Use of Biomarkers to Predict Cardiac Risk from Medications: Getting to the Heart of the Matter

In May 1999, the US Food and Drug Administration approved rofecoxib, the first nonsteroidal antiinflammatory drug (NSAID) with specific cyclooxygenase II (COX-II) activity. Soon to follow were the approvals of other COX-II inhibitors, including celecoxib. The hypothetical advantage of COX-II inhibitors over standard NSAIDs was that COX-II inhibitors reportedly caused fewer gastrointestinal complications, thanks to their avoidance of COX-I inhibition.

Not long after the release of COX-II agents, however, concerns were voiced about the theoretical potential for cardiovascular risk associated with their use. This concern was based on the fact that although nonselective NSAIDs inhibit both COX-I and COX-II, COX-II agents had little to no inhibitory effect on COX-I, which might be accompanied by a relative prothrombotic risk due to the suppression of prostacyclin, in the absence of inhibition of thromboxane A₂. Also voiced were concerns about increased blood pressure and fluid retention—2 side effects described for COX-II inhibitors. It is interesting that less concern existed at the time about the potential cardiac risk of nonselective NSAIDs.

The prescient concerns about cardiac risk related to COX-II inhibitor use were subsequently supported by the release of clinical trial results that demonstrated significant cardiovascular risk associated with the use of these drugs (1, 2), a risk that appeared to be dose dependent and to be present even when the results were adjusted for the baseline risk of the study participants. Following the release of these findings, the manufacturer of rofecoxib ultimately withdrew the drug from the market, and sales of COX-II inhibitors (previously blockbuster drugs) fell dramatically as the public responded to fears of the cardiac risk associated with use of these nonetheless excellent pain relievers. Interestingly, subsequent data indicated that similar and perhaps less severe cardiovascular side effects may follow therapy with non–COX-II NSAIDs (3).

This experience of unexpected cardiovascular risk associated with drugs is not limited to COX-II inhibitors; indeed, other examples exist in modern medicine, such as volume overload/heart failure associated with thiazolinedione therapy for diabetes mellitus (4) and hemorrhage from unexpected sensitivity to the anticoagulant warfarin sodium (5).

In this context, it is not surprising that clinicians are justified in wondering and worrying about what might follow after they reach for their prescription pad to write for a potentially useful drug. Furthermore, it is not a stretch to assert that we are lagging behind in our ability to recognize patients who might be at risk for adverse consequences from such drugs’ potentially avoidable side effects. Having tools at our disposal to predict such events would certainly allay fears about otherwise unexpected and undesirable consequences from therapy with an agent such as an NSAID.

In this issue of Clinical Chemistry, Brune and colleagues present the results of a provocative study that examined the value of amino-terminal pro–B type natriuretic peptide (NT-proBNP) for predicting adverse events from NSAID therapy (6). In this nonrandomized, retrospective analysis from a study conducted to analyze the efficacy of a metalloproteinase inhibitor for the treatment of osteoarthritis, the authors concluded that an NT-proBNP concentration ≥100 ng/L was able to identify patients who had a nearly 2-fold risk for a cardiovascular adverse event. Furthermore, the addition of more than one NSAID to the therapeutic program of patients with an increased NT-proBNP concentration led to a cardiac risk that was higher than in similar patients who were taking only one NSAID. Even more interestingly, the cardiovascular risk associated with an increased NT-proBNP concentration was even more exacerbated in patients taking a COX-II inhibitor, with a nearly 7.5-fold excess risk compared with those with an NT-proBNP concentration <100 ng/L. Consistent with other studies that showed that the negative predictive value of natriuretic peptides to exclude risk typically exceeds their positive predictive value to predict it (7, 8), the negative predictive value of an NT-proBNP concentration of 100 ng/L for excluding adverse events was a robust 85%.

1 Nonstandard abbreviations: NSAID, nonsteroidal antiinflammatory drug; COX-II, cyclooxygenase II; NT-proBNP, amino-terminal pro–B type natriuretic peptide.
These interesting results should be taken with a measure of caution, however, because the findings are based on a retrospective analysis of a nonrandomized cohort of patients. Given that it is clearly not feasible or ethical to propose a prospective, randomized clinical trial to evaluate such an association, we are left to accept this limitation. Furthermore, the use of a rather compounded composite endpoint (including a wide range of cardiovascular complications, such as myocardial infarction, stroke, worsening hypertension, heart failure, and others) runs the risk of obtaining positive findings by chance. Nonetheless, the data pass the “gut check” in that the results do make sense in light of prior studies of NSAIDs and cardiovascular risk, the trends of outcomes appear to follow a logical direction, and, furthermore, they are consistent with the ability of NT-proBNP to predict hard cardiovascular events in an at-risk population.

What remains unclear is whether all—or only some—of the potential side effects of NSAID drugs would be detectable by monitoring NT-proBNP. Indeed, although this extremely versatile biomarker has been shown to be useful for predicting heart failure, stroke, and death, from apparently healthy patients all the way to patients with end-stage heart failure, studies have consistently shown that natriuretic peptides are generally unable to predict myocardial infarction (9), a major mechanism of cardiac risk associated with NSAID treatment, and particularly COX-II use. The work of Brune and colleagues leaves us guessing, because it does not provide a more granular breakdown of the cardiovascular adverse events.

Although clinicians frequently use the results of biomarker tests in making medication choices (fine examples would be the avoidance of acetaminophen in the context of an increased serum aspartate aminotransferase concentration or the discontinuation of angiotensin-converting enzyme inhibitors in the face of an increased serum creatinine concentration), such a practice most often relates to changing therapeutic strategies to avoid exacerbation of a complication that is already present. The use of biomarkers to predict complications from drug therapy is a different concept and represents a promising future application for markers such as NT-proBNP. Indeed, in reference to the examples given earlier, existing data now suggest that natriuretic peptides may be helpful in identifying patients who would be expected to experience volume overload after therapy with thiazolinedinedione agents (10). Furthermore, in issuing a bold relabeling of warfarin sodium in 2007, the Food and Drug Administration recommended the use of currently available (and quite predictive) genetic testing to help guide initial dosing of this anticoagulant to reduce the risk of catastrophic hemorrhage (5). These first small steps of using markers to personalize medical care are exciting and have been long awaited. Although the implication of the results from Brune and colleagues can only be called hypothesis generating, the use of biomarkers to tailor a patient’s medical program is an exciting hypothesis nonetheless, and clearly in need of further exploration.

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Editorial


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