Can Natriuretic Peptide Levels Predict the Cardiovascular Complications of COX-2 Inhibitors and Nonsteroidal Anti-inflammatory Drugs?

Robert P. Blankfield, MD, MS

There is evidence that fluid retention, whether due to a disease process or due to a medication, is associated with a number of cardiovascular diseases, including heart failure, strokes, coronary artery disease, and cardiovascular death. There is additional evidence that fluid retention that manifests as increased intravascular volume adversely affects cardiovascular outcomes. Because natriuretic peptide levels reflect intravascular volume and pressure, it is hypothesized that when patients are prescribed medications that promote fluid retention—such as non-selective nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors—monitoring natriuretic peptide levels before and after initiating the medication may allow these medications to be used more safely. (J Am Board Fam Med 2006;19: 178–82.)

Several diseases that are associated with fluid retention are also associated with cardiovascular diseases. Likewise, some medications that promote fluid retention are associated with, and in some instances contribute to, cardiovascular morbidity and mortality. Because natriuretic peptide levels reflect intravascular volume, and because elevated natriuretic peptide levels are a risk factor for a number of adverse cardiovascular outcomes, there is a scientifically based rationale for the hypothesis of this paper that monitoring natriuretic peptide levels before and after starting medications that cause fluid retention—such as non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors—might allow these medications to be used more safely.

Natriuretic Peptides and Cardiovascular Disease

Data involving natriuretic peptides provides the primary evidence that fluid retention in the form of increased intravascular volume is a cardiovascular risk factor. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are secreted by the myocytes of the atria and ventricles in response to stretch and pressure. Serum levels of ANP and BNP reflect intravascular volume or pressure, with higher levels of ANP and BNP indicating increased intravascular volume or pressure.

While abnormally elevated levels of natriuretic peptides imply a diagnosis of heart failure, even when natriuretic peptide levels fall within the normal range, higher than average levels of BNP and ANP predict a number of adverse cardiovascular events: death from any cause, first major cardiovascular event, heart failure, atrial fibrillation, and stroke or transient ischemic attack, but not coronary heart disease.[1]

Disease States and Cardiovascular Disease

Heart Failure

Heart failure is characterized by fluid retention. Patients with heart failure are more likely to die suddenly compared with persons with normal left ventricular ejection fractions,[2,3] and the lower the left ventricular ejection fraction, the higher the mortality rate.[4] In addition, heart failure increases the risk for the development of a stroke,[2,3,5–8] with the risk increasing as the left ventricular ejection fraction decreases.[9,10]

Sleep-disordered Breathing

Obstructive sleep apnea (OSA) is associated with, and can cause, fluid retention.[11,12] OSA is associated with increased levels of ANP, primarily during

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From the Department of Family Medicine, Case Western Reserve University School of Medicine, Berea, OH.

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Corresponding author: Robert P. Blankfield, MD, 201 Front Street, Suite 101, Berea, OH 44017 (E-mail address: blankfield@adelphia.net).

the hours of sleep.[13–19] Following appropriate treatment of OSA with nasal continuous positive airway pressure, ANP levels decrease.[16–19]

Prospective studies indicate that OSA is a risk factor for hypertension, heart failure, strokes, fatal cardiovascular disease, and coronary artery disease, whereas treating the OSA reduces the risk of developing these cardiovascular diseases.[20–24]

Diabetes Mellitus II and the Metabolic Syndrome

Insulin resistance with concomitant hyperinsulinemia is a hallmark of type 2 diabetes mellitus and the metabolic syndrome.[25] One of the properties of insulin is fluid and sodium retention.[26,27] Fluid retention may help explain why diabetes mellitus II is associated with increased levels of ANP.[28]

Heart failure, OSA, and type 2 diabetes mellitus are all associated with endothelial dysfunction.[28–33] Stimulation of the sympathetic nervous system, activation of the renin-angiotensin system, effects on endothelial nitric oxide, and, in the case of type 2 diabetes mellitus, atherogenic properties of insulin itself, have been invoked as possible explanations as to why these disease states are associated with endothelial dysfunction.[28–34]

Medications and Cardiovascular Disease

Antihypertensive Medications

Antihypertensive medications that are associated with fluid reduction (diuretics and angiotensin-converting enzyme inhibitors [ACEIs]) are associated with better cardiovascular outcomes than antihypertensive medications that promote fluid retention (calcium channel blockers [CCBs] and α-adrenergic receptor blockers [α-blockers]).[35] Thiazide diuretics are more effective than ACEIs, CCBs, and α-blockers at preventing heart failure, and thiazide diuretics are more effective than ACEs and α-blockers at preventing strokes.[36–40] When compared with β-adrenergic receptor blockers and ACEIs, CCBs are less effective at reducing myocardial infarctions and heart failure.[36,37]

Non-selective NSAIDs

Non-selective NSAIDs cause fluid retention, raise blood pressure,[41,42] are associated with the development of heart failure,[43–45] and are associated with an increased likelihood of having an ischemic stroke.[46] A number of studies have failed to identify a relationship between non-selective NSAIDs and myocardial infarctions.[47–55]

Rofecoxib

The COX-2 inhibitor rofecoxib (Vioxx) causes more fluid retention than either non-selective NSAIDs or celecoxib (Celebrex).[56,57] In the prospective Vioxx Gastrointestinal Outcomes Research (VIGOR) study, rofecoxib was associated with a higher frequency of myocardial infarctions than naproxen,[58] and a different prospective study found that subjects treated with rofecoxib had more than twice the incidence of cardiovascular death, myocardial infarctions, unstable angina, and cerebrovascular disease as subjects in the placebo group.[59] A meta-analysis combining 18 prospective and 11 retrospective studies found that rofecoxib increases the risk of myocardial infarctions compared with placebo, naproxen, or non-naproxen NSAIDs.[60]

Celecoxib

One prospective study showed that, compared with placebo, celecoxib increased the risk of myocardial infarction, stroke, heart failure, or death from cardiovascular causes.[61] However, a pooled analysis of prospective studies found that, compared with placebo and compared with non-selective NSAIDs, celecoxib is not associated with an increased incidence of cardiovascular events (myocardial infarctions, strokes, and cardiovascular death).[62]

Valdecoxib

A pooled analysis found that valdecoxib (Bextra) does not increase the risk of cardiovascular thrombotic events (cardiac, cerebrovascular and peripheral vascular, or arterial thrombotic events) compared with non-selective NSAIDs and compared with placebo.[63] However, coronary bypass graft surgery subjects treated with intravenous parecoxib (an intravenous prodrug of valdecoxib) followed by oral valdecoxib had increased cardiovascular and thromboembolic events (cardiovascular death, myocardial infarctions, strokes, deep venous thrombosis, and pulmonary emboli) compared with subjects treated with placebo.[64]

A Strategy to Improve Patient Safety

Although it has been argued that the adverse cardiovascular events resulting from selective COX-2

inhibitors are due to their mechanism of action,[65–67] it is equally plausible that fluid retention is to blame. If it were possible to predict which patients are at increased risk for adverse cardiovascular events following the use of NSAIDs or selective COX-2 inhibitors, prescribing these medications would become safer. One might expect that measuring markers of endothelial dysfunction before and after initiating the medication might help to identify those patients at increased risk. However, because rofecoxib can lower levels of C-reactive protein and interleukin-6,[68] this approach is fallible.

A more promising strategy might be to measure natriuretic peptide levels in patients before and after they start using selective COX-2 inhibitors and non-selective NSAIDs. One would anticipate that persons who experience an increase in natriuretic peptide levels would be the ones most at risk for adverse cardiovascular outcomes. If a rise in natriuretic peptide levels does predict an increased risk for cardiovascular disease, patient safety could be improved by monitoring natriuretic peptide levels before and after starting non-selective NSAIDs and selective COX-2 inhibitors. Physicians could then discontinue the medication for those persons who experience an increase in the level of natriuretic peptide.

Summary

There is evidence linking fluid retention with coronary heart disease, heart failure, strokes, and cardiovascular death, but a causal relationship between fluid retention and these cardiovascular diseases has not been established. It is hypothesized that because increased intravascular fluid volume may heighten the risk of adverse cardiovascular events, then monitoring natriuretic peptides before and after patients use medications that cause fluid retention—such as COX-2 inhibitors or non-selective NSAIDs—may allow these medications to be used more safely.

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