

MEDICAL RESEARCH COUNCIL PRESS RELEASE

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SMALL INCREASE IN HEART RISK FROM COMMON PAINKILLERS

New study provides clarification about the risks of prolonged use of NSAIDs

With prolonged use, some widely used painkillers called non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of heart attacks by a small but significant amount, according to research published online in today's *The Lancet*.

The large international study was funded by the Medical Research Council and the British Heart Foundation, and coordinated by researchers at the MRC Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) at the University of Oxford.

The study found that high doses of diclofenac and ibuprofen increased the risk of a major vascular event (heart attack, stroke or dying from cardiovascular disease) by around one third. Most of this additional risk was due to an increased risk of heart attacks.

In contrast, high doses of naproxen did not appear to increase the risk of heart attacks. The researchers say this may be because naproxen also has protective effects that balance out any extra risk of heart attacks.

Concerns about the possible heart risks of NSAIDs, many of which have been on the market for several decades, arose after randomised trials showed that a newer class of NSAIDs known as COX-2 inhibitors or coxibs increased the risk of heart attacks.

Professor Colin Baigent, the MRC scientist who led the research at the University of Oxford, said: "The research shows that, when used in high doses, diclofenac and ibuprofen increase the risk of cardiovascular disease, on average causing about 3 extra heart attacks a year in every 1000 patients treated, one of which would be fatal.

"We would emphasise that the risks are mainly relevant to people with arthritis who need to take high doses over a long period. A short course of lower dose tablets purchased without a prescription, for example, for a muscle sprain, is not likely to be hazardous."

The research also showed that the risks of ulcer bleeding were increased by between 2- and 4-fold, depending on the NSAID regimen, but the consequences of such bleeding were not usually serious.

The study team gathered detailed data, including information on admissions to hospital for cardiovascular or gastrointestinal disease, from all randomised trials that have previously tested NSAIDs. The researchers brought together the results of 639 randomised trials involving over 300,000 people, and re-analysed the data in order to predict the magnitude of the adverse effects of NSAIDs in particular types of patients.

The availability of detailed data from so many studies allowed the researchers to predict accurately the size of any increased risk of heart attacks and ulcer bleeding in particular types of patients, including those at increased risk of such adverse effects.

Professor Baigent said: "For many arthritis patients, NSAIDs reduce joint pain and swelling effectively and help them to enjoy a reasonable quality of life. This new research shows how to calculate the likely size of any risks of NSAIDs for an individual patient, which should help doctors and their patients when they consider the treatment options."

In England in 2010, there were 17 million prescriptions for NSAIDs, with approximately one third of them diclofenac, one third ibuprofen, and one sixth naproxen.

Dr Shannon Amoils, Research Advisor at the BHF said: "This study supports previous findings showing that taking high doses of some NSAIDs such as diclofenac and ibuprofen for a prolonged period leads to a small increase in the risk of heart attack and stroke.

"Based on this research, we would reiterate the advice that people should take the lowest effective dose of these drugs for the shortest time necessary to control symptoms. Although people who take painkillers infrequently needn't be overly concerned, those who need regularly prescribed painkillers should speak to their doctor about which drug is the most suitable choice for them."

Professor David Lomas, Chair of the MRC's Population and Systems Medicine Board, said: "Large-scale randomised and observational studies such as this one are crucial in identifying adverse drug reactions in patients – even where the risk might be very small. This kind of work, along with the relatively new approaches of stratified medicine and the linkage of electronic health records, is improving understanding of why different patients respond differently to treatments, allowing us to more accurately target different groups of patients with treatments that are both effective and safe."

Professor Alan Silman, medical director of Arthritis Research UK, said: "NSAIDs are a lifeline for many millions of people with arthritis, and when used appropriately can be extremely effective in relieving pain. However, because of their potential side-effects, in particular the increased risk of cardiovascular complications which has been known for a number of years, there is an urgent need to find alternatives that are as effective, but safer. GPs are aware of the risks of NSAIDs, and there has been a marked reduction in the use of diclofenac and a switch to naproxen in recent years. For patients with arthritis, not smoking, a healthy diet and having their blood pressure checked regularly are more important factors in reducing the risk of a heart attack. We would advise people with arthritis who are taking NSAIDs not to be unduly concerned by these latest findings and to seek the advice of their GP."

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For further information, or to arrange an interview with Colin Baigent, contact the MRC Press Office on 0207 395 2345 (out of hours: 07818 428297) or email press.office@headoffice.mrc.ac.uk.

Notes:

1. NSAIDs are used for their pain-relieving and anti-inflammatory properties in a wide range of conditions, but the main indications in the trials were osteoarthritis or rheumatoid arthritis.
2. The adverse cardiovascular and gastrointestinal effects of NSAIDs are thought to be largely attributable to inhibition of an enzyme called cyclo-oxygenase (COX)-2. Naproxen, however, is unique in that it also blocks the related enzyme COX-1 in

blood platelets sufficiently to make blood less likely to clot. This antiplatelet effect of high-dose naproxen offsets any excess risk of heart attacks, but the new research also showed that it also makes naproxen more likely to cause ulcer bleeding, which may diminish its advantage over other NSAIDs.

3. Although the randomised trials in this study only provide information about a limited number of NSAIDs, the results suggest that the adverse effects of NSAIDs are a result of inhibition of the COX-2 enzyme, an action that is common to all NSAIDs. For this reason, the researchers believe that all NSAIDs (other than naproxen) are likely to cause some increase in cardiovascular risk.
4. The Medical Research Council has been at the forefront of scientific discovery to improve human health. Founded in 1913 to tackle tuberculosis, the MRC now invests taxpayers' money in some of the best medical research in the world across every area of health. Twenty-nine MRC-funded researchers have won Nobel prizes in a wide range of disciplines, and MRC scientists have been behind such diverse discoveries as vitamins, the structure of DNA and the link between smoking and cancer, as well as achievements such as pioneering the use of randomised controlled trials, the invention of MRI scanning, and the development of a group of antibodies used in the making of some of the most successful drugs ever developed. Today, MRC-funded scientists tackle some of the greatest health problems facing humanity in the 21st century, from the rising tide of chronic diseases associated with ageing to the threats posed by rapidly mutating micro-organisms. www.mrc.ac.uk. The MRC Centenary Timeline chronicles 100 years of life-changing discoveries and shows how our research has had a lasting influence on healthcare and wellbeing in the UK and globally, right up to the present day. www.centenary.mrc.ac.uk