Cardiac Resynchronization Therapy: An Overview on Guidelines

Giuseppe Boriani, MD, PhD[a,*], Martina Nesti, MD[b], Matteo Ziacchi, MD, PhD[a], Luigi Padeletti, MD[c]

KEYWORDS

• Atrial fibrillation • Bundle branch block • Cardiac resynchronization therapy • Guidelines • Heart failure • QRS interval

KEY POINTS

- Cardiac resynchronization therapy (CRT) is included in international consensus guidelines as a treatment with proven efficacy in well-selected patients on top of optimal medical therapy. Although all the guidelines strongly recommend CRT for LBBB with QRS duration greater than 150 milliseconds, lower strength of recommendation is reported for QRS duration of 120 to 150 milliseconds, especially if not associated with LBBB. CRT is not recommended for a QRS of less than 120 milliseconds.
- The process of translating consensus guidelines into "real-world" practice is incomplete. Efforts should be dedicated to "synchronize" the competence and expertise of many physicians in order to deliver this treatment to the right patient, at the right time, and in the appropriate setting.

INTRODUCTION

Clinical guidelines are systematically developed statements and recommendations regarding clinical decision making to help practitioners and patients to make the most appropriate decisions about management and treatment of specific clinical conditions and diseases. Clinical guidelines are produced on the basis of a systematic revision process of the medical literature and opinion of experts and should provide extensive, critical, and well-balanced information on the benefits and limitations of a series of therapeutic and diagnostic choices to assist in taking decisions in individual cases. Application of guidelines to the management of individual patients always requires rational judgment and informed considerations, even when guidelines recommendations are properly linked to evidence.

Since the mid 1980s, national and international guidelines focused on different diseases have been developed. The reasonable expectation included an improvement in the process of health care provision by making it more effective and efficient. Despite the great efforts dedicated to development and implementation of evidence-based guidelines, contradictory results emerge by analysis of guidelines implementation and medical decisions in the "real world." A series of surveys indicate that around 30% to 40% of patients do not receive treatments based on scientific evidence, and around 20% to 25% receive treatments that may be unnecessary and sometimes even harmful.[1]

With regard to pacemaker and implantable electrical devices, the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (formerly the North American

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[a] Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S. Orsola-Malpighi University Hospital, Via Giuseppe Massarenti 9, Bologna 40138, Italy; [b] Electrophysiology and Pacing Centre, Heart and Vessels Department, University of Firenze, Largo Brambilla 3, Firenze 50134, Italy; [c] Specialty School in Cardiovascular Diseases, University of Firenze, Largo Brambilla 3, Firenze 50134, Italy
* Corresponding author.
E-mail address: giuseppe.boriani@unibo.it

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Society of Cardiac Pacing and Electrophysiology) published the first guidelines for the implantation of cardiac pacemakers and antiarrhythmia devices in 1984.[2] Since that time, major advancements in technology and clinical evidence of benefit occurred with regard to device therapy and these developments have led to periodic updating of the guidelines in 1991, 1998, 2002, 2008, and 2012.[3] The European Society of Cardiology released the first document including recommendations on use of implantable cardioverter defibrillators in 1992[4] and then released guidelines on pacing and cardiac resynchronization therapy (CRT) in 2006 and 2013.[5,6]

CARDIAC RESYNCHRONIZATION THERAPY AS AN EFFECTIVE TREATMENT IN HEART FAILURE

CRT was proposed as the result of pioneering experiences performed in France around 20 years ago.[7–9] CRT is an electrical treatment based on biventricular or left ventricular-only pacing that was initially applied as a last resort therapeutic solution for patients with severe heart failure (HF) associated with left bundle branch block (LBBB). Despite the novelty of the approach and the technical limitations of implantable leads in the first phases of clinical use, the evaluation of CRT moved rapidly from isolated case reports and small case series or uncontrolled studies to randomized controlled trials (**Table 1**). Multisite Stimulation in Cardiomyopathy (MUSTIC) was the first randomized study on CRT[21] and was followed by a randomized controlled trial with blinded assessment of the effects, namely, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study.[10,11] The MIRACLE trial included implant of a CRT device followed by randomization to biventricular pacing "on" or "off" for 6 months with blinded assessment of the presence/absence of improvement in symptoms, HF status, and quality of life.[10] A paradigm shift in obtaining solid evidence in favor of CRT use in patients with moderate to severe HF were the Cardiac Resynchronization—Heart Failure (CARE HF) and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trials[13,14] that randomized patients to optimal medical therapy versus CRT (with a pacemaker in CARE HF, with or without a defibrillator in COMPANION), using "hard endpoints"[13,14] as primary endpoints of efficacy (all-cause mortality or hospitalization).

As a result of the randomized controlled trials performed in the last 15 years (see **Table 1**), CRT has been proposed by all the international consensus guidelines as a treatment with proven efficacy in improving symptoms, reducing hospitalizations, inducing reverse remodeling, and reducing mortality in well-selected patients with wide QRS (and LBBB), left ventricular dysfunction, and moderate to severe (New York Heart Association [NYHA] class III-IV) or mild (NYHA class II) HF, on top of optimal medical therapy.[6] More recently, patients with conventional indications for pacing, a left ventricular ejection fraction of 50% or less and NYHA class I to III resulted to benefit from biventricular pacing in a relatively long follow-up,[19] although with a number needed to treat, much higher than that of others CRT trials.[22]

GUIDELINES ON CARDIAC RESYNCHRONIZATION THERAPY

In the present review, we analyze the recommendations for CRT implant included in the guidelines on pacing and CRT delivered by the European Society of Cardiology and in the guidelines by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society, as well as the recommendations for CRT included guidelines on HF delivered by the same societies. Moreover, we analyze the guidelines on CRT delivered by the Canadian Cardiovascular Society and by National Institute for Health and Care Excellence (NICE; **Table 2**). These guidelines have some differences with regard to the grading of recommendations (see **Table 2**), which is very explicit and associated with a predefined wording of recommendations in both European and American guidelines. Conversely, NICE does not report in the guidance specific explanations focused on grading of recommendations, implying that the reader can find some information in another NICE publication.[27] The recent NICE guidelines on implantable cardioverter defibrillators (ICDs) and CRT are in some way unique, because they are based on individual patient data network meta-analyses, based on 12,638 patients from 13 clinical trials, taking into account not only evidence but also cost-effectiveness estimates.[28] The approach of NICE of considering cost effectiveness is quite original because, even if economic evaluations are an important aspect of health technology assessment,[29–32] economic estimates were deliberately excluded from clinical recommendations in guidelines delivered by the European Society of Cardiology[33] and has never been considered in guidelines from North America.

We analyze the recommendations delivered from these guidelines with regard to class of recommendation and level of evidence, if available, taking into account different categories of patients, on the basis of clinical aspects (severity