tients a lower body mass index and a decrease in body weight are associated with worse outcome (4). Treatments that are clearly beneficial in CHF have also been shown to prevent weight loss (angiotensin-converting enzyme inhibitors and beta-blockers [4]) or even increased body fat mass (beta-blockers) (5). Until today there are no data on changes in body weight or body composition following CRT. We agree with Bax et al. (1) that much more research remains to be done regarding CRT. We believe that metabolic pathways should be an important focus of these investigations. This will promote our understanding of the pathophysiology of CHF and of the response to CRT and may help to better guide patient selection for cardiac resynchronization therapy.

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REPLY

We thank Dr. Karhausen and colleagues for their constructive comments concerning our manuscript of the unresolved issues in cardiac resynchronization therapy (CRT) (1). As the researchers point out, there are many such issues concerning CRT. The most difficult issue remains the prediction of response to CRT (2). It has become evident that the current selection criteria are not sufficient, as 20% to 30% of patients do not respond to CRT. The most promising techniques to better select the potential responders are the different sophisticated tissue Doppler imaging (TDI) techniques. However, as pointed out in part 1 of our review on CRT (2), many techniques have been proposed. In total, 24 studies with TDI to predict response to CRT have been published; only 2 (8%) demonstrated that interventricular dyssynchrony was useful to predict response, whereas all 24 studies demonstrated some value of intraventricular (within the left ventricle) dyssynchrony for the prediction of response to CRT. How to precisely assess the intraventricular dyssynchrony is currently not clear, and the extent of dyssynchrony (in ms) needed to result in response to CRT is also uncertain.

Moreover, this uncertainty is further complicated by the fact that a precise definition of a responder to CRT is lacking. As emphasized by Dr. Karhausen and colleagues, various end points have been used. In addition, a single patient may show improvement in a certain end point, but not in another end point. This has been highlighted recently by Bleeker et al. (3) showing a discrepancy between improvement in clinical markers and echocardiographic markers in patients undergoing CRT.

Finally, Dr. Karhausen and colleagues raise an even more complicated issue, namely changes in metabolic status after CRT. Indeed, this is a very important concern, and data on this topic are virtually nonexistent. We fully agree with Dr. Karhausen and colleagues that more work is needed, including in the field of metabolic response to CRT.

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Allergic Reactions Following Implantation of Drug-Eluting Stents: A Manifestation of Kounis Syndrome?

In the very interesting study (1) and editorial (2) published in the January 3, 2006 issue of the *Journal*, the investigators reported and commented on 17 patients who developed allergic reactions after implantation of drug-eluting stents (DES). These reactions included rash, hives, itching, dyspnea, and fever. However, four patients developed in-stent thrombosis and died at 4, 5, 18, and 18 months after implantation, respectively. Eosinophilia and elevated immunoglobulin E (IgE) titers accompanied the allergic reactions. One patient had implanted a TAXUS (Boston Scientific Corp., Natick, Massachusetts) stent impregnated with the antineoplastic agent paclitaxel, and the other three had CYPHER (Cordis Corp., Miami Lakes, Florida) stents impregnated with the anti-

inflammatory agent rapamycin. The other components of the stents include the polymer coating and the metal stent itself. The investigators concluded that hypersensitivity to DES is a real entity that causes serious clinical sequelae, and they recommended continuous vigilance and surveillance for any allergic reactions in patients receiving DES.

The Kounis syndrome (3) was described 15 years ago as the concurrence of acute coronary events with allergic or hypersensitivity reactions as well as anaphylactic or anaphylactoid insults. Arachidonic acid metabolites such as leukotrienes and thromboxane; proteolytic enzymes such as chymase and tryptase; histamine and a variety of cytokines and chemokines released during the activation of various interrelated and interacting inflammatory cells such as macrophages, T-lymphocytes, and mast cells have all been incriminated to induce Kounis syndrome. Two variants of Kounis syndrome have been described recently (4). The type I variant, includes patients with normal coronary arteries and represents a manifestation of endothelial dysfunction; the type II variant, includes patients with culprit but quiescent preexisting atheromatus disease. Causes of Kounis syndrome (5) include various conditions, a variety of environmental exposures, and many drugs such as antibiotics, contrast media, intravenous anesthetics, analgesics, skin disinfectants, corticosteroids, thrombolytics, antiinflammatories, and antineoplastics. Antineoplastics capable of inducing acute coronary syndrome (5) are the antimetabolite 5-fluorouracil (Adrucil, UpJohn Pharmaceuticals, Kalamazoo, Michigan), its prodrug capecitabine (Xeloda, Roche Laboratories, Nutley, New Jersey), the alkaloid cisplatin (Platinol, Bristol-Myers Squibb, Princeton, New Jersey), the antimicrotubule paclitaxel (Taxol, Bristol-Myers Squibb), the interleukin-2 agent denileukin difitox (Ontak, Ligand Pharmaceuticals, San Diego, California), the vinca alkaloids, and interferons.

All three components of DES could be responsible for inducing allergic reactions and Kounis syndrome. Polymers, like those in latex and vinyl gloves, have been reported to induce allergic reactions and Kounis syndrome (6). Antineoplastics and antiinflammatory drugs can also induce Kounis syndrome (6). Patients positive for allergic patch-test reactions to stent metal components nickel and molybdenum appear to have increased rates of in-stent thrombosis (7). The inflammatory cells found at autopsy to infiltrate the intima, the media, and the adventitia in one of the patients who died from in-stent thrombosis (8) were the same—namely lymphocytes, plasma cells, macrophages, and eosinophils—with those participating in the process of Kounis syndrome. Indeed, the proportion of 262 cases of allergic reactions in 2 million DES insertions is very low, but it seems likely that some cases might go unreported; thus, it is anticipated that many more cases will be encountered in the coming years.

Responding, therefore, to the appeal of the RADAR (Research on Adverse Drug events And Reports) project and until further studies characterizing the incidence and the course of the reactions and confirming or predicting the DES allergy are undertaken, we recommend, especially in atopic individuals, the following: 1) careful history of adverse drug reactions and allergies in patients receiving DES; 2) intradermal skin tests for every DES component and desensitization strategies; 3) antibody testing including enzyme-linked immunosorbent assay and radioallergosorbent test for every DES component; 4) monitoring the levels of tryptase, histamine, and arachidonic acid products immediately after the allergic reaction appears; and 5) considering the use of corticosteroids and mast-cell stabilizers when the allergic reaction appears. The latter have also abrogated late thrombotic events experimentally (9).

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REPLY

We appreciate the letter by Dr. Kounis and colleagues that expands upon our discussion of the literature on stent-associated hypersensitivity (1). In conjunction with the RADAR (Research on Adverse Drug events And Reports) project (2), we have started a protocol that incorporates some of the suggestions of Dr. Kounis and colleagues. This protocol includes skin tests to stent components and laboratory tests. It also features a methodical approach to dechallenge and rechallenge (3) for concomitant medication while maintaining antiplatelet coverage. To refer patients, please contact Dr. Marc Feldman, Associate Professor, Department of medicine, University of Texas, San Antonio (E-mail: feldmanm@uthscsa.edu).

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