths. In the same investigation, celecoxib was in tenth place for causing disability or other serious outcome, with 4822 instances reported.[24] These data, derived from voluntary reports, are likely to underestimate the true scale of the problem.

To quantify the size of the morbidity and mortality risks associated with coxibs and t-NSAIDs, our study used a different data source that was not reliant on voluntary reporting. While the clinical course of patients who have stroke or AMI induced by coxibs may potentially be different from that from more traditional etiologies, we have used published case fatality rates to estimate the potential mortality attributable to coxibs during the period of study. These case fatality rates have to be taken in the context that they are derived from populations that

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are not necessarily representative of the study population.

To put the coxib mortality figure of 26 603 in context, it is equal to the mortality of motorists in motor vehicle accidents in the USA over a 9-month period.[25] Yet, one might argue that motor vehicle deaths, while unfortunate, reflect an explicit trade-off made by society between increasing the speed-limit enabling faster travel and, at the same time, elevating the risk of crashes. These risks are accepted by the public who can make choices with regards to both speed and alternate modes of transport. Additionally, given certain roads (highways) are safer than others (inner city streets), speed limits are adjusted accordingly.

An analogy can be drawn between the way in which traffic crashes are managed by the community and the way medication safety is regulated in light of the coxib experience analysed in this paper. The rapid diffusion of coxibs into clinical practice is likely to be at least partly responsible for the large mortality reported. As in the case of motoring, rapid diffusion has both benefits and costs and neither of these are the same across drugs. This suggests that society (and policy makers) ought to be making more informed and explicit determinations about the trade-offs between the benefits of faster diffusion and higher risks.

Undoubtedly part of the reason for the rapid diffusion of the coxibs was the vigorous marketing campaign including high levels of sampling and direct-to-consumer advertising. Our data show that 15% of all administered coxibs between 1999 and 2004 were samples (as opposed to 3% of all drugs). This is one area where more stringent regulation might be justified.

Conclusions

We found substantial morbidity and nearly 27 000 deaths associated with coxibs. The scale of cardiovascular and GI haemorrhage risks might have been smaller if the massive market penetration of coxibs had not occurred, and the adverse effects could have been detected sooner through effective surveillance. From the public health perspective, there would have been a population benefit from either regulating the diffusion of these new drugs into the market or performing more effective postmarketing surveillance. This may be a lesson relevant to all new drugs, particularly when the iatrogenic adverse effects have the potential to negate or reverse the gains from successful public health interventions such as obesity and cholesterol reduction. The results presented here, and in particular the stroke risk, suggest that coxibs have potentially serious effects on patients and that very careful consideration by physicians and patients alike is needed before choosing coxibs over other analgesic and anti-inflammatory therapies.

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