National Prescribing Centre

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MeReC Publications

A2RAs associated with an increased risk of cancer

A meta-analysis[1] of RCTs found that the risk of new cancer diagnoses increased in patients randomised to receive angiotensin-II receptor antagonists (A2RAs), compared with controls who were not taking them. This increase in absolute risk of cancer was 1.2% over an average of 4 years. However, even this relatively small absolute increase in risk could, **if true**, produce a large number of additional cancers given the large number of people taking A2RAs.

Action

Clinicians should review A2RA prescribing on an individual patient basis at the next routine appointment to ensure it is in line with NICE guidance. This meta-analysis provides a safety signal about a possible increased risk of associated cancer in people who are taking A2RAs, but this does not prove that A2RAs cause cancer. The finding of a 1.2% increase in the absolute risk of new cancer diagnosis over an average of four years needs to be interpreted in the context of the estimated 41% lifetime risk of cancer.

So what?

Regulatory authorities are examining these data to clarify whether there is an increased risk of cancer in patients taking A2RAs. In the meantime, this safety concern adds weight to the NICE recommendations that ACE inhibitors, not A2RAs, continue to be **the first-line choice when a renin-angiotensin system drug is indicated.** ACE inhibitors have a more robust evidence base than A2RAs for all indications in terms of evidence for efficacy, safety and most patient factors (e.g. dosing regimens, monitoring requirements). The major benefit of A2RAs over ACE inhibitors is a lower rate of cough. Hence, A2RAs are an alternative where a renin-angiotensin system drug is indicated, but an ACE inhibitor has to be discontinued because of an intolerable ACE inhibitor-induced cough.

For further details on this study and its limitations, see *MeReC Rapid Review Blog No. 1525*. More information on renin-angiotensin system drugs can be found on NPCi and in a recent *MeReC Bulletin*.

Reference

1. Sipahi I, et al. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncology 2010;11:627–36

CV risk of diclofenac similar to rofecoxib

A large cohort study[1] found that individual NSAIDs have different levels of CV risk. In particular, this study found that diclofenac and rofecoxib were associated with a similar increase in CV mortality and morbidity in healthy individuals. Naproxen was found to have a safer CV risk profile. Although this observational study has important limitations, these findings are similar to previously published evidence. Diclofenac is still the most widely prescribed of all NSAIDs (39% of all NSAID prescriptions in primary care in England). Therefore, this study re-emphasises the need for prescribers to regularly review patients treated with NSAIDs, particularly diclofenac.

Action

Health professionals should assess both the cardiovascular (CV) and gastrointestinal (GI) risks on an individual patient basis and carefully consider the balance between benefit and risk before starting treatment with any NSAID. However, this study re-emphasises that even in healthy individuals, diclofenac appears to be associated with increased CV risk, which may be similar to that of rofecoxib, while naproxen appears to be associated with lower CV risk than other NSAIDs. Prescribers should continue to review their prescribing of all NSAIDs, particularly diclofenac, and follow our previous recommendations given in *MeReC Extra 30*.

All information was correct at the time of publication (August 2010)

So what?

Despite its limitations, this was a very large, well conducted study, which supports the findings from RCTs and other observational studies. The MHRA has previously advised that diclofenac has a CV thrombotic risk profile similar to that of licensed doses of etoricoxib▼, and that naproxen is associated with a lower risk than coxibs. This study suggests that even short-term NSAID use increases CV risk, which supports the MHRA view that some increase in CV risk may apply to **all NSAID users, irrespective of their baseline CV risk, and not only to chronic users**. However, the increase in absolute risk for an individual 'healthy' user is very low.

Over recent years there have been encouraging trends in NSAID prescribing showing a reduction in the overall volume of prescribing, a significant decline in diclofenac prescribing and a significant increase in the proportion of naproxen prescribing (see **Figure 1** below). However, diclofenac is still the most commonly prescribed NSAID (39% of all NSAID prescriptions in primary care in England). This may potentially expose a substantial number of individuals to the risk of CV adverse events, as we have discussed previously.

Figure 1. The proportions of NSAIDs prescribed in general practice in England December 2005 to November 2006, compared with December 2008 to November 2009.

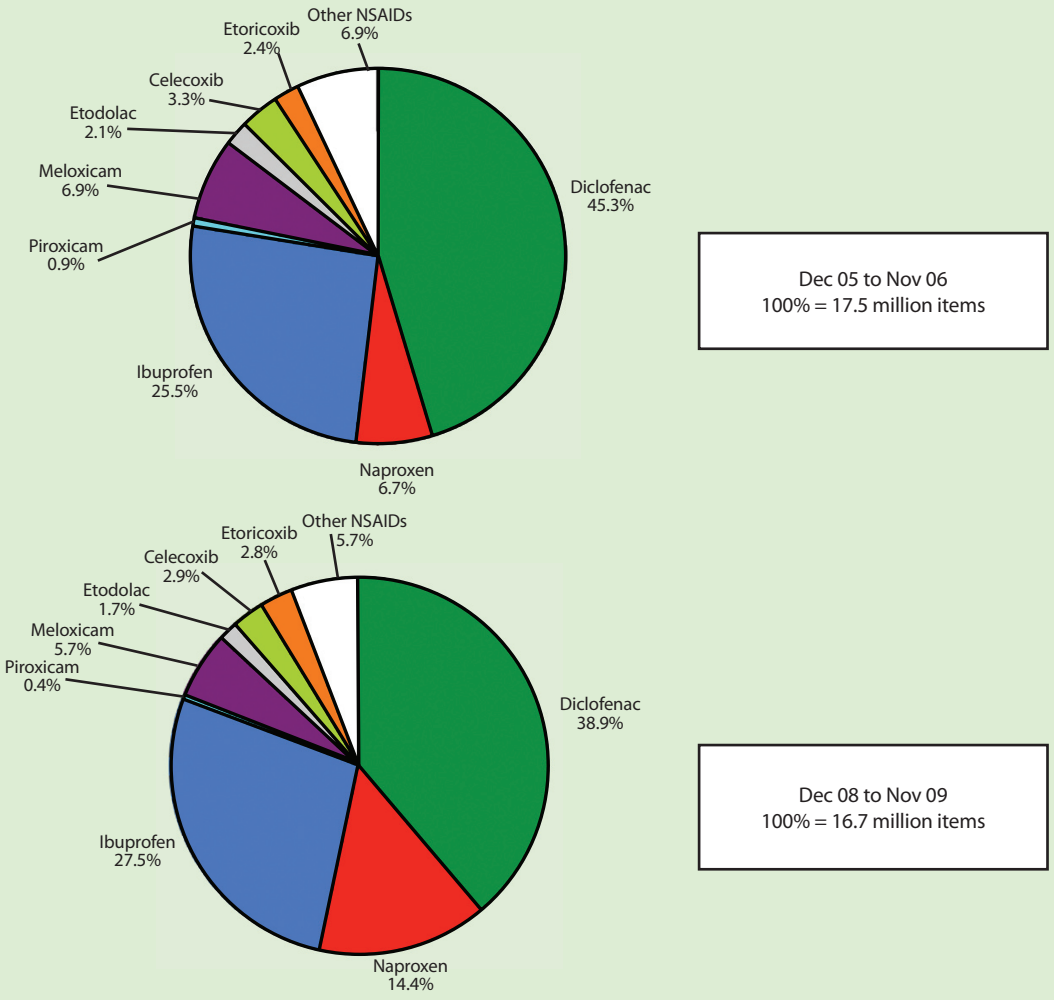

Figure prepared from data supplied by NHS Business Services Authority

See *MeReC Rapid Review Blog No. 1597* for further details on this study. More background information on the CV and GI safety of NSAIDs can be found in *MeReC Extra 30* and on the musculoskeletal pain floor of NPCi.

Reference

1. Fosbøl EL, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes 2010;3:395–405

Fewer GI events (mainly anaemia) with celecoxib vs. diclofenac plus PPI, but no difference in GI complications

The CONDOR study[1] found a lower risk of clinically significant GI events with celecoxib compared with diclofenac plus a PPI. However, this result was entirely driven by differences in the rates of anaemia (mainly of presumed occult GI origin). Rates of GI haemorrhage, obstruction or perforation were identical between the two treatments. Taking into account the increased CV risks of many NSAIDs, including celecoxib and diclofenac, using lower dose ibuprofen or naproxen, plus a PPI is likely to present the lowest overall risk of serious adverse events for most patients.

Action

This study does not change recommendations for practice. Health professionals should continue to follow existing NICE and other guidance and use a proton pump inhibitor (PPI) for gastroprotection in obligate NSAID users, especially those at increased risk of adverse GI events. The MHRA has warned about an increased risk of CV events with coxibs (including celecoxib) and many traditional NSAIDs (including diclofenac). Considered together, if an NSAID is essential, the lowest GI and CV risks are associated with ibuprofen 1200mg/day or less, especially if a PPI is co-prescribed. The next lowest CV and GI risks overall are probably associated with naproxen 1000mg/day plus a PPI. There is no robust evidence that prescribing a coxib plus a PPI offers any significant advantage over prescribing a traditional NSAID plus a PPI in preventing GI complications.

What are the limitations of this study?

This study has a number of limitations. In particular, anaemia, the main driver of the composite outcome, is not a true patient-oriented outcome (POO); it does not provide **direct** evidence as to whether or not patients are likely to live longer or better with one treatment rather than the other. Further studies are required to identify whether these differences in anaemia translate into POOs.

See *MeReC Rapid Review Blog No. 1630* for further details. More information on NSAIDs and gastroprotection can be found on the musculoskeletal pain floor of NPCi.

Reference

1. Chan FKL, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet 2010;376:173–79

New antiplatelets floor on NPCi — why not take a look?

A new suite of rooms, which discusses antiplatelet treatment for the primary and secondary prevention of CV disease, is now available on NPCi.

The materials include a <60minute eLearning event, two sets of key slides, a quiz, two case studies, a data focussed commentary and two patient decision aids. In addition, the library contains details of MeReC publications relating to antiplatelet treatment. We continue to develop materials for NPCi, and are continually updating existing materials.

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