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Cardiac Resynchronization Therapy in Patients With Narrow QRS

We read with great interest the report by Achilli et al. (1) on cardiac resynchronization therapy (CRT) in patients with heart failure (HF) and narrow QRS: the clinical implication of those data is huge in light of the rapidly expanding indications for CRT.

Achilli et al. (1) described the "long-term" efficacy of CRT in 52 patients (all preselected by echocardiographic recognition of inter- and intraventricular dyssynchrony) affected by HF, 14 of them with a QRS ≤120 ms. Positive results were obtained both from a clinical and echocardiographic point of view.

The fact that the mean follow-up was ~565 days, but that the "clinical and echocardiographic results" refer to the six-month follow-up, could be a bit confusing. This may be misleading, and no doubt the definition of "mid-term" rather than "long-term" would be more appropriate in describing the follow-up by Achilli et al. (1).

Our larger experience (158 patients, mean follow-up 1 year) (2), published just a year before Achilli et al. (1) study (and probably overlooked by the investigators) also confirms positive results of CRT in patients with narrow QRS. Based purely on basal QRS duration, without preselection by any echocardiographic parameter, our patients were defined as wide QRS (≥150 ms, 128 patients) and narrow QRS (<150 ms, 30 patients, 13 with QRS ≤120 ms, a number comparable to the Achilli et al. [1] narrow QRS cohort). Our data confirm that, in both groups, CRT significantly improved clinical and echocardiographic parameters; in our series these good results were sustained for at least one year.

The most relevant difference between Achilli et al's. (1) and our population concerns the mortality rate in the narrow QRS group; in fact, the 21.4% reported by Achilli et al. (1) in patients with narrow QRS strongly contrasted with no deaths in our series. In addition, the mortality rate reported by the investigators was similar in patients with both narrow and wide QRS duration, being substantially higher than other reported series.

Finally, we agree that echocardiographic indicators of dyssynchrony can be useful; nonetheless, our data on patients with narrow QRS have clearly demonstrated that the use of pure "clinical" selection criteria (i.e., drug refractoriness, severe HF, low ejection fraction, large diameters) has permitted us to identify patients who can substantially benefit from CRT in the long term.

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REPLY

We appreciate the interest of Dr. Gasparini and colleagues in our report (1) and respond to their specific points as follows. First, as regards our follow-up, we are of the opinion that the definition of "long-term" is correct considering a mean observation period for our patient population of 546 days, but clinical and echocardiographic data were collected at 6 months as this reflected the minimum follow-up for all patients and we believed that this guaranteed a homogeneous data evaluation. Nevertheless, the latter definition obviously reflects a "mid-term" follow-up.

Second, we agree that the data published by Gasparini et al. (2) concur with ours in underscoring the benefit of cardiac resynchronization therapy (CRT) in patients with heart failure and narrow QRS. However, the definition of a "narrow" QRS is substantially different in the two studies (110 ± 10 ms vs. 133 ± 15 ms), thus making the confrontation between patient populations inappropriate as regards the electrical asynchrony profile. Moreover, we acknowledge with pleasure that 13 patients in the Gasparini et al. (2) series had a QRS duration ≤120 ms, but this issue was not cited in the original report.

The major difference between the two populations is in the criteria used for the selection of patients. We required the presence of inter- and intraventricular asynchrony documented by echocardiography, whereas the Gasparini et al. (2) patients were selected solely on the basis of clinical features.

Third, the high mortality rate of our patients might be due to a disproportionate percentage of New York Heart Association (NYHA) functional class IV (40%) patients with respect to previous studies and the absence of functional class II patients in our study; this is because we had decided, at least in the initial phase of our experience, to reserve CRT for very ill patients. Conversely, the subgroup with a narrow QRS from the Gasparini et al. (2) series included 40% of NYHA functional class II patients.

Moreover, our selection criteria with respect to intraventricular asynchrony were highly restrictive and may have led to selection of patients with a very unfavorable prognosis.

Fourth, we agree with Dr. Gasparini and colleagues that the screening of patients suitable for CRT based on merely clinical criteria may be sufficient in specific settings. However, we are of the opinion that this simplification could increase the number of non-responders to CRT: this issue is critical, and current research for the identification of responders is in active development. There is evidence that left intraventricular asynchrony detected at echocardiography may represent the best parameter for the identification of responders to CRT (3,4). Therefore, we are convinced that the selection of patients for CRT should necessarily include the evaluation of mechanical asynchrony, the latter representing the pathophysiologic substrate for resynchronization pacing in heart failure patients.

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Cerebroprotection Mediated by Angiotensin II

I read with great interest the provocative study by Fournier et al. (1) on cerebroprotection mediated by angiotensin II. The investigators state that beta-blockers are remarkably ineffective in reducing the risk of stroke; however, they cite three studies all performed with one beta-blocker, atenolol, which has never been proven to reduce sudden death.

In general, the results of multiple studies with one drug cannot be interpreted as representing the class of that drug. In the case of beta-blockers in particular, publication of the Beta-blocker Evaluation of Survival Trial (BEST) (2), which failed to replicate the mortality reduction demonstrated by bisoprolol, metoprolol extended release, and carvedilol in systolic heart failure, clearly established the fallacy of assuming a class effect for the benefit of beta-blockers for that particular indication. Furthermore, in the recently published Carvedilol Or Metoprolol European Trial (COMET) (3), the stroke rate was reduced significantly (67%) with carvedilol compared with the short-acting metoprolol tartrate (4). Thus, the investigators need to limit their conclusion of the ineffectiveness of beta-blockers to atenolol and avoid invoking beta-blockers as a class in this argument.

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REPLY

Dr. Ghali raises an interesting point about our study (1) that deserves to be scrutinized. In hypertension, beta-blockers as a class have never been shown to reduce heart attacks or strokes (2,3). This is true for atenolol in several prospective placebo-controlled randomized trials, but also for propranolol in the Medical Research Council (MRC) study (4) and for oxprenolol in the International Prospective Primary Prevention Study in Hypertension (IPPPSH) (5). In Cardiac Insufficiency Bisoprolol Study (CIBIS-II), the rate of hospitalization for a stroke was almost twice as high in the bisoprolol arm as in the placebo arm (6). Thus, there are several prospective randomized studies with atenolol, propranolol, oxprenolol, or bisoprolol documenting that beta-blockers are not efficacious in reducing strokes.

A notable exception that Dr. Ghali mentioned is the Carvedilol Or Metoprolol European Trial (COMET) in congestive heart failure patients (7). However, carvedilol is a drug that is distinctly different from traditional beta-blockers in that it does have some alpha-blocking properties and other features that exert a more favorable effect on systemic hemodynamic, metabolic endocrine findings, and target organ disease than do traditional beta-blockers (8). We also should emphasize that a stroke reduction in congestive heart failure without hypertension cannot necessarily be extrapolated to uncomplicated hypertension. Indeed, heart failure per se is a risk factor for stroke, but the pathogenesis is different from the one in hypertension and often involves emboli of cardiac origin. Because carvedilol was superior to metoprolol in preventing congestive heart failure and sudden death, it is likely that it