1 2 9 0

FACULDADE DE MEDICINA
UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

RODRIGO MIGUEL PEREIRA MARTINS

Cardiac Resynchronization Therapy – predictors of echocardiographic response: Systematic Review with Meta-Analysis

ARTIGO DE REVISÃO SISTEMÁTICA COM META-ANÁLISE

ÁREA CIENTÍFICA DE CARDIOLOGIA

Trabalho realizado sob a orientação de:

PROFESSORA DOUTORA BÁRBARA CECÍLIA BESSA DOS SANTOS OLIVEIROS PAIVA

PROFESSORA DOUTORA NATÁLIA SOFIA CLÁUDIO ANTÓNIO

ABRIL/2021

Curso de Mestrado Integrado em Medicina da Faculdade de Medicina da Universidade de Coimbra, Portugal

Cardiac Resynchronization Therapy – predictors of echocardiographic response: Systematic Review with Meta-Analysis

Investigadores:

Rodrigo Miguel Pereira Martins[1]

Dra. Helena Margarida de Miranda Lemos Romão Donato

Professora Doutora Natália Sofia Cláudio António

Professora Doutora Bárbara Cecília Bessa Dos Santos Oliveiros Paiva

[1]**Email:** rodrigom97@gmail.com

Para os meus pais, Paula e Luís

Table of contents

Tables and figures

1 Abbreviations

adj p - adjusted p-value for False Discovery Rate in multiple comparisons

AF - atrial fibrillation

CENTRAL - Cochrane Central Register of Controlled Trials

CRT - cardiac resynchronization therapy

CRT-D - cardiac resynchronization therapy and defibrillator

CRT-P - cardiac resynchronization therapy and pacemaker

ESC - European Society of Cardiology

GFR - glomerular filtration rate

HF - heart failure

HFrEF - heart failure with reduced ejection fraction

HT - hypertension

LBBB - left bundle branch block

LV - left ventricle

LVEF - left ventricular ejection fraction

LVESV - left ventricular end-systolic volume

MRI - magnetic resonance imaging

NICM - non-ischemic cardiomyopathy

NOS - Newcastle-Ottawa Scale

NYHA - New York Heart Association

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

RBBB - right bundle branch block

RCT - randomized controlled trial

ROC - receiver operating characteristic

2 Resumo

Introdução: A terapêutica de ressincronização cardíaca (TRC) é uma opção comprovada para pacientes com insuficiência cardíaca (IC) selecionados adequadamente. Contudo, pelo menos 30% dos pacientes não apresentam os resultados esperados. Vários estudos já abordaram este problema, tentando identificar preditores de resposta à TRC, mas, à luz do conhecimento dos autores, ainda não existe uma revisão sistemática com meta-análise, usando dados do mundo real, a abordar este tema.

Objetivos: Identificar potenciais preditores de resposta à TRC, usando dados do mundo real.

Métodos: Uma pesquisa sistemática foi realizada, recorrendo às bases de dados *PubMed*, *Embase* e *Cochrane Central Register of Controlled Trials* (CENTRAL), com um limite temporal relativo às publicações entre 31 de outubro de 2010 e 31 de outubro de 2020, pesquisando-se estudos observacionais prospetivos com um desenho de estudo que, de alguma forma, envolvesse a avaliação de resposta à TRC, definida como uma diminuição do volume telessistólico do ventrículo esquerdo ≥ 15%, aos 6 meses de follow-up, através de ecografia bidimensional. A avaliação da elegibilidade dos artigos, primeiro através dos títulos e resumos, depois através do texto completo, foi realizada, de forma independente, pelos autores, de acordo com os critérios de inclusão. Após colheita e processamento dos dados relevantes, foram aplicadas meta-análise e análise de curvas ROC (*Receiver Operating Characteristic*), seguidas da identificação do ponto de corte ótimo pelo índice de Youden, com análise de concordância (Kappa de Cohen) aplicada à tabela de classificação, ponderadas de acordo com a precisão dos estudos. É apresentada a probabilidade de resposta à terapêutica dada a presença ou ausência de cada uma das características identificadas.

Resultados: 2462 citações foram encontradas e um total de 24 estudos foram incluídos nas análises qualitativa e quantitativa. A meta-análise mostrou que o género feminino ($p = 0.018$; adj $p = 0.077$), a cardiomiopatia de etiologia não-isquémica (CMNI) ($p < 0.001$; adj $p = 0.023$), o bloqueio de ramo esquerdo (BRE) ($p = 0.001$; adj $p = 0.046$), o QRS longo ($p < 0.001$; adj $p = 0.023$) e a classe *New York Heart Association* (NYHA) II ($p = 0.014$; adj $p = 0.062$) parecem favorecer a resposta à TRC. Após análise ROC e regressão logística, o género feminino (kappa = 0.450; $p < 0.001$), a CMNI (kappa = 0.636; $p < 0.001$), o BRE (kappa = 0.935; $p < 0.001$), e a classe NYHA II (kappa = 0.647; $p < 0.001$) foram identificados como preditores independentes de resposta à TRC, sendo o BRE o mais fiável (sensibilidade = 97.24%; especificidade = 98.86%).

Conclusões: Género feminino, CMNI, BRE e classe NYHA II são as variáveis basais com uma aparente capacidade de predizer, de forma independente e com elevada acuidade, a resposta à TRC – populações com proporções maiores de pacientes com estas características

têm maior probabilidade de apresentar benefício com esta terapêutica. De acordo com os dados, o BRE é o preditor mais fiável de resposta à TRC.
Palavras-chave: terapêutica de ressincronização cardíaca; preditores; resposta; remodelagem do ventrículo esquerdo; bloqueio de ramo esquerdo

3 Abstract

Introduction: Cardiac resynchronization therapy (CRT) is an established device therapy for appropriately selected patients with heart failure (HF). However, at least 30% of the patients do not achieve the expected outcomes. Many studies have addressed this problem by trying to identify predictors of response to CRT, but, to the authors' knowledge, it still does not exist a systematic review with meta-analysis of real-world data assessing this topic.

Objectives: To identify potential predictors of response to CRT, using real-world evidence.

Methods: A systematic search was conducted in PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL), from October 31st of 2010 to October 31st of 2020, for observational prospective studies, referring, somehow, a study design that involved the evaluation of response to CRT, defined as a decrease in left ventricle end-systolic volume (LVESV) ≥ 15% at 6-month follow-up, via two-dimensional echocardiography. Screening, first of titles and abstracts, then from full text, was performed independently by the authors, according to the inclusion criteria. After collection and processing of the relevant data, meta-analysis techniques were applied and also Receiver Operating Characteristic (ROC) curve analysis, followed by optimal threshold identification by Youden Index, with concordance analysis (Cohen's kappa) applied to the classification table, were conducted, weighted by studies precision. Probability of response is given according to the presence or absence of each one of the identified characteristics.

Results: 2462 citations were retrieved, being a total of 24 studies included in qualitative and quantitative synthesis. The meta-analysis showed that female gender ($p = 0.018$; adj $p = 0.077$), non-ischemic cardiomyopathy (NICM) ($p < 0.001$; adj $p = 0.023$), left bundle branch morphology (LBBB) ($p = 0.001$; adj $p = 0.046$), longer QRS ($p < 0.001$; adj $p = 0.023$) and New York Heart Association (NYHA) class II ($p = 0.014$; adj $p = 0.062$) appear to favor response to CRT. After ROC analysis and logistic regression procedures, female gender (kappa = 0.450; $p < 0.001$), NICM (kappa = 0.636; $p < 0.001$), LBBB (kappa = 0.935; $p < 0.001$), and NYHA class II (kappa = 0.647; $p < 0.001$) were identified as independent predictors of response to CRT, being LBBB the most reliable one (sensitivity = 97.24%; specificity = 98.86%).

Conclusions: Female gender, NICM, LBBB and NYHA class II are baseline variables with an apparent capability to independently predict response to CRT – populations with higher proportion of patients with these characteristics are more likely to benefit from this therapy. According to these data, LBBB is the most reliable predictor of CRT response.

Keywords: cardiac resynchronization therapy; predictors; response; left ventricular remodeling; left bundle branch block

4 Introduction

Cardiac resynchronization therapy (CRT) is a clinically proven therapeutic option in properly selected patients with heart failure with reduced ejection fraction (HFrEF), that improves functional status and LV systolic function, and reduces morbidity and mortality. [1,2] As a concept, conventional CRT (also known as biventricular pacing) entails a modality in which both ventricles are submitted to electrical stimulation, correcting the existent mechanical desynchrony. [3] Even though CRT is recognized as an effective treatment in this context, at least 30% of patients do not benefit from it, and some of them even worsen their health status. [4] Therefore, it is crucial to improve patients' selection for CRT, in order to achieve better outcomes from it in these patients.

Over the last decade, observational studies and several randomized clinical trials, including a meta-analysis of clinical trials, [5] reported some patients' characteristics that increase the chance of response to CRT and that are present on current guidelines. [6] However, to our knowledge, it still does not exist a systematic review with meta-analysis of real-world evidence assessing predictors of response to CRT.

This paper aims to synthesize the large quantity of real-world data regarding predictors of echocardiographic response to CRT, by conducting a meta-analysis of the available prospective CRT studies. Real-world evidence meta-analysis on this issue could provide valuable insights to confirm predictors of CRT response in routine clinical practice.

5 Methods

5.1 Protocol and registration

The design of this study respected all the standards present on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. At inception, a registration in the PROSPERO database (identified as CRD42020211520) was completed (Appendix I).

5.2 Eligibility criteria

Regarding eligibility criteria, the following were considered: (1) observational prospective studies, referring, somehow, a study design that involved the evaluation of response to CRT, defined, for the purpose of this study, as a decrease in LVESV ≥ 15%; (2) a responder had to be defined, at no other time period than 6 months of follow-up, and with no other method than a two-dimensional echocardiography, as a patient that achieved a decrease in LVESV ≥ 15%, and a non-responder as a patient that did not achieve a decrease in LVESV ≥ 15%; (3) patients included had to be older than 18 years old, have a wide QRS duration (not below than 120 ms) and be submitted, for the first time in their lives, to a conventional CRT method (biventricular pacing); and (4) baseline data, comparing responders and non-responders, had to be present and explicit, with, at least, the following variables: age, gender, etiology of cardiomyopathy, QRS duration, left ventricle ejection fraction (LVEF) and LVESV. Studies that included patients with a previous cardiac device (such as pacemaker), only one cardiomyopathy subtype (ischemic or non-ischemic), only a specific type of desynchrony and sarcoidosis were excluded. Articles that considered non-responders, besides not reaching the response definition at 6 months of follow-up, as the patients that died before the considered follow-up period, were also excluded.

This specific criterium of response was chosen based on the fact that is considered one of the most reliable parameters to assess cardiac reverse remodeling after CRT. [7]

5.3 Information Sources and Search Strategy

A systematic search was conducted in PubMed®, Embase® and Cochrane Central Register of Controlled Trials (CENTRAL), for articles written in English and published from October 31st of 2010 to October 31st of 2020. MeSH terms were used to improve the search, as well as specific filters of each database, when appropriate.

The following search equation was applied in PubMed®: ("Cardiac Resynchronization Therapy"[Mesh] OR "Cardiac Resynchronization Therapy Devices"[Mesh] OR "cardiac resynchronization therapy"[Title/Abstract] OR "biventricular pacing"[Title/Abstract] OR "biventricular pacemaker"[Title/Abstract] OR CRT[Title/Abstract]) AND

("Echocardiography"[Mesh] OR echocardiography[Title/Abstract]) AND ("response"[Title/Abstract] OR "responders"[Title/Abstract] OR "reverse remodelling"[Title/Abstract] OR "clinical improvement"[Title/Abstract]). As search limits, the next were applied: articles written in English, published in the last 10 years. This search strategy was applied for the other considered databases, adapting it to the specifications of each one.

5.4 Data Collection and Management

Regarding study selection, two authors (RM and NA) screened, independently and systematically, titles and abstracts of obtained publications from the already explained search strategy, with studies that satisfied the criteria mentioned above being included for further full-text evaluation. Subsequently, the full text assessment of the eligible articles was, again, carried out by the same two review team members, independently. Disagreements between individual judgements were solved by consensus, including a third author (BO). Data regarding the following baseline variables were collected, concerning responders and non-responders: age, gender, cardiomyopathy subtype, bundle branch block morphology, rhythm status, QRS duration, ejection fraction, LVESV, NYHA functional classes, diabetes, hypertension, dyslipidemia, and chronic renal insufficiency. All the variables were considered for meta-analyses, except dyslipidemia and chronic renal insufficiency, since a rapid statistical analysis did not reveal relevant findings. Some articles only reported data relative to LVEF and LVESV via other methods than 2D echography (3D echography [8] and MRI [9,10]), while another had data regarding only LVESV index, instead of LVESV. [9,11] Therefore, values from these articles corresponding to the referred variables were not used in the meta-analyses.

5.5 Risk of bias assessment

Only prospective observational studies were included on this manuscript. Therefore, the Newcastle-Ottawa Scale (NOS) for non-randomized studies was used, independently, by two review team members (RM and BO), to appraise the risk of bias of the included articles. Using this tool, three domains were assessed, based on a ‘star system’: selection of the study groups (it implies four items, and each one can value one star, depending on the study’s characteristics); comparability of them (it can value a total of two stars); and the evaluation of the outcome (it implies three items, and each one can value one star). The Newcastle-Ottawa Scale summary (Table 1) presents the quality appraisal for each study.

5.6 Statistical Analysis – Synthesis of Results and Additional Analyses

Initially, it was performed a meta-analysis applying a random effects model and using as effect size the standardized mean difference of each one of the variables in analysis. For the quantitative ones, the Cohen’s d was computed, and for the binary ones the approximation of the binomial distribution to a z score was achieved. Heterogeneity of the results was evaluated through the I^2 measure and plotted the overall summary measures in a summary forest plot with a lateral table, where confidence intervals and either original p-values and adjusted p-values are described (using Benjamini-Hochberg correction assuming a false discovery rate of 20%). With this analysis, performed in R, version 4.0.3 through the *metaphor* package, it was possible to identify which variables presented statistical differences between response and non-response to CRT.

Afterwards, a ROC analysis was applied to each variable identified in the previous meta-analyses as presenting statistically significant differences (considering $p < 0.05$ and adj $p < 0.10$), in order to identify eventual thresholds for quantitative variables which may discriminate groups, and also for binary ones presented as a percentage of the characteristic of interest in papers used in analysis. For each variable considered as discriminating groups (defined as an area under the ROC curve above 0.5 with a statistical significance), the variable was dichotomized according to the threshold defined by the highest Youden index and the sensitivity, specificity, positive and negative predictive values were obtained. Predictive values may be used to determine the probability having a response when the characteristic that is in analysis is present or absent. Also, the Cohen's kappa was calculated to accomplish concordance between predictions and observed classification for response. These former analyses were performed in IBM SPSS®, version 26, using study precision as weights for analysis. Study precision is defined as the inverse of the sampling variance, and weights were determined as the percentage of sampling variance of each study relative to the total sampling variance, which is the sum of study individual sampling variances. Sampling variance is defined as the squared standard error, but there were two studies in which it was not reported. In one of them it was the variation range, which was approximated to 6 standard deviations; in another study, it was reported the interquartile range and it was decided to approximate it to 2 standard deviations. For binary variables, expressed as percentages, and using the Bernoulli distribution, it was assumed that the sampling variance is given by $p(1-p)$, where p is the percentage of cases satisfying that condition.

All the analyses were evaluated at a 5% significance level and confidence intervals were determined for 95% confidence level.

Table 1 - Newcastle-Ottawa summary

	Selection	Comparability	Outcome	Total score
Abdelhamid 2017	***	*	***	7
Ahmed 2016	***	*	***	7
Almeida-Morais 2018	***		***	6
Auger 2014	***	*	***	7
Bertini 2010	***	*	***	7
Brunet-Bernard 2014	****	**	***	9
Carlomagno 2015	***		***	6
Cochet 2013	***	*	***	7
Fournet 2017	***	*	***	7
Ibrahim 2019	***	*	***	7
Jackson 2014	***	*	***	7
Klimusina 2011	***	*	**	6
Maffè 2015	***	*	***	7
Mastenbroek 2016	***	*	***	7
Modi 2017	***		***	6
Petrovic 2016	***		***	6
Risum 2012	***	*	***	7
Shanks 2010	***	**	***	8
Sunman 2016	***	*	***	7
Wang 2010	***	**	***	8
Wita 2015	***	*	***	7
Wong 2013	***	*	***	7
Zaremba 2019	***	**	***	8
Zhu 2019	***	**	***	8

6 Results

6.1 Study Selection and Search Results

A total of 2462 publications were identified through the already mentioned literature search strategy (Figure 1). After removal of duplicates, 1773 records were screened based on their title and abstract, applying the criteria stated previously, being 1576 of these excluded. At this stage, 197 papers were considered for full-text assessment, resulting in the exclusion of 173, for the following reasons: forty-two were conference abstracts; nineteen were retrospective studies (or included data collection in that way); nineteen did not have the all the demanded baseline variables to be included on this systematic review; fifty-two did not have the pretended data regarding, explicitly, responders and non-responders; thirty-one considered other definition of response; five had other definition of non-response (considering patients that died before the 6-month evaluation as non-responders); ten evaluated patient's response at other follow-up period than six months; fifteen included patients with a previous cardiac device; two considered other pacing modality (than conventional biventricular pacing); one study only included patients with a specific cardiomyopathy subtype; two had the presence of desynchrony as an inclusion criteria; two included patients with sarcoidosis; one included patients with narrow QRS; and two were only available in other language (Russian). At this point, twenty-five studies fulfilled all the inclusion criteria for the systematic review, being twenty-four observational prospective studies and only one an RCT. Given this fact, and to study only "real-world" patients, the RCT was also excluded. Therefore, twenty-four studies were included in the qualitative synthesis, and all of them contributed to the quantitative synthesis (with the variables present on each article).

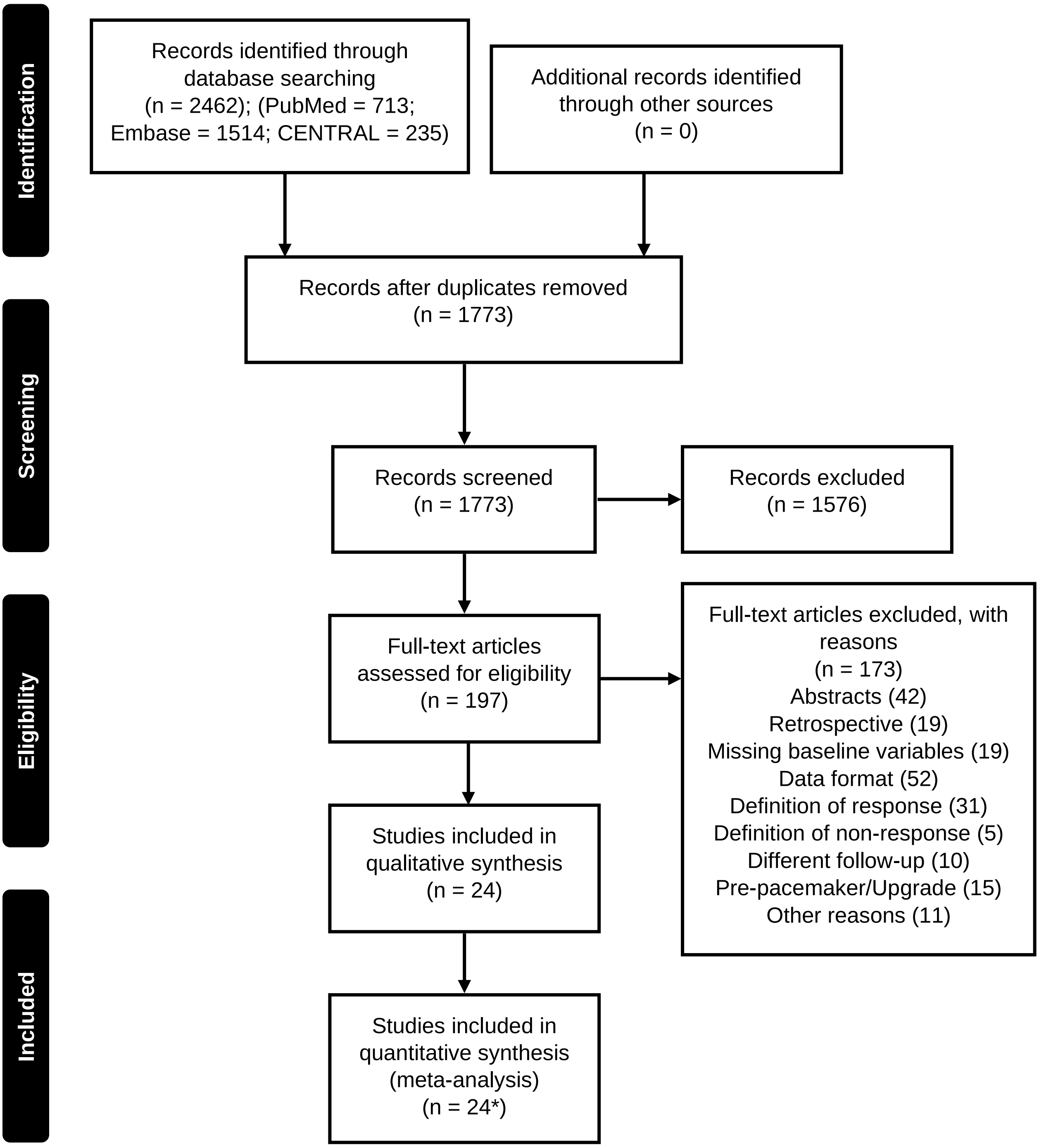

Figure 1 - PRISMA flow diagram of search strategy

*Not all the 24 studies contributed with data to all the studied variables.

Table 2 - Studies characteristics

Author	Year	Multicenter	No.		Inclusion criteria					Relevant exclusion criteria/ Other important notes
			Responders	Non-responders	QRS (ms)	LVEF (%)	NYHA	Sinus rhythm [a)]	LBBB [b)]	
Abdelhamid [12]	2017	No	63	31	≥ 120 (with LBBB); ≥ 150 (with non-LBBB)	≤ 35	III/IV	Yes		Decompensated NYHA class IV; sustained atrial arrhythmias
Ahmed [13]	2016	No	19	11	> 120	≤ 35	III/IV			Recent myocardial infarction (≤ 3 months); AF
Almeida-Morais [14]	2018	No	59	56	2013 ESC Guidelines [6]					
Auger [15]	2014	No	177	115	> 120	≤ 35	III/IV			Recent myocardial infarction (≤ 3 months); AF/ Only CRT-D devices were implanted
Bertini [16]	2010		91	68	≥ 120	≤ 35	III/IV	Yes		Only CRT-D devices were implanted
Brunet-Bernard [17]	2014	Yes [c)]	98	64	≥ 120 (if NYHA III/IV); ≥ 150 (if NYHA II)	≤ 35	II/III/IV	Yes [d)]		
Carlomagno [18]	2015	No	33	20	> 120	≤ 35	III/IV	Yes	Yes	Non-LBBB morphology; any kind of myocardial/ pericardial disease (such as recent myocardial infarction or significant organic valve disease)/ Only CRT-D devices were implanted
Cochet [9]	2013	No	42	18	≥ 120 (if NYHA III/IV); ≥ 150 (if NYHA II)	≤ 35	II/III/IV			AF
Fournet [19]	2017	Yes	34	14	2010 ESC Guidelines [20]					RBBB
Ibrahim [21]	2019	No	20	10	≥ 120 (if LBBB); ≥ 150 (if non-LBBB)	≤ 35	II/III/IV			Life expectancy < 1 year; AF/ Only CRT-P devices were implanted
Jackson [22]	2014	No	25	12	≥ 130 for women; ≥ 140 for men	≤ 35	II/III/IV		Yes	

Klimusina [23]	2011	Yes	30	20	≥ 120	≤ 35	III/IV			Life expectancy < 1 year (due to non-cardiac cause)
Maffè [24]	2015	No	61	16	> 120	< 35	II/III/IV			AF
Mastenbroek [25]	2016	No	45	39	2012 ESC Guidelines for treatment of acute and chronic heart failure [26]					Only CRT-D devices were implanted
Modi [27]	2017	No	35	7	≥ 120	≤ 35	II/III/IV		Yes	Recent myocardial infarction (≤ 1 month) or revascularization procedure (≤ 3 months)
Petrovic [28]	2016	No	28	18	> 120	≤ 35	III/IV		Yes	Recent myocardial infarction (≤ 3 months)
Risum [29]	2012	No	43	23	≥ 120	≤ 35	II/III		Yes	Significant primary valve disease; AF; acute coronary syndrome/ revascularization (≤ 3 months)/ Only CRT-D devices were implanted
Shanks [11]	2010	No	169	97	> 120	≤ 35	III/IV			AF
Sunman [30]	2016	No	34	23	≥ 120	< 35	II/III		Yes [e)]	Recent acute coronary syndrome or revascularization procedure (≤ 1 month)/ Only CRT-D devices were implanted
Wang [31]	2010	No	18	12	> 120	≤ 35	III/IV			
Wita [32]	2015	Yes	39	18	≥ 130	≤ 35	III/IV			AF; life expectancy < 1 year
Wong [10]	2013	No	42	18	≥ 120	≤ 35	II/III/IV			Recent myocardial infarction or revascularization procedure (≤ 3 months)/ Only CRT-D devices were implanted
Zaremba [33]	2019	Yes	66	23	≥ 120				Yes	
Zhu [8]	2019	No	27	13	≥ 130	≤ 35	III/IV			RBBB

a) On the referred article, if it is expressly mentioned that patients had to be in sinus rhythm, then the respective box is filled in with ‘Yes’; b) On the referred article, if it is expressly mentioned that patients had to have LBBB, then the respective box is filled in with ‘Yes’; c) The considered cohort is from only one center; d) It was not an inclusion criterium referred in the article, but all patients were in sinus rhythm; e) Only patients with LBBB and intraventricular conduction delay were included.

6.2 Results of Individual Studies

Baseline variables between groups

Age, gender, etiology of cardiomyopathy, QRS duration, LVEF and LVESV were present as baseline variables, in the comparison between responders and non-responders, in all the twenty-four studies included in this systematic review. [8–19,21–25,27–33]

Regarding other variables in the comparison, information regarding NYHA functional class was presented in seventeen studies, [8–12,14–18,21,24,25,27,30,31,33] diabetes mellitus in ten, [8,10,11,13,14,25,27,28,30,32] hypertension in eight, [8,10,13,14,27,28,30,32] dyslipidemia in five, [10,14,27,28,32] and chronic renal insufficiency in five. [8,10,16,25,33] For the electrocardiographic variables, information about atrial fibrillation (AF) was present in six studies, [10,14,23,25,27,30] and LBBB morphology in nine. [8,10,15,17,19,21,25,28,30]

Age

A significant statistically difference was found in only one study, [15] in which the responders where younger than the non-responders. The same trend was also identified in other study, but with a borderline significance. [33]

Gender

Women were responders more frequently, with statistical significance in two studies, [17,19] and with near statistical significance in other two studies. [10,27]

Etiology of cardiomyopathy

NICM was more often present in the responder group, with a reported significant statistically difference in eight studies. [9,10,15,17,24,28,29,31] A similar tendency was verified in other two studies, with near statistical significance. [16,18]

QRS duration

Also, in what concerns this variable, as in every one of the studies mentioned so far, all of them present the same proclivity. Five studies verified, with significant statistically difference, that a wider QRS duration is encountered more regularly in responders, [15,16,18,21,29] and three studies demonstrated the same fact, but with near statistical significance. [10,22,30]

LVEF

Considering LVEF, data was somewhat contradictory. A higher LVEF was more often present in responders, with a significant statistically difference in two studies, [19,32] whilst one study, [28] with statistical significance, and two studies, [15,16] with near statistical significance, showed that, in the responder group, LVEF was lower.

LVESV

As for the previous variable, a sure inference regarding LVESV is difficult to achieve. Three studies verified that the responder group had lower LVESV, with significant statistically difference, [10,19,25] whereas one study demonstrated the opposite. [14] With near significant statistically difference, one study showed that responders had lower LVESV, [8] whereas two studies verified the opposite. [15,29] The results from Wong et al. [10] and Zhu et al. [8] should be carefully interpreted, since the reported results were assessed via MRI and 3D-echography, respectively, although they fulfilled the criteria to be included in this study.

NYHA

Only one study verified, with statistical significance, that a higher NYHA functional class is more often present in non-responders. [10] The opposite trend was verified in another study, but with borderline significance. [11]

Diabetes

Only one study showed that non-responders are more frequently diabetic, but with near statistical difference. [28]

Hypertension

No studies verified relevant differences (whether with statistical significance or borderline significance) regarding the prevalence of hypertension between responders and non-responders to CRT.

Dyslipidemia

As for the hypertensive patients, the same conclusion applies to the dyslipidemic patients.

Chronic renal insufficiency

Regarding patients suffering from chronic renal insufficiency, two studies verified, with statistical difference, that a higher glomerular filtration rate (GFR) is more prevalent in the responder group. [10,16] Accordingly, another study showed that the incidence of this pathology is lower in the responder group, with borderline significance. [33]

Atrial fibrillation

Among the studies that included patients with this condition and assessed it as a baseline variable, only one study verified, with near statistical significance, that there is a trend of AF to be more prevalent in the non-responder group. [27]

Left bundle branch block

Regarding LBBB, three studies, [15,17,21] with significant statistically difference, and one study, [30] with borderline statistical significance, showed that LBBB is more frequent in the responder group.

Univariate and Multivariate analyses

LBBB is the most relevant baseline variable that stands out from the analyses reported from the various studies, both in univariate and multivariate analyses (Appendix II).

Table 3 - Summary of comparisons of baseline variables between responders and non-responders, in all the included studies

		Abdelhamid 2017	Ahmed 2016	Almeida-Morais 2018	Auger 2014	Bertini 2010	Brunet-Bernard 2014	Carlomagno 2015	Cochet 2013	Fournet 2017	Ibrahim 2019	Jackson 2014	Klimusina 2011	Maffè 2015	Mastenbroek 2016	Modi 2017	Petrovic 2016	Risum 2012	Shanks 2010	Sunman 2016	Wang 2010	Wita 2015	Wong 2013	Zaremba 2019	Zhu 2019
Younger patients					●																			○	
Female gender							●			●						○							○		
NICM					●	○	●	○	●					●			●	●	●				●		
Longer QRS					●	●		●			●	○						●		○			○		
LVEF	Higher									●												●			
	Lower				○	○											●								
LVESV	Higher			●	○													○							
	Lower									●					●								●		○
NYHA class	Higher																		○						
	Lower																						●		
Diabetes																	□								
Better renal status						●																	●	○	
AF																□									
LBBB					●		●				●									○					

●; ○ - higher presence of the corresponding characteristic, in the responder group, with significance or with near significance, respectively.
□ - higher presence of the corresponding characteristic, in the non-responder group, with near significance.

6.3 Additional Analyses – Meta-analysis and Classification

A meta-analysis was conducted for each variable, if values corresponding to it were present in, at least, two of the twenty-four articles considered for qualitative analysis. However, given the quantity of data available for analysis and subsequent discussion, it was decided to present the results deemed more relevant for this manuscript (all the meta-analyses made are present in the Appendix III). Some articles only reported data relative to LVEF and LVESV via other methods than 2D echography (3D echography [8] and MRI [9,10]) – these values were not used in meta-analyses. One study [24] reported values of LVEF and LVESV via 3D echography, however it was also used 2D echography on the same study, and the differences of measurement between the two methods were non-significant. Therefore, those values were considered for meta-analysis. A forest plot with the summary of the more important meta-analyses results obtained for each variable, as a screening of the tendencies reported from all studies, is presented in Figure 2. All the information regarding the meta-analyses conducted is present in the Appendix III.

Female gender, NICM and LBBB appears to favor response to CRT, as well as the presence of a longer QRS duration and a NYHA functional class II (Figure 2). In figure 3 are presented the studies that contributed for each meta-analyses regarding female gender, NICM, LBBB and NYHA class II.

Thereby, considering the variables that presented relevant tendencies on meta-analyses, a ROC analysis was performed using those in an univariate way, so that important studies were not placed out. As defined in the methods section, the weight of each study was considered in order to ascertain which baseline variables are able to discriminate responders from non-responders.

As shown in table 4, it is possible to infer that study samples that have more than about 40% of subjects with NICM, have more than three quarts of subjects with LBBB and have more than about one fifth of women (≥ 20.66%) and NYHA class II patients (≥ 22.17%) are more likely to discriminate responders from non-responders to CRT. This means that the presence of those characteristics may, in advance, identify patients who will benefit more in terms of reverse remodeling from CRT.

Therefore, the classification was carried out for studies in which previous mentioned baseline variables were identified as discriminators of response to CRT, after dichotomization according to the threshold defined in table 4. The weight of each study was considered. Among those variables, it was found that four of them may be considered as independent predictors of response to CRT. As observed in table 5, the concordance between what is observed and what is predicted (based on the cut-off points resulted from the ROC analysis), regarding the response to CRT, is higher in the presence of the following characteristics: female gender (kappa = 0.450; $p < 0.001$), NICM (kappa = 0.636; $p < 0.001$), LBBB (kappa = 0.935; $p < 0.001$), and NYHA class II (kappa = 0.647; $p < 0.001$). Of note, since these variables were considered in a binary form, it can be said that, within the deemed variables, the presence of LBBB is the most potent predictor of response to CRT by far, with an almost perfect concordance between the CRT response that occurs in fact and what is predicted by the ROC analysis, and with both sensitivity and specificity higher than 95%. From this data, it is suggested that, in a certain sample, with more than about 75% of patients with LBBB, the probability of response to CRT is almost certain if this characteristic is present (99.69%), and clearly drops to 8.65% if LBBB is absent. The same logic can be applied to the other variables with significant both thresholds and kappa, however with less reliability.

	I^2 (num. studies)	Num. subjects	Std Effect	95% CI	p	adj p
Age	36,83% (24)	2044	-0,020	-0,13 to 0,08	0,665	0,169
Female (%)	98,81% (24)	2044	0,820	**0,14 to 1,5**	**0,018**	0,077
Non-ischemic Etiology (%)	99,21% (24)	2044	2,410	**1,53 to 3,29**	**< 0.001**	**0,023**
Left bundle branch block (%)	98,85% (8)	773	2,250	**0,88 to 3,63**	**0,001**	**0,046**
Atrial fibrillation (%)	99,49% (5)	358	-0,530	-2,2 to 1,13	0,530	0,123
QRS duration (ms)	0,01% (24)	2044	0,240	**0,12 to 0,36**	**< 0.001**	**0,023**
Ejection faction(%)	0% (21)	1884	0,000	-0,24 to 0,25	0,976	0,192
LVESV (ml)	97,25% (20)	1618	-0,060	-0,24 to 0,12	0,537	0,138
% NYHA II	95,21% (7)	591	1,850	**0,37 to 3,33**	**0,014**	0,062
% NYHA III	98,96% (14)	1317	-0,810	-2,16 to 0,53	0,235	0,100
% NYHA IV	98,75% (8)	765	0,020	-1,44 to 1,48	0,976	0,192
% Diabetes	99,16% (10)	797	-0,790	-2,09 to 0,51	0,235	0,100
% HT	98,06% (8)	447	-0,300	-1,62 to 1,02	0,652	0,154

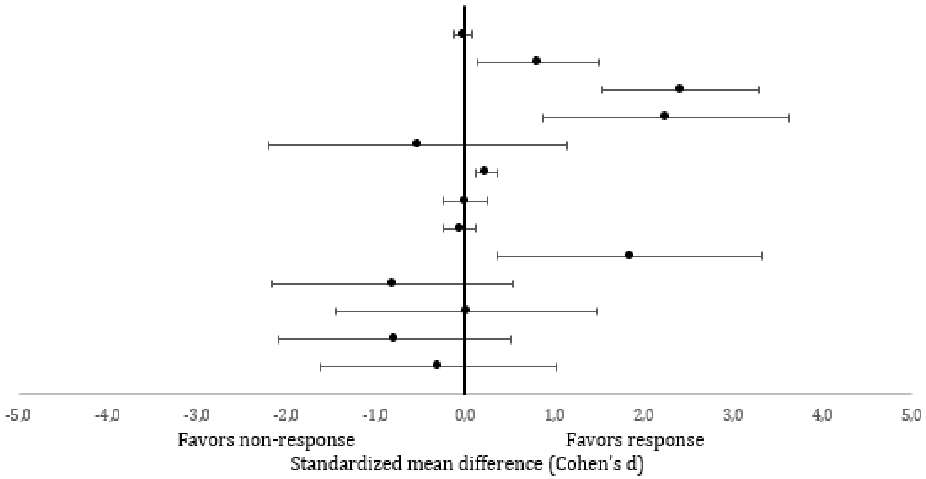

Figure 2 - Forest plot with the summary of all the meta-analyses performed

Descriptive forest plot summarizing results for each one of the meta-analysis performed using a random-effects model, presenting the summary measures of each one (standardized mean difference – Std. Effect) and its 95% confidence interval, significance statistics (p-value and Benjamini-Hochberg adjusted p-value) and heterogeneity statistics (I^2).

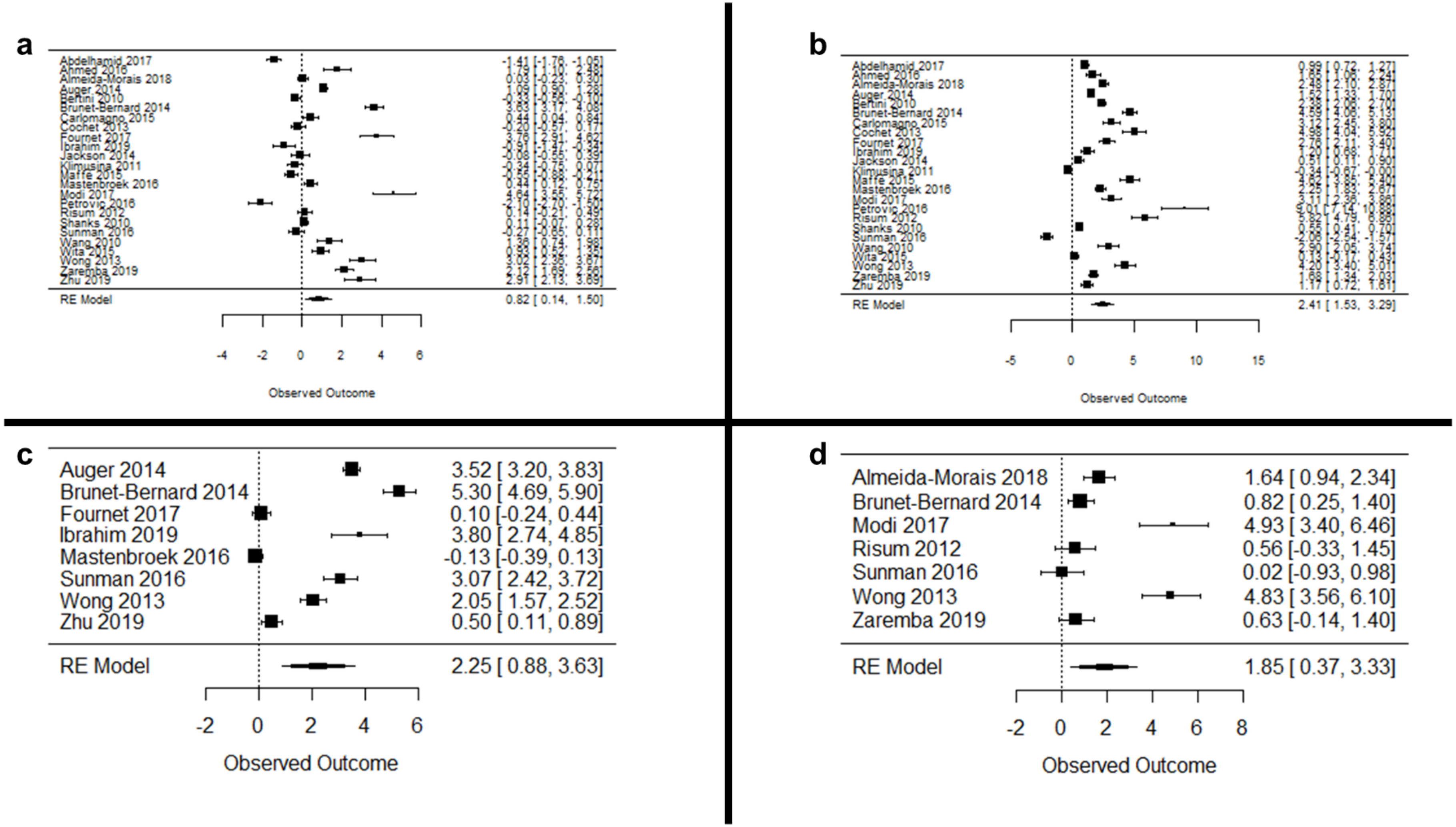

Figure 3 – Forest plots for the most relevant meta-analyses, with all the contributing studies and synthetic overall measure considering a random-effects model (a) Female gender; (b) NICM; (c) LBBB; (d) NYHA II.

Table 4 - Results from ROC analysis

	AUC (SE)	95%CI	P	Cut-off	S	E
Female gender (%)	0.721 (0.031)	0.782 - 0.782	< 0.001	≥ 20,66%	90.50%	51.06%
NICM (%)	0.773 (0.032)	0.710 - 0.837	< 0.001	≥ 39.65%	99.58%	55.17%
LBBB (%)	0.969 (0.011)	0.947 - 0.991	< 0.001	≥ 73.96%	97.24%	98.96%
QRS duration (ms)	0.555 (0.038)	0.480 - 0.630	0.096	-	-	-
NYHA II (%)	0.815 (0.028)	0.759 - 0.871	< 0.001	≥ 22.17%	75.95%	96.15%

Table 5 - Results from the classification through the thresholds obtained from the ROC analysis

Characteristic	Kappa (p)	Sensitivity	Specificity	P(Resp) if characteristic present (PPV)	P(Resp) if characteristic absent (1-NPV)
Female gender	0.450 (< 0.001)	90.50%	51.06%	81.30%	30.43%
NICM	0.636 (< 0.001)	99.58%	55.17%	85.92%	2.04%
LBBB	0.935 (< 0.001)	97.24%	98.96%	99.69%	8.65%
NYHA II	0.647 (< 0.001)	75.95%	96.15%	97.56%	33.63%

7 Discussion

7.1 Summary of Evidence

This meta-analysis of real world evidence demonstrates that: (1) female gender, NICM, LBBB morphology and NYHA class II are baseline variables more frequent in responders than in non-responders to CRT, with an apparent capability to independently predict the response to CRT - populations with higher proportion of patients with these characteristics are more likely to benefit from CRT; (2) LBBB morphology appears to be the most reliable independent predictor of CRT response.

The tendency of responders to have baseline characteristics that are vastly studied as potential predictors of response to CRT in the current literature is confirmed by this meta-analysis. A previous systematic review on this topic showed that NICM, LBBB, longer QRS, and female gender are associated with improvement in various outcomes after CRT. [34] In consonance with previous studies, [35–38] the present meta-analysis confirmed, with data from real-world studies, the importance of these clinical variables to achieve the desired left ventricular reverse remodeling with CRT.

There is weak evidence, due to lack of large randomized trials, regarding the benefit of CRT in patients with permanent AF. The systematic review Rickard J et al. points out that eligible patients with sinus rhythm have better outcomes following CRT. [34] However, regarding reduction in ventricular volume (reverse remodeling) after CRT, the present meta-analysis suggests that AF is not so determinant for response to CRT, supporting the recommendation of experts in favor of CRT in permanent AF patients with NYHA class III and IV with the same indications as for patients in sinus rhythm.

One of the most interesting and, to our knowledge, innovative findings of this study is that NYHA II may be an independent predictor of response to CRT. This means that, the higher proportion of NYHA class II patients, the higher is the probability of response to CRT in a certain population. This conclusion corroborates, in some way, the results reported by Sze et al., that described that delaying access to CRT in detrimental of trying medical management first, in an eligible heart failure patient for CRT, has no benefit at all, being, possibly, even harmful for the patient. [39] Bank et al. also reported that LV reverse remodeling tend to improve more in patients with fewer symptoms. [40] A lesser symptomatic patient represents, in principle, less advanced stages of the disease and the presence of a more preserved myocardial structure with less scar tissue, which, in turn, makes cardiac reverse remodeling more likely to happen, fact that can explain this finding.

Other additional interesting finding of this study is that LBBB morphology, in an eligible patient for CRT, may be the most potent independent predictor of response, by far. Several studies have demonstrated that patients with LBBB morphology are more likely to respond favorably to CRT than their non-LBBB morphology counterparts. Sipahi et al. [41] conducted a meta-analysis in which they evaluated the impact of QRS morphology on clinical outcomes after CRT, and it was verified that a baseline LBBB was associated with a 36% risk reduction, and such benefit was not observed in patients with non-LBBB morphologies.

Although it is consensual that patients with larger QRS and LBBB benefit from CRT, it is still unclear which is the key predictor of response, since LBBB frequently coexists with longer QRS. [42] Even though there is evidence showing that QRS morphology do not give important information regarding clinical response (after adjustment for QRS duration), [5] the opposite is also reported. [43] Results of three landmark CRT clinical trials (MADIT-CRT, REVERSE trial and RAFT) indicate that all patients with baseline LBBB morphology benefit from CRT, regardless of QRS duration. [37,44,45] The fact that this meta-analysis identifies LBBB as a such important predictor suggests that the major impact of CRT is on the electro-mechanical resynchronization of the LV.

7.2 Limitations

This analysis is based on data from study samples, and not from individual patient data. Therefore, the results should not be extrapolated to an individual patient, but rather to populations. Also, it has to be pointed out that data heterogeneity is high, and that variability of two studies was estimated from their range and interquartile range instead of their standard deviations. Moreover, it was not possible to conduct a multivariate logistic regression, since a great quantity of data would be excluded and it would be difficult to attribute weights based on different variables. Finally, some of the included studies had data about specific mechanical desynchrony parameters and they could have been analyzed, as well. However, that goal was not pursued since they had so many variations, and that fact raised concerns about the reliability and practicality of the evidence that could possibly be concluded from that data.

7.3 Conclusions

This systematic review with meta-analysis filled a gap that persisted on the literature: compiles several important potential predictors of response to CRT, in a systematic way, and conducts a cohesive statistical analysis, giving insights of the importance of each one. Female gender, NICM, LBBB and NYHA class II are baseline variables with an apparent capability to independently predict the response to CRT in real-world clinical practice – populations with higher proportion of patients with these characteristics are more likely to benefit from this therapy. From these variables, LBBB is the most reliable to predict cardiac reverse remodeling, by far. Future studies can address the application of CRT in patients in contexts that were not so focused until these days: CRT in earlier heart failure stages and populations with large proportions of AF.

8 Funding and Conflicts of Interest

Nothing to declare.

9 Acknowledgments

I thank both Professor Doctor Bárbara Oliveiros and Professor Doctor Natália António for the guidance and support given throughout the execution of this work. I thank Professor Helena Donato for the support given on the searching process.

I am grateful to my friends, especially Alexandre Alferes, family, especially my parents, and Marta Neves for all the strength.

10 References

1. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004/05/21. 2004;350(21):2140–50.

2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005/03/09. 2005;352(15):1539–49.

3. Moreira C. Terapia de Ressincronização Cardíaca em Doentes com Insuficiência Cardíaca [Master's dissertation]. 2013.

4. Thomas G, Kim J, Lerman BB. Improving Cardiac Resynchronisation Therapy. Arrhythm Electrophysiol Rev. 2019/08/30. 2019;8(3):220–7.

5. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J [Internet]. 2013 Jan;34(46):3547–56. Available from: https://doi.org/10.1093/eurheartj/eht290

6. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association . Eur Hear J. 2013/06/27. 2013;34(29):2281–329.

7. Boidol J, Średniawa B, Kowalski O, Szulik M, Mazurek M, Sokal A, et al. Many response criteria are poor predictors of outcomes after cardiac resynchronization therapy: validation using data from the randomized trial. EP Eur [Internet]. 2013 Jan;15(6):835–44. Available from: https://doi.org/10.1093/europace/eus390

8. Zhu M, Chen H, Fulati Z, Liu Y, Su Y, Shu X. The value of left ventricular strain–volume loops in predicting response to cardiac resynchronization therapy. Cardiovasc Ultrasound [Internet]. 2019;17(1). Available from: https://doi.org/10.1186/s12947-019-0153-3

9. Cochet H, Denis A, Ploux S, Lumens J, Amraoui S, Derval N, et al. Pre- and intra-procedural predictors of reverse remodeling after cardiac resynchronization therapy: an MRI study. J Cardiovasc Electrophysiol. 2013/02/27. 2013;24(6):682–91.

10. Wong JA, Yee R, Stirrat J, Scholl D, Krahn AD, Gula LJ, et al. Influence of pacing site

characteristics on response to cardiac resynchronization therapy. Circ Cardiovasc Imaging. 2013/06/07. 2013;6(4):542–50.

11. Shanks M, Bertini M, Delgado V, Ng AC, Nucifora G, van Bommel RJ, et al. Effect of biventricular pacing on diastolic dyssynchrony. J Am Coll Cardiol. 2010/10/30. 2010;56(19):1567–75.

12. Abdelhamid MA, Ghanem MT, Abdelmotaleb AM. Assessment of right ventriclular systolic function prior to cardiac resynchronization therapy: Does it make any difference? Indian Hear J. 2017/11/28. 2017;69(6):731–5.

13. Ahmed W, Samy W, Tayeh O, Behairy N, Fattah AA El. Temporal changes of left ventricular synchronization parameters and outcomes of cardiac resynchronization therapy. Egypt J Crit Care Med [Internet]. 2016;4(2):105–12. Available from: https://doi.org/10.1016/j.ejccm.2016.04.001

14. Almeida-Morais L, Abreu A, Oliveira M, Silva Cunha P, Rodrigues I, Portugal G, et al. Impact of cardiac resynchronization therapy on inflammatory biomarkers and cardiac remodeling: The paradox of functional and echocardiographic response. Rev Port Cardiol [Internet]. 2018;37(2):105–13. Available from: http://repositorio.chlc.min-saude.pt/bitstream/10400.17/3138/1/RPC 2018 105.pdf

15. Auger D, Hoke U, Thijssen J, Abate E, Yiu KH, Ewe SH, et al. Effect of cardiac resynchronization therapy on the sequence of mechanical activation assessed by two-dimensional radial strain imaging. Am J Cardiol. 2014/01/28. 2014;113(6):982–7.

16. Bertini M, Delgado V, den Uijl DW, Nucifora G, Ng AC, van Bommel RJ, et al. Prediction of cardiac resynchronization therapy response: value of calibrated integrated backscatter imaging. Circ Cardiovasc Imaging. 2009/11/19. 2010;3(1):86–93.

17. Brunet-Bernard A, Maréchaux S, Fauchier L, Guiot A, Fournet M, Reynaud A, et al. Combined score using clinical, electrocardiographic, and echocardiographic parameters to predict left ventricular remodeling in patients having had cardiac resynchronization therapy six months earlier. Am J Cardiol. 2014/05/06. 2014;113(12):2045–51.

18. Carlomagno G, Iengo R, Sordelli C, Martiniello AR, Ascione R, Severino S, et al. Recoordination of opposing walls drives the response to cardiac resynchronization therapy: a longitudinal study using a strain discoordination index. J Cardiovasc Med. 2014/07/16. 2015;16(11):736–42.

19. Fournet M, Bernard A, Marechaux S, Galli E, Martins R, Mabo P, et al. Pilot study using 3D-longitudinal strain computation in a multi-parametric approach for best selecting

responders to cardiac resynchronization therapy. Cardiovasc Ultrasound. 2017/06/19. 2017;15(1):15.

20. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Develo. Eur Hear J. 2010/08/31. 2010;31(21):2677–87.

21. Ibrahim M. The utility of echocardiographic right ventricular parameters in predicting response to cardiac resynchronization therapy in patients with heart failure: A proof of concept. Ann Clin Anal Med. 2019;10(5).

22. Jackson T, Sohal M, Chen Z, Child N, Sammut E, Behar J, et al. A U-shaped type II contraction pattern in patients with strict left bundle branch block predicts super-response to cardiac resynchronization therapy. Hear Rhythm. 2014/06/10. 2014;11(10):1790–7.

23. Klimusina J, De Boeck BW, Leenders GE, Faletra FF, Prinzen F, Averaimo M, et al. Redistribution of left ventricular strain by cardiac resynchronization therapy in heart failure patients. Eur J Hear Fail. 2010/11/26. 2011;13(2):186–94.

24. Maffè S, Paffoni P, Dellavesa P, Perucca A, Kozel D, Paino AM, et al. Role of echocardiographic dyssynchrony parameters in predicting response to cardiac resynchronization therapy. J Cardiovasc Med. 2014/07/09. 2015;16(11):725–35.

25. Mastenbroek MH, Van't Sant J, Versteeg H, Cramer MJ, Doevendans PA, Pedersen SS, et al. Relationship Between Reverse Remodeling and Cardiopulmonary Exercise Capacity in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy. J Card Fail. 2015/09/13. 2016;22(5):385–94.

26. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur J Hear Fail. 2012/07/26. 2012;14(8):803–69.

27. Modi S, Yee R, Scholl D, Stirrat J, Wong JA, Lydell C, et al. Ventricular pacing site separation by cardiac computed tomography: validation for the prediction of clinical response to cardiac resynchronization therapy. Int J Cardiovasc Imaging. 2017/03/31. 2017;33(9):1433–42.

28. Petrovic I, Stankovic I, Milasinovic G, Nikcevic G, Kircanski B, Jovanovic V, et al. The Relationship of Myocardial Collagen Metabolism and Reverse Remodeling after Cardiac Resynchronization Therapy. J Med Biochem. 2017/03/31. 2016;35(2):130–6.

29. Risum N, Jons C, Olsen NT, Fritz-Hansen T, Bruun NE, Hojgaard M V, et al. Simple regional strain pattern analysis to predict response to cardiac resynchronization therapy: rationale, initial results, and advantages. Am Hear J. 2012/04/24. 2012;163(4):697–704.

30. Sunman H, Özkan A, Yorgun H, Canpolat U, Maharjan N, Asil S, et al. Vitamin D levels predict the response to cardiac resynchronization therapy in patients with systolic heart failure. Turk Kardiyol Dern Ars. 2017/01/04. 2016;44(8):670–6.

31. Wang CL, Wu CT, Yeh YH, Wu LS, Chang CJ, Ho WJ, et al. Recoordination rather than resynchronization predicts reverse remodeling after cardiac resynchronization therapy. J Am Soc Echocardiogr. 2010/04/27. 2010;23(6):611–20.

32. Wita K, Mizia-Stec K, Płońska-Gościniak E, Wróbel W, Gackowski A, Gąsior Z, et al. Low-dose dobutamine stress echo for reverse remodeling prediction after cardiac resynchronization. Adv Med Sci. 2015/06/29. 2015;60(2):294–9.

33. Zaremba T, Tayal B, Riahi S, Thøgersen AM, Bruun NE, Emerek KJG, et al. Index of contractile asymmetry improves patient selection for CRT: a proof-of-concept study. Cardiovasc Ultrasound. 2019/10/12. 2019;17(1):19.

34. Rickard J, Michtalik H, Sharma R, Berger Z, Iyoha E, Green AR, et al. Predictors of response to cardiac resynchronization therapy: A systematic review. Int J Cardiol. 2016/10/19. 2016;225:345–52.

35. Yin F-H, Fan C-L, Guo Y-Y, Zhu H, Wang Z-L. The impact of gender difference on clinical and echocardiographic outcomes in patients with heart failure after cardiac resynchronization therapy: A systematic review and meta-analysis. PLoS One [Internet]. 2017;12(4):e0176248. Available from: https://dx.doi.org/10.1371/journal.pone.0176248

36. Chen J-S, Niu X-W, Chen F, Yao Y-L. Etiologic impact on difference on clinical outcomes of patients with heart failure after cardiac resynchronization therapy: A systematic review and meta-analysis. Medicine (Baltimore) [Internet]. 2018;97(52). Available from: https://journals.lww.com/md-journal/Fulltext/2018/12280/Etiologic_impact_on_difference_on_clinical.20.aspx

37. Gold MR, Thébault C, Linde C, Abraham WT, Gerritse B, Ghio S, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left

Ventricular Dysfunction (REVERSE) study. Circulation. 2012/07/12. 2012;126(7):822–9.

38. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Hear J. 2012/02/07. 2012;163(2):260-7.e3.

39. Sze E, Samad Z, Dunning A, Campbell KB, Loring Z, Atwater BD, et al. Impaired Recovery of Left Ventricular Function in Patients With Cardiomyopathy and Left Bundle Branch Block. J Am Coll Cardiol [Internet]. 2018;71(3):306–17. Available from: https://www.sciencedirect.com/science/article/pii/S0735109717416342

40. Bank AJ, Rischall A, Gage RM, Burns K V, Kubo SH. Comparison of cardiac resynchronization therapy outcomes in patients with New York Heart Association functional class I/II versus III/IV heart failure. J Card Fail. 2012/05/05. 2012;18(5):373–8.

41. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med. 2011/06/15. 2011;171(16):1454–62.

42. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of. Eur Hear J. 2016/05/22. 2016;37(27):2129–200.

43. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. Heart. 2015/08/14. 2015;101(22):1800–6.

44. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: Results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Hear Fail. 2013/09/03. 2013;6(6):1190–8.

45. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, et al. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011/03/02. 2011;123(10):1061–72.

11 Appendices

The following link provides access to the Appendices:

https://drive.google.com/drive/folders/1zYxdHaFkui6PrS6RoMfEmV1YBkLyepn0?usp=sharing