Dear Sir,

Circulation has very recently published the above scientific statement. While it is without doubt that such an advisory article is needed in this area, and while the first section of this piece is a succinct description of clinical data regarding NSAIDs, the “Background Scientific Information on COX Inhibitors” is in its most important areas misleading and turns basic pharmacological data from groups such as our own on their head.

Firstly, and of extreme significance in discussing the cardiovascular effects of NSAIDs, it is absolutely not true that “it is now recognized that COX-2 is expressed in normal endothelial cells in response to shear stress and that inhibition of COX-2 is associated with suppression of prostacyclin synthesis”. Despite being oft repeated in the most important journals, such as your own, there is hardly any evidence for COX-2 being normally expressed in healthy blood vessels and endothelial cells (try searching PubMed!). With the exception of indirect measures of prostacyclin production through urinary metabolites the only conclusion that can be drawn from all other vascular biology and immunohistochemistry is that normal blood vessels and endothelial cells express COX-1. For some reason a single paper (Topper et al., 1996) is continually referenced in current review articles as showing that shear stress causes COX-2 expression in endothelial cells. This single paper is not representative of the results in this area (again as easily demonstrated by a search of PubMed). Shear stress can influence, up and down, the expressions of both COX-1 and COX-2. Shear stress for any periods of longer than 24h does not increase COX-2 expression. Endothelial cells in the body are exposed to shear for periods greatly in excess of the few hours used in studies such as those of Topper and colleagues. Thus in repeating the assertion that COX-2 is expressed in endothelial cells because of the influences of shear stress this scientific statement ignores the vast majority of scientific data.

Secondly, as is often the case in articles addressing NSAIDs, attention is focussed upon the actions of these drugs upon COX-2. This is absolutely misleading and absolutely the wrong way to interpret the basic pharmacology of these drugs. All NSAIDs, from the oldest to the newest COX-2 selective, are used at therapeutic doses that produce substantial inhibition of COX-2. They differ little in efficacy as anti-pyretics, analgesics and anti-inflammatories as in clinical use they are all inhibiting COX-2. The greatest variation in activity is upon COX-1 – COX-2-selective drugs are in use COX-1-sparing drugs. So, if one believes that inhibition of COX-2 will cause cardiovascular events then one must conclude that all NSAIDs will cause cardiovascular events at standard doses as all are COX-2 inhibitors at standard doses. If one believes that NSAIDs produce different cardiovascular events one cannot explain it upon different “selectivities” for COX-2 – all NSAIDs are used at COX-2 inhibiting doses. If they exist, different cardiovascular events would be better explained by differences upon COX-1 as that is where the pharmacological differences lie. So Figure 7 would much more accurately define the class of drugs “non COX-2-selective NSAIDs” as “COX-1 inhibiting drugs at standard dose”, the class of drugs “NSAIDs with some COX-2 activity” as “NSAIDS that partly inhibit COX-1 at standard dose”, and the class of drugs “COX-2-selective drugs” as “drugs that do not inhibit COX-1 at standard dose”. None of these classes differ in use by their actions on COX-2! Although it seems largely forgotten now in the frenzy surrounding COX-2, more than a decade ago it was clearly understood that standard doses of NSAIDs produced anti-thrombotic effects through inhibition of platelet COX-1 (e.g. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol. 1995 Mar;35(3):209-19).

Could it be possible that a journal such as yours would publish an article setting out the overwhelming science for a better understanding of the influences of NSAIDs on thrombotic processes than simply COX-2 in the blood vessel wall? The repetition of misleading scientific interpretations and extrapolations and the ignoring of the greater body of scientific evidence cannot assist us in arriving at the best understanding of how to use NSAIDs.

Best regards.

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Response to Dr. Warner and Dr. Mitchell

In response to the recent AHA Scientific Statement on the use of nonsteroidal antiinflammatory drugs,[1] Dr. Warner and Dr. Mitchell bring up the issue of the expression of COX isoforms in endothelial cells. Given the editorial constraints, the statement only gave a cursory background to the complex issue of COX isoform expression in the variety of cell types that are involved in the atherogenic process. This led to some selectivity in the scope of scientific discussion and citation.

The expression of COX1 and COX2 in endothelial cells has been examined in several cell culture and in vivo studies. The in vitro studies consistently demonstrate that endothelial cells cultured under static conditions express COX1, and do not express COX2.[2-5] Although endothelial cells do not express COX2 under basal conditions, several factors promote its expression and activity including endogenous interleukin-1alpha, [6] interleukin 1beta, [5,7] thromboxane A2, [3] LDL, [8] HDL3, [9] hypoxia,[10,11] and non confluency.[4]

While is it indisputable that endothelial cells have the capacity to express COX2, we have been asked to address the issue of hemodynamic influences on COX2 in cultured cells and its relevance to the whole organism. In the statement, we noted COX2 can be induced in normal endothelium by the application of laminar shear stress. We only cited the original article to demonstrated this response. This is the highly cited study of Topper et al [12] in which COX2 mRNA and protein was not present in cells cultured under static conditions, but was upregulated by laminar shear stress in cultured human umbilical endothelial cells (HUVECs). Turbulent shear stress had no effect on COX2 expression. COX1 was expressed under basal conditions, but was not influenced by the application of laminar shear stress.

Dr. Warner and Dr. Mitchell assert that this publication is not representative of the field. However, the induction of COX2 mRNA and protein after shear stress loading in HUVECs was confirmed by other groups [13,14] and have been sustained for 24 hours. In contrast to Topper et al,[12] Okahara et al[13] observed that shear stress also augmented COX1 expression. This augmentation was modest at the mRNA level, but profound at the protein level. However, Inoue et al[14] also failed to observe any effects of shear stress on endothelial COX1 expression. The application of laminar shear stress has also been shown to increased COX2 mRNA abundance in cultured endothelial cells in several gene array studies.[15-17]

The regulation of endothelial COX2 has also been studied in intact vessels. High shear stress perfusion of human umbilical veins at elevated luminal pressure lead to a biphasic response with peaks of COX2 mRNA abundance at 1.5 and 6 hours with a reduction between these intervals.[18] COX1 followed a similar temporal pattern of expression. Elevated pressure also promotes an increase in COX2 mRNA abundance in human umbilical veins that was sustained for the 6 hours of the experiment.[19]

These studies demonstrate that there are different responses on endothelial COX2 expression that are determined by the complexities of the applied shear stress. For example, in contrast to the consistent effects of laminar shear stress to promote COX2 mRNA expression in endothelial cultured cells, there is no enhancement by other forms of flow, such as turbulent and those promoted by asynchronous mechanical forces.[12,20]

While several groups have detected the presence of COX2 under selected hemodynamic conditions in cultured cells, there have been only a few studies of the expression of COX isoenzymes in grossly normal arterial regions. These have consistently detected COX1 in normal regions of arteries from rat,[21,22] dog,[22] and humans.[22-24] In contrast, most studies have either failed to detect, or show only weak expression, of COX2 in endothelium overlying grossly normal areas. One exception to this has been the immunostaining of COX2 in endothelium of aged rats.[21] This scant expression of endothelial COX2 in vivo may be in concordance with Dr. Mitchell and Dr. Warner's recent publication in which they note that the acute application of laminar shear stress for relatively brief intervals in cultured cells may not mimic the chronic exposure of endothelium to shear stresses in vivo.[25] These discrepancies may also be resolved by a systematic study of the spatial expression of COX2 through an normal arterial bed that contains regions of atherosclerosis susceptibility and resistance.

Perhaps the most important issue to emphasized is the presence of COX2 in the endothelium overlying atherosclerotic lesions. In this respect, there are consistent demonstrations of COX2 protein, as determined by immunostaining, in endothelial cells overlying atherosclerotic lesions from apoE -/- mice [26-29] rabbits,[30] and humans.[23] The function of endothelial COX2 expression overlying atherosclerotic lesions has yet to be determined. This consistentcy of COX2 expression may be indicative of a protective adaptive mechanism that is attempting to attenuate the atherogenic process.

Overall, it is clear that endothelium has the capacity to express COX2. However, we would acknowledge that further studies are needed to determine the importance of COX2 in this cell type on the cardiovascular manifestations that have been attributed to NSAID administration.

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