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Quarterly Medical Review - Innovations in heart failure therapies

Electrical therapies in heart failure: Evolving technologies and indications



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ABSTRACT

Device therapy for heart failure has rapidly evolved over 2 decades. The knowledge of indications, assessment lead and device technology has expanded to include CRT, leadless pacing and conduction system pacing such as His bundle and left bundle branch area pacing. But there is still a lack of evidence for these new technologies as well as for common indications such as atrial fibrillation and upgrading from a previous device. The role of personalized medicine will become increasingly important when selecting candidates for CRT, primary preventive ICD ablation procedures and emerging new devices such as cardiac contractility modulation (CCM). Rapidity of therapy is associated with outcome which will be a challenge. If properly implemented devices and drugs will have a large positive affect of HF outcomes.

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1. Introduction

Heart Failure (HF) has poor prognosis despite moderns HF therapy with a five -year mortality rate of 50 %. In recent years we have seen great advances in HF medication [1]. Still many remain symptomatic and one in three have electrical dyssynchrony and may indicated for additional therapies such as cardiac resynchronisation (CRT) [2]. The increasing knowledge of HF epidemiology, imaging evaluation techniques and effective therapies has led to universal definitions of HF-phenotype based on left ventricular (LV) ejection fraction (EF) into heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) [3]. This definition has not affected the indications for CRT which are limited to patients with HFrEF and based on LVEF < 35 % or < 40 % depending on indication [4].

CRT developed in late 1990s emerged as a promising therapy for HFrEF and electrical dyssynchrony defined by the presence of wide QRS on the 12 lead ECG. Initially the therapy was called biventricular pacing but soon cardiac resynchronisation (CRT) became the accepted term. CRT has been shown to improve survival, reduce heart failure hospitalisations, improve exercise tolerance and quality of life in patients with HFrEF with wide QRS who remain symptomatic despite guidelines indicated medical therapy (GMDT) [5–11]. The discovery that the lateral wall of the LV could be stimulated by pacing from the coronary sinus was a major achievement [12]. The lateral wall of the LV is the area of latest electrical activation in dyssynchrony including in left bundle branch block. Pacing the LV and the

right ventricle partly overcame the dyssynchrony which resulted in reverse LV remodeling and clinical improvements.

In later years there has been many major breakthroughs in HF medication reflected in recent guidelines including the introduction of sacubitril- valsartan and SGLT2 inhibitors. In addition the sequential approach to initiate HF drugs is being replaced by rapid initiation of all four guidelines indicated drugs within the first month of treatment [13]. Most of these drugs also reduce the risk for sudden cardiac death (SCD) making the choice to provide a primary preventive defibrillator in the CRT (CRT-D) especially challenging.

2. Indications according to the ESC 2021 guidelines on cardiac pacing and CRT

Guidelines state that CRT is indicated in patients with left bundle branch block (LBBB) and wide QRS with a class I level of evidence A for QRS width ≥ 150 ms and with a class IIa for QRS width 130–149 ms [4]. For patients without LBBB the recommendations are class IIa or IIb depending on QRS width. Importantly, CRT is contraindicated in QRS width < 130 ms [14] because normal or near normal conduction and activation of the ventricles is always superior to that induced by pacing including biventricular pacing.

CRT is effective in symptomatic HF patients meaning NYHA class II–IV [5–11]. One of the main mechanism of action is left ventricular (LV) reverse remodeling. This process starts immediately after CRT is turned on [15] and further evolves over a 2 year time period [16]. In the REVERSE trial a randomised controlled study in patients with mild HF symptoms sustained LV reverse remodeling over a 5 year period could be demonstrated [17]. In practise this means that CRT both reverses remodeling and delays disease progression depending

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on disease severity. In spite of very strong evidence patients with CRT indication do not get access to therapy [18,19]. Women appear particularly underserved [19,20].

3. Choice of CRT- D or CRT- P in primary prevention of sudden cardiac death

With the evolution of HF modifying medication and CRT, the relative risk of sudden cardiac death (SCD) has been reduced more than 40 % [21]. With each added guidelines indicated HF medication the risk of both total mortality and SCD decrease [22]. CRT per se also reduces the risk of sudden cardiac death [23]. Following the negative results of the DANISH trial [24] comparing ICD with or without CRT to no ICD the decision to implant a CRT-P or CRT-D has become even more challenging especially in patients with non-ischemic HF etiology. Finally, not all SCD is due to ventricular tachy-arrhythmia and thus preventable with ICD. Preventive models to evaluate the risk of SCD against that of total mortality have been introduced and may be helpful [25]. ESC 2021 guidelines on pacing and CRT also include such a help and take presence of myocardial scar tissue into account [4]. Ongoing projects to build models to predict risk for SCD after acute myocardial infarction such as PROFID will determine the value of clinical prediction model in neural networks (profid-project.eu)

Ultimately there is a need for a randomized study comparing CRT-P to CRT- D such as the ongoing RESET CRT. The investigators already published a prelude to this study: the RESET CRT project which applied the inclusion criteria in the RESET CRT to a German registry. They found no survival benefit in CRT- D over CRT -P treated patients after comorbidity and age adjustment [26] again highlighting competing risks for mortality in older patients. These results further emphasizes that each decision to implant a primary preventive ICD in conjunction with CRT needs to be personalized to the individual patient.

4. CRT in patients in need of RV pacing

Right ventricular pacing may induced HF and should be avoided whenever possible. RV pacing $\geq 20\%$ is enough to increase the risk of developing LV dysfunction and by time HF as evidenced in the DAVID [27] and MOST trials [28]. The BLOCK-HF study showed that CRT to patients in need of RV pacing is superior to RV pacing for mortality and HF hospitalisations and LV function [29] which is reflected in the guidelines but not widely adopted in clinical practise [4,30]. One reason may be use of algorithms adjusting AV delay to allow intrinsic conduction and thus minimize level of RV pacing in patients with intermittent high degree AV- block. But this approach will require careful monitoring and documentation since extent of RV pacing as well as LV function may change over time. As many patients are followed by remote monitoring, special attention must be given to detect increases in extent of RV stimulation and to monitor LVEF. For the future, the risk of RV pacing induced HF may decline by the potential greater use of conduction system pacing when such techniques such as His pacing are commonly available and feasible. But at present and according to the 2021 ESC EHRA pacing and CRT guidelines conduction system pacing are nor recommended [4].

5. Lead- less pacing

Leadless pacing is a way of to reduce lead and pocket related problems [31]. It is a small device inserted intravenously and screwed into the RV septum. Ideal candidates are older patients with intermittent RV pacing need such as in sinus arrest or intermittent high degree AV block. Long term results of the MICRA trial indicate excellent results [32] with 38 % lower rates of re-interventions and 31 % lower risk of chronic complications compared to transvenous VVI pacing but costs remain high. Until recently AV synchronous pacing

could not be delivered by leadless pacing but this is being resolved [33]. Cantillon et al. just recently reported that 3 months safety and performance data of leadless AV synchronous pacing using one device in the right atrium and one in right ventricle. Of 300 patients 2/3rd had sinus node disease and 1/3rd had high degree AV block . Implantation was successful in 98 %. At least 70 % AV synchrony was achieved in 95 % exceeding the goal of 83 % [33]. Electrical performance was similar to dual chamber transvenous pacing systems. This study needs to be confirmed in a larger material with longer follow up time. Whether leadless systems can also be combined with LV stimulation remains to be demonstrated.

6. Enhancement of CRT therapy

Continuous optimization for CRT with stimulating of the LV to fuse of with intrinsic right bundle conduction is a concept called synchronized LV stimulation which has been studied [34] with favorable results on outcome and AF in patients with LBBB and normal AV conduction [35] compared to conventional CRT. In the Adapt response global trial [34] patients with NYHA class II-IV HF, LVEF $\leq 35\%$, LBBB using the Strauss criteria with QRS duration ≥ 140 ms (men) or ≥ 130 ms (women) and baseline PR interval ≤ 200 ms were randomly assigned to synchronized LV stimulation or conventional CRT. The primary outcome was a composite of all-cause death or intervention for HF decompensation. The study was interrupted for futility in the third interim analysis with 59 month follow up and the results reported by at the European Heart Rhythm association (EHRA) annual congress in March 2023. The primary endpoint of mortality and hospitalizations was not met with HR 0.89 and a p-value of 0.077 with a small trend in favor synchronized LV stimulation. Results were consistent among subgroups. Nonetheless, there are many important observations in this trial. It is the largest RCT to date and included 3617 patients and with more than 40 % females. It reports the lowest mortality rate 16 % at 5 years ever irrespective of randomization arm. In a subgroup of patients in whom LV pacing had been delivered $\geq 85\%$ of the time there was a significant 24 % relative reduction in the primary endpoint ($p = 0.0037$). In summary, there were benefits by LV pacing only especially in those patients with high extent of such pacing. We need the paper for further knowledge of the study results. For now the positive results of the Adapt response trial is a call for higher implementation of CRT and for separate QRS criteria in women and men.

7. CRT in atrial fibrillation

Atrial fibrillation accompanies heart failure and its prevalence increases in patients with more severe HF symptoms meaning that 10–50 % of those with HFrEF have AF. Yet efficacy of CRT in AF patients has not been studied in CRT randomised controlled studies and the results are still conflicting. The MUSTIC-AF was a small cross-over study of HF patients with permanent AF. Comparing RV to CRT pacing, the study showed improved exercise tolerance but only modest LV remodeling with CRT compared to RV pacing [36]. In the much larger RAFT trial, there were 229 HF patients with permanent AF patients randomized to CRT-ICD or ICD alone [37]. In a post-hoc analysis no benefit in the combined primary endpoint of all-cause mortality and HF hospitalizations was shown in AF patients but the trial was not powered to show clear treatment effects in patients with AF. The results of a meta-analysis of retrospective studies suggest CRT benefit may be attenuated in patients with a history of AF [38]. Although AF has been an exclusion criterium in many CRT recipients many study patients had history of AF at the time of randomization. In a post hoc analysis of the COMPANION trial there was no benefit of CRT in patients with a history of AF [39]. One probable contributing factor is lack of CRT therapy delivery since intrinsic conduction overrides biventricular stimulation for example during exercise. AV junction

ablation is recommended to ascertain delivery of biventricular pacing in such AF patients [4,40].

Despite clear lack of evidence, the CRT Survey II shows that as much as 1 in 4 of those who receive CRT therapy are AF patients [19] reflecting that many cardiologists are convinced that CRT is beneficial despite lack of evidence. In conclusion, there is a clear need for a randomised study of CRT in AF patients.

8. Upgrading

Patients who develop HF and LVEF < 35 % during treatment with an ICD or a RV based pacemaker and who have RV pacing ≥ 20 % of the time should be considered for upgrading to CRT (Level of evidence IIa B) based on current guidelines [4]. From the CRT Survey II we know that upgrading is common across the ESC countries with no apparent excess perioperative risk in conjunction with the implantation procedures compared to de novo CRT implantation despite older age in upgraded patients [40].

The Budapest CRT upgrade study [41] is a prospective randomised trial which randomised RV paced patients with LVEF < 35 % and ≥ 20 % RV pacing without having intrinsic LBBB to be upgrade to CRT from RV pacing or ICD. The baseline characteristics have been published [42] and show that patients are in their early 70 s with severe HF, multiple comorbidities and are almost exclusively men. In addition, they have a history of having been subject to 85 % RV pacing for at least 6 months. The primary outcome is time to all-cause mortality, HF events, and echocardiographic response. The results may contribute to a more precise definition and extension of the current guidelines for CRT upgrade. The study is unique and will hopefully elucidate the value of upgrading to CRT for outcome.

9. CRT response

Response to CRT therapy traditionally has been categorized as improved, unchanged or worsened [43] based on a combination of mortality, HF hospitalization, NYHA class and patients global assessment. No individual response has been required in HF drug therapy. In contrast, cardiology has only accepted improvements as response to CRT despite the fact that HF is a chronic disease just like many cancers (Fig. 1) [44] and that CRT is always given on top of HF medication. In oncology *partial* remission has long been recognized as an acceptable response to therapy.

Using the definition 30–40 % of patients treated with CRT as non responders encompassing both unchanged or worsening by CRT. Such a high “nonresponse rate” may deter physicians for referring patients for CRT and may contribute to underimplementation of this therapy. But lately, the response definition is in transition. There is now evidence that an unchanged condition (often called stabilization or non progression) is as positive for the patient as an “improvement”. For example it has long been known that CRT to patients with ischemic HF etiology improves outcome despite limited extent of reverse remodeling [10]. REVERSE was a multinational RCT comparing CRT to non CRT in NYHA class II HF patients a disease state for which “improvements” may be more difficult to demonstrate especially early on in treatment. In the trial design LVESVi change was the secondary powered endpoint and the primary endpoint was the composite Packer endpoint. The Packer combined endpoint was significant after 2 year results [16] but only borderline significant after one year [7] reflecting the mild disease state on randomised patients. In a subsequent substudy a similar probability of death was found in those stabilized as in those who improved. (Fig. 2). In contrast, patients who worsened had significantly worse prognosis [45,46]. The conclusion is twofold. Firstly, lack of early improvement in LVESVi or clinical improvement does not preclude subsequent outcome benefit. Secondly and importantly, patients who deteriorate during CRT need to be considered for advanced therapies [45,46].

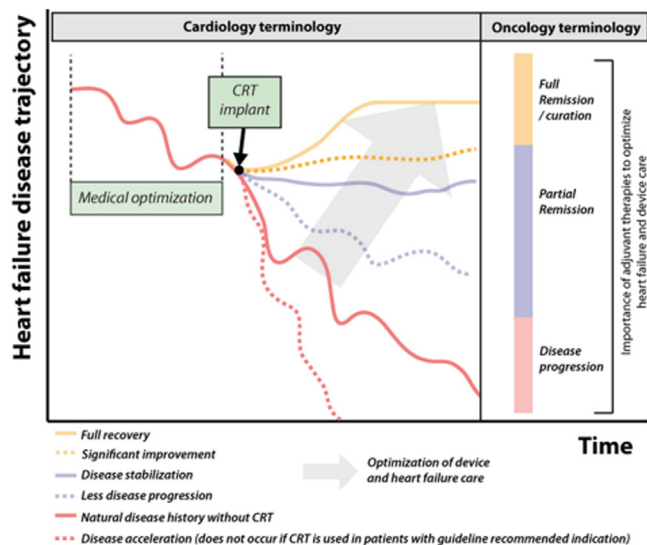


Fig. 1. Role of CRT in disease modification of the heart failure trajectory. Reprinted with permission from Mullens W et al. Eur J Heart fail 2020;22:2349
CRT: Cardiac resynchronization therapy.

But we do have recent indicators for patients not expected to benefit from CRT. A very recent additional evidence from a large patient based meta-analysis of nine studies clearly shows that right bundle branch block (RBBB) patients *do not* benefit from CRT and conversely that patients in intraventricular conduction disturbance IVCD who often have underlying ischemic heart disease benefit to the same extent and those with LBBB [47]. The results have immediate implications since RBBB patients should be given other therapies and patients in ischemic cardiomyopathy who often present with IVCD should not be withheld from CRT.

In conclusion to much emphasis has been given to stress that improvement is the only acceptable response to CRT which is now being replaced by improvement/stabilization. Instead of emphasizing the need for the patient to have LBBB to benefit from CRT it now becomes apparent that RBBB distinguishes a group who is not suitable for CRT whereas LBBB and IVCD patients benefit.

10. Women and body size

Women are undertreated [19] but also less often have HFref [48] raising the question whether the reported 25 % in clinical studies and registries is appropriate. Women also have prerequisites for great response to CRT such as LBBB [49] and dilated cardiomyopathy. But women have smaller QRS widths than men even in the presence of LBBB and may therefore not fulfill guidelines Class I recommendations [4] for CRT not the QRS width inclusion criteria in many studies contributing to underimplementation. In a pooled metaanalysis based on 4076 patients in 2 RCT women as opposed to men [49] with LBBB and QRS width 130–149 ms benefited from CRT-D. This stresses the importance of considering sex and body size when assessing a patient for CRT. The relationship between QRS width and CRT benefit for outcome has been clearly demonstrated [50] and in a subsequent publication from the same group *height* was shown to be more important for response than *sex per se* with greater CRT response in shorter persons [51]. Thus, shorter men (median 167 cm) responded better to CRT and at smaller QRS widths just like women whereas taller men only benefited at QRS widths > 150 ms. A later case based meta-analysis [52] confirmed greater CRT response in with smaller or medium height, body weight and body surface area (BSA) (Fig. 3) [52]. In conclusion: we need to move into precision medicine taking not only sex but body size and possibly ethnicity into account in clinical decision making for CRT.

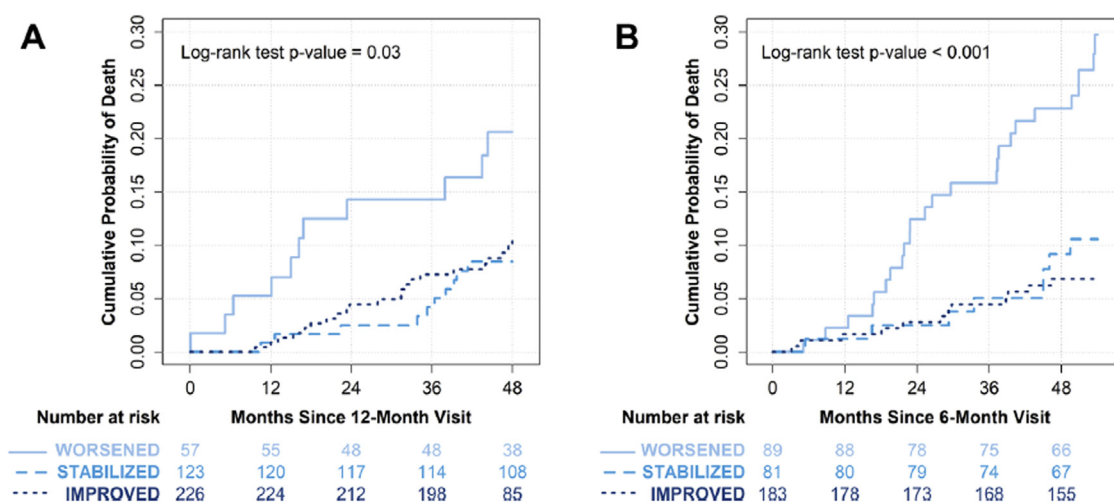


Fig. 2. Long term mortality in patients assigned to CRT ON in the REVERSE study according to one year response either worsened, stabilized or improved. Reprinted with permission from Gold et al. JACC Clin Electrophysiol. 2021 Jul;7(7):871–880. Doi 10.1016/j.jacep.2020.11.010.

Finally, there may be a reluctance to give women CRT since in CRT Survey II had a higher procedural complication rate, related to vascular access as evidenced by pneumothorax (1.4 %), coronary sinus dissection (2.1 %), and pericardial tamponade (0.3 %) [53]. The probable reason is the smaller dimensions of vessels in women compared to men [53].

11. Conduction system pacing

His bundle pacing (HBP) is appealing since the lead is inserted to the His bundle achieving normal or near normal ventricular activation pattern [54,55] perceived as a marker of clinical response. But HBP may come at the expense more complex implantation procedure than RV pacing, a higher pacing threshold and there is a lack of evidence from RCTs and long-term results. Vinther et al. [56] in the randomised comparison between HBP and CRT in HF patients with LBBB found similar physical and clinical improvements over 6 months. The 2021 Guidelines on cardiac pacing and CRT are cautious on HBP and state that it may be considered as an alternative to RV pacing in patients with AV block and LVEF >40 %, who are anticipated to have >20 % ventricular pacing (Class of recommendation IIb Level of evidence C [4]). They also state that HBP with a ventricular backup lead may be considered in patients in whom a “pace-and-ablate” strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when intrinsic QRS is narrow. For CRT HBP can only be seen as a backup when coronary sinus cannot be reached.

In patients with LBBB left bundle area pacing LBBA may become an alternative to conventional CRT [57] but lacks scientific evidence from RCTs. This technique is theoretically attractive since the LV lead inserted in the LV septum to pace the left bundle area. The block in LBBB is often in the proximal part of the left bundle and hence accessible by this technique. Although the technique is simpler than HBP there is a learning curve around 200 implantations [58]. The lead stability is greater than in HBP and the stimulation threshold lower but there are other hazards. In a large European registry MELOS complications included septal perforation and coronary perforation and the success rate of implanting the lead in the septum was lower in HF patients. [58]. As earlier stated, HBP and LBBA pacing have different patient targets. Patients with bradyarrhythmia and RBBB may be candidates for His pacing. A CRT indicated patient with LBBB can be eligible for LBBA pacing. But the technique cannot be widely adopted without scientific evidence. There are ongoing RCT comparing CRT to LBBA pacing and we need these results. The 2021 ESC guidelines [4] do not make a recommendation for LBBA Pacing but state that

conduction system pacing is very likely to play a growing role in the future.

12. AV nodal ablation, pulmonary vein isolation and cardiac contractility modulation therapy

Tachycardia mediated cardiomyopathy patients often present with palpitations, HF symptoms and severe LV systolic dysfunction and have rapid atrial tachyarrhythmia. Pulmonary vein isolation (PVI) should be strongly considered in such patients [59] and patients should then be carefully followed for need of further therapies. HF patients with AF who are expected to tolerate PVI should be to improve outcome [60,61]. But, in elderly individuals who are not suitable for PVI AV junction ablation and CRT improves outcome in terms of longevity and reduced need for hospitalizations according to the results of the APAF CRT trial [62] and thus should be preferred over PVI.

As much of 70 % of HFrEF patients do not have wide QRS duration. In such patients a cardiac contractility modulation device may be an alternative additive therapy au lieu de CRT. Cardiac contractility modulation (CCM) consists of the delivery of nonexcitatory electrical signals in the absolute ventricular refractory period to the RV septum [63] but does not pace. It is associated with improved Calcium handling, reversal of fetal gene program and improved contractility and diastolic function [63] in human and animal studies. The FIX trials were performed in patients with NYHA class III-IV HF, with an LVEF >25 % to <45 % and QRS duration <130 ms and all show improvements in peak VO₂, NYHA class quality of life accompanied by reductions in HF hospitalizations [64,65] with results comparable to those of the early CRT trials [5]. Long term open studies also indicate benefit in HF patients with AF [66]. The results on mortality remain to be studied in the ongoing AimHigher study (clinicaltrials NCT05064709). CCM is recommended by the FDA in NYHA II-III HF patients with LVEF 25–45 % on optimal medical therapy, with no indication for pacing or CRT. In Europe the guidelines committee consider the scientific evidence insufficient for recommendation [1].

13. HF therapy implementation and timing

Timing of HF therapies is key for the survival of the HF. But the greatest challenge is to properly ensure that HF medications are given to HFrEF patients. Betablockers, ARNi, MRA all reduce the risk of sudden cardiac death through reverse remodeling [67,68]. Therefore, swift introduction of these disease modifying drugs is needed and with through evaluation of clinical findings, echocardiography

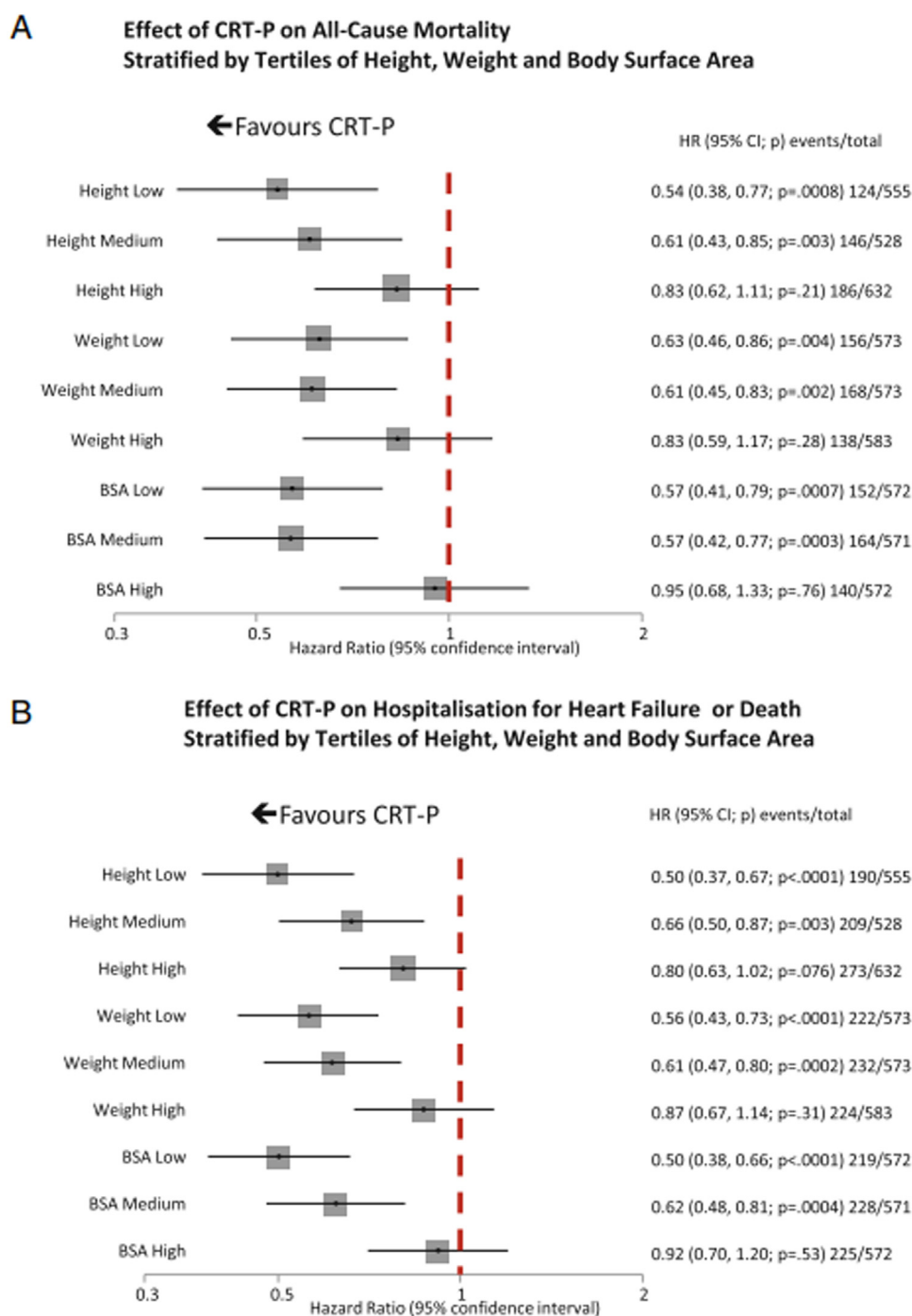


Fig. 3. Effect of CRT on all-cause mortality and all cause mortality and heart failure hospitalizations stratified by height, weight and body surface area (BSA) tertiles
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before deciding on device implantation. Mebazaa [13] recently in the Strong HF study showed that institution of all four guidelines indicated HF medication in connection with a HF hospitalization was associated with superior 180 days outcome compared to conventional care. The results indicate rapid response already within 30 days. Recent evidence from a nationwide study indicates that introduction of CRT therapy should not be delayed [69]. In a nationwide study in the UK Levya et al. showed that receiving CRT early before a patient being hospitalized for HF or during a first HF hospitalization (HFH) was associated with superior survival to delayed onset of therapy. 64,968 first CRT implantations 2010–2019 were analyzed and divided into CRT implantation with no previous HFH,

CRT implantation during HFH or after ≥ 1 HFH. Time in years after first HFH was associated with increasingly higher risk of total mortality (HR, 1.19; CI 1.17–1.20). An additional aspect of not waiting with CRT in indicated patients is that patients with electrical dyssynchrony such as LBBB have been shown to respond less to HF medication for reverse remodeling. In the NEOLITH, [70] marginal improvements in LVEF after 3 months of medical therapy was found in patients with LBBB. Similar observations were made by Sze et al. [70].

This rapid introduction of HF therapies including device therapy will require good organization of HF care. HF-care including device therapy heavily hinges of multidisciplinary HF team with a care plan for each patient with rapid revision according to the disease state of

the individual. Results from the Swedish HF National registry show that therapy implementation including CRT is increased in such care and which in turn is linked to improved outcome [71,72].

Disclosure of interest

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