Heart failure (HF) is a medical problem of huge socioeconomic importance, mainly due to the increasing life expectancy in our societies and the strides in the treatment of ischemic heart disease which resulted in improved prognosis of our patients. These medical and socioeconomic issues may explain why HF poses a significant financial burden on our health care systems. It is estimated that acute decompensated HF accounts for 2.9% of all emergency room visits, its prevalence is steadily increasing in epidemic proportions and in age-dependent manner, reaching an incidence of almost 10% in patients aged >65 years.²

There has been considerable improvement in our therapeutic armamentarium over the years with significant benefit obtained with use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and β-blockers. However, there is still a large population of HF patients who remain refractory to current therapeutic approaches and this therapeutic gap has recently been bridged by the newer mode of electrical therapy known as cardiac resynchronization therapy (CRT), effected by biventricular pacing.²⁻³ CRT has been shown to improve symptoms and prognosis of patients with HF. The pathophysiological rationale for the development of CRT was the observation that some patients with advanced HF presented asynchronous contraction of the left ventricle (LV) on echocardiography. Asynchronous contraction due to cardiac conduction abnormalities, often described as cardiac dysynchrony, reflected by the presence of left bundle branch block (LBBB) on the electrocardiogram (ECG), occurring in 20-30% of patients afflicted by HF, has been documented to adversely affect the function of the failing heart.⁴ Furthermore, it has been shown that cardiac dys synchrony has an unfavorable influence on prognosis in patients with HF.⁵⁻⁶

CPT aims to improve the mechanical function of the failing heart. Biventricular pacing is an effective way to achieve CRT and restore electromechanical synchrony by simultaneously pacing at different sites of the heart, classically at the right ventricular apex and the lateral wall of the LV. This is accomplished by inserting the LV pacing lead via the coronary sinus and placing it into a lateral cardiac vein tributary. In a large number of studies, it is a consistent finding that biventricular pacing increases LV ejection fraction (LVEF) and cardiac output and most importantly, improves quality of life, functional class and exercise capacity in the majority of the treated patients.⁷⁻¹⁰

In terms of pathophysiology, CRT has a unique characteristic among other therapies for HF. Its favorable influence on cardiac performance has not been associated with increased oxygen consumption, an issue of profound importance especially in patients with ischemic cardiomyopathy.¹¹ These striking beneficial effects of CRT, had not been accompanied by any detectable survival benefit in the large number of small randomized trials that were published during the initial period of biventricular pacing.⁷⁻¹⁰ Of course, these studies were not designed to detect a survival benefit and thus,
they were underpowered to study the effects of biventricular pacing on overall mortality. However, the lack of statistical significance should not be considered synonymous to the lack of clinical significance. In the case of CRT, this fact was firstly supported by a meta-analysis of four large randomized trials, which showed that CRT therapy significantly reduced all-cause mortality (relative risk=0.77).12 Thereafter, the results of the two randomized studies having as primary end-point total mortality, the COMPANION13 and the CARE-HF14 trials, verified the aforementioned findings and provided the necessary evidence for the recommendations and guidelines on CRT use for patients with symptomatic HF, which were published three years ago by the American Heart Association (AHA)/American College of Cardiology (ACC)15 and by the European Society of Cardiology (ESC).16

The accumulating evidence from the recently published studies resulted in the revised recommendations by the ESC and the European Heart Rhythm Association.17 According to these recommendations, CRT is considered class I (level of evidence A) therapy for the HF patients who remain symptomatic in NYHA classes III–IV despite optimal treatment, with LVEF ≤35%, LV dilatation, normal sinus rhythm and wide QRS complex (≥120 ms). Although this general classical indication includes the majority of patients studied in everyday clinical practice, the authors of these guidelines tried to provide practical answers to a number of problematic unresolved clinical issues that raised questions regarding appropriate use of CRT.17 Indeed, the authors of the 2007 ESC/EHRS guidelines devoted a great effort to analyze these unresolved issues which are expected to be enlightened by some large ongoing randomized trials (Table 1).

Thus, trying to provide a reasonable clinical approach to these unsolved issues despite the lack of solid evidence, they suggested that CRT can be a reasonable therapeutic option in HF patients with NYHA classes III–IV symptoms, low LVEF ≥35%, LV dilatation and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker) (Class IIa: level of evidence C). In addition CRT is considered appropriate for HF patients with a Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA classes III–IV despite optimal treatment, with low LVEF ≤35%, LV dilatation and wide QRS complex (≥120 ms)(Class I: level of evidence). Finally, heart failure patients with permanent atrial fibrillation who remain symptomatic in NYHA classes III–IV despite optimal treatment, with low LVEF ≤35%, LV dilatation and indication for AV junction ablation are considered candidates for CRT according to the latest guidelines (Class IIa: level of evidence C). A synopsis of the 2008 ESC/EHRA guidelines on CRT in comparison to the previous (published at 2005) ACC and ESC guidelines is presented at Table 2.

### COMMENTS ON UNSOLVED ISSUES AND POTENTIAL NEW INDICATIONS

CRT is a rapidly evolving therapeutic strategy which is expected to be influenced by the accumulation of evidence derived by ongoing studies, by the accumulation of increasing operator and centers’ experience and by the development of new tools and modalities that can be used to achieve biventricular pacing. In this context, the current situation regarding indications and patients’ selection criteria is expected to change. Many of the unsolved issues, which are presented in Table 1 are now considered as “non-classical indications”. Some of them will possibly be included in future widely accepted indications, while others will be rejected in the light of new evidence. Although preliminary data may support the so called “non-classical indications” any comments on their applicability in everyday clinical practice will inevitably be, at least partly, subjective.

Although currently existing evidence from large scale studies is based on selection criteria solely related to the duration of QRS complex, it is well-known that electrical dysynchrony does not always accompany mechanical dysynchrony.18 Taking into consideration that CRT through biventricular pacing aims to restore mechanical dysynchrony, we believe that it should be directed only to those patients who present both electrical and mechanical dysynchrony, simply because there are no data or even convincing assumptions that have associated the beneficial effects afforded by biventricular pacing with any other characteristic of patients with advanced HF apart from the mechanical dysynchrony. Although preliminary results from the PROSPECT study19 showed that no echocardiographic measure of mechanical dysynchrony was found to be useful for identifying patients more likely to respond to CRT, we should not apply CRT in

<table>
<thead>
<tr>
<th>TABLE 1. Unresolved issues in CRT indications</th>
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</thead>
<tbody>
<tr>
<td>1. Lack of electromechanical dyssynchrony</td>
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<td>2. Narrow QRS on surface ECG</td>
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<td>3. Atrial fibrillation</td>
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<td>4. Right bundle branch block</td>
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<tr>
<td>5. Indication for permanent pacing in patients with mild heart failure or asymptomatic left ventricular systolic dysfunction</td>
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<tr>
<td>6. Patients with a previously implanted conventional pacing device and severe left ventricular dysfunction</td>
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<tr>
<td>7. Co-existing right heart failure</td>
</tr>
<tr>
<td>8. Heart failure and pacing in the pediatric population</td>
</tr>
<tr>
<td>9. Planned cardiac surgery and classical CRT indication.</td>
</tr>
</tbody>
</table>
patients who lack electromechanical dyssynchrony given the lack of a relevant pathophysiological mechanism that could support the notion that improvement of LV function can be achieved by biventricular pacing independently of preexisting mechanical dyssynchrony.

On the other hand, another “non-classical” indication for CRT would be the application of biventricular therapy in patients with advanced refractory HF in the absence of prolonged QRS duration (<120 ms) but in the presence of echocardiographically documented inter- or/and intraventricular dyssynchrony. Again our enthusiasm should be tempered by the lack of convincing evidence. Notably, recently, Beshai et al evaluated this issue in a prospective, double-blind, randomized, controlled clinical trial (RethinQ study). A total of 172 HF patients with a SCD-HeFT indication for ICD, NYHA class III functional class, QRS duration <130 ms and evidence of mechanical dyssynchrony as measured by echocardiography, were randomized to either CRT or no CRT. The presence of mechanical dyssynchrony was identified by using echocardiographic imaging methods. In 96% of cases the tissue Doppler-defined presence of an opposing wall delay ≥65 ms was used as a qualifying criterion, while the rest 4% of patients exhibited a significant mechanical delay in the septal-to-posterior wall, obtained by M-mode in the parasternal long-axis view. After 6 months, among 156 patients assessed (76 in the CRT and 80 in the control group), CRT was not shown to confer any benefit in patients with QRS duration < 120 ms, as evidenced by lack of improvement in peak oxygen consumption. However, we should keep in mind that the results of the RethinQ study are not conclusive and mostly, underline the need for further large-scale prospective, adequately powered, double-blind trials that could delineate the potential beneficial effect of CRT on the subpopulation of HF patients with narrow QRS as well as the optimal echocardiographic imaging method which enables the most accurate definition of cardiac dyssynchrony and the selection of responders. Amongst others, we have suggested that until results from these studies are available, we should follow the recently published guidelines of the ESC/EHRA routinely precluding patients with narrow QRS from CRT, even in the case of echocardiographically determined cardiac dyssynchrony.

For the first time, the authors of the 2007 ESC/EHRA guidelines addressed the dilemma of providing CRT versus conventional pacing in patients with indication for permanent pacing, with mild heart failure or asymptomatic LV systolic dysfunction and the dilemma of CRT in patients with a previously implanted conventional pacing device and severe LV dysfunction. In both cases accumulating data suggest that the detrimental role of pacing-induced dyssynchrony may justify the use of biventricular pacing in these patients. Regrettably, the authors of the recent guidelines included advanced NYHA class (III-IV) as a perquisite for this indication. However, it would be logical to hypothesize that a large proportion of NYHA II patients who will be implanted a conventional pacemaker or ICD, will deteriorate due to pacing-induced dyssynchrony and will need to upgrade to biventricular systems with profound consequences on efficacy, safety and cost-effectiveness of the management of the patient.

In conclusion, the classical indications for CRT have evolved considerably, while the non-classical should not be

### Table 2. CRT guidelines in chronic heart failure patients according to the recently published ESC/EHRA recommendations in comparison to the guidelines published in 2005 by the ACC/AHA and by the ESC.

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Clinical end-point</th>
<th>Class and level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA Guideline Update for Chronic Heart Failure (2005 update)</td>
<td>NYHA class III-IV, LVEF ≤35%, Sinus rhythm, Symptoms despite optimal medical therapy, Cardiac dyssynchrony (currently defined as QRS &gt;0.12 ms)</td>
<td>Symptoms, Hospitalizations, Mortality</td>
<td>I (A) 15</td>
</tr>
<tr>
<td>ESC guidelines for Chronic Heart Failure (2005 update)</td>
<td>NYHA class III-IV, Reduced LVEF, Symptoms despite optimal medical therapy, Cardiac dyssynchrony (QRS&gt;0.12 ms)</td>
<td>Symptoms, Hospitalizations</td>
<td>I (A) 16</td>
</tr>
<tr>
<td>ESC/EHRA guidelines for pacing and CRT (2007)</td>
<td>NYHA class III-IV, LVEF ≤35%, Symptoms despite optimal medical therapy, Wide QRS complex (QRS&gt;0.12 ms)</td>
<td>Morbidity and Mortality</td>
<td>I (A) 17</td>
</tr>
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</table>
routinely included in everyday clinical practice, despite the fact that they may represent reasonable therapeutic options in selected cases.

REFERENCES


