All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

CEPP National Audit

Towards Appropriate Non-steroidal Anti-inflammatory Drug (NSAID) Prescribing

March 2010 (updated June 2015)

This report has been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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CONTENTS

1.0 INTRODUCTION 2
1.1 Prescribing 2
1.2 Risks versus benefits 4
1.3 Useful resources 4
2.0 AUDIT 5
2.1 Aim of the audit 5
2.2 Audit criteria 5
2.3 Method 5
2.4 Results and reflection 9
2.4.1 Notes on medication review for NSAIDs and good practice points 9
DATA SUMMARY SHEET 1 12
DATA SUMMARY SHEET 2 13
PRACTICE REVIEW SHEET 14
REFERENCES 15
APPENDIX A: AWMSG NSAID AUDIT UPDATE DECEMBER 2010 17
APPENDIX B: RECOMMENDED READ CODES 19
APPENDIX C: SAMPLE SELECTION 23

1.0 INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are licensed and prescribed for a range of indications. They include traditional NSAIDs (including aspirin), meloxicam, etodolac and selective cyclo-oxygenase (COX)-2 inhibitors ("coxibs"). The majority of NSAID use is for musculoskeletal pain, particularly osteoarthritis, and prescribing for older people is common. However, other treatment options such as paracetamol, topical NSAIDs and non-drug treatments such as exercise may be just as effective in some conditions such as osteoarthritis[1].

There are no important differences in efficacy between NSAIDs in the management of musculoskeletal disorders. The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued advice that applies to all traditional NSAIDs and selective COX-2 inhibitors. All are associated with gastrointestinal (GI) toxicity and some are associated with an increased risk of thromboembolic events[2,3]. NICE CKS NSAIDs – prescribing issues provides information on cardiovascular and GI safety of NSAIDs[4]. These medicines are also recognised as having nephrotoxic potential, and their use may be a contributory factor in the development of acute kidney injury[5].

1.1 Prescribing

In line with the aims of the AWMSG National Prescribing Indicator, there has been a downward trend in overall NSAID prescribing across the seven health boards in Wales (Figure 1). Prescribing of ibuprofen and naproxen (NSAIDs with a lower cardiovascular risk) as a proportion of all NSAIDs has increased (Figure 2)[6], with these medicines accounting for 80% of all NSAID prescribing in the quarter ending December 2014.

Figure 1. Trend in total NSAID prescribing

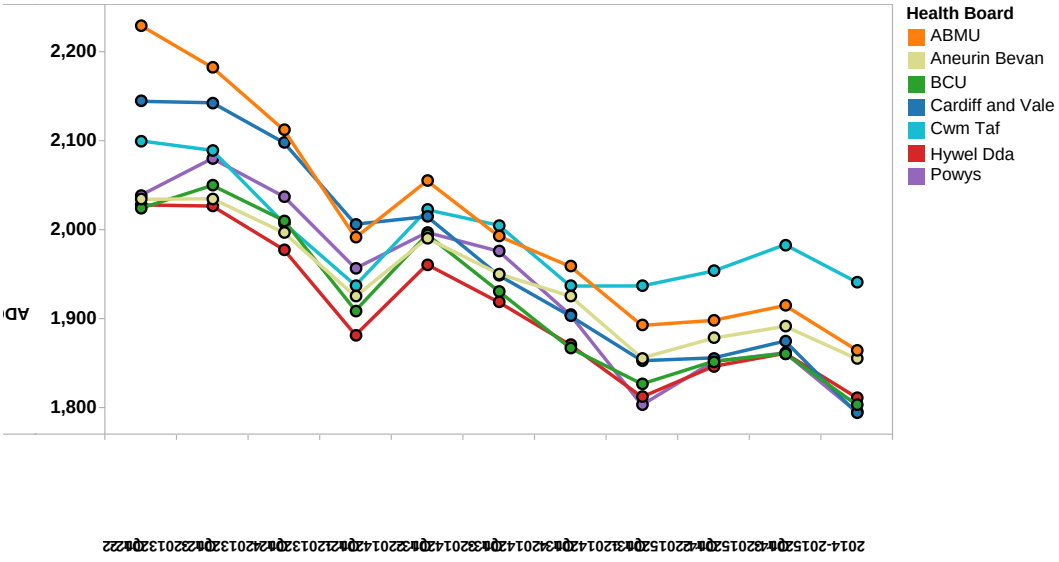
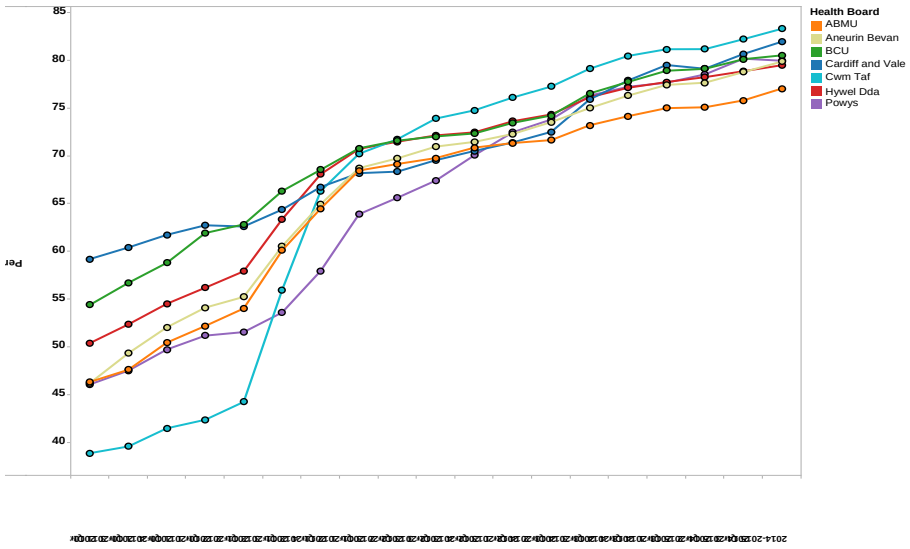


Figure 2. Trend in ibuprofen and naproxen prescribing



Prescribers are reminded that:

- GI and cardiovascular risks of NSAIDs may be minimised by selecting the lowest dose of NSAID for the shortest duration of treatment[2,4].
- The risks of GI and other adverse effects are higher in the elderly[2,7]. NSAIDs are considered high-risk medications, and their use in combination with other high-risk medicines should be reviewed and avoided where possible[7].
- Aspirin and other NSAIDs should only be used together when absolutely necessary – the combination substantially increases GI risk. Patients taking long-term aspirin should be reminded to avoid NSAIDs, including those bought without prescription[2].
- Ibuprofen is associated with the lowest GI risk of the traditional NSAIDs; however, serious and fatal GI reactions have been reported with its use.
- Clinical trial data suggest that selective COX-2 inhibitors have GI safety advantages over standard NSAIDs. Serious and fatal GI reactions have, however, been associated with these medicines. NICE osteoarthritis guidance states that gastroprotection with a PPI should be offered to all patients on regular NSAID and COX-2 inhibitors[1].
- Renal function can be impaired by NSAIDs and should be monitored in patients on long-term treatment[8]. Patients with pre-existing renal impairment are especially at risk, and doses of NSAIDs should be kept as low as possible in such patients. Patients with acute illness, who have used NSAIDs (or other potentially nephrotoxic medicines) within the past week should be investigated for acute kidney injury especially if hypovolaemic[5].
- Prescribing should be based on the safety profiles of individual NSAIDs and COX-2 inhibitors and on individual patient risk profiles (e.g. GI and cardiovascular).
- Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products, a patient's individual risk factors, and patient preference.
- Prescribers should check for a history of hypersensitivity to aspirin or any other NSAIDs, including any worsening of asthma, urticaria or rhinitis with aspirin or NSAIDs.
- Many drugs interact with NSAIDs (see Method; **(E)** Risk factors): increased bleeding with selective serotonin reuptake inhibitors (SSRIs) is of note. Other medicines such as angiotensin converting enzyme inhibitors (ACEIs) and diuretics increase the risk of renal impairment. Medicines with a narrow therapeutic range such as lithium and antiepileptics can be affected by NSAIDs.

1.2 Risks versus benefits

A summary of the 2010/2011 All Wales audit results confirms that many patients across Wales prescribed repeat NSAIDs in primary care are at increased risk of adverse events due to age, co-morbidities and drug interactions[9]. In the sample studied, 30% of patients were over 65, 30% were hypertensive and 40% were on drugs which potentially interact with NSAIDs (Appendix A).

COX-2 selective inhibitors are associated with an increased risk of thrombotic events[10] (e.g. myocardial infarction [MI] and stroke) and should not be used in preference to non-selective NSAIDs except when specifically indicated (i.e. for patients at a particularly high risk of developing gastroduodenal ulceration or bleeding) and after assessing their cardiovascular risk.

Non-selective NSAIDs are also associated with a small increased risk of thrombotic events even when used short-term in those with no cardiovascular risk factors. Diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic events. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib. Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of MI[10].

The lowest effective dose of NSAID or COX-2 selective inhibitor should be prescribed for the shortest period to control symptoms and the need for long-term treatment should be reviewed periodically.

All NSAIDs are associated with serious GI toxicity; the risk is higher in the elderly. Evidence on the relative safety of seven non-selective NSAIDs indicates differences in the risks of serious upper GI side-effects. Azapropazone is associated with the highest risk and ibuprofen with the lowest; piroxicam, ketoprofen, indometacin, naproxen and diclofenac are associated with intermediate risks[10].

Recommendations:

- NSAIDs associated with a low risk, e.g. ibuprofen, are generally preferred.
- Start at the lowest recommended dose.
- Do not use more than one oral NSAID at a time.
- Remember that all NSAIDs (including selective inhibitors of COX-2) are contra-indicated in patients with active peptic ulceration. Non-selective NSAIDs are contra-indicated in patients with a history of peptic ulceration[10].
- The combination of an NSAID and low-dose aspirin can increase the risk of GI side-effects; this combination should be used only if absolutely necessary, and the patient should be monitored closely[10].
- All patients offered regular NSAID treatment should be co-prescribed a proton pump inhibitor (PPI)[1,10].

1.3 Useful resources

- Welsh Backs campaign[11], including GP desk aid[12] and the “Back Book” available through NPHS[13].
- Clinical Knowledge Summaries: NSAIDs – prescribing issues[4]; available at: http://cks.nice.org.uk/nsaids-prescribing-issues#!topicsummary
- Drug and Therapeutics Bulletin. Volume 48. Number 3. March 2010[14].
- AWMSG information leaflet: Medicines for mild to moderate pain relief[15]

2.0 AUDIT

The following audit was developed in 2009 by the All Wales Prescribing Advisory Group (AWPAG) and Primary Care Quality and Information Service (PCQIS) part of Public Health Wales. It was endorsed by AWMSG at their meeting on the 3 March 2010. This version was updated by AWPAG in 2015, with support for read code information provided by PCQIS. This document is for use by primary care general practitioners to highlight safety issues associated with NSAID prescribing, particularly in patients with a higher risk of side effects.

2.1 Aim of the audit

- To estimate how many patients have received an NSAID on their repeat prescription record in the last 12 months. An NSAID repeat is used as a marker for long-term and/or intended long-term NSAID use.
- To encourage practices to review their NSAID prescribing in line with the MHRA recommendations and the agreed audit criteria.
- To ensure all repeat NSAID prescribing is appropriate.
- To ensure those older patients or those with established ischaemic heart disease (IHD), cerebrovascular disease, peripheral vascular disease, renal disease, hypertension, diabetes or peptic ulcer disease, for whom an NSAID is considered essential, have had their risks adequately assessed and minimised.

2.2 Audit criteria

- All patients prescribed an NSAID as a repeat prescription should have a linked indication/diagnosis Read Coded.
- No patient receiving an NSAID on repeat medication should have any contraindication to such medication.
- All patients prescribed an NSAID as a repeat medication should have a record of a risk/benefit assessment with the patient documented in the medical record in the past 12 months.
- All patients prescribed an NSAID as a repeat medication should have a PPI co-prescribed.
- All patients prescribed an NSAID as a repeat medication should have a record of renal function in the past 12 months.

2.3 Method

1. Find the total number of patients prescribed an NSAID as a repeat medication within the past 12 months (A):
Search the practice computer system for all patients with an NSAID (remember to search for *branded* products as well) prescribed as a "repeat" in the past 12 months. Include COX-2 selective drugs in your search. Enter the figures for the total number of patients on the Data Summary Sheet(s).

Table 1. Generic names for NSAIDs
Please see Appendix B for a full list of Read Codes to aid in searching for this information.

NSAID	
Acemetacin	Nabumetone
Aceclofenac	Naproxen (includes Napratec®)
Dexibuprofen	Piroxicam
Dexketoprofen	Sulindac
Diclofenac (includes Arthrotec®)	Tenoxicam
Diflunisal	Tiaprofenic acid
Fenbufen	

Fenoprofen	**COX-2 selective NSAIDs:**
Flurbiprofen	Celecoxib
Ibuprofen	Etodolac
Indometacin	Etoricoxib
Ketoprofen	Meloxicam
Mefenamic acid	

(Tip: Remember to exclude low-dose aspirin from your list of NSAIDs.)

2. Sample (B):
Select a number of patients from the total number of patients prescribed an NSAID **(A)** to sample; sample size will depend on the number of patients in your list. Appendix C indicates a sample size that would give statistically significant results. The proportion of patients to sample may alternatively be decided at local level. Randomly select these patients from this list of patients to the required number.

3. Complete patient data collection:
Use the patients' medical records to complete the Patient Data Collection Sheet for these patients. Include the indications, contraindications and any risk factors which the patients have.

See Appendix B for a full list of Read Codes to aid in searching for the data.

Search for Read Code for NSAID risk/benefit assessment.

If this Read Code is not in general use in a practice, the medical records would need to be reviewed for any relevant documented discussion with the patient.

4. Complete Data Summary Sheet 1. Use Data Summary Sheet 2 to collate data from the Data Summary Sheet 1.

5. Complete Practice Review Sheet (see points below and data from the Data Summary Sheets to inform discussion).

6. Return Data Summary Sheet 1 (and Sheet 2 if applicable) and the Practice Review Sheet (localities to insert contact).

(C) Indications
Continuous or regular pain associated with inflammation:
Rheumatoid arthritis and other inflammatory polyarthropy
Osteoarthritis and allied disorders
Gout
Ankylosing spondylitis
Other:
Back pain and soft tissue disorders
Migraine
Dental and orofacial pain
Short term management of post operative pain

(D) Contraindications
Peptic ulceration or GI bleed:
History of peptic ulcer, peptic ulcer symptoms, peptic ulcer of oesophagus
Personal history of peptic ulcer, peptic ulcer – site unspecified, acute peptic ulcer
Chronic peptic ulcer
Unspecified peptic ulcer

Peptic ulcer – not otherwise specified
NSAID induced gastric ulcer, NSAID induced duodenal ulcer
Acute renal failure:
Acute renal failure
Heart failure:
Heart failure
Congestive heart failure
Left ventricular failure
Acute heart failure
Heart failure – not otherwise specified
Heart failure confirmed
NSAID/aspirin hypersensitivity

(E) Risk factors
Age over 65 years
IHD:
IHD
Acute MI
Other acute and subacute IHD
Old MI
Angina pectoris
Other chronic IHD
Subsequent MI
Cardiac syndrome
Other specified IHD
IHD NOS
Cerebrovascular disease:
Cerebrovascular disease
Intracerebral haemorrhage
Other and unspecified intracranial haemorrhage
Precerebral arterial occlusion
Cerebral arterial occlusion
Transient cerebral ischaemia
Stroke and cerebrovascular accident unspecified
Other cerebrovascular disease
Other specified cerebrovascular disease
Cerebrovascular disease NOS
Peripheral vascular disease
Chronic kidney disease:
Chronic renal failure
Chronic renal impairment
End stage kidney disease
Chronic kidney disease monitoring
Renal failure unspecified
Diabetes:
H/O: diabetes mellitus
Type 1 diabetes mellitus
Type 2 diabetes mellitus
Hypertension:
H/O: hypertension
Hypertensive disease
Hypertensive heart disease

Drugs increasing risk of bleeding when co-prescribed with NSAIDS:
Antiplatelets:
abciximab
aspirin 75 mg dispersible tablets
aspirin 75 mg tablets
aspirin 75 mg e/c tablets
clopidogrel
clopidogrel prophylaxis
dipyridamole
eptifibatide
prasugrel
ticagrelor
tirofiban
Anticoagulants:
apixaban
dabigatran
rivaroxaban
acenocoumarol
phenindione
warfarin sodium
warfarin therapy started
SSRIs:
citalopram
escitalopram
fluoxetine
fluvoxamine
paroxetine
sertraline
venlafaxine
Glucocorticoids:
betamethasone
cortisone
deflazacort
dexamethasone
hydrocortisone
methylprednisolone
prednisolone
prednisone
triamcinolone
Other medicines:
erlotinib
iloprost
pentoxifylline
Drugs increasing nephrotoxicity when co-prescribed with NSAIDS:
Renin-angiotensin system drugs:
ACE inhibitor prophylaxis
angiotensin II receptor antagonist prophylaxis
Diuretics:
loop diuretics
osmotic diuretics
thiazide diuretics
mercurial diuretics
potassium sparing diuretics

Other medicines:
tacrolimus
penicillamine
ciclosporin
lithium
phenytoin
Other NSAIDS: (see list above – Table 1)

(F) NSAID risk/benefits assessment completed
Read Code for 'NSAID drug risk assessment completed' 9OhB

(G) PPI co-prescribed:
esomeprazole
lansoprazole
omeprazole
pantoprazole
rabeprazole sodium

(H) Renal function test in last 12 months :
Renal function tests

2.4 Results and reflection

When completing the Practice Review Sheet consider:

- Are the results what we expected?
- Can we make any improvements?
- What might be stopping us getting better?

Discuss the results of the audit within the practice. Details from Data Summary Sheet 2 may help identify groups of patients to prioritise for review, or indicate patterns of prescribing to comment on.

Identify areas for improvement – formulate an action plan to optimise prescribing:

- Decide what it is that you want to achieve.
- Think about how you will know if you are improving or not.
- Generate ideas for the things that you could do differently.
- Use some of the reference material to inform debate and discussion.
- Record your progress.

2.4.1 Notes on medication review for NSAIDs and good practice points

Medication reviews of NSAIDs should address the following questions:

- Has alternative treatment been tried, e.g. paracetamol (regular dosing may be required)[10]?
- Is an NSAID still necessary?
- Have the risks as well as the benefits of NSAIDs been assessed and communicated to the patient and has this been recorded?
- Is the NSAID prescribed the one with the lowest cardiovascular risk suitable for this particular patient?
- Is the NSAID prescribed the one with the lowest GI risk suitable for this particular patient?
- Has the patient's renal function been assessed in the last 12 months?
- Should a PPI be co-prescribed to reduce adverse GI effects?
- When should treatment and the prescribed dose next be reviewed?

PATIENT DATA COLLECTION SHEET

(A) Number of patients in the practice with repeat NSAID prescription recorded in past 12 months _____

(B) Number of patients in sample taken from **(A)** _____

Patient ID	NSAID/indication recorded		Contraindications					Risk factors										Risk/benefit assessment recorded? (F)	Proton pump inhibitor co-prescribed? (G)	Renal function test in last 12 months? (H)
	Name of NSAID or COX-2 inhibitor prescribed recorded	Clear indication for NSAID prescribing recorded (see list in 'Method' section) (C)	History of peptic ulcer/GI bleed	Heart failure	Acute renal failure (in past 12 months)	NSAID/aspirin hypersensitivity	One or more contraindications (D)	Over 65 years of age	Ischaemic heart disease	Cerebrovascular disease	Peripheral vascular disease	Chronic kidney disease 1–5	Diabetes	Hypertension	Taking other drugs with increased GI bleeding risk when co-prescribed with NSAIDs (see list in 'Method' section)	Taking drugs that increase nephrotoxicity when co-prescribed with NSAIDs (see list in 'Method' section)	One or more risk factors (E)			

PATIENT DATA COLLECTION SHEET (CONTINUED)

Patient ID	NSAID/indication recorded		Contraindications					Risk factors										Risk/benefit assessment recorded? (F)	Proton pump inhibitor co-prescribed? (G)	Renal function test in last 12 months? (H)

DATA SUMMARY SHEET 1

Practice: _____
Date of audit: _____

	Number	Percentage of practice population
Practice list size		100%
(A) Number of patients in the practice with repeat NSAID prescription recorded in past 12 months		

	Number	Percentage of the audit sample	Suggested audit standard*
(B) Sample size i.e. number of patients with a repeat NSAID prescription included in the audit		100%	NA
(C) Number of patients with a clear indication for NSAID prescribing documented and recorded in their record			90%
(D) Number of patients with 1 or more NSAID contraindications recorded			0%
(E) Number of patients with 1 or more risk factors for NSAID prescribing recorded			No national audit standard set.
(F) Number of patients with assessment of prescribing risk/benefit documented in notes			90%
(G) Number of patients with PPI co-prescribed			75%
(H) Number of patients with urea and electrolytes documented in past 12 months			75%

*These represent realistic standards based on clinicians' discussions as objectives for the time of the audit cycle.

Please send Data Summary Sheet 1 (and Sheet 2 if applicable) and the Practice Review Sheet to your local Head of Pharmacy and Medicines Management who will compile the local information.

DATA SUMMARY SHEET 2

Factor	Number of patients with this characteristic
Total sampled	
Acute renal failure contraindication	
Peptic ulcer disease/GI bleed contraindication	
Heart failure contraindication	
Age > 65 years of age	
IHD	
CVD	
Peripheral vascular disease	
Chronic kidney disease 1–5	
Diabetes	
Hypertension	
Number of patients on interacting drugs	
Number of patients taking ibuprofen	
Number of patients taking naproxen	
Number of patients taking diclofenac	
Number of patients taking other NSAID	
Number of patients taking COX-2 inhibitor	

Please send Data Summary Sheet 1 (and Sheet 2 if applicable) and the Practice Review Sheet to your local Head of Pharmacy and Medicines Management who will compile the local information.

PRACTICE REVIEW SHEET

A. What lessons did the practice discover from carrying out this audit?

B. What discussion/activities did the practice undertake as a result of the audit?

C. What changes have the practice agreed to implement as a result of this audit?

This audit was completed by:

Name(s) _____

Signature(s) _____

Practice (name and address)

Please send Data Summary Sheet 1 (and Sheet 2 if applicable) and the Practice Review Sheet to your local Head of Pharmacy and Medicines Management who will compile the local information.

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1 National Institute for Health and Care Excellence. Clinical Guideline 177. Osteoarthritis: Care and management in adults (CG177). 2014. Available at: http://www.nice.org.uk/guidance/cg177. Accessed Feb 2015.

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APPENDIX A: AWMSG NSAID AUDIT UPDATE DECEMBER 2010

Summary

As of December 2010, data have been analysed for 9,397 patients from 86 practices across seven of the former local health board regions[9]. There do not appear to have been any significant problems when using the audit in practice. Areas where practices are performing well against the agreed standards include documentation of indications for NSAID treatment, and to a lesser extent urea and electrolyte monitoring. Areas where improvement is needed include co-prescription of PPIs and documentation of risk benefit discussions with patients. A significant proportion of patients had at least one risk factor associated with increased incidence of NSAID induced adverse events. Overall, diclofenac and ibuprofen are the most widely prescribed NSAIDs in the sample studied.

Audit findings

Data are presented from 86 practices and include a total of 9,397 patients. Findings are presented in the tables below:

Audit criterion	Sample size	Patients meeting criterion n (%)
Indication documented	9397	8226 (88)
Patients with 1 or more contraindication	9397	144 (2)
Patients with 1 or more risk factor	9397	5372 (57)
Patients with risk/benefit documented	7400	1625 (22)
Patients co-prescribed a PPI	9397	3560 (38)
Patients with urea and electrolytes in last 12 months	9397	5253 (56)

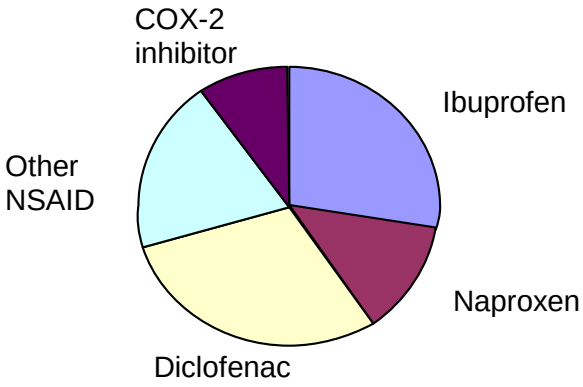
The number (and percentage) of patients with each contra-indication and risk factor is shown below:

	Patients n (%)
Contraindication:	
Gastrointestinal bleed/ulcer	110 (1)
Heart failure	24 (0.25)
Acute renal failure	10 (0.11)
Risk factor:	
Age > 65 years	2858 (30)
Ischemic heart disease	466 (5)
Cerebrovascular disease	146 (2)
Peripheral vascular disease	70 (1)
Chronic kidney disease 1–5	829 (9)
Diabetes	809 (9)
Hypertension	2770 (29)
Drug interaction	3769 (40)

Number of patients receiving each NSAID

Data for 9,157 patients from 83 practices was included for analysis, and results are summarised below:

	Patients n (%)
Ibuprofen	2542 (28)
Naproxen	1164 (13)
Diclofenac	2724 (30)
Other NSAID	1845 (20)
COX-2	882 (10)



Discussion

The proportion of patients with a documented indication for NSAID use was high (88% versus audit standard 90%). Whilst only a small proportion of patients had contra-indications (2%), this represents 144 patients in whom use of these drugs is unlicensed. Documentation of risk benefit discussion was low, although in part this may have been due to the unavailability of a Read Code for this audit criterion. The rate of PPI co-prescribing was also somewhat low, ranging from 21% to 46% across the local health boards (suggested standard 75%). Monitoring of urea and electrolytes came closer to meeting the agreed target, with 56% of patients meeting this criterion versus the 75% standard.

The proportion of patients with at least one risk factor for NSAID associated adverse events was 57%. The most common risk factors were age > 65 yrs, hypertension and drug interactions. This is a concern, as increasing age and drug interactions involving low dose aspirin and SSRIs have a significant effect on the relative risk of GI complications. Lanas et al* suggest an age adjusted odds ratio for upper GI bleeding of 6.1 when using NSAIDs in combination with low-dose aspirin. Addition of an SSRI was found to increase the risk of GI bleed with an odds ratio of 6.3 in one study†. Although no recommended standard has been established for risk factors, the audit has highlighted this problem. Patients at increased risk of GI adverse events should be co-prescribed a PPI, or alternative forms of analgesia considered.

Diclofenac and ibuprofen were the two most commonly prescribed NSAIDs accounting for 30% and 28% of usage respectively. Amongst the non-selective NSAIDs there is meta-analysis and observational evidence that diclofenac is associated with greater cardiovascular risk. Based on current data diclofenac should be avoided in patients at high risk of cardiovascular toxicity and naproxen considered first-line‡.

* Lanas A, Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006, 55: 1731-1738

† Loke YK et al., Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2006, 27: 31-40

‡ Ray WA. Cardiovascular safety of NSAIDs. BMJ 2011 342:c6618

APPENDIX B: RECOMMENDED READ CODES

NSAID	Read Code CTV2
Acemetacin	j2j..
Aceclofenac	j2m..
Dexibuprofen	j2t..
Dexketoprofen	j2q..
Diclofenac (includes Arthrotec®)	j22..
Diflunisal	j23..
Fenbufen	j25..
Fenoprofen	j26..
Flurbiprofen	j27..
Ibuprofen	j28.. j2p..
Indometacin	j29..
Ketoprofen	j2a..
Mefenamic acid	j2b..
Nabumetone	j2k..
Naproxen (includes Napratec®)	j2c..
Piroxicam	j2e..
Sulindac	j2f..
Tenoxicam	j2l..
Tiaprofenic acid	j2g..
Celecoxib	jA2..
Etodolac	j24..
Etoricoxib	jA5..
Meloxicam	j2n..
Indications	**Read Code (CTV2)**
Rheumatoid arthritis and other inflammatory polyarthropy	N04..
Osteoarthritis and allied disorders	N05..
Gout	C34..
Ankylosing spondylitis	N100.
Pain in thoracic spine	N141.
Pain in lumbar spine	N142.
Sciatica	N143.
Thoracic and lumbosacral neuritis	N144.
Backache unspecified	N145.
Intervertebral disc disorders	N12..
Backache symptom	16C..
Migraine	F26..
H/O Migraine	1474.
Dental and orofacial pain:	
Toothache	JO5y. 1912.
Dental swelling	1914.
Post operative pain	SP2y2
Contraindications	**Read Code (CTV2)**
Peptic ulcer symptoms	1956.
Peptic ulcer of oesophagus	J1020
Peptic ulcer, site unspecified	J13..
Acute peptic ulcer	J130.
Chronic peptic ulcer	J131.
Unspecified peptic ulcer	J13y.

Peptic ulcer – not otherwise specified	J13z.
NSAID induced gastric ulcer	J113.
NSAID induced duodenal ulcer	J126.
History of peptic ulcer	14C1.
History of GI bleed	14CA.
Acute renal failure	K04..
Heart failure	G58..
Congestive heart failure	G580.
Left ventricular failure	G581.
Acute heart failure	G582.
Heart failure – not otherwise specified	G58z.
Heart failure confirmed	1O1..
Personal history of aspirin allergy	ZV148
Risk factors	**Read Code (CTV2)**
IHD	G3...
Acute MI	G30..
Other acute and subacute IHD	G31..
Old MI	G32..
Angina pectoris	G33..
Other chronic IHD	G34..
Subsequent MI	G35..
Cardiac syndrome X	G37..
Other specified IHD	G3y..
IHD NOS	G3z..
Cerebrovascular disease	G6...
Intracerebral haemorrhage	G61..
Other and unspecified intracranial haemorrhage	G62..
Precerebral arterial occlusion	G63..
Cerebral arterial occlusion	G64..
Transient cerebral ischaemia	G65..
Stroke and cerebrovascular accident unspecified	G66..
Other cerebrovascular disease	G67..
Other specified cerebrovascular disease	G6y..
Cerebrovascular disease NOS	G6z..
Other peripheral vascular disease	G73..
Chronic renal failure	K05..
Chronic renal impairment	1Z1..
End stage kidney disease	K0D..
Chronic kidney disease monitoring	66i..
Renal failure unspecified	K06..
H/O: diabetes mellitus	1434.
Type 1 diabetes mellitus	C10E.
Type 2 diabetes mellitus	C10F.
H/O: hypertension	14A2.
Hypertensive disease	G2...

Hypertensive heart disease	G21..
NSAID Drug risk assessment completed	9OhB
Medicines increasing risk of bleeding when co-prescribed with NSAIDs	
Antiplatelets	**Read Code (CTV2)**
abciximab	bu3..
aspirin 75 mg dispersible tablets	bu23.
aspirin 75 mg tablets	bu25.
aspirin 75 mg e/c tablets	bu2B.
clopidogrel	bu5..
clopidogrel prophylaxis	8B6P.
dipyridamole	bu1..
eptifibatide	bu7..
prasugrel	buA..
ticagrelor	buB..
tirofiban	bu8..
Anticoagulants	**Read Code (CTV2)**
apixaban	bs7..
dabigatran etexilate	bs4..
rivaroxaban	bs6..
acenocoumarol	bs2..
phenindione	bs3..
warfarin sodium	bs1..
warfarin therapy started	66Q6.
SSRIs	**Read Code (CTV2)**
citalopram	da9..
escitalopram	daC..
fluoxetine	da4..
fluvoxamine	da3..
paroxetine	da6..
sertraline	da5..
venlafaxine	da7..
Glucocorticoids	**Read Code (CTV2)**
betamethasone	fe1..
cortisone	fe2..
deflazacort	fe9..
dexamethasone	fe3..
hydrocortisone	fe4..
methylprednisolone	fe5..
prednisolone	fe6..
prednisone	fe7..
triamcinolone	fe8..
Other medicines:	**Read Code (CTV2)**
erlotinib	hhC..
iloprost	bn7..
pentoxifylline	bn4..

Other medicines which interact with NSAIDs	
Renin-angiotensin system medicines	**Read Code (CTV2)**
ACE inhibitor prophylaxis	8B6B.
Angiotensin II receptor antagonist prophylaxis	8B6E.
Diuretics	**Read Code (CTV2)**
loop diuretics	b3…
osmotic diuretics	b6…
thiazide diuretics	b2…
mercurial diuretics	b7…
potassium sparing diuretics	b4…
Other medicines:	**Read Code (CTV2)**
tacrolimus	h83..
penicillamine	j52..
ciclosporin	h82
lithium salts	d6…
phenytoin	dn8..
phenytoin sodium	dn9..
PPIs co-prescribed	**Read Code (CTV2)**
esomeprazole	a6h..
lansoprazole	a6c..
omeprazole	a6b..
pantoprazole	a6e..
rabeprazole sodium	a6f..
Renal function tests	**Read Code (CTV2)**
Renal function test	**451..**

APPENDIX C: SAMPLE SELECTION

Total number of patients at risk prescribed NSAID	Sample size: 95% confidence; +/-5%
50	44
100	79
150	108
200	132
500	217
1000	278
2000	322