Featured research

Abstracts and commentaries

Elevated C-reactive protein in atherosclerosis–chicken or egg?

Schunkert H, Samani NJ. *N Engl J Med*. 2008;359:1953–1955.

Increased concentrations of the inflammatory biomarker, high-sensitivity C-reactive protein, predict cardiovascular events. As statins decrease the concentrations of high-sensitivity C-reactive protein in addition to those of cholesterol, we hypothesized that people with increased concentrations of high-sensitivity C-reactive protein, but without hyperlipidemia, might benefit from treatment with statins. We randomly assigned 17 802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol concentrations less than 130 mg/dL (3.4 mmol/L) and high-sensitivity C-reactive protein concentrations of 2.0 mg/L or more to receive rosuvastatin 20 mg daily or placebo. They were followed for the occurrence of the combined primary endpoint of myocardial infarction, stroke, arterial revascularization, admission to hospital because of unstable angina, or death from cardiovascular causes. The trial was stopped after a median follow-up of 1.9 years (maximum 5.0 years). Rosuvastatin reduced LDL cholesterol concentrations by 50% and high-sensitivity C-reactive protein concentrations by 37%. The rates of the primary endpoint were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin 0.56, 95% confidence interval [CI] 0.46 to 0.69; $P < 0.00001$), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio 0.46, 95% CI 0.30 to 0.70; $P = 0.0002$), 0.18 and 0.34 for stroke (hazard ratio 0.52, 95% CI 0.34 to 0.79; $P = 0.002$), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio 0.53; 95% CI 0.40 to 0.70; $P < 0.00001$), 0.45 and 0.85 for the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio 0.53, 95% CI 0.40 to 0.69; $P < 0.00001$), and 1.00 and 1.25 for death from any cause (hazard ratio 0.80, 95% CI 0.67 to 0.97; $P = 0.02$). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not exhibit a significant increase in myopathy or cancer, but did have a greater incidence of physician-reported diabetes. In this trial of apparently healthy persons without hyperlipidemia but with increased high-sensitivity C-reactive protein concentrations, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Commentary

An association between a biomarker (eg, C-reactive protein) and disease (eg, atherosclerotic diseases) may represent a causal relationship (causation), an increase in the biomarker as a consequence of the disease or its treatment (reverse causation), or an association that is spurious because both the biomarker and the disease are affected independently by another known or unknown factor (confounding). Several clinical studies have demonstrated the association between increased concentrations of these inflammatory markers and the risk of myocardial infarction, yet it has been debated whether the inflammatory state detected by these markers is a primary process that predisposes to atherothrombosis or a consequence of existing subclinical atherosclerosis.

What also is unclear is whether the widespread heightened cardiac inflammation is the culmination of an inflammatory process leading to plaque rupture, a consequence of plaque rupture, or both. Thus, akin to the ancient riddle of which came first, the chicken or the egg, C-reactive protein comes both before *and* after atherothrombosis.

Mario Marzilli

C-terminal provasopressin (copeptin) is a strong prognostic marker in patients with heart failure after an acute myocardial infarction: results from the OPTIMAAL study

Voors AA, von Haehling S, Anker SD, et al, for the OPTIMAAL investigators. *Eur Heart J*. 2009 Apr 3 [Epub ahead of print].

The aim of this study was to compare the prognostic value of a novel and promising marker, copeptin, with those of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) on death or a composite cardiovascular endpoint in patients who developed

heart failure after an acute myocardial infarction (AMI). From a subset of 224 patients (mean age 67 ± 10 years) of the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) study, blood samples were drawn at a mean of 3 days after AMI when all patients had signs, symptoms, or both, of heart failure, or a left ventricular ejection fraction <0.35. Endpoints of interest were mortality (the primary endpoint of OPTIMAAL) and a composite cardiovascular endpoint, including death, myocardial infarction, stroke, or resuscitated cardiac arrest. Mean follow-up was 33 ± 7 months. Use of univariable Cox proportional hazards survival analysis revealed that higher concentrations of copeptin, BNP, and NT-proBNP were all significantly related to both mortality and the composite cardiovascular endpoint (all $P < 0.01$). In a multivariable Cox proportional hazards model, including all three biomarkers and other relevant covariates, a doubling of copeptin concentration was related to a 1.83 (range 1.26–2.64) times increased risk of mortality ($P < 0.0001$) and a 1.35 (range 1.05–1.72) times increased risk of the composite cardiovascular endpoint ($P = 0.018$). Receiver operating characteristic curves indicated that copeptin [area under curve (AUC) 0.81] was a stronger predictor of mortality than either BNP (AUC 0.66; $P = 0.0063$ compared with copeptin) or NT-proBNP (AUC 0.67; $P = 0.0016$ compared with copeptin). Finally, changes in copeptin concentrations after 1 month significantly added prognostic information to the baseline value. We conclude that copeptin is a strong and novel marker for mortality and morbidity in patients with heart failure after AMI. In this population, the predictive value of copeptin was even stronger than those of BNP and NT-proBNP.

Commentary

The use of the biomarkers, BNP and NT-proBNP, is increasingly common in the diagnosis and prognosis of patients with heart failure and in the risk stratification of adverse events in patients with a history of myocardial infarction. The blood concentrations of copeptin (the C-terminal portion of provasopressin), are also increased immediately after a myocardial infarction and are quickly and easily measured nowadays. Previous studies (eg, the Leicester Acute Myocardial Infarction Peptide [LAMP] study [1]) have already shown that the values of copeptin, NT-proBNP, and BNP measured during the hospital stay in patients with AMI were significantly greater in those who developed congestive heart failure, who were admitted to hospital again, and who died. These biomarkers overlapped each other, suggesting an additive effect of copeptin to those of BNP and NT-proBNP.

In the LAMP study, copeptin was even more predictive of death and of major adverse cardiovascular events than were BNP and NT-proBNP in patients with AMI, congestive heart failure, or moderate-to-severe left ventricular systolic dysfunction (or combinations thereof). This fact opens interesting possibilities as to adverse mechanisms of vasopressin acting through V1 and V2 receptors, and thus subsequent treatment protocols (eg, use of vaptans).

The findings of the OPTIMAAL study, reported in the paper by Voors et al, suggest that the role of these biomarkers remains weak in some ways. This study tested the effectiveness of two different therapeutic strategies – the first (drugs indicated for the treatment of heart failure according to current guidelines) based on the symptoms, and the second based on concentrations of BNP – in a population aged 60 years or older and with heart failure. Effectiveness (assessed in the 18 months following the start of the study) was judged in terms of overall survival, hospital-free survival, and hospital-free survival after heart failure. The study has not provided substantial evidence to show a superiority of BNP-guided treatment over symptom-guided treatment.

REFERENCE

1. Khan SQ, Dhillon OS, O'Brien RJ, et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction. Leicester Acute Myocardial Infarction Peptide (LAMP) Study. *Circulation*. 2007;115:2103–2110.

Mario Marzilli

Prognostic utility of ApoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22

Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. *Arterioscler Thromb Vasc Biol*. 2009;29:424–430.

The purpose of this study was to compare the prognostic utility of apolipoprotein (apo)B/AI, total cholesterol/high-density lipoprotein (HDL) ratio (TC/HDL), non-HDL cholesterol (non-HDL-C), or C-reactive protein (hs-CRP) as predictors of clinical risk among patients receiving statin treatment after acute coronary syndromes (ACS). In the PROVE IT-TIMI 22

trial, patients with ACS were allocated randomly to groups to receive either pravastatin 40 mg or atorvastatin 80 mg. Cox regression models adjusting for confounders were used to assess the relationship between on-treatment lipids or hs-CRP and risk of death or acute coronary events. At 4 months, a 1-SD increment in apoB/AI (hazards ratio 1.10, 95% confidence interval [CI] 1.01 to 1.20), TC/HDL (hazards ratio 1.12, 95% CI 1.01 to 1.24), and non-HDL-C (hazards ratio 1.20, 95% CI 1.07 to 1.35) predicted events to a similar extent as did low-density lipoprotein (LDL)-C (hazards ratio 1.20, 95% CI 1.07 to 1.35). Risk prediction models that included LDL-C were not improved by the inclusion of apoB/AI, TC/HDL, or non-HDL-C. In contrast, the addition of hs-CRP significantly improved risk prediction models, irrespective of the lipid parameters included, with a 29–30% increased risk observed per 1-SD increment in log CRP. In this study of patients with ACS receiving statin therapy, on-treatment apoB/AI, TC/HDL, and non-HDL-C offered prognostic information similar to that obtained with LDL-C. However, the addition of hs-CRP to lipid-based measurements significantly improved risk prediction. On-treatment measurement of CRP may therefore offer additive prognostic information to that derived from lipid measurements in patients with ACS.

Commentary

The evaluation of risk and monitoring of treatment efficacy in hypercholesterolemic patients is traditionally based on the characterization of LDL-cholesterol values only. Of note, the measurement of atherogenic lipoproteins, such as intermediate-density lipoprotein and very-low-density lipoprotein, in addition to the balance between proatherogenic (apoB) and antiatherogenic (apoAI) activity, should provide a more accurate definition of the risk profile in patients with ACS. The present large trial sought to evaluate whether intensive treatment with atorvastatin (80 mg/day), rather than standard-dose statin therapy (pravastatin 40 mg/day), in patients with ACS could affect the composite endpoint of death and non fatal acute coronary events.

Despite the encouraging observation that intensive treatment with atorvastatin reduced the ratios of apoB/apoAI and total cholesterol/HDL-C, in addition to the level of non-HDL-C, compared with standard-dose treatment in patients with ACS, measurements of the concentrations of each lipid provided information on risk prediction similar to that provided by LDL-C alone.

In contrast, the observations from this trial suggest that measurement of hs-CRP concentrations improves risk prediction and is only weakly related with each lipid parameter. Hs-CRP probably helps to identify the ''synergy'' between conventional risk factors and the inflammatory status of the body, thus improving the detection of dynamic processes related to coronary artery disease. It may therefore represent an independent, powerful risk predictor in patients with ACS.

Mario Marzilli

BNP-Guided vs Symptom-Guided Heart Failure Therapy. The trial of intensified vs standard medical therapy in elderly patents with congestive heart failure (TIME-CHF) randomized trial

Pfisterer M, Buser P, Rickli H, et al, *JAMA*, 2009;301:383–392.

Commentary

It sounds very attractive to have an objective index of efficacy and appropriateness when treating a serious illness. BNP is a peptide secreted by the heart in response to hemodynamic stress that increases sodium and chloride excretion and urine volume, decreases blood pressure, and reduces sympathetic nervous system activity and the activities of the renin–angiotensin system. In heart failure, BNP has been proposed as a marker of the presence and severity of the disease. In the emergency setting, it has been used to differentiate the cause of dyspnea, and at discharge after admission to hospital because of heart failure, it can predict adverse outcomes and re-admissions. What is more controversial is the use of BNP to monitor treatment.

Previous studies using BNP concentrations as a guide to treatment reported a significant reduction in events related to heart failure, including cardiovascular deaths or decompensation. Conversely, in this trial of intensified vs standard medical therapy in elderly patents with congestive heart failure (TIME-CHF) study, BNP-guided treatment had no advantage compared with symptom-guided treatment: the primary endpoint of 18 months of survival free of all-cause admission to hospital and the quality of life were similar between the two groups. In older patients, BNP-guided therapy was sometimes even harmful.

Thus the TIME-CHF trial places BNP-guided treatment of heart failure in perspective, and introduces

important caveats in the use of BNP in clinical practice. Treatment of heart failure is a matter of uptitration of medication and frequent re-assessment of the patient's symptoms and signs – challenging the persistence and patience of the physician. There are no easy answers, no easy solutions, no short cuts.

As for others biomarkers, it is not their reduction that counts, but how we obtain the reduction. Biomarker concentrations should no longer be considered as surrogate endpoints.

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