Reply to Letter to the Editor from Surdacki et al.,

The COX-2/ADMA axis: relevance to arthritis, anti-inflammatory and anti-thrombotic therapy

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We thank Professor Surdacki and colleagues for their interest in our work. Our work published recently in Circulation\(^1\) shows that genetic deletion or pharmacological inhibition of cyclooxygenase-2 with nonsteroidal anti-inflammatory drugs (NSAIDs) increases plasma levels of the naturally occurring NO synthase inhibitors asymmetric dimethylarginine (ADMA) and monomethyl-L-arginine (LNMMA). In light of our data we hypothesized that ADMA may represent a biomarker and a mechanistic bridge between cyclo-oxygenase-2/vascular NO and cardiovascular risk, explaining the cardiovascular side effects associated with NSAIDs. The use of NSAIDs globally is a phenomenon – with billions of doses taken each year in the USA alone. They are the single most commonly used over the counter medications and represent the first line therapy for the majority of patients with arthritis. The risk of cardiovascular side effects with NSAIDs is relatively small but, considering the number of people taking these drugs, represents a global health problem. Furthermore the fear and anxiety surrounding the cardiovascular risk of using NSAIDs, particularly selective inhibitors of cyclooxygenase-2, has slowed research into new drugs and virtually stopped progress in the use of these drugs to prevent cancer. For these reasons it is vitally important that we find biomarkers, mechanisms and treatments to protect those individuals most at risk.

Our data is entirely consistent with that published by Professor Surdacki’s group\(^2\) showing elevated ADMA levels in patients with rheumatoid arthritis, who, as would be expected, were all taking NSAIDs\(^2\). Interestingly in their paper the levels of ADMA correlated with atherosclerosis\(^2\), an observation that is in line with the idea that ADMA is a meaningful biomarker and mediator of cardiovascular disease. The authors rightly point out that proton pump inhibitors (PPIs), now commonly co-prescribed with NSAIDs, increase ADMA via an inhibitory action on one of its removal systems, dimethylarginine dimethylaminohydrolase-1 (DDAH-1)\(^3\). The idea that NSAIDs together with PPIs might cause an additive increase in ADMA levels is
concerning and one that should be addressed not least because some evidence suggests that PPIs may increase cardiovascular events in some patient groups.

Professor Surdacki and colleagues also rightly point out the implications of our work for what we know pharmacologically of the powerful synergy between NO and prostacyclin on platelet function. Other recent work from our group has established that NO not only synergizes with prostacyclin but also with P2Y12 blockers such as prasugrel and clopidogrel. When we consider that P2Y12 blockers are amongst the most widely prescribed medication for people at risk of cardiovascular disease, some of who will also be taking NSAIDs, the idea that inhibition of COX-2 can indirectly affect NO formation in vessels needs to be studied carefully. Our findings together with those of Professor Surdacki provide a potential biomarker to identify those individual patients at risk but also a rescue therapy in the form of L-arginine supplementation. These ideas need to be fully explored using both preclinical models, such as those described in our study, and in the form of comprehensive clinical trials.

Disclosure Statement.

Disclosures: None.

