Biomarker discovery sheds new light on heart attack risk of arthritis drugs

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A class of drug for treating arthritis - all but shelved over fears about side effects - may be given a new lease of life, following the discovery of a possible way to identify which patients should avoid using it.

The new study, led by Imperial College London and published in the journal *Circulation*, sheds new light on the 10-year-old question of how

COX-2 inhibitors - a type of non-steroidal anti-inflammatory drug (NSAID) - can increase the risk of heart attack in some people.

NSAIDs - which include very familiar drugs such as ibuprofen, diclofenac and aspirin - are widely-used treatments for debilitating inflammatory conditions such as arthritis as well as being used for general pain relief worldwide. NSAIDs are also being investigated for their potential to prevent cancer. COX-2 inhibitors, which include Vioxx and Celebrex, were developed in the 1990s to avoid the risk of stomach ulcers caused by some NSAIDs, but after they were linked to an increased risk of heart attacks, they rapidly fell out of favour and some brands, including Vioxx, were withdrawn.

The new study, in mice and human volunteers, was led by Professor Jane Mitchell and Dr James Leiper. Professor Mitchell, from the National Heart and Lung Institute at Imperial, said: "Although the majority of arthritis sufferers could safely use COX-2 inhibitors, the fear of heart attacks has left some patients confused and worried about their medication and GPs nervous about prescribing them. This problem is made worse because we now know that most NSAIDs, not just COX-2 selective drugs, carry a similar risk of heart attacks in some patients.

"If we could identify which people have an increased risk, these patients could be offered more appropriate treatments - and we can start to look at ways of reducing or averting the risk entirely."

NSAIDs work by preventing the production of prostaglandins - the chemical messengers in tissues and joints that trigger pain and inflammation. Prostaglandins are produced by two different enzymes, known as COX-1 and COX-2, which are found at sites of inflammation as well as in other sites around the body.

The study, funded by the Wellcome Trust, the British Heart Foundation

and the Medical Research Council (MRC), looked at where and how removing COX-2 caused changes in gene activity in mice. They found that knocking out COX-2 caused changes in three genes in the kidney which predicted a rise in levels of a molecule linked to cardiovascular disease, called ADMA. In subsequent tests, the researchers found that taking NSAIDs led to a rise in ADMA levels in mice and in 16 human volunteers.

Dr James Leiper, from the MRC Clinical Sciences Centre at Imperial, said: "ADMA is an independent risk factor for cardiovascular disease. In people increases of ADMA similar to those we found are linked with significant increases in cardiovascular disease and death. Our discovery that COX-2 inhibitors raise ADMA levels provides a plausible mechanism for the increased cardiovascular risk associated with these drugs and provides insights into how this risk might be mitigated'

Professor Mitchell thinks that higher ADMA levels might work as an indicator of which patients are at greater risk of a heart attack.

"If we are right," said Professor Mitchell, "ADMA could be used as a biomarker in a simple blood test to identify who may be at risk, and regular screening would allow GPs to monitor patients' ADMA levels to ensure these remain within safe limits whilst taking the drug." The team are planning a clinical trial to test their idea.

ADMA interferes with the normal function of an amino acid called L-arginine, which plays a key protective role in heart health.

Professor Mitchell said: "In some settings, giving more L-arginine can offset the damaging effects of ADMA, so it's possible that supplements containing L-arginine could provide an antidote to the heart attack risk of NSAIDs. This would be simple to test as L-arginine is already widely available in health food shops as a sports and cardiovascular health

supplement. More work is needed for which we would need major funding, but I believe it's worth looking at whether these types of supplements could protect those at risk."

More information: Blerina Ahmetaj-Shala, Nicholas S. Kirkby et al. 'Evidence That Links Loss Of Cyclo-oxygenase-1 2 With Increased Asymmetric Dimethylarginine: Novel Explanation of Cardiovascular Side Effects Associated With Anti-inflammatory Drugs.' *Circulation*, 9 December 2014. circ.ahajournals.org/content/e … .114.011591.abstract

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