retrospective studies performed in centers with a particularly large experience with the myectomy operation have shown that survival in patients with obstructive hypertrophic cardiomyopathy and heart failure symptoms who underwent myectomy is similar to that of patients with the nonobstructive form of the disease, and substantially more favorable than that of nonoperated obstructive patients (3,4). Both studies raise the important question of whether young patients with obstructive hypertrophic cardiomyopathy, a marked outflow gradient, and a dilated left atrium should be operated earlier, without waiting for the development of severe symptoms of heart failure unresponsive to medical treatment. On the basis of these recent results, cardiac surgeons with a large experience and very low operative mortality for the myectomy operation are now confronted with the dilemma of whether to operate young patients with outflow obstruction earlier in their clinical course, without waiting for progression to severe heart failure symptoms.

Therefore, we would like to take this opportunity to stress the need for a large international multicenter registry of the clinical course and management of patients with the obstructive form of hypertrophic cardiomyopathy, focused not only on the comparison of the results of myectomy operation versus alcohol septal ablation, but also on the selection of the proper candidates to surgery.

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Reply

We are grateful to Dr. Ferrazzi and colleagues for their thoughtful comments and interest in our work (1). The primary issue raised in their letter is indeed an important one; should surgical septal myectomy for obstructive hypertrophic cardiomyopathy (HCM) be offered to patients with less than severe drug-refractory symptoms, instead of waiting for the progression to New York Heart Association (NYHA) functional class III to IV? At this time, however, we believe that there is no compelling evidence to allow for such radical liberalization of the established selection criteria for surgical septal myectomy (or alcohol septal ablation) (2).

For example: 1) Patients with NYHA functional class III to IV symptoms of heart failure improve measurably after myectomy, often achieving functional class I (2–4). Obviously, symptomatic improvement cannot represent a clinical target in NYHA functional class I to II patients. 2) Postoperatively, patients with class III to IV symptoms have a long-term survival benefit equivalent to that of the general population (4). 3) There are few (if any) available data documenting irreversible heart failure despite adequate myectomy, due to an excessive period of NYHA functional class III to IV symptoms. 4) No consistent data support the advantage of myectomy in reducing left atrial size and the propensity for atrial fibrillation (2,5). For example, in the paper by Woo et al. (3), a substantial proportion of operated patients still went on to develop atrial fibrillation during follow-up.

On the other hand, we agree with Dr. Ferrazzi and colleagues that is probably not necessary or advisable to require symptomatic patients with obstructive HCM to prolong decisions regarding operative intervention until they are essentially disabled. Indeed, once symptoms related to obstruction become fixed and unresponsive to conventional pharmacologic treatment, further medical treatment is unlikely to result in clinical improvement equivalent to that expected following myectomy.

Finally, it is tantalizing to consider earlier intervention with surgical myectomy, given the very low operative mortality now reported by major centers (4). Nevertheless, we hesitate to promote myectomy for asymptomatic or mildly symptomatic patients with obstructive HCM, given that open-heart procedures are never without a mortality and morbidity risk, even at particularly experienced centers (2,4,5). Therefore, we welcome the suggestion of expanding the multicenter registry for obstructive HCM that we have proposed, as a tool to identify ideal candidates for septal reduction therapies (1). However, such registry may ultimately prove of limited value in establishing the need for earlier intervention in HCM patients.

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Early Breast Cancer Therapy and Cardiovascular Injury

The paper by Jones et al. (1) provides an excellent review of the cardiovascular toxicity incurred during treatment for breast cancer. Late cardiotoxicity from anthracyclines has been recognized in survivors of childhood cancer (2) and is more recently being addressed in survivors of breast cancer. The section by Jones et al. on "Prevention and/or Treatment" contains many important approaches. It is surprising, however, that dexrazoxane is not mentioned.

Dexrazoxane was shown in the 1980s to afford protection from cardiotoxicity in women with breast cancer (3). Its use was limited after a multicenter trial, in advanced breast cancer, reported by Swain et al, confirmed cardioprotection, but showed, in 1 of the 5 study arms, a better tumor response in the control patients compared with those treated with dexrazoxane (4). As a result, the indication for breast cancer was restricted to patients who had already received 300 mg/m^2 doxorubicin, pending further trials.

Further trials were subsequently conducted in patients with pediatric cancers, including Ewing's sarcoma, osteosarcoma, Hodgkin's lymphoma, and leukemia. These trials demonstrated cardioprotection, with no decrease in anticancer efficacy, when dexrazoxane was added to chemotherapeutic protocols. It is therefor used with initial therapy in pediatric patients. It has allowed treatment with cumulative doxorubicin doses up to 600 mg/m^2, without cardiac failure (5). It is, therefore, time for the use of dexrazoxane to be investigated again in women with breast cancer during initial treatment, to provide them with protection against future cardiotoxicity.

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Reply

We thank Dr. Steinherz for the important comments regarding the use of dexrazoxane as a prevention/treatment strategy for anthracycline-induced cardiotoxicity in cancer patients. The primary focus of our paper was to examine the risk of and preventive/treatment strategies for long-term global cardiovascular disease (CVD) as opposed to the specific entity of anthracycline-induced cardiotoxicity (1). We feel that this is important to stress because the risk of late-occurring CVD in women diagnosed with early breast cancer likely far exceeds the risk of symptomatic anthracycline-induced cardiac dysfunction during therapy. Clearly, prevention/treatment of cardiac toxicity is of major clinical importance in breast and several other cancer populations, as highlighted by Dr. Steinherz. Further, acute and delayed cardiac toxicity likely contribute to the risk of late-occurring CVD as a component of the "multiple-hit" hypothesis as described in our paper (1). To this end, we agree with Dr. Steinherz that clinical trials of dexrazoxane are required in women receiving chemotherapy in the early stages of disease. However, we wanted to highlight strategies for the treatment of risk factors for the global prevention of CVD in women (e.g., lifestyle modification in conjunction with pharmacotherapy) which has not, in our opinion, received adequate attention in oncology.

Finally, to our knowledge, dexrazoxane has only been investigated and approved by the Food and Drug Administration among breast cancer patients in the metastatic (advanced) setting who have received a cumulative dose of 300 mg/m^2 (2). Given that the focus of our paper was cardiovascular injury among women diagnosed with early-stage disease, we felt inclusion of this approach was not warranted.

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