

Cardiovascular and gastrointestinal safety of NSAIDs



Summary

- All non-steroidal anti-inflammatory drugs (NSAIDs) carry the risk of side effects, which can be serious and life-threatening. Although the risks may vary between individual NSAIDs, important side effects include gastrointestinal (GI) complications (e.g. perforation, ulcer, bleeding) and cardiovascular (CV) (e.g. stroke, myocardial infarction). This article summarises current evidence of relative CV and GI risks for non-aspirin NSAIDs and highly selective COX-2 inhibitors (coxibs), and provides prescribing advice which is consistent with previous advice from the Commission on Human Medicines.

CV risk

- Coxibs (celecoxib, etoricoxib[▼]), as a class, are associated with a small excess risk of thrombotic events compared with no treatment (about three per 1000 users treated for one year), and they are contraindicated in patients with established CV disease.
- Traditional NSAIDs may also be associated with an increased risk of thrombotic events. Diclofenac 150mg/day appears to be associated with a similar excess risk to that of coxibs, whereas low-dose ibuprofen (≤ 1200 mg/day) and naproxen 1000mg/day appear to be associated with a lower risk.

GI risk

- Coxibs, as a class, are associated with a lower GI risk than traditional NSAIDs. However, their GI-safety advantage is diminished when they are co-administered with aspirin.
- Of the traditional NSAIDs, low-dose ibuprofen is associated with a lower GI risk than diclofenac or naproxen.
- Use of a proton pump inhibitor (PPI) with any NSAID significantly reduces the risk of GI side effects.
- Benefits from gastroprotection largely depend on the individual patient's baseline risk of GI complications. There is, as yet, no good evidence that adding a PPI to a coxib is more beneficial, equivalent or a worse option than adding a PPI to a traditional NSAID.

What does this mean in practice?

- Where NSAIDs are required, prescribing should be based on the safety profiles of individual NSAIDs and on individual patient risk factors. All NSAIDs should generally be used at the lowest effective dose and for the shortest period of time necessary to control symptoms.
- The ideal anti-inflammatory prescribing choice will vary from patient to patient, depending on individual risk factors, therapeutic response, patient preference, and the patient's attitude to the risk of adverse events.
- Low-dose ibuprofen (≤ 1200 mg per day) is an appropriate first choice NSAID in view of its low risk of GI and CV side effects.
- Low-dose ibuprofen or naproxen 1000mg would appear more appropriate than other NSAIDs for patients in whom CV risk is a significant consideration in decision making.
- Consider prescribing a PPI with any NSAID to reduce the risk of adverse GI effects, particularly in those who are at high GI risk (includes anybody aged 65 years or older) and long-term NSAID users.
- Although coxibs are associated with a lower risk of GI side effects than traditional NSAIDs, there is no good evidence to support the use of coxibs alone ahead of traditional NSAIDs co-prescribed with a PPI. Coxibs also have a higher CV risk than ibuprofen ≤ 1200 mg per day or naproxen 1000mg.
- Medication reviews of NSAIDs should consider:
 - Is an NSAID still necessary?
 - Is the NSAID prescribed appropriate based on the patient's CV risk?
 - Is the NSAID prescribed the one with the lowest GI risk suitable for that patient?
 - Should a PPI be co-prescribed to reduce the risk of adverse GI effects?
 - When should treatment/dose next be reviewed?
- When reviewing the treatment of patients already receiving diclofenac, some patients, after discussion, may decide to continue treatment with diclofenac. However, in some cases (especially patients with significant risk factors for CV disease) it may be appropriate to consider alternatives:
 - Patients who change from diclofenac 150mg/day to 1200mg ibuprofen/day would probably reduce both their GI and CV thrombotic risk, especially if the opportunity is taken to introduce a PPI. High doses of ibuprofen (e.g. 2400mg/day) are not prescribed frequently in clinical practice. However, the BNF states that 1600mg to 2400mg daily of ibuprofen is required for conditions where inflammation is prominent. The relative risks of these doses versus diclofenac 150mg/day are unclear.
 - Patients who change from diclofenac 150mg/day to naproxen 1000mg/day would reduce their CV thrombotic risk, but may slightly increase their risk of GI complications. However, if the opportunity is taken to introduce a PPI, the GI risks may also be reduced. There is less evidence for the balance of risks with lower doses of diclofenac and naproxen.

This publication was correct at the time of preparation: November 2007

Compared to no treatment, prescribing of coxibs may be responsible for approximately 240 additional or premature CV events per year in England alone

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), regardless of their cyclo-oxygenase (COX)-2 selectivity (see **footnote** on page 3), are similarly effective for reducing pain in musculoskeletal conditions.^{1,2} However, other treatment options (e.g. paracetamol, topical NSAIDs, and some non-drug treatments such as exercise) may be just as effective for some conditions (e.g. osteoarthritis) in many patients and are associated with fewer adverse effects.^{1,2} All NSAIDs are associated with gastrointestinal (GI) side-effects, which may be serious (e.g. perforation, ulcer, bleeding), although there are important differences between agents in the level of risk. Other class-specific adverse effects, which may occur in addition to GI adverse effects, are hypersensitivity or skin reactions, cardiovascular (CV) effects, renal effects and hepatotoxicity.³ Rofecoxib was withdrawn in 2004 due to its increased risk of thrombotic events. Following this, considerable attention has been paid to the CV safety of coxibs, and, more recently, to traditional NSAIDs such as diclofenac, naproxen and ibuprofen. In the light of this emerging evidence, we consider which NSAIDs are most appropriate to prescribe for people at significant risk of CV and GI events.

Cardiovascular risk

Long-term, randomised controlled trials (RCTs) have demonstrated that coxibs cause a small increased risk of thrombotic events in comparison with placebo. The excess risk was estimated to be about three cases per 1000 users treated for one year.³ This risk appears to increase with dose and persists throughout treatment. This estimate was based on a meta-analysis (MA) of RCTs by Kearney and colleagues, which identified an increase from 0.9% to 1.2% per year, corresponding to a 42% (95%CI 13% to 78%) proportional increase in the incidence of a first serious vascular event for coxibs compared with placebo.⁶ This estimate is supported by data from observational studies.³ Although the Kearney MA reported no

heterogeneity between individual coxibs, it included trials that used drugs at non-equivalent and/or unlicensed doses and it was under-powered to detect dose- or drug-specific effects.

An increased risk with meloxicam and etodolac can also not be ruled out, as there are insufficient data to examine the risks with these agents fully.³ An MA of three case-control studies suggests that meloxicam is associated with a 25% elevation of vascular risk (relative risk [RR] 1.25; 95%CI 1.00 to 1.55).⁷

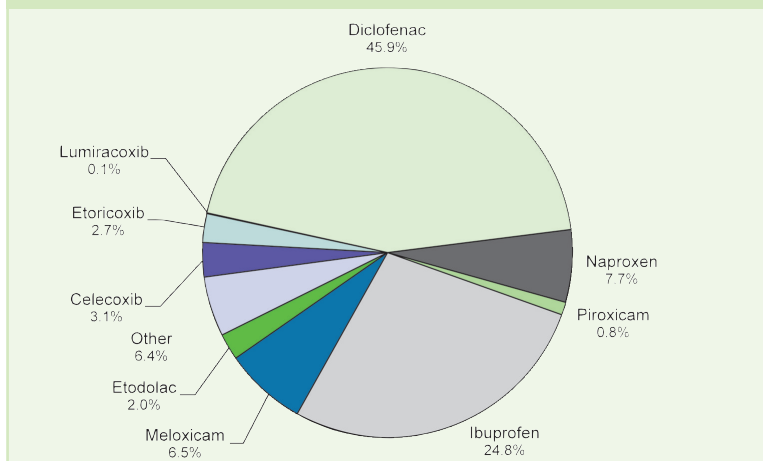
The absolute risk for individual patients depends on their baseline CV risk. All coxibs are now contraindicated for patients with established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.⁸

From a peak of more than five million items per quarter throughout 2004, prescribing of NSAIDs in primary care in England has fallen to 4.3 million items in the first quarter of 2007/2008.⁹ Coxibs account for 6% of these items (see **Figure 1**) and etodolac/meloxicam 8%. Assuming that each prescription is for 28 days and that prescribing continues in the same group of patients over the quarter, about 80,000 people in England are taking a coxib. Assuming a risk of three extra thrombotic events per 1000 users per year (or one per 4,000 users per month), this means that the prescribing of coxibs may be responsible for approximately 240 additional or premature CV events per year in England alone compared to no treatment. This estimate assumes that patients in clinical practice are at the same baseline risk of CV events as those involved in clinical trials.

The evidence is less clear regarding the CV risk of other NSAIDs. However, following a review in October 2006, the Commission on Human Medicines (CHM) advised that there was sufficient evidence to suggest that traditional NSAIDs may also be associated with a small increased risk of thrombotic events when used at high doses and for long-term treatment.¹⁰ Furthermore, they identified that not all traditional NSAIDs carried the same CV risk:

- Naproxen 1000mg/day may be associated with a lower risk of thrombotic events than coxibs. Although some risk with naproxen can not be entirely ruled out, epidemiological evidence suggests that naproxen is not associated with an excess risk of myocardial infarction (MI).^{8,10}
- Ibuprofen may be associated with a small thrombotic risk at high doses (e.g. 2400mg/day), whereas at low doses (e.g. 1200mg/day) evidence does not suggest an increased thrombotic risk in the short-term¹⁰
- Diclofenac 150mg/day has a thrombotic risk profile similar to that of etoricoxib* 60mg or 90mg/day, and possibly other coxibs.¹⁰

Figure 1. The prescribing of NSAIDs in England from April to June 2007: % total items (4.3 million)⁹



The MA by Kearney and colleagues quantified the RRs of vascular events versus placebo as 1.63 (95%CI 1.12 to 2.37) for diclofenac, 1.51 (95%CI 0.96 to 2.37) for ibuprofen and 0.92 (95%CI 0.67 to 1.26) for naproxen. The RR for vascular events for coxibs (combined) was 1.42 (95%CI 1.13 to 1.78).⁶

Epidemiological evidence also suggests that diclofenac is associated with an elevated risk of MI compared with non-use that is similar to that of the coxibs. An MA of 13 observational studies in 2006 identified the RRs for MI from diclofenac, naproxen or ibuprofen compared with non-use as 1.35 (95%CI 1.24 to 1.47), 1.02 (95%CI 0.92 to 1.13), and 1.11 (95%CI 1.01 to 1.22), respectively. [Personal communication, MHRA, August 2007] There were insufficient data to establish if there was any dose effect, although studies examining low doses of ibuprofen did not identify any increased risk of MI. For comparison, an MA of case-control and cohort studies, which identified similar increases in risks for CV events for diclofenac as the Medicines and Healthcare Products Regulatory Agency (MHRA) MA, found the RR of CV events for rofecoxib compared with non-use as 1.35 (95%CI 1.15 to 1.59).⁷

The MEDAL programme (three RCTs, n=34,701) found rates of CV events for etoricoxib 60mg or 90mg/day and diclofenac 150mg/day of 1.24 and 1.30 per 100 patient-years, respectively (hazard ratio [HR] 0.95, 95%CI 0.81 to 1.11).¹¹ Although a placebo was not included in the studies, the rate of these events appeared similar to that of other coxibs.¹² Importantly, this study showed that the risk of thrombotic events was constant over time (up to about two years) for both drugs, i.e., there was no safe period over which there was no increased risk of events for either drug. This has important implications when considering the population CV risk resulting from diclofenac use (see below), as prescribing data suggest that many patients take the drug for short-periods of time. For example, in the year from July 2005, of the 3.5 million patients who were prescribed diclofenac, 80% received three or fewer prescriptions. [Personal communication, MHRA, August 2007]

Diclofenac accounted for 46% of all NSAID prescribing (1.96 million items) in primary care in England in the first quarter of 2007/2008 (see **Figure 1**).⁹ Assuming these prescriptions were for 28 days this equates to nearly 8 million treatment months. If the excess risk for CV events is the same as coxibs (three per 1000 patients per year, or one per 4,000 patients taking diclofenac for a month) then approximately 2000 additional or premature CV events per year could be caused by diclofenac prescribing, compared with no treatment. However, this is likely to be an overestimate of risk as many patients who take short-term diclofenac may be suffering from acute musculo-skeletal conditions rather than chronic arthritis, and might

not have the same baseline risk of CV events as those patients seen in clinical trials. On the other hand, some patients will have a greater baseline risk than those included in the RCTs since patients recruited to RCTs are generally younger and have fewer co-morbidities. In addition, the absolute risk for diclofenac at doses less than 150mg/day remains uncertain.

Does ibuprofen interfere with the cardio-protective effect of aspirin?

Although there is ex-vivo evidence of an interaction between aspirin and ibuprofen, there is inadequate clinical evidence to suggest that there is a loss in the cardioprotective effect of aspirin when given with ibuprofen.^{8,13} The US Food and Drug Administration (FDA) advises that when used together the doses of ibuprofen and aspirin should be staggered to minimise any interaction (e.g., ibuprofen at least 30 minutes after and 8 hours before aspirin).¹³ The MHRA and other EU Regulators keep this issue under continual review; however, in view of the lack of supportive clinical evidence no updated prescribing advice has been issued in Europe.

Cardiorenal effects

Cardiorenal effects of NSAIDs (e.g. oedema, hypertension, heart failure) may be important contributors to long-term CV risk; however, current evidence does not suggest that COX-2 selectivity per se is an important determinant of risk.⁹ Clinical studies suggest that individual NSAIDs may differ in their cardiorenal effect. The MEDAL program suggests that etoricoxib 60mg or 90mg/day may be associated with a poor cardiorenal profile relative to diclofenac 150mg/day,^{8,11} whereas the CLASS study suggests that high-dose ibuprofen (2400mg/day) may have an inferior cardiorenal profile relative to celecoxib.⁸

GI risk

All NSAIDs carry a risk of GI side effects, which can be serious and life threatening. Options to reduce the risk of GI complications include use of non-drug therapies, alternative analgesia (e.g. paracetamol), co-prescription of a gastro-protectant, using an NSAID with a lower risk or GI side effects, and/or prescribing the lowest possible dose of NSAID for the shortest possible time. There is limited evidence on the value of

Not all traditional NSAIDs carry the same CV risk

Compared to no treatment, approximately 2000 additional or premature CV events per year could be caused by diclofenac prescribing

Footnote: The classification of NSAIDs

The classification of NSAIDs is controversial, often guided by historical development rather than clinical effect, and can be confusing. Different NSAIDs differ in their COX-2/COX-1 selectivity; however, the measured degree of selectivity can depend on the assay system used. Furthermore, clinical effects are subject to variability from patient to patient.⁴ Traditional (sometimes called standard) NSAIDs (e.g. diclofenac, ibuprofen, naproxen) differ considerably in the degree of selectivity. Etoricoxib and meloxicam, although sometimes termed partially selective and categorised with traditional NSAIDs as non-selective, were included alongside the newer 'coxibs' (e.g. rofecoxib, celecoxib, etoricoxib) in the NICE technology appraisal of selective COX-2 inhibitors.⁵ Arguably, diclofenac might also be considered together with this class as, unlike ibuprofen and naproxen, it preferentially inhibits COX-2 rather than COX-1.⁴ The Medicines and Healthcare products Regulatory Agency (MHRA) include only the 'coxibs' in their definition of selective COX-2 inhibitors, and it is important to note that the evidence-base for relative GI and CV safety relates largely to the coxibs.

On 19th November 2007 the Medicines and Healthcare products Regulatory Agency suspended the marketing authorisation for lumiracoxib with immediate effect. This follows interim advice restricting its use earlier in 2007 following safety concerns about liver damage.

Greater use of a PPI with any NSAID reduces the risk of adverse GI side effects

enteric-coating of NSAIDs, but it appears ineffective for aspirin.¹⁴ The evidence for *H. pylori* eradication is contradictory.¹⁵

Of the commonly used traditional NSAIDs, ibuprofen appears to be associated with the lowest risk of GI side effects.¹⁶ There is a widely held view that naproxen is associated with a greater GI risk than diclofenac. However the evidence supporting this assertion is not strong and there are no comparative RCTs. An MA of RCTs identified no apparent difference in the rates of GI complications between diclofenac and naproxen. The risk relative to non-users was 1.83 (95%CI 1.25 to 2.68) for naproxen, 1.73 (95%CI 1.21 to 2.46) for diclofenac and 1.19 (95%CI 0.93 to 1.54) for ibuprofen.¹⁷ However, an MHRA GI safety review in 2005 found that the majority of epidemiological evidence and reports of spontaneous adverse drug reactions suggest that naproxen is associated with a higher GI risk than diclofenac. [Personal communication, MHRA. October 2007]. An MA of three retrospective case-control studies in Spain, England and Scotland, and Sweden identified the odds ratios (OR) for serious upper GI events as 1.7 (95%CI 1.1 to 2.5) for ibuprofen, 4.9 (95%CI 3.3 to 7.1) for diclofenac, and 9.1 (95%CI 6.0 to 13.1) for naproxen.¹⁸ Across the entire NSAID class, risk was greatest during the first week of use (OR 11.7, 95%CI 6.5 to 21.0), decreased thereafter with continuing use (OR 5.6, 95%CI 4.6 to 7.0), and was reduced one week after discontinuing use (OR 3.2, 95%CI 2.1 to 5.1).

Expectations that coxibs would eliminate the GI side effects associated with the use of traditional NSAIDs have not been fulfilled. Coxibs are also associated with serious and sometimes fatal GI reactions. Nevertheless, there is reasonable evidence to suggest that coxibs (when considered as a class) are associated with a reduction in the risk of GI symptoms and complications compared with traditional NSAIDs.

A recent Cochrane Collaborative systematic review of eight studies (n=73,449) found that, compared with non-selective NSAIDs, coxibs produced significantly fewer clinically important ulcer complications (RR 0.39, 95%CI 0.31 to 0.50), with an absolute risk reduction of 0.4%.¹⁹ There are no good long-term RCTs comparing the GI safety of meloxicam or etodolac with traditional NSAIDs.

As with traditional NSAIDs, it is possible that individual coxibs may vary in their propensity to cause GI effects, and the effects may vary with dose and duration of treatment. However, there are no studies that directly compare the GI risk of coxibs. In the CLASS study, celecoxib 800mg/day did not demonstrate a statistically significant advantage over either diclofenac 150mg/day or ibuprofen 2400mg/day for the primary endpoint of complicated ulcers.² In the MEDAL programme, rates of upper GI events

(perforation, obstruction, bleeding, ulcer) were lower with etoricoxib 60mg or 90mg/day than diclofenac 150mg/day (0.67 vs. 0.97 per 100 patient years, HR 0.69, 95%CI 0.57 to 0.83), but the rate of complicated GI events were similar (0.32 vs. 0.30 per 100 patient years, respectively).¹¹

The Cochrane Collaborative review¹⁹ also considered subgroups of patients in clinical trials who received aspirin with NSAIDs. Patients (n>21,000) receiving both coxibs and aspirin were at a significantly greater risk of ulcer complications than those taking coxibs but not taking concomitant aspirin (RR 4.12, 95%CI 2.40 to 7.06), whereas coadministration of aspirin did not have a significant effect on the GI risk of traditional NSAIDs (RR 1.27, 95%CI 0.88 to 1.83).¹⁹

What about gastroprotection?

There is evidence from observational studies that the use of a proton pump inhibitor (PPI) in combination with an NSAID is associated with a significant reduction in upper GI ulcers and complications compared with NSAID treatment alone. For example, a Canadian retrospective cohort study of 332,491 patients aged 65 years or older found that the rate of hospital admissions for GI perforations or bleeding for those receiving a PPI plus NSAID was approximately half that of those receiving an NSAID alone (HR 0.47, 95%CI 0.32 to 0.69).²¹

A case-control study in Spain found that the use of an NSAID plus a PPI was associated with a lower risk of GI complications than an NSAID alone. The study, which reviewed the cases of 2777 patients admitted to hospital with major upper GI bleeding, identified a RR of 5.3 (95%CI 4.5 to 6.2) for current NSAID use compared to non-use, whereas there was no increased risk when using an NSAID plus PPI (RR 0.9, 95%CI 0.7 to 1.3).²²

An MA of four RCTs (duration 12 to 24 weeks) identified a RR for dyspeptic symptoms with an NSAID plus PPI compared with NSAID alone of 0.34 (95%CI 0.22 to 0.54 — a number needed to treat [NNT] of 11).²³

An RCT of 224 patients with a history of NSAID-related complicated peptic ulcers found no significant difference in the proportion of patients who developed recurrent ulcer complications on celecoxib or on naproxen plus PPI (lansoprazole) (4% vs. 6%, respectively, P=0.37). However, significantly more patients receiving celecoxib developed dyspepsia (15% vs. 6%, P=0.02) than those taking naproxen plus PPI.²⁴

Two RCTs of similar design (n=844 and 585) studied the effect of giving a PPI (esomeprazole 20 or 40mg) to people who were currently taking NSAIDs (including coxibs) who were at significant risk of GI ulcers (age 60 years or older and/or a history of gastric or duodenal

ulcers). After a period of 6 months, a pooled analysis demonstrated significantly fewer ulcers in those receiving either dose of PPI with coxibs and other NSAIDs compared with placebo (see **Table 1**).¹

Table 1. The development of gastric or duodenal ulcers in high-risk patients prescribed NSAIDs with or without esomeprazole¹

	Proportion of patients developing gastric or duodenal ulcers (95%CI):		
	Placebo	Esomeprazole 20mg	Esomeprazole 40mg
Coxibs	16.5% (9.7 to 23.4)	0.9% (0.0 to 2.6)*	4.1% (0.6 to 7.6)**
Other NSAIDs	17.1% (12.6 to 21.6)	6.8% (3.9 to 9.7)*	4.8% (2.3 to 7.2)*

*P vs. placebo <0.001; **P vs. placebo =0.002

In an RCT of 273 patients at very high risk of recurrent ulcer bleeding, celecoxib (200mg twice a day) plus PPI (esomeprazole 20mg twice a day) was compared with celecoxib alone. Over 13 months, there was a 9% recurrence rate of ulcers in the celecoxib group, whereas there were no recurrent ulcers in the group receiving celecoxib plus PPI (P=0.0004).²⁵ This study highlights the importance of providing gastroprotection if coxibs are used in patients at high GI risk.

The benefits from gastroprotection largely depend on the individual patient's baseline risk of GI complications. There is, at present, no good evidence that a coxib plus PPI is more beneficial, equivalent or a worse option for preventing GI complications over the use of a traditional NSAID plus PPI. There is also no good evidence to suggest that any PPI is more effective than another and prescribers should use the least expensive option.²⁶

The draft NICE guideline for adults with osteoarthritis suggests that, when offering treatment with an NSAID, all patients at low GI risk under the age of 65 should be offered a standard NSAID (not a coxib), co-prescribed with a PPI. Patients with any GI risk factors (including those aged over 65 years) may be offered a coxib (other than etoricoxib) co-prescribed with a PPI or a standard NSAID co-prescribed with a PPI.¹

Medication audit

Recent audit data from one Primary Care Trust in England in March 2007 (data on file), if typical of UK prescribing as a whole, indicate that a significant proportion of patients may be being prescribed NSAIDs inappropriately. Of the 4% of patients (range 2 to 8%) older than 75 who were taking NSAIDs on a long term basis, approximately:

- 40% had hypertension
- 20% had a history of CV disease or heart failure

- 20% had existing renal disease
 - Only 35% were prescribed gastroprotection
- Overall, of patients older than 75 who were taking NSAIDs long-term, 21% had contraindications to NSAIDs, and a further 52% required a risk assessment.

What does this mean in practice?

All NSAIDs carry a risk of serious side effects. To minimise the risk to an individual where an NSAID is required, the lowest effective dose should generally be used for the shortest time necessary to control symptoms, and the need for long-term treatment should be reviewed regularly. Prescribing should be based on the safety profiles of individual NSAIDs and on individual patient risk factors (including both GI and CV risk).¹⁰

Gastroprotection with a PPI should be considered for all patients who are at high risk of GI complications and who require any NSAID.¹ These include patients aged 65 years or older, those with a past history of peptic ulcer disease or serious GI complications, those receiving concomitant medications known to increase the likelihood of upper GI complications (e.g. steroids and anticoagulants), and those with serious comorbidity (including CV disease, renal or hepatic impairment, diabetes or hypertension).⁵ CKS guidance suggests that full dose misoprostol (800micrograms/day) is an alternative to a PPI.²⁷

Coxibs, because of their risk of adverse CV effects, would appear to have a limited role in clinical practice - they are inappropriate to prescribe to patients who require aspirin for prophylaxis of CV disease because any GI benefits compared to traditional NSAIDs are diminished when they are co-prescribed with aspirin, and they are contraindicated in patients with existing coronary, cerebrovascular or peripheral artery disease. Co-prescription of a traditional NSAID with a PPI appears at least as effective as a coxib alone in reducing GI side effects, and is a less expensive option. The NICE draft guidance for osteoarthritis suggests coxibs in combination with a PPI as an option for people at high risk of GI disease.¹ However, there is, as yet, no good evidence to suggest this approach more beneficial, equivalent or a worse option than traditional NSAIDs plus PPI with regard to GI side effects. Compared with low-dose ibuprofen or naproxen, use of a coxib may put the patient at greater risk of a CV event.

Low dose ibuprofen (400mg three times a day) is an appropriate first choice NSAID in view of its low CV and GI risks at this dose. The risk of GI effects can be reduced still further by co-prescription of a PPI. Naproxen 1000mg/day is an alternative to ibuprofen 1200mg/day and may be preferable to NSAIDs other than ibuprofen 1200mg/day in patients at significant risk of adverse CV effects. Co-prescription of a PPI

Prescribing of NSAIDs should be based on the safety profiles of individual NSAIDs and on individual patient risk factors

All NSAIDs should be prescribed at the lowest possible dose and for the shortest possible time

Prescribing of diclofenac should be reviewed in patients at risk of CV disease

seems advisable especially in patients at particular risk of serious GI effects. The apparently increased rate of CV events with diclofenac and high dose ibuprofen suggests that, like coxibs, these are less appropriate options for patients in whom CV risk is a significant consideration in decision making.

The high use of diclofenac in the UK indicates a need for reconsideration of its use ahead of low-dose ibuprofen or naproxen (with a PPI if appropriate), in people at significant risk of CV disease who require an NSAID. Current advice from the CHM is that patients should not switch between NSAIDs without careful consideration of the overall safety profile of the products and a patient's individual risk factors and preferences.¹⁰ Although the risks to an individual may be low, when used widely in the population the NSAID-related GI and CV effects constitute significant risks and at the next routine review the choice of NSAID should be reviewed.

The ideal anti-inflammatory prescribing choice will vary from patient to patient, depending on individual risk factors, therapeutic response and individual attitude to increased GI and CV risks with medication. Patients should use the lowest effective dose, and the shortest duration of therapy necessary to control symptoms.

When reviewing the treatment of patients already receiving diclofenac, some patients, after discussion, may decide to continue treatment. However, in some cases (especially patients with significant risk factors for CV disease) it may be appropriate to consider alternatives:

- Patients who change from diclofenac 150mg/day to ibuprofen 1200mg/day would probably reduce both their GI and CV thrombotic risk, especially if the opportunity is taken to introduce a PPI. However, the BNF states that 1600mg to 2400mg daily of ibuprofen is required for conditions where inflammation is prominent. High doses of ibuprofen (e.g. 2400mg/day) are not prescribed frequently in clinical practice, and the relative cardiovascular risks of such doses versus diclofenac 150mg/day are unclear.
- Patients who change from diclofenac 150mg/day to naproxen 1000mg/day would reduce their CV thrombotic risk, but may slightly increase their risk of GI complications. However, if the opportunity is taken to introduce a PPI, the GI risks may also be reduced. There is less evidence for the balance of risks with lower doses of diclofenac and naproxen.

References

1. National Institute for Health and Clinical Excellence. Osteoarthritis: the care and management of osteoarthritis in adults. Draft full guideline. July 2007. Accessed from <http://guidance.nice.org.uk/page.aspx?o=440442> on 08/07/2007
2. Chou R, Helfand M, Peterson K, et al. Comparative effectiveness and safety of analgesics for osteoarthritis. Agency for Healthcare Research and Quality Publication No. 06-EHC009-EF. September 2006. Accessed from www.ahrq.gov on 15/05/07
3. European Medicines Agency. Public CHMP assessment report for medicinal products containing non-selective non-steroidal anti-inflammatory drugs (NSAIDs). EMEA/CHMP/442130/2006. November 2006. Accessed from <http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf> on 16/05/07
4. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase 2. *New Engl J Med* 2001;345:433-42
5. National Institute for Clinical Excellence. Guidance on the use of cyclooxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. Technology Appraisal Guidance No. 27. July 2001. Accessed from <http://guidance.nice.org.uk/TA27/guidance/pdf/English> on 16/05/07
6. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase 2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? A meta-analysis of randomised trials. *BMJ* 2006;332:1302-5
7. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase. A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296:1633-44
8. Medicines and Healthcare products Regulatory Agency. Cardiovascular safety of COX-2 inhibitors and non-selective NSAIDs. Accessed from www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON019582 on 18/10/07
9. Prescription Pricing Division, Business Services Authority. ePACT data. Accessed from www.epact.ppa.nhs.uk on 22/08/07
10. Duff G, Chaiman, Commission of Human Medicines. Safety of selective and non-selective NSAIDs. Letter. October 2006. Accessed from www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON1004257&ssSourceNodeid=227&ssTargetNodeid=221 on 15/05/07
11. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;368:1771-81
12. Garcia Rodriguez LA, Patrignani P. The ever growing story of cyclo-oxygenase inhibitors. *Lancet* 2006;368:1745-7
13. US Food and Drug Administration. Center for Drug Evaluation and Research. New information for healthcare professionals Concomitant use of ibuprofen and aspirin. September 2006. Accessed from http://www.fda.gov/cder/drug/InfoSheets/HCP/ibuprofen_aspirinHCP.htm on 21/06/07
14. Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413-6
15. Anon. *H pylori* eradication in NSAID-associated disorders. *DTB* 2005;43:37-40
16. McCarthy DM. Comparative toxicity of nonsteroidal anti-inflammatory drugs. *Am J Med* 1999;107:37S-47S
17. Richey F, Bruyere O, Ethgen O, et al. Time dependent risk of GI complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. *Ann Rheum Dis* 2004;63:759-66
18. Lewis SC, Langman MJS, Laporte J-R, et al. Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002;54:320-6
19. Rostom A, Muir K, Dube C, et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane collaboration systematic review. *Clin Gastroenterol Hepatol* 2007;5:818-28
20. Schnitzer TJ, Burmester GR, Mysler E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004;364:665-74
21. Rahme E, Bardou M, Dasgupta K, et al. Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study. *Rheumatology* 2007;46:265-72
22. Lanas A, Garcia-Rodriguez LA, Arroya MT, et al. 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;55:1731-8
23. Spiegel BMR, Farid M, Dulai GS, et al. Comparing rates of dyspepsia with coxibs vs NSAID+PPI: a meta-analysis. *Am J Med* 2006; 119: e27-36
24. Lai K-C, Chu K-M, Hui W-M, et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *Am J Med* 2005;118:1271-8
25. Chan FKL, Wong VWS, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* 2007;369:1621-6
26. National Prescribing Centre. The management of dyspepsia in primary care. MeReC Briefing 2006;32:1-8. Accessed from http://www.npc.co.uk/MeReC_Briefings/2006/dyspepsia_briefing_no_32.pdf on 08/07/07
27. CKS. Nonsteroidal anti-inflammatory drugs (NSAIDs) (Topic Review). 2007. Accessed from http://cks.library.nhs.uk/nonsteroidal_anti_inflammatory_drugs_nsaids on 18/10/07

Update on the CV risk of glitazones

In *MeReC Extra 29* (August 2007) we reviewed the concerns over the cardiovascular (CV) safety of rosiglitazone. These arose from a meta-analysis (MA) of 42 randomised controlled trials (RCTs) (n=27,843) by Nissen and Wolski.¹ Although the methodology of this MA has been questioned,² its results are consistent with another recently published MA of four RCTs (n=14,291) with at least 12 months follow up³ and an independent analysis by the US Food and Drug Administration (FDA), which included 42 short-term trials (n=14,237).^{4,5} The FDA analysis identified an increased risk of myocardial ischaemic events (serious and non-serious) for rosiglitazone compared with controls (odds ratio [OR] 1.4, 95%CI 1.1 to 1.8; P=0.02), although effects for serious ischaemic events did not reach statistical significance (OR 1.4, 95%CI 1.0 to 2.1, P=0.06).⁵ An FDA Advisory Committee, convened to consider the issue, concluded that rosiglitazone was associated with a greater risk of myocardial ischaemic events than placebo, metformin and sulfonylureas, and suggested measures to increase awareness of the increased risk.⁵

CV disease is by far the most common cause of death among people with diabetes⁶ and an effective antidiabetic drug would be expected to reduce long-term macrovascular complications, as was the case for metformin in the UKPDS.⁷ None of the MAs suggests that a reduction in CV risk with rosiglitazone is likely.

What about pioglitazone and CV risk?

Published data so far suggests that pioglitazone may offer less CV risk than rosiglitazone. A recent MA (19 RCTs, n=16,390) identified a statistically significantly lower risk for the combined outcome of death, myocardial infarction (MI) or stroke (4.4% vs. 5.7%; HR 0.82, 95%CI 0.72 to 0.94, P=0.005) for pioglitazone compared with controls (placebo or alternative oral antidiabetic therapy), but not for the individual outcome components.⁸ A retrospective cohort study (n=29,911) found that pioglitazone was associated with a lower risk of hospitalisation for

MI than rosiglitazone (1.1% vs. 1.4%, adjusted HR 0.78, 95%CI 0.63 to 0.96).⁹

But don't forget the risk of heart failure

There is consistent evidence that both rosiglitazone and pioglitazone can cause weight gain, fluid retention, and lead to new or worsening heart failure. This is not a rare occurrence, and it can be serious and sometimes fatal.⁴ A recent MA of seven RCTs found that pioglitazone or rosiglitazone increased the risk of congestive heart failure compared with controls (placebo or another oral antidiabetic agent) across a wide range of cardiac risk, with no heterogeneity between studies (relative risk [RR] 1.72, 95%CI 1.21 to 2.42, P=0.002).¹⁰ However, there was no increased risk of cardiovascular death (RR 0.93, 95%CI 0.67 to 1.29; P=0.68). Another MA of three RCTs (n=10,731) estimated that about 1 in every 50 patients taking a glitazone for 26 months would experience heart failure compared with those taking placebo or another oral antidiabetic agent.¹¹

EMA review of risk-benefit

In October 2006, after a review of the available clinical trial data, glitazone product information for prescribers and patients was updated to reflect more fully the risk of heart failure and to include a warning about the potential small increased risk of MI in patients receiving rosiglitazone compared with those receiving placebo. A year later, following a Europe wide review, the European Medicines Agency (EMA) issued a statement, with the advice that the benefits of both rosiglitazone and pioglitazone in the treatment of type 2 diabetes continue to outweigh their risks. However, the statement goes on to say that prescribing information should be updated to include a warning that, in patients with ischaemic heart disease, rosiglitazone should be used only after careful evaluation of each patient's individual risk. In addition, the combination of rosiglitazone and insulin should be used only in exceptional cases and under close supervision.¹²

Pioglitazone may offer less CV risk than rosiglitazone. However, both pioglitazone and rosiglitazone are associated with an increased risk of heart failure

Drug safety e-bulletin from the MHRA

A new monthly electronic bulletin from the MHRA, Drug Safety Update, was launched in August. This contains a summary of the latest information and clinical advice from the MHRA and the Commission on Human Medicines, and replaces *Current Problems in Pharmacovigilance* that was previously sent in hardcopy to certain healthcare professionals. You can receive an e-mail notification when new issues are published by subscribing to the e-mail alerting service (http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodeld=340).

References

- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–71
- Diamond GA, Bax L, Kaul S. Uncertain effects of rosiglitazone on the risk of myocardial infarction and cardiovascular death. *Ann Intern Med* 2007;147:578–81
- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone. *JAMA* 2007;298:1189–95
- FDA Briefing Document. Division of Metabolism and Endocrine Products and Office of Surveillance and Epidemiology. Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. July 30, 2007. Accessed from www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf on 23/10/07
- Rosen CJ. The rosiglitazone story — lessons from an FDA advisory committee meeting. *N Engl J Med* 2007;357:844–6
- British Heart Foundation. Mortality from diabetes. Accessed from www.heartstats.org/datapage.asp?id=1113 on 23/10/07
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–65
- Lincoff AM, Wolski K, Nicholls SJ, et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomised controlled trials. *JAMA* 2007;298:1180–8
- Gerrits CM, Bhattacharya M, Manthena S, et al. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. *Pharmacoeconom Drug Saf* 2007;16:1065–71
- Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised controlled trials. *Lancet* 2007;370:1129–36
- Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure. A teleo-analysis. *Diabetes Care* 2007;30:2148–53
- Medicines and Healthcare products Regulatory Agency. Press statement: Europe wide review confirms positive benefit-risk balance for rosiglitazone and pioglitazone. Accessed from www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2032783&ssTargetNodeld=387 on 23/10/07

The ADVANCE study

Lowering blood pressure saves lives in people with type 2 diabetes

What does this study claim?

The ADVANCE study examined the effect of a fixed dose combination of an angiotensin converting enzyme inhibitor (ACEI) and a diuretic on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus.¹ The combination showed some benefits over placebo and is being suggested by the authors and the media as the preferred regimen in such patients.^{1,2} Are these claims justified?

What were the details of the study?

This was an RCT of 11,140 patients aged 55 years and older with type 2 diabetes. Patients also had either a history of CV disease (including stroke and MI) or at least one other CV risk factor (e.g. age \geq 65 years, smoking, history of major microvascular disease). Active treatment with a combination of perindopril and indapamide (initially 2mg/0.625mg, doubled to 4mg/1.25mg after 3 months) was compared with placebo. While taking the combination during the run-in phase, 1,737 other recruited patients withdrew, at least 29% of these due to adverse effects. The primary endpoints were composites of major macrovascular events (death from CV disease, non-fatal stroke or non-fatal MI) and major microvascular events (new or worsening renal disease or new or worsening diabetic eye disease), analysed jointly and separately.

After 4.3 years, the combined endpoint of major macrovascular and microvascular events was reduced by 1.3% (number needed to treat [NNT]=77; relative risk reduction [RRR] 9%, 95%CI 0% to 17%; P=0.04). However, when major macrovascular events or major micro-

vascular events were analysed separately, differences were not statistically significant. Death from CV disease was significantly reduced by 0.8% (NNT=125 over 4.3 years; RRR 18%, 95%CI 2% to 32%; P=0.03) and death from any cause was reduced by 1.2% (NNT= 83; RRR 14, 95%CI 2% to 25%; P=0.03).

How does this relate to existing evidence?

The United Kingdom Prospective Diabetes Study has already shown that tight blood pressure control reduces the risk of macro-vascular and microvascular complications in type 2 diabetes.^{3,4} Similar evidence does not exist for tight control of blood glucose.⁵ NICE guidance for managing blood pressure in type 2 diabetes provides treatment thresholds, targets and advice on the choice of antihypertensive agent.⁶

So what?

The authors of the paper conclude that, "routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death". This is true. But the mean blood pressure in patients in the active arm was 5.6/2.2mmHg lower than that in patients in the placebo arm and this was highly statistically significant (p<0.0001). It is therefore possible that the differences observed were an effect of lower blood pressure rather than any drug specific action. It is also notable that the study did not set a blood pressure target but simply added in the study drugs to existing therapy.

Action

This study adds to the body of evidence that lowering blood pressure in patients with type 2 diabetes reduces CV complications and deaths. NICE guidance should be followed, with patients encouraged to try and control their blood pressure to national targets or as close to these as possible, while taking into account adverse effects and individual patient preferences and circumstances. Some have questioned the use of thiazides in people with type 2 diabetes.⁷ However, this study backs up advice from a recent *MeReC Bulletin* that, based on their safety, efficacy, tolerability and cost, thiazide diuretics are a good first choice agent for most people, including those with type 2 diabetes.⁸

This article is adapted from a blog on the recently launched NPCi website (www.npci.org.uk). NPCi is a new and radically different NHS learning resource designed specifically for busy health care professionals and managers. The content covers prescribing, therapeutics and medicines management. The information is contained within a virtual building, which makes searching via the lift simple and quick.

The blog provides a succinct commentary on a recent newsworthy health issue related to prescribing and medicines. It may be an important piece of evidence that may change our practice, or something that has been in the news headlines (but perhaps isn't so important, once carefully examined and set in the context of the rest of the evidence base).

The blog is written by the NPC team according to our in-house quality assurance procedure. There are lots of websites that highlight news items involving medicines, but not many set the evidence in context. We aim to do just that to help busy people concentrate on the information that matters to them as patients, healthcare professionals or managers.

Please visit the NPCi virtual building and try out our educational materials, including the blog (www.npci.org.uk/blog/). Also feel free to discuss this in our NPCi discussion rooms (www.npci.org.uk/discuss/) or give us feedback (www.npci.org.uk/feedback.php).

References

1. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial). *Lancet* 2007;370:829-40
2. Medical Editor. Cheap pill 'cuts death from diabetes'. Accessed from www.telegraph.co.uk/news/main.jhtml?xml=/news/2007/09/03/ndiabetic103.xml on 22/10/07
3. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703-13
4. Type 2 diabetes: the management of cardiovascular risk factors. MeReC Briefing 2004;26. Accessed from www.npc.co.uk/MeReC_Briefings/2003/briefing_no_26.pdf on 22/10/07
5. Type 2 diabetes: the management of blood glucose. MeReC Briefing 2004;25. Accessed from www.npc.co.uk/MeReC_Briefings/2003/briefing_no_25.pdf on 22/10/07
6. The National Institute for Health and Clinical Excellence. Management of type 2 diabetes – management of blood pressure and blood lipids (Guideline H). Accessed from <http://guidance.nice.org.uk/CGH/?c=91500> on 22/10/07
7. National Library for Health. Diabetes alert over blood pressure pills. Hitting the Headlines 18/02/04. Accessed from www.library.nhs.uk on 22/10/07
8. The management of hypertension in primary care: updated guidance from NICE. MeReC Bulletin 2006;17(1). Accessed from www.npc.co.uk/MeReC_Bulletins/MeReC_Bulletin_Vol17_Index.htm on 22/10/07

The National Institute for Clinical Excellence (NICE) is associated with MeReC Publications published by the NPC through a funding contract. This arrangement provides NICE with the ability to secure value for money in the use of NHS funds invested in its work and enables it to influence topic selection, methodology and dissemination practice. NICE considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery. This publication represents the views of the authors and not necessarily those of the Institute.