

have added to the area under the receiver-operator characteristic curve for the standard risk factors' ability to prognosticate. We think that there has not been and will not be a major breakthrough in prevention, akin to what has dramatically occurred in diagnostic testing and intervention, until risk factors are used not for risk assessment, but to identify treatable causal factors after risk has more accurately been established by the level of subclinical atherosclerosis (5).

- To those who raise cost effectiveness concerns related to widespread screening for subclinical atherosclerosis, reduction in the cost of calcium scanning to the level of mammography will make it the most cost-effective modality.
- Finally, in both secondary and primary prevention, there has been a misplaced focus on simple changes in the treated risk factors, for example, low-density lipoprotein, rather than on measures of subclinical atherosclerosis and disease activity and endothelial function to evaluate the response of the disease, rather than the risk factors, to treatment.

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## No Benefit From Cardiac Resynchronization Therapy in Asymptomatic Patients

We congratulate Linde et al. (1) on the meticulously carried out REVERSE (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) trial that addressed the question of the clinical benefit of cardiac resynchronization therapy (CRT) in patients with New York Heart Association (NYHA) functional class II and I heart failure (1). Unfortunately, the composite primary end point as defined per the study protocol was negative. Still, the authors conclude that CRT, in combination with optimal medical treatment ( $\pm$  defibrillator), reduces the risk for heart failure hospitalizations and improves ventricular structure and function in NYHA functional class II and I. In our opinion, the

later statement is not supported by the presented data, which shows no benefit for NYHA functional class I patients (odds ratio: 0.87; 95% confidence interval: 0.37 to 2.03) in their subgroup analysis (Fig. 4 of Linde et al. [1]).

This disagreement raises the more philosophical question: whether these subgroup analyses make sense if the primary end point is negative—maybe due to a lack of statistical power? It seems that the well-known players such as wide QRS and low left ventricular ejection fraction are positive predictors for CRT success but not NYHA functional class I. Another intriguing finding of this subgroup analysis is that patients on diuretics did improve, whereas those not on diuretics did not. However, the use of diuretics reduced mortality and prevented hospital admissions in this patient population, which raises the question of whether the use of diuretics by themselves may have accounted for the documented beneficial effect (clinical composite end point, hospitalizations) in the CRT ON group and whether this confounding variable was corrected for in the main analysis (2).

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## Reply

We thank Dr. Osswald and colleagues for their interest in our paper (1). The REVERSE (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) study was designed as one population of New York Heart Association (NYHA) functional class I to II heart failure (HF) patients. We agree that the primary end point did not reach statistical significance (2), with 16% of patients worsened in the cardiac resynchronization therapy (CRT) ON group and 21% in the CRT OFF group ( $p = 0.10$ ). The clinical composite response was designed for severe HF patients and, to our knowledge, has not previously been used in mildly symptomatic or asymptomatic HF patients (3).

The fact that the primary end point did not reach statistical significance despite substantial improvement in left ventricular (LV) dimensions accompanied by a significantly reduced time to first HF related hospitalization might be due to the difference in utility of this end point or that the observation period was not long enough to demonstrate effects in NYHA functional class I to II patients. Dr. Osswald and colleagues are concerned about the

subgroup analysis in a neutral study and more specifically by the “lack of benefit” in NYHA functional class I patients and in those not on diuretics (1). We understand their concern but want to point out that subgroup analyses are performed in larger studies to clarify whether a presumed treatment effect can be generalized over many clinically relevant conditions.

The main finding was an overall positive effect over nearly all subgroups, with an odds ratio of 0.70 in favor of CRT. The study was not powered to show a benefit in NYHA functional class I patients alone and, therefore, statistical significance for this small group of patients should not be expected. Nonetheless, the results indeed favor CRT ON in NYHA functional class I patients with an odds ratio of 0.87. Improvements in left ventricular end-systolic volume index between NYHA functional class I and II patients were substantial in both NYHA functional class I and II groups as well as for patients with and without diuretics. Diuretics were not randomized in any way. The on-diuretics group included both CRT ON and CRT OFF patients, so if “diuretics by themselves may have accounted for the documented beneficial effect,” then both CRT ON and CRT OFF patients would have shown the same improvement. Therefore, this is not a confounding variable.

We thus believe that our conclusion, that CRT reduces the risk for HF hospitalization and reverses LV remodeling over the course of 12 months in patients with American College of Cardiology/American Heart Association stage C, NYHA functional class I and II HF, raising the possibility that CRT might delay disease progression in HF patients with mild HF through LV reverse remodeling, is valid. Because the REVERSE study was not dimensioned as a morbidity/mortality trial we will have to wait for the ongoing MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) and RAFT (Resynchronization/defibrillation for Ambulatory heart Failure Trial) studies and the 24-month REVERSE study results to obtain the final answer as to whether CRT may modify disease progression in mildly symptomatic HF patients (4,5).

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## Early Repolarization in the Athlete

An “abnormal” resting electrocardiogram is common in top-ranking, endurance-trained athletes (1). These abnormalities belong to physiological changes induced by training, as sinus bradycardia, high QRS and T-wave voltages, and early repolarization (ER), consisting of an elevation of QRS–ST junction, or a QRS notching/slurring. Until now, ER has been considered benign (2).

In a previous article (3), we underlined differences between ventricular repolarization anomalies in top-level athletes and those present in patients with Brugada syndrome. ER was observed in 89% of athletes, a value largely different from what was recently observed by Rosso et al. (4) in a young athletic group (22%).

The difference in ER prevalence between our athletes and those studied by Rosso et al. (4) could be that the former were competitive athletes and the Rosso et al. (4) subjects were noncompetitive. Moreover, in this study, different from the control group, the athletic patients were not age-matched with patients with idiopathic ventricular fibrillation (IVF) and were younger (range 17 to 19 years vs. 24 to 70 years). So, the difference in the prevalence of J-point elevation in IVF subjects (42%) may be due more to the younger age than to athletic conditioning. We observed a similar ER prevalence (36%) in our young nonathletic controls (mean age, 25 years) (3).

Recently, it was suggested that, in some cases, ER may not be benign (4,5). We would like to stress that top-level endurance-trained athletes represent a peculiar group of subjects in whom ER and some other electrocardiogram anomalies are almost the rule. None of our athletes has suffered from major ventricular arrhythmias from the time of the study onward (3). In this way, the meaning of ER, in particular, in left pre-cordial leads, especially when associated with high QRS and T-wave voltages, must be considered a complete benign phenomenon, reversible after a few months of detraining.

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