ROLE OF ELECTROCARDIOGRAPHY IN SPECIAL CLINICAL SITUATIONS

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LIST OF PUBLICATIONS RELATED TO THE THESIS

Pilecky D, Vamos M, Bogyi P, Muk B, Stauder D, Racz H, Nyolczas N, Duray GZ, Zacher G, Zima E. Risk of cardiac arrhythmias after an electrical accident: a single-centre study of 480 patients. Clin Res Cardiol. 2019 Aug;108(8):901-908. **IF 4,14**

Pilecky D, Duray GZ, Elsner D, Israel CW, Erath-Honold JW, Vamos M. Association between electrical and mechanical remodeling after cardiac resynchronization therapy: systematic review and meta-analysis of observational studies. Heart Fail Rev. 2022 Nov;27(6):2165-2176. **IF 5,06**

1 | INTRODUCTION

Cardiac arrhythmias are among the most common cardiovascular diseases. Arrhythmias can have sequelae that range from life-shortening to inconsequential. Sudden cardiac death, chronic disability, and heart failure are among the most frequent serious complications resulting from arrhythmias [1]. The prevalence of arrhythmias can be estimated at 2% in the community. The incidence of cardiac rhythm disturbance is about 0.5% per year, similar to the yearly rates for stroke, myocardial infarction, and heart failure. The most common arrhythmias are atrial fibrillation, followed by bradyarrhythmias, conduction disturbances, and supraventricular and ventricular arrhythmias. Older age, male sex, traditional cardiovascular risk factors, chronic kidney disease, and heart failure are the most common risk factors of rhythm disorders [2]. Cardiac arrhythmias and conduction disorders typically occur as a consequence of structural heart disease and electrolyte or metabolic abnormality. However, external injuries may also trigger arrhythmias. In the first case, the molecular mechanisms responsible for cardiac arrhythmias are traditionally divided into two major categories: enhanced or abnormal impulse formation (reduced or increased automaticity; triggered activity) and conduction disturbances (reentrant arrhythmias) [3]. Among the external injuries leading to cardiac arrhythmias, the most relevant are electrical injuries. The heart is an electrically active tissue, and the effects of electrical current on the heart vary from beneficial and life-saving (e.g., cardiac pacing, radiofrequency catheter ablation, defibrillation) to harmful and fatal (e.g., electrocution, ventricular fibrillation leading to sudden death). Regarding adverse myocardial effects due to electrical injury, several mechanisms appear to be involved: depolarisation of myocytes, myocardial necrosis due to electroporation or electrothermal conversion, vasoconstriction through catecholamine release, coronary spasm or thrombosis, anoxia (respiratory muscle paralysis), coronary hypoperfusion due to severe arrhythmia-induced hypotension and traumatic contusion of the heart [4].

Cardiac arrhythmias cannot be diagnosed and evaluated without electrocardiography. ECG is one of the most commonly conducted medical diagnostic procedures and plays a fundamental role not only in the recognition and treatment of cardiac arrhythmias but also in the diagnostic and prompt initiation of therapy in patients with acute coronary syndromes. Furthermore, ECG may lead to the recognition of electrolyte abnormalities, particularly of serum potassium and calcium, and permit the detection of some forms of genetically mediated electrical or structural cardiac abnormalities. ECG is routinely used to monitor patients treated with antiarrhythmic and other drugs potentially affecting the heart's electrical activity [5]. Moreover, ECG plays a crucial role in the follow-up of patients after the implantation of a cardiac implantable electric device [6]. Although ECG is a simple,

widely available, and relatively cheap diagnostic tool, accurate recording techniques and correct and precise interpretation are essential. Besides conventional 12-lead ECG, many devices (wearable devices, smartphones, and other ambulatory sensors) have been developed which, subject to certain limitations, have expanded the possibility of ECG monitoring of cardiac rhythm disturbances [7].

This thesis investigates rhythm disorders and ECG changes in special clinical situations, such as electrical injury and the assessment of electrical remodeling during the follow-up of patients who have undergone implantation of a cardiac resynchronization therapy device.

1.1 │ Electrical injury and cardiac arrhythmias

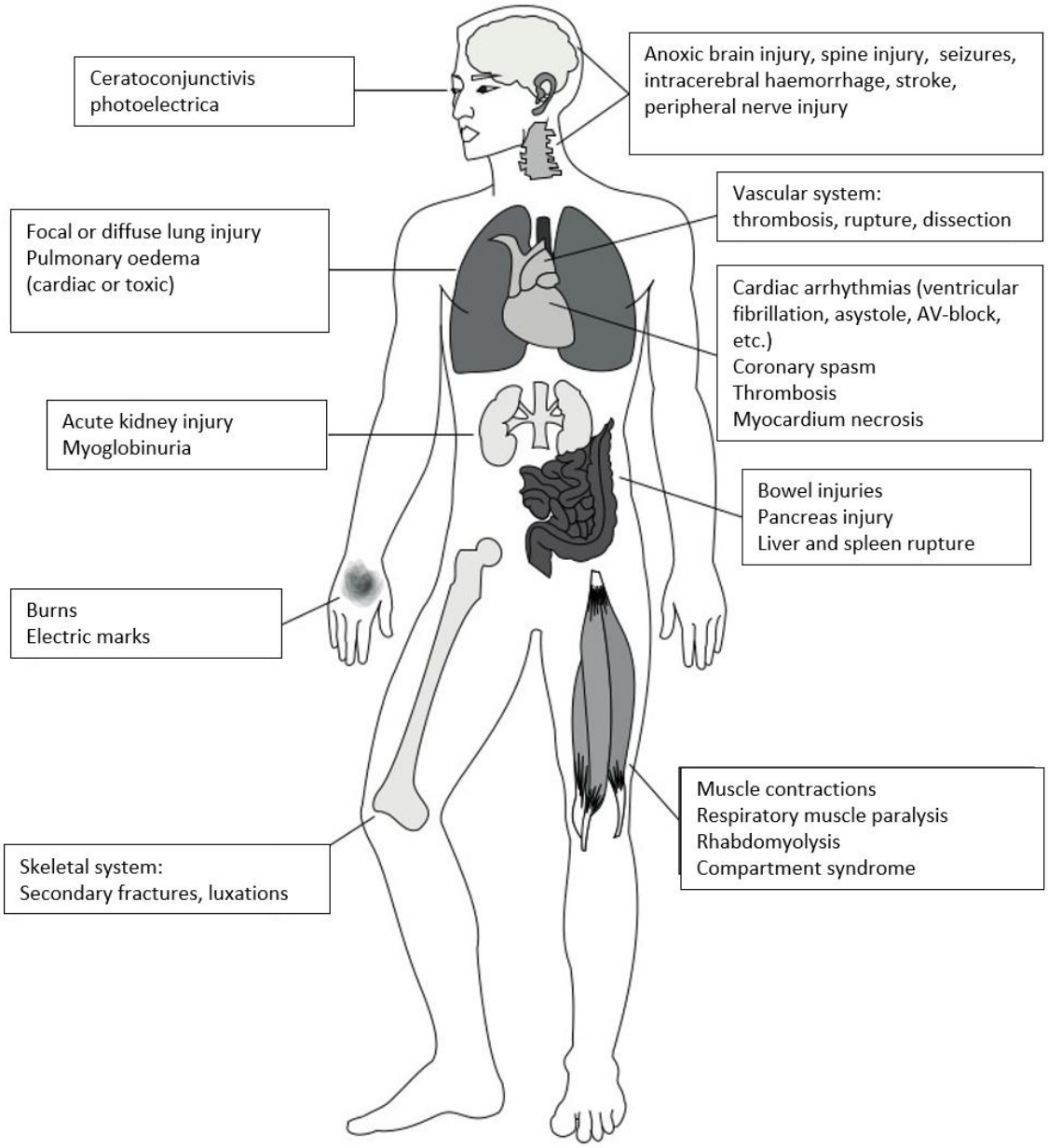
Electrical contact protection measures have improved over the years, decreasing the number of serious electrical accidents (EA) in developed Western countries, although the latter still account for 5-6% of fatal workplace events [8]. The severity of burns and the potential for damage to internal organs are primarily influenced by factors such as the body's resistance, the voltage, the duration of the electrical current, whether the current is direct or alternating, and the path it takes through the body. According to Joule's law, the magnitude of the energy delivered to the body is directly proportional to the body's resistance, exposure duration, and the square of the current ($W = R \times T \times I^2$). In the case of direct current, the flow of electrons in a single direction can cause the victim to be 'pushed' away from the source of the current. However, with alternating current, a sustained muscle contraction may occur, preventing the victim from releasing the current source and prolonging the exposure [9]. Table 1 illustrates the physiological effects of the 60 Hz alternating current typical of households, depending on current strength.

Table 1. Estimated effects of 60Hz alternating current depending on current strength [10]

1 mA	Barely perceptible
16 mA	Maximum current an average person can grasp and then "let go"
20 mA	Paralysis of respiratory muscles
100 mA	Ventricular fibrillation threshold
2 Amps	Cardiac standstill and internal organ damage
15/20 Amps	Common fuse or breaker opens circuit

The conductivity of the human body's tissues is different: the skin, bone, and fat tissue have the highest resistance, while blood vessels and nerves are the best conductors due to their higher fluid and electrolyte content. Wet skin has a lower resistance than dry skin, so although burns may be milder with wet skin, the current reaches deeper tissues and internal organs more efficiently [11]. Complications caused by electric shock sorted by organ system are illustrated in Figure 1.

Figure 1. Complications resulting from electrical accidents, categorized by organ systems [9]



Transthoracic current may lead to cardiac complications, which manifest predominantly as arrhythmias, conduction disturbances, and myocardial tissue damage. Arrhythmias resulting from the proarrhythmic effect of electric shock usually occur immediately after the electrocution. If

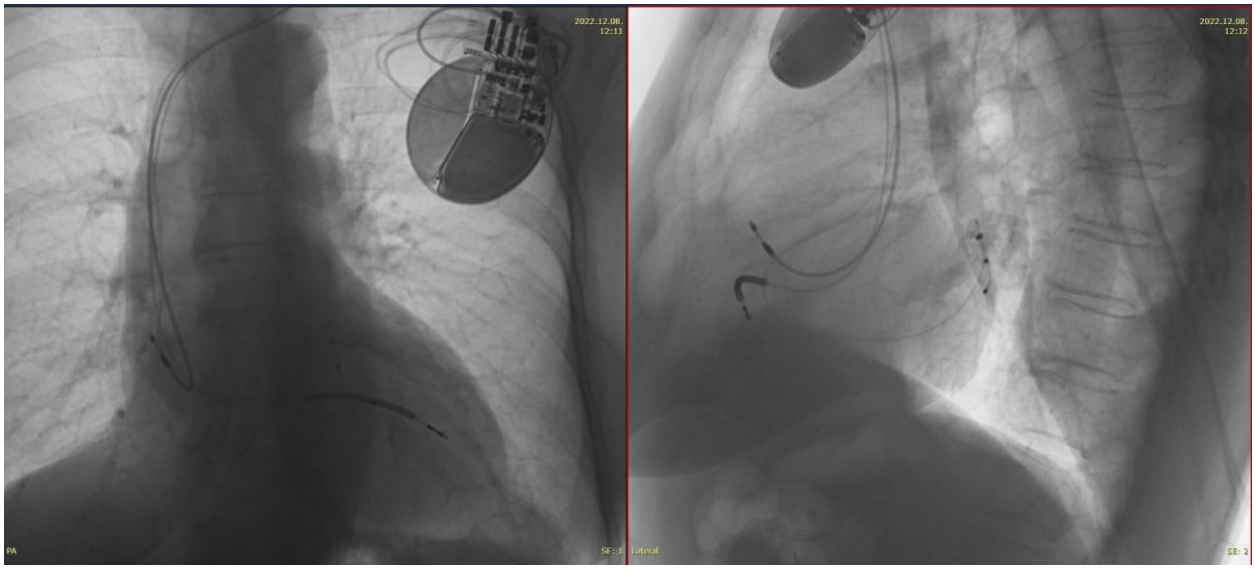
electric current reaches the heart within the vulnerable period, it may also trigger ventricular fibrillation (VF), which is the most common cause of death after EA. The clinical experience is that while the magnitude of the reported energy mostly correlates with the degree of burn injuries, the ventricular fibrillation threshold is mostly determined by the current strength [4].

In patients presenting at emergency units after EA, the most commonly diagnosed arrhythmias are sinus tachycardia, sinus bradycardia and premature atrial and ventricular complexes (PACs and PVCs) [12–14]. Various degrees of atrioventricular block and intraventricular conduction disorders like bundle branch block may also occur [15,16]. Late-onset malignant arrhythmias are infrequent after EA. Only a few case reports have described delayed VF, and only two of these cases have been documented with an initial ECG [15,17]. Delayed ventricular arrhythmias can remain subclinical: in a patient with a previously implanted pacemaker multiple non-sustained polymorphic tachycardia episodes were registered in the pacemaker memory after the electrical accident [18]. Risk stratification of patients after EA remains challenging. According to the guidelines of the European Resuscitation Council (ERC), ECG monitoring is recommended after EA for patients with known heart disease or one or more of the following risk factors: loss of consciousness, initial cardiac arrest, soft tissue damage and burns, or ECG-abnormalities at the time of admission [19]. However, these recommendations rely only on a few, primarily retrospective studies, case reports and expert opinion.

1.2 │ Electrical remodeling in cardiac resynchronization therapy

About one-third of patients with heart failure have a prolonged QRS duration (> 120ms), which is an independent risk factor for all-cause mortality [20]. It has also been shown that an incremental increase in QRS duration is common in heart failure and also predicts worse outcomes [21]. Cardiac resynchronization therapy (CRT) is a cornerstone of the treatment of patients with chronic heart failure and wide QRS complex [22,23]. Several randomized controlled trials have demonstrated the positive effects of CRT on morbidity and mortality in heart failure patients [24]. The main goal of CRT is the restoration of atrioventricular, intraventricular, and interventricular dyssynchrony. Accordingly, three transvenous leads are usually implanted: one right atrial lead (usually in the right atrial appendage), one right ventricular pacing/sensing or pacing/sensing and defibrillator lead, and one left ventricular lead via the coronary sinus (see Figure 2).

Figure 2. Anteroposterior and lateral chest X-ray after implantation of a CRT-D device. The quadripolar left ventricular lead is placed in one posterolateral side branch of the coronary sinus.

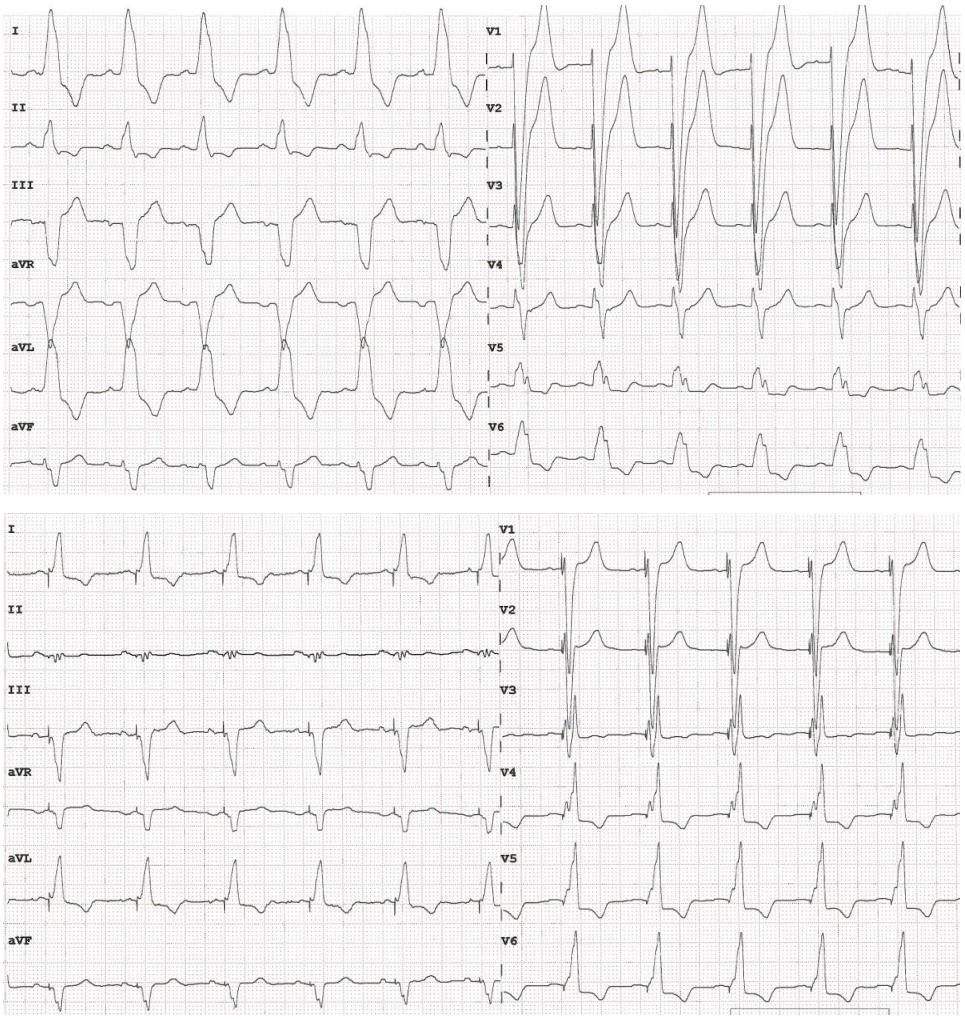


In patients with wide QRS due to left bundle branch block, the electrical activation of the left ventricle is prolonged with delayed activation and contraction of the lateral wall. The key point of successful CRT device implantation is the proper implantation of the left ventricular lead in one lateral or posterolateral side branch of the coronary sinus to ensure stable pacing on the delayed cardiac segments. The implantation of a CRT device, especially the left ventricular lead, may be technically complex and challenging. The feasibility of transvenous lead positioning is determined by anatomical and technical factors, including coronary sinus anatomy, the accessibility of the vein, pacing threshold, lead stability, and the absence of phrenic nerve stimulation [25].

For optimal patient selection, clinical, echocardiographic, and electrocardiographic features should be evaluated. Regarding clinical and echocardiographic criteria, CRT should be considered in symptomatic heart failure patients with left ventricular ejection fraction ≤ 35% despite optimized medical treatment. Regarding electrocardiographic criteria, QRS duration, as well as QRS morphology, should be evaluated. It is well-known that patients with a left bundle branch block (LBBB) pattern benefit more than those with right bundle branch block (RBBB) or non-specific intraventricular conduction delay (IVCD) patterns [26]. Patients with a combination of a normal PR interval and non-LBBB morphology may even have a higher mortality risk after CRT[27]. The definition of "true" LBBB is not uniform due to various criteria used in CRT trials and clinical practice. *Strauss et al.* suggested that for optimal patient selection for CRT, the following criteria should be met: a QRS duration of ≥ 140 ms for men and ≥ 130 ms for women, along with mid-QRS notching or slurring in at least two contiguous leads [28]. Further criteria, like the absence of q

waves in the lateral leads and the absence of R waves in lead V1, should also be considered [29]. It is important to note that CRT may even be harmful in patients with narrow QRS (< 130ms) [30]. In summary, according to current guidelines, CRT is indicated as a class I indication in patients with LBBB and QRS ≥ 150ms and as a class IIa indication for patients with LBBB and QRS between 130 and 149ms. The indication is weaker for patients without LBBB and QRS duration ≥ 150 ms (recommendation class IIa) and for patients without LBBB and QRS between 130 and 149 ms (recommendation class IIb) [23]. Electrocardiography plays an important role not only in the indication but also in the follow-up of patients with CRT devices (Figure 3a).

Figure 3a. 12-lead ECG before and after CRT implantation. Baseline LBBB morphology resolves during biventricular pacing, and QRS duration becomes shorter.

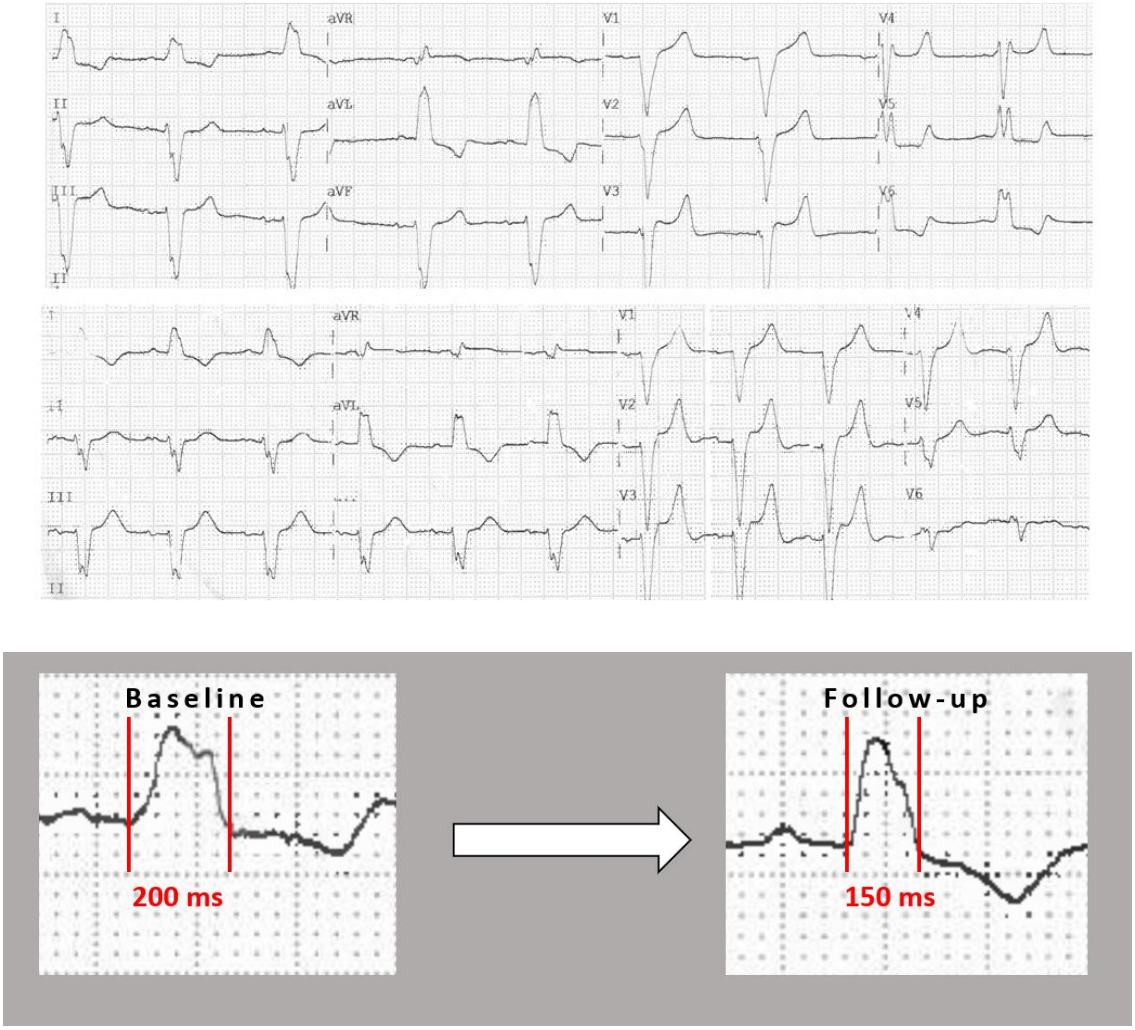


During left ventricular (LV) pacing from the appropriate site in the coronary venous system, a correctly positioned lead V1 often registers a right bundle branch block pattern. During biventricular stimulation associated with right ventricular (RV) apical pacing, the QRS is often positive in lead V1, but can be also monophasic negative in RV septal or LV only pacing. The

frontal plane QRS axis is usually in the right superior quadrant and occasionally in the left superior quadrant [6]. 12-lead ECG performed during follow-up can help detect loss of true biventricular pacing, a rise in pacing threshold, lead failure, or the suboptimal timing of pacing [31].

Approximately 30% of patients do not respond to CRT, as assessed clinically or echocardiographically, even following successful CRT device implantation [32]. The most commonly used measurable indicators of reverse mechanical remodeling in CRT recipients are a reduction in left ventricular dimensions and an improvement in left ventricular ejection fraction (LVEF). Further, CRT may lead to the reverse remodeling of the native conduction system (i.e., electrical remodeling), most simply detected by the shortening of intrinsic QRS duration (iQRS)[33,34] (Figure 3b). Evidence regarding the prevalence and clinical impact of this finding is limited, primarily because changes in intrinsic QRS during CRT have not been studied within large randomized controlled trials.

Figure 3b. 12-lead ECG before CRT implantation and during follow-up (ECG was registered during temporary inhibition of pacing). Intrinsic QRS duration became shorter by 50ms.



2 │OBJECTIVES

2.1 We aimed to analyze the data of consecutive patients who presented at the emergency unit after an electrical accident to determine the rate of arrhythmias and electrocardiographic abnormalities. The predictive value of some presumed risk factors of arrhythmias was evaluated, and finally, we assessed the risk of late-onset malignant arrhythmias and in-hospital and 30-day mortality.

2.2 We sought to describe the incidence and extent of electrical response to CRT measured by shortening of intrinsic QRS complex on 12-lead electrocardiogram and its correlation with echocardiographic and clinical response by performing a systematic review and meta-analysis of published studies related to this topic.

3 │ METHODS

3.1 │ Risk of arrhythmias after electrical accident

3.1.1 │ Patient population

Consecutive patients who were admitted with EA (ICD diagnosis T75.4, effects of electric current) to the Emergency Department of the Medical Centre - Hungarian Defence Forces (Budapest, Hungary) between 01.01.2011 and 31.12.2016 were included in the analysis. This department is one of Budapest's largest multidisciplinary emergency centres and is prepared for all types of major adult emergencies, including burn victims. Clinical data of patients were collected from the hospital information system and patient records. Baseline demographics, medical history, and antiarrhythmic medication were registered along with the time, location and other circumstances of the EA. Furthermore, clinical parameters which are deemed to be risk factors for cardiac arrhythmias based on the ERC criteria were summarized. We also recorded presenting symptoms, severity of burns, and other injuries.

3.1.2 │ Biochemical and electrocardiographic analysis

The following laboratory parameters were identified: high-sensitive cardiac troponin I (cTnI), creatine kinase (CK), and creatine kinase muscle-brain ratio (CK-MB%). The upper limit of the normal level of these parameters was defined at our institution as 0.04ng/ml for cTnI, 190U/ml for CK and 5% for CK-MB%. Pre-hospital and in-hospital ECGs were blind analyzed by two independent cardiologists, who were unaware of the clinical presentation or the purpose of the study. In the case of disagreement, a third expert was involved. Length of ECG monitoring, arrhythmic events during ECG monitoring, length of stay at the emergency department (ED) and the disposition decisions were also reviewed.

3.1.3 │ Survival analysis

Data for all-cause and arrhythmic cause in-hospital and 30-day mortality were collected. Mortality data were obtained from the hospital records and from database of the National Health Insurance Fund of Hungary.

3.1.4 │ Statistical analysis

All relevant patient data were recorded in an anonymized form in a Microsoft Excel 2007 spreadsheet (Microsoft, Redmont, WA). We used the statistical program R (The R Foundation for Statistical Computing, version 3.5.0) for statistical analysis. Descriptive statistics for categorical variables are shown as percentages, while continuous variables are represented by their means and standard deviations. We used multivariable logistic regression to determine independent risk

factors for the occurrence of arrhythmias. The clinical parameters analyzed in this model were structural heart disease, loss of consciousness, high voltage electric shock, transthoracic current, burns and soft tissue injuries. Our observational study was approved by the local ethical committee and (EPC-HK/ 11-01-2018) and was undertaken in conformity with the Helsinki Declaration.

3.2 │ Electrical remodeling in cardiac resynchronization therapy

3.2.1 │ Study selection for the meta-analyis

A systematic search in PubMed and Cochrane Library databases was performed through May 2021 without any limitations using the following key terms: 'electrical remodeling' OR 'electrical remodelling' OR 'QRS duration' AND 'cardiac resynchronization therapy'. We evaluated the title and abstract of all records and applied the following inclusion criteria to identify eligible studies for the meta-analysis:

1. prospective or retrospective observational studies providing data on **(a)** incidence of reverse electrical remodeling defined as a shortening of intrinsic QRS duration during follow-up or **(b)** studies providing data on any association between reverse electrical remodeling and mechanical and/or clinical response to CRT
2. only full-text, English-language and human studies published in peer-reviewed journals were considered.

We excluded studies where RER was not measured by conventional 12-lead electrocardiogram and papers including patients with CRT upgrade. Reference lists of selected manuscripts were manually checked for additional eligible publications. Two reviewers independently conducted the systematic search, and any disagreement was subsequently resolved by consensus. Data were extracted using a predefined form. Data extraction included information about publications' details, baseline demographic and clinical parameters of patients, definition of electrical and mechanical response and proportion of patients in each group, detailed data on iQRS changes in different subgroups, duration of follow-up and mortality if available.

3.2.2 │ Endpoints of interest

The primary outcome of the meta-analysis was the incidence and extent of RER and its association with mechanical response to CRT assessed by echocardiography. Furthermore, we investigated the association of RER with clinical response (defined by improvement in NYHA functional class) and all-cause mortality. Conventional predictors of CRT-response such as female sex, left bundle block (LBBB) and non-ischaemic cardiomyopathy (NICMP) and their association with RER were also analyzed. Moreover, the impact of acute narrowing of paced QRS (defined as baseline iQRS - paced QRS) on later RER was investigated.

3.2.3 │ Statistical analysis

The meta-analysis was performed using a random effect model with the help of Review Manager (RevMan 5.4.1, Cochrane Collaboration, Nordic Cochrane Center, and Copenhagen, Denmark). Comprehensive Meta-Analysis (version 3, Biostat, Englewood, USA) software was used for assessment of publication bias. Categorical variables were pooled as an odds ratio (OR) with 95% confidence interval (CI). For the continuous variable, mean difference was calculated with corresponding 95% confidence intervals. All-cause mortality was calculated by pooled risk ratio (RR). The p-value <0.05 (two-tailed) was considered statistically significant. Study heterogeneity was evaluated by Cochrane's Q and I^2 index. In the minority of the studies mean with standard deviation of continuous variables were not available and were replaced by their median with interquartile range. Since there was significant heterogeneity in the design and patient characteristics of the included studies, it was assumed that the true effect size varies from one study to the other, and hence the random-effect model was applied. The methodological quality of studies was assessed using the methodological index for non-randomized studies (MINORS)[35]. Only one study contained a comparator group [36], all other studies were non-comparative. For these studies only items 1 to 8 of MINORS score (maximal point of 16) were applied. A study was defined high quality if the MINORS score was ≥ 12 out of 16 or ≥ 18 out of 24, respectively. Publication bias was assessed using the funnel plot, the trim and fill method of Duval and Tweedie [37], and an adjusted rank correlation test according to Begg and Mazumdar [38].

This meta-analysis was performed according to the Guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered at Internal Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021253336).

4 │ RESULTS

4.1 │ Risk of arrhythmias after electrical accident

4.1.1 │ Patient population

During the study period, 559 patients were admitted to the ED with a first diagnosis of EA. Seventy-nine patients were excluded for various reasons. The final analysis assessed 480 patients (287 males) with a mean age of 34.3 years (Table 2). Workplace accidents accounted for 38.3% of cases; in most of these work-related accidents, men were affected (72%). More than 60% of patients had no complaints on admission, while the most common complaints were as follows: numbness of extremities (19.6%), burns (17.5%), and chest pain (5.8%). Circumstances of EA are also detailed in Table 2. Minor electric marks or mild first-degree burns were found in 75 patients (15.6%). Eight patients had second-degree, one patient third-degree, and two patients had fourth-degree burn injuries. Treatment by a burn care specialist was needed in eight cases (Table 2). In further eight patients concomitant traumatic injuries were observed, such as contusions, fractures, or ceratoconjunctivitis photoelectrica.

Table 2. Demographic characteristics, anamnesis and circumstances of electrical accident

Number of patients (male)	480 (287)
Age (years; mean±SD)	34.3 ±11.6
Medical history (n; %)	
Hypertension	45 (9.4%)
Asthma/COPD	10 (2.1%)
Structural heart disease	7 (1.5%)
Atrial fibrillation	1 (0.2%)
Actual pregnancy	6 (1.3%)
Antiarrhythmic medication (n; %)	
Beta-blockers	22 (4.6%)
Other antiarrhythmic agents	0 (0%)
Circumstances of accident and admission (n; %)	
Self-admission	231 (48.1%)
Admission via ambulance car	245 (51.0%)
Admission via emergency helicopter	4 (0.8%)
Time from accident to admission (hours; mean±SD)	2.9 ±3.9
Workplace accident	184 (38.3%)
Suicide attempt	5 (1.0%)
High voltage accident (>1000V)	18 (3.8%)
Resuscitation on site	1 (0.2%)
Loss of consciousness	13 (2.7%)

Transthoracic current	104 (21.7%)
Complaints at admission (n; %)	
No complaints	298 (62.1%)
Numbness of extremities	94 (19.6%)
Burns	84 (17.5%)
Chest pain	28 (5.8%)
Pain of the extremities	21 (4.4%)
Headache	14 (2.9%)
Dizziness	13 (2.7%)
Palpitations	9 (1.9%)
Nausea	6 (1.3%)
Other	14 (2.9%)
Severity of burns (n; %)	
I° or electrical marks	75 (15.6%)
II°	8 (1.7%)
III°	1 (0.2%)
IV°	2 (0.4%)
Concomitant injuries	8 (1.7%)

4.1.2 Arrhythmias at admission

Pre-hospital ECG was performed on 205 patients (42.7%). ECG on admission was available for almost all patients (n=475); however pre-discharge ECG was performed only in 76 cases (Table 3). The most frequent supraventricular arrhythmias on admission were mild sinus bradycardia (<60 bpm, n=50, 10.4%) and sinus tachycardia (>100 bpm, n=21, 4.1%). All patients with sinus bradycardia were asymptomatic and did not require any intervention. Atrial fibrillation was detected in two cases on the admission ECG. One of these patients had AF as a first diagnosis. A few hours later, this patient had a spontaneous conversion to sinus rhythm. In one young patient, frequent multifocal PACs were observed on the pre-hospital and admission ECGs, and these PACs spontaneously resolved during monitoring. In two other patients, intermittent sinus arrest with an atrial escape rhythm without haemodynamic instability was observed.

The detected ventricular arrhythmias were as follows: one male patient was resuscitated due to VF at the site of the accident (high-voltage injury). On admission, this patient had sinus tachycardia, but no malignant arrhythmias occurred during further monitoring in the ICU. In another patient, ventricular bigeminia was found on the admission ECG, which became less frequent during monitoring, and only single PVCs were seen on the control ECG before discharge. This patient did not have a known history of PVC. In another patient with a history of severe alcohol abuse but

without known heart disease, recurrent non-sustained ventricular tachycardia (nsVT) was observed. Electrolyte disorder and myocardial necrosis were excluded, while transthoracic echocardiography did not show significant abnormalities. After administration of a single dose of amiodarone (150mg iv.), nsVTs were terminated. The patient was monitored for 18 hours and then left the hospital of their own volition, against medical advice. Further ECG abnormalities observed on admission are summarized in Table 3.

Table 3. Arrhythmias and electrocardiographic changes (n; %)

Prehospital ECG available	205 (42.7%)
ECG on admission available	475 (99.0%)
Control ECG before discharge available	76 (15.8%)
Arrhythmias	
Sinus bradycardia (<60 bpm)	50 (10.4%)
Sinus tachycardia (>100 bpm)	21 (4.4%)
Sinus arrest with atrial escape rhythm	2 (0.4%)
Newly diagnosed atrial fibrillation	1 (0.2%)
Frequent multifocal atrial premature complexes	1 (0.2%)
Supraventricular tachycardia during monitoring	1 (0.2%)
Ventricular fibrillation before admission	1 (0.2%)
Non-sustained ventricular tachycardia	1 (0.2%)
Ventricular bigeminy	1 (0.2%)
Further electrocardiographic observations	
Non-specific ST-T changes	41 (8.5%)
Incomplete RBBB	19 (4.0%)
PR depression	9 (1.9%)
Non-specific IVCD	6 (1.3%)
Single PVC	5 (1.0%)
RBBB (QRS duration ≥0.12sec)	4 (0.8%)
Left anterior hemiblock	3 (0.6%)
Single PAC	2 (0.4%)
First-degree AV block	1 (0.2%)
Trifascicular block	1 (0.2%)
Ventricular preexcitation syndrome	1 (0.2%)

AV = atrioventricular, IVCD = intraventricular conduction delay, PAC = premature atrial complex
PVC = premature ventricular complex, RBBB = right bundle branch block,

The most common ECG changes were non-specific mild ST-T differences (e.g., early repolarization) and incomplete right bundle branch block. We also compared ECG curves in cases where more than one ECG was available (n=246). In 12 cases intermittent incomplete right bundle

branch block was detected. Except for the cases reported here, we found no further dynamic ECG changes.

4.1.3 | Arrhythmias during ECG monitoring

Asymptomatic patients without risk factors and without ECG abnormalities were discharged directly from the ED. ECG monitoring was performed in 182 (37.9%) patients for 12.7±7.1 hours at the observation unit of the ED. Only one case of clinically relevant arrhythmia was detected during monitoring (a symptomatic regular supraventricular tachycardia that was terminated via vagal maneuver), although this patient suffered from recurrent palpitations even before the EA. Multivariable logistic regression indicated no statistically significant association between the most important baseline clinical parameters and the occurrence of arrhythmias; however, for high-voltage injury, borderline significance was detected (OR 2.94 (0.91 – 9.53); p = 0.07) (Table 4). Similar results were found when patients presenting with sinus tachycardia or sinus bradycardia were excluded from the regression model.

Table 4. Association between various clinical parameters and arrhythmias

Variable	OR (95% confidence interval)	p-value
Structural heart disease	0.90 (0.11 – 7.60)	0.92
LOC	2.82 (0.75 - 10.60)	0.13
High voltage	2.94 (0.91 – 9.53)	0.07
Transthoracic current	1.49 (0.85 - 2.63)	0.13
Burns	0.14 (0.01 – 1.55)	0.11

OR=odds ratio, LOC=loss of consciousness

4.1.4. Biochemical analysis

Results of laboratory tests are presented in Table 5. High-sensitive cTnI and CK was available in 354 (73.8%) patients performed at an average of 4.6 (± 4.3) hours after the EA. In most patients (n = 347) cTnI was below the upper limit of normal (<0.04 ng/ml). Slightly elevated cTnI (0.04-0.4 ng/ml) was found in six patients, while one patient had moderate cTnI elevation at 5.40 ng/ml. This patient was resuscitated by the emergency service on-site due to ventricular fibrillation. Patients with mild cTnI elevation showed no ECG abnormalities. CK elevation (>170 U/L) was detected in 120 patients and may be explained by soft tissue injuries, burns, muscle pain, or transthoracic current in 74 patients. The CK-MB ratio was <5% in all patients.

Table 5. Assessment of cardiac biomarkers

Time from EA to blood sample (hours; mean±SD)	4.6±4.3
cTnI available (n; %)	354 (73.8%)
cTnI slightly elevated (0.04 - 0.4ng/ml)	6 (1.25%)
cTnI significantly elevated (>0.4ng/ml)	1 (0.2%)
CK available (n; %)	354 (73.8%)
CK (U/L; mean ±SD)	305±1356
CK elevated (>170U/L)	120 (25.0%)
CK-MB% available (n; %)	291 (60.6%)
CK-MB% (mean±SD)	1.1±0.6
CK-MB% elevated (>5%)	0 (0%)

EA = electrical accident, cTnI = cardiac troponin I, CK = creatine kinase, CK-MB = creatine kinase muscle and brain, SD = standard deviation

4.1.5 In-hospital and post-discharge follow-up

The overwhelming majority of patients (n=468; 97.5%) were discharged from the ED, while only 12 patients were admitted for further observation or treatment. Among them, four patients were admitted to the multidisciplinary intensive care unit, one to the burn unit, four to the psychiatric ward, two to the cardiology ward, and one to the general internal medicine ward. All hospitalized patients were discharged from hospital to home. A thirty-day follow-up was undertaken for 477 patients, while three patients were lost to follow-up. At the end of this period, every patient was assumed to be alive (Table 6).

Table 6. Disposition of patients and survival

ED length of stay (hours; mean±SD)	6.9±5.7
ECG monitoring at ED (n; %)	182 (37.9%)
duration of ECG monitoring at ED (hours; mean±SD)	12.7±7.1
admitted for further observation/treatment (n; %)	12 (2.5%)
patients discharged from hospital (n; %)	480 (100%)
follow-up completed (n; %)	477 (99.4%)
30-day survival (n; %)	477 (100%)

ED = emergency department, SD = standard deviation

4.2 │ Electrical remodeling in cardiac resynchronization therapy

4.2.1 │ Studies included in the meta-analysis

Figure 4 shows the PRISMA flowchart for the search of the literature and study selection for the meta-analysis. After completion of screening, a total of 16 studies fulfilling the aforementioned selection criteria were included. According to MINORS criteria, nine papers could be classified as high-quality and five as medium-quality studies (Table 7, Supplementary Table 1). The eligible studies included 930 heart failure patients (range of included patients per study 17 – 110, 64.1% male) who all underwent CRT. The weighted mean age was 64.0±11.2 years. 35.7 % of patients had ischaemic cardiomyopathy (ICMP), and baseline ECG showed LBBB morphology in 748 (80.4%) patients. Non-LBBB morphology at baseline was an exclusion criterion in eight studies. Of the 16 included studies, three studies provided data only on incidence of RER, and these studies could not be included in the further meta-analytic calculations [36,39,40]. Up to two retrospective studies [40,41], all other studies were prospective observational trials. The vast majority of studies were single-center observations with the exception of one dual-center [40] and one multicenter study [34]. Tables 7–8 provide further details on each study included in the meta-analysis. Intrinsic QRS duration was measured by conventional 12-lead electrocardiogram before implantation and during follow-up by temporary inhibition of ventricular pacing. The mean timepoint of follow-up echocardiogram and ECG was between 6 and 15 months in most of the included studies.

Figure 4. Flowchart of the literature search and study selection.

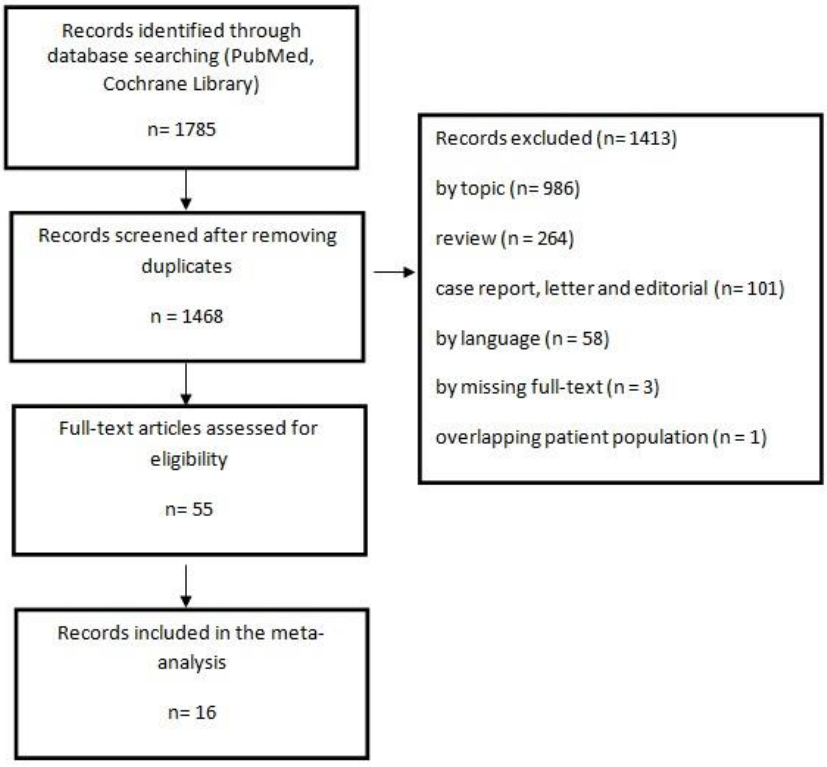


Table 7. Characteristics of the studies included in the meta-analysis

First author	Year	Study type	Time of ECG follow-up (months±SD)	QRS measuring method	Definition for echocardiographic response	Definition for clinical response	Definition for electrical response	Quality assessment (MINORS)
Henrikson	2007	P	14	mean of 12 standard leads	increase in LVEF	NA	reduction in iQRS > 0ms	low
Stockburger	2008	P	21 ± 14	50mm/s, automated measurement	decrease in LVEDD	NA	reduction in iQRS > 0ms	low
Tereschenko	2010	P	13 ± 7	lead II	decrease in LVESV ≥ 15%	NA	reduction in iQRS ≥ 10ms	moderate
Mischke	2011	P	6, 12	50mm/s	relative increase in LVEF of > 25%	≥1 decrease in NYHA	NA	high
Sebag	2012	P	12	25mm/s, widest complex	decrease in LVESV ≥ 15% and/or absolute increase in LVEF ≥10%	≥1 decrease in NYHA, no HF hospitalization	reduction in iQRS ≥ 20ms	high
Yang	2014	R	13 (range 6–36)	25mm/s, widest QRS, 200% magnitude	absolute increase in LVEF ≥ 10 %	NA	reduction in iQRS > 0ms	moderate
Diab*	2014	P	15±6	25mm/s	decrease in LVESV ≥15% and/or absolute increase in LVEF ≥10% and ≥1 decrease in NYHA		reduction in iQRS ≥ 20ms	moderate
Aslani	2015	P	at least 14	50mm/s, widest QRS	decrease in LVESV ≥ 15% or increase in LVEF ≥ 10%	NA	reduction in iQRS > 0ms	high
Zhang	2015	P	24	50mm/s, lead II	decrease in LVEDD >5 mm	NA	NA	high
Cvijic	2016	P	1 (3, 6, 9, 12)	25mm/s, lead V2, 400% magnification	decrease in LVESV ≥15%	NA	reduction in iQRS ≥ 10ms	high
Karaca	2016	P	6	50mm/s, widest QRS	decrease in LVESV ≥15%	≥1 decrease in NYHA	reduction in iQRS > 0ms	moderate
Cheng	2017	P	> 6	25mm/s, widest QRS	improvement in LVEF ≥ 25%	NA	reduction in iQRS ≥ 10ms	high
Sunman	2018	P	12	25mm/s	decrease in LVESV ≥15%	≥1 decrease in NYHA and no HF hospitalization	reduction in iQRS ≥ 20ms	high
Suszko	2019	P	6	25mm/s, from earliest onset to latest offset	improvement in LVEF ≥ 5%	NA	NA	high
Kwon	2020	P	33±18	25mm/s	decrease in LVESV ≥15%	NA	NA	high
Li	2020	R	40 ± 25	25mm/s, widest QRS	LVEF ≥50% (super-response)	NA	reduction in iQRS > 0ms	moderate

HF: heart failure; iQRS: intrinsic QRS; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association class; P: prospective; R: retrospective.

*In the study of Diab et al. CRT-responders fulfilled both echocardiographic and clinical criteria.

Table 8. Baseline patient characteristics and follow-up data of the studies included in the meta-analysis

First author	Number of patients	Mean age (years±SD)	Males (%)	LBBB (%)	AF (%)	ICMP (%)	Mean LVEF (%)	Mean NYHA	Baseline iQRS (ms)	Paced QRS width (ms)	Echo responders (%)	Electrical responders (%)
Henrikson	25*	NA	16 (64)	16 (64)	0	8 (32)	19 ± 6	3 ± 0.5	155 ± 29	NA	10 (67)	10 (67)
Stockburger	21**	65 ± 9	17 (81)	21 (100)	NA	8 (38)	23 ± 7	NA	165 ± 22	NA	17 (81)	11 (52)
Tereschenko	69	66 ± 13	50 (72)	41 (59)	39 (57)	37 (54)	24 ± 9	3 ± 0	150 ± 26	166 ± 40	36 (46)	22 (32)
Mischke	38	66±8	26 (68)	38 (100)	NA	18 (47)	26 ± 7	3.2 ± 0.4	175 ± 30	161 ± 25	22 (58)	NA
Sebag	85	65 ± 11	61 (72)	85 (100)	10 (12)	32 (38)	27 ± 8	2.9 ± 0.4	168±20	NA	45 (53)	43 (51)
Yang	74	61 ± 9	48 (65)	35 (47)	0	17 (23)	26 ± 6	3.0 ± 0.7	163±24	160 ± 18	47 (64)	30 (41)
Diab	30	55 ± 7	21 (70)	NA	0	15 (50)	29 ± 3	3.3 ± 0.4	146± 16	NA	23 (77)	16 (53)
Aslani	48	NA	NA	48 (100)	0	16 (34)	NA	NA	150±14	NA	32 (66)	0
Zhang	80	59 ± 12	57 (71)	69 (86)	9 (11)	15 (19)	29 ± 3	2.8 ± 0.6	165±27	135±20	52 (65)	NA
Cvijic	62	66 ± 10	50 (81)	40 (65)	0	25 (40)	27 (24 - 31)	2.8 ± 0.4	185 (175 - 194)	169±20	31 (50)	24 (39)
Karaca	110	66 (61 - 75)	70 (64)	94 (85)	30 (27)	47 (43)	27 ± 6	2.9 ± 0.6	161 ± 21	156±25	71 (65)	48 (44)
Cheng	83	67 ± 12	54 (65)	83 (100)	12 (14)	32 (39)	22 ± 6	3.3 ± 0.5	175±24	144±22	49 (59)	38 (46)
Sunman	41	61 ± 12	28 (68)	41 (100)	0	16 (39)	27 ± 5	2.9 ± 0.3	155 (142 - 178)	142 (130 - 161)	29 (71)	16 (39)
Suszko	47	62 ± 14	30 (64)	41 (87)	8 (17)	16 (34)	23 ± 7	2.6 ± 0.6	173±32	NA	28 (60)	NA
Kwon	100	66 ± 12	57 (57)	80 (80)	0	30 (30)	24 ± 6	NA	166±36	134±21	71 (71)	NA
Li	17	63 ± 11	11 (65)	16 (94)	0	0	33 ± 5	3.3 ± 0.5	175±12	136 (17)	17 (100)	14 (82)

LBBB: left bundle branch block; AF: atrial fibrillation; ICMP: ischaemic cardiomyopathy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association classification

Mean LVEF and NYHA represent baseline pre-implantation values. Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range.

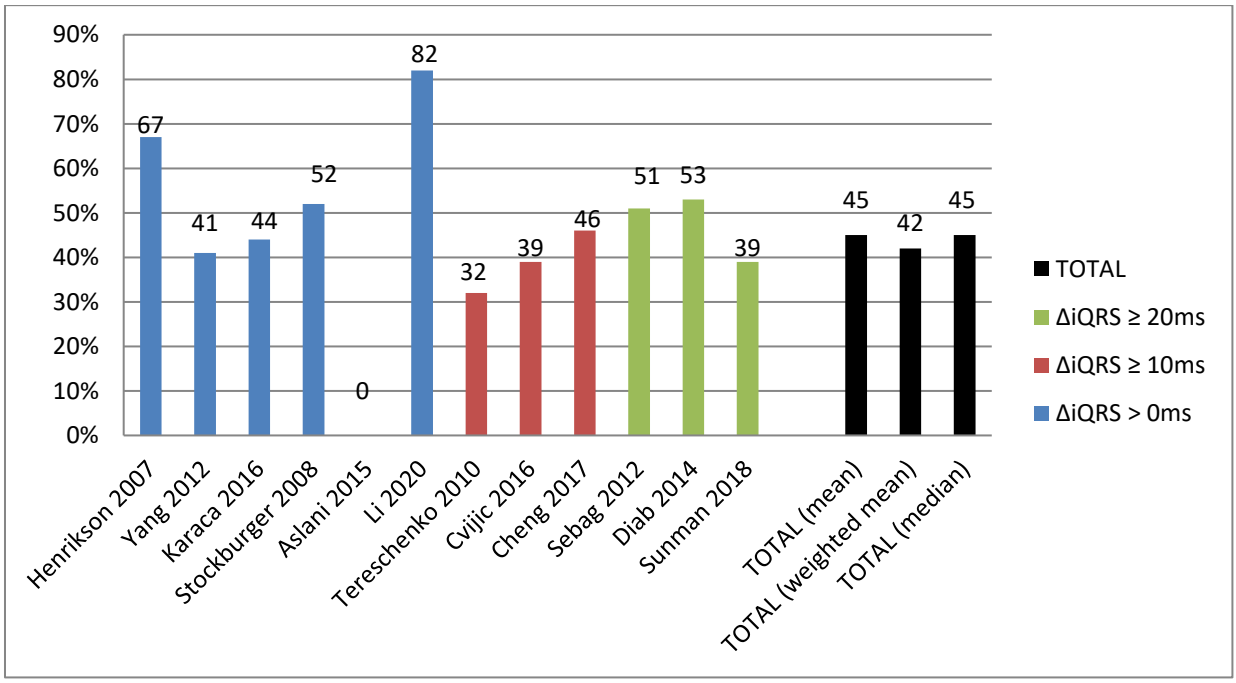
* Complete echocardiographic and ECG data only for 15 patients available. ** Only patient characteristics of patients receiving CRT are given.

4.2.2 | Incidence and extent of reverse electrical remodeling

The incidence of RER was reported in 12 studies [33,34,36,39–47]. For note, no universal definition of RER was used in these studies. Cut-off values for iQRS shortening of >0 ms, ≥10 ms, or ≥20 ms were applied in six, three, and three studies, respectively (Table 7). The incidence of RER sorted by the used cut-off value of iQRS shortening is depicted in Figure 5. The mean, weighted mean, and median overall incidence of RER in CRT recipients were 45%, 42% and 45% (range 0–82%). The baseline QRS duration was similar in patients with and without RER (169 ± 25 ms vs. 166 ± 25 ms). Mean baseline and follow-up iQRS duration were reported in four studies, including 294 participants. Patients with RER had a mean iQRS narrowing of 12.2 ms, whereas iQRS became broader by 4.6 ms in patients without RER ($p < 0.01$).

Figure 5. Incidence of RER sorted by degree of iQRS shortening defined by each study

ΔiQRS = change in intrinsic QRS duration



4.2.3 | Association between electrical and mechanical response

Nine studies reported detailed echocardiographic data on mechanical response in patient groups with and without RER (Table 7)[33,34,41–47]. Mechanical response was more frequently observed in patients with RER (75.7%) compared to patients without RER (46.6%) and this difference was statistically significant (OR 3.7; 95% CI 2.24–6.09, $p < 0.01$, $I^2 = 37\%$, Figure 6). In addition, we compared the extent of iQRS duration change in patients with mechanical response versus those without mechanical response. Data were extracted from six studies with 356

participants, of whom 231 (64.9%) were defined as mechanical responders [41,46,48–51]. We found that while mechanical responders had a mean of iQRS shortening of 6.4 ms, mechanical non-responders experienced a widening of iQRS by a mean of 5.2 ms (p=0.005). Sensitivity analysis including only high-quality studies showed similar results (Supplementary Figure 1).

Figure 6. Reverse electrical remodeling (RER) and mechanical response

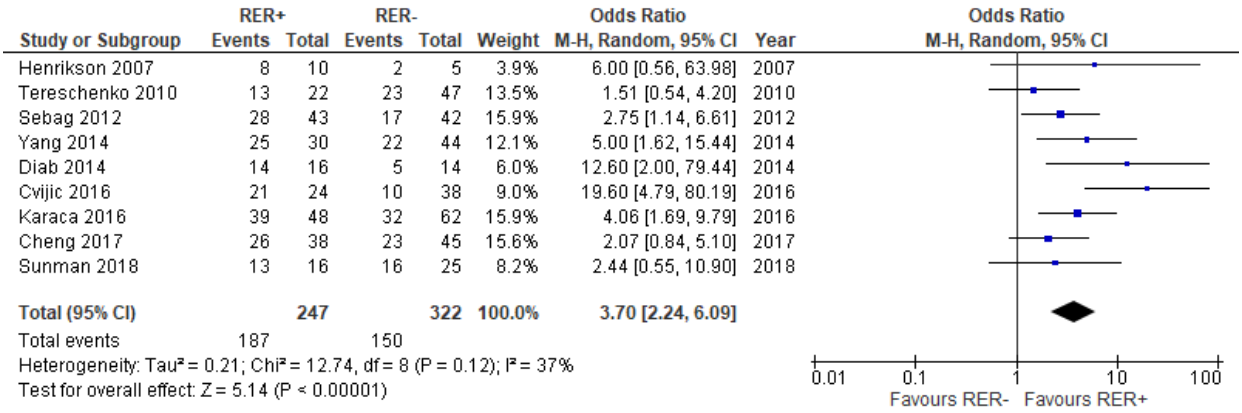
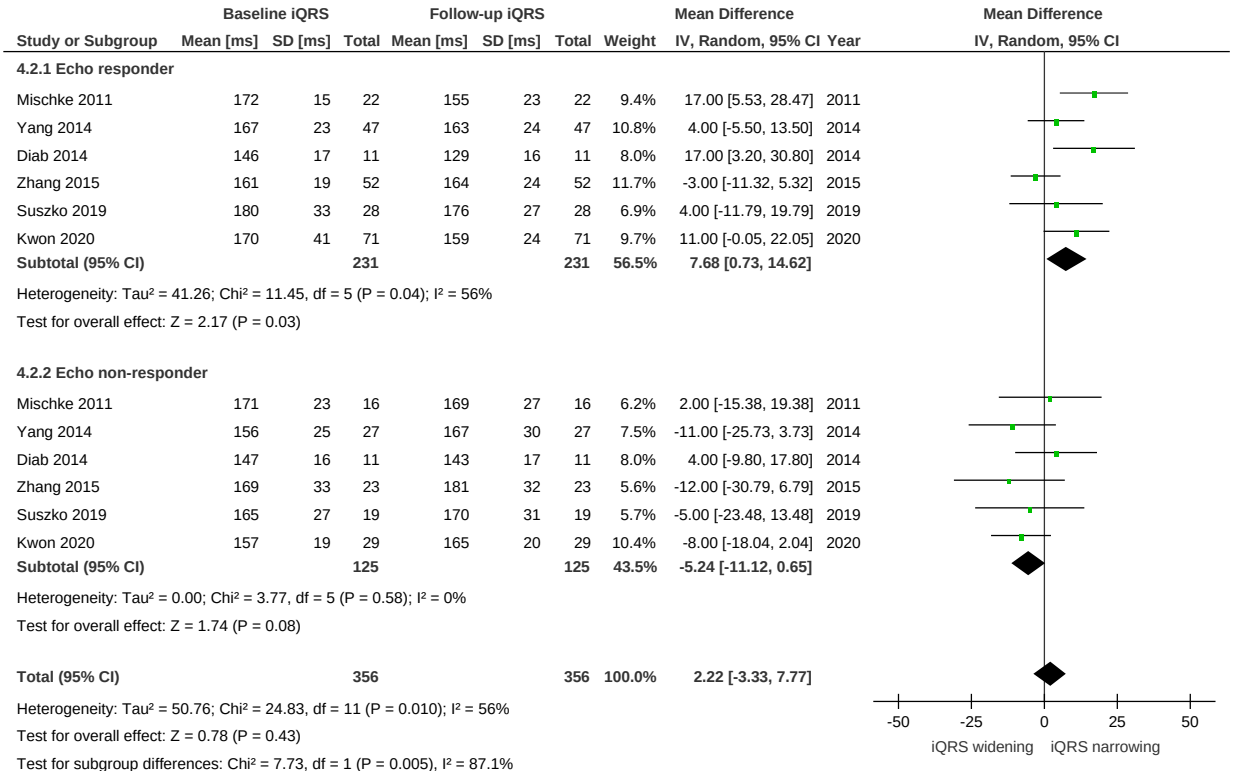


Figure 7. Intrinsic QRS narrowing in mechanical responders vs. non-responders subgroups



4.2.4 | Clinical response and mortality

Regarding the clinical response, we analyzed four studies (266 patients) [34,44,46,47]. Clinical response was defined as ≥1 decrease in NYHA functional class and in two studies an additional criterion of absence of HF hospitalisation was determined. The pooled analysis demonstrated that clinical improvement was more frequent in patients with RER vs. patients without RER (82.9% vs. 49.0%; OR 5.26; 95% CI 2.92-9.48; $p < 0.001$; $I^2 = 0\%$, Figure 6).

Regarding all-cause mortality, we analyzed five studies including 409 participants [33,34,43–45]. In one study, no death occurred during follow-up [34]. Three studies reported significantly reduced mortality in patients with RER [33,43,44], whereas one study [41] showed no association/neutral results. In the pooled analysis, we found no significant difference in all-cause mortality between patients with and without RER (6.3 vs. 15.4%, RR 0.47; 95% CI 0.18-1.21; p =0.12; I^2 = 38%, Figure 7). Sensitivity analysis, including only high-quality studies, showed similar results for both clinical response and mortality (Supplementary Figures 2-3).

Figure 6. Reverse electrical remodeling and clinical response

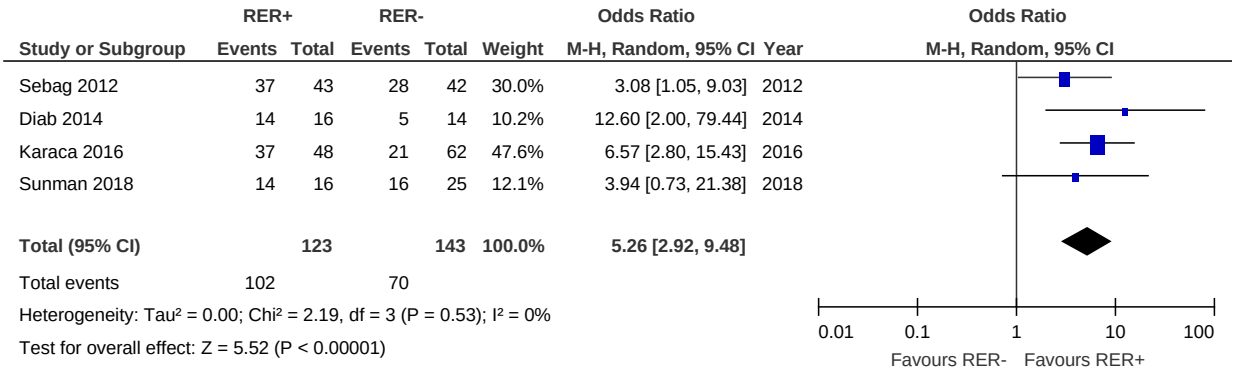
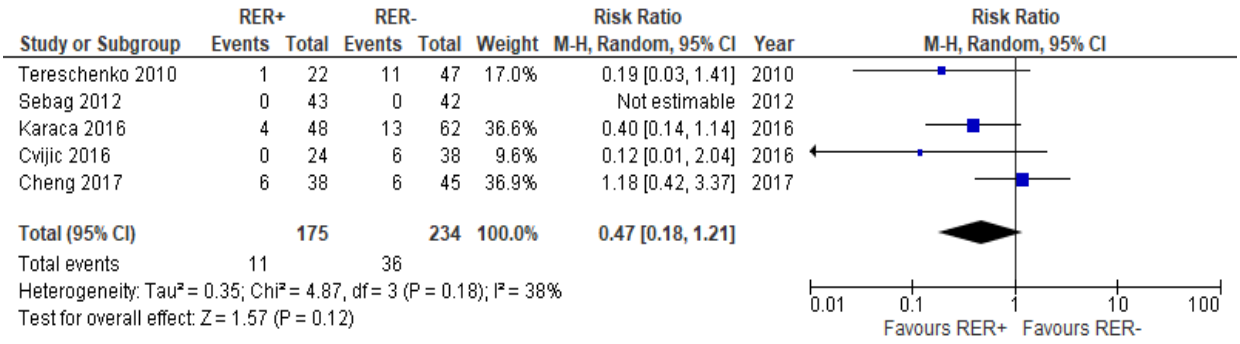


Figure 7. Reverse electrical remodeling and all-cause mortality

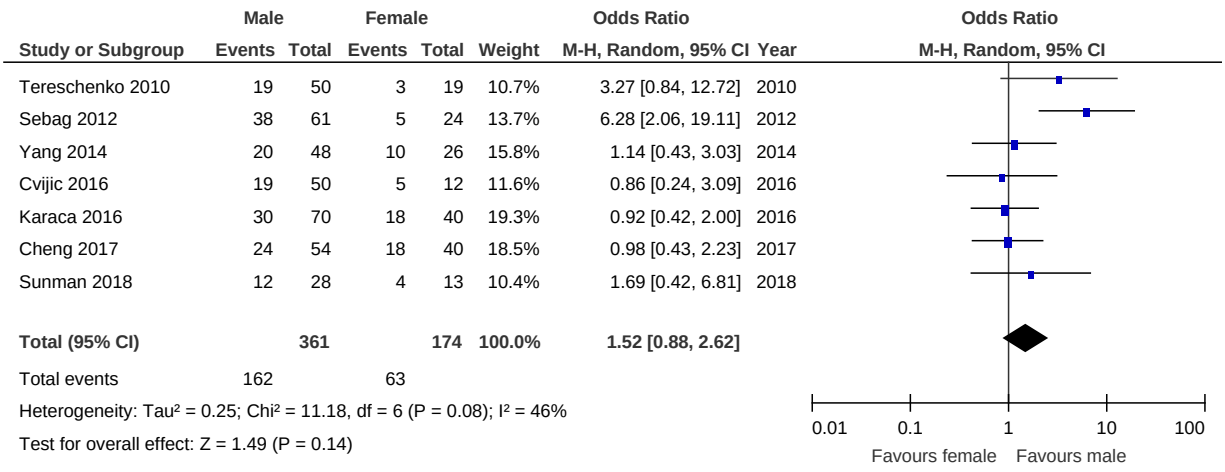


4.2.5 | Predictors of reverse electrical remodeling

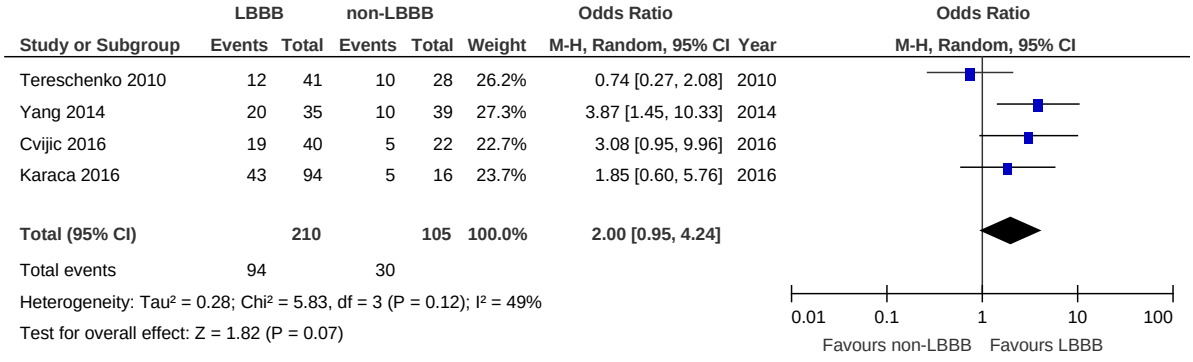
Analysis of the association between RER and gender, QRS morphology and heart failure aetiology was applicable in seven (n=225), four (n=124) and seven (n=221) studies, respectively (Figures 8a-c). The proportion of RER numerically higher in males than in females (44.9% vs. 36.2%; OR 1.52; 95% CI 0.88-2.62; p = 0.08; I^2 = 46%) [33,34,41,43–45,47]. RER was more frequent if the baseline QRS showed LBBB morphology, but the difference was not significant (44.8% vs 31.4%; OR 2.00; 95% CI 0.95-4.24; p = 0.07; I^2 = 49%) [33,41,43,44]. Regarding heart failure etiology no significant association was found between underlying heart disease (ICMP vs. NICMP) and occurrence of RER (OR 1.36; 95% CI 0.91-2.04; p = 0.13; I^2 = 14%) [33,34,41,43–45,47]. Also, only non-significant trend toward greater narrowing of iQRS in NICMP patients could be observed (-12.0 ms (-24.7, 0.8) vs -1.5 ms (-9.5, 6.6); p = 0.08, Figure 9).

Figure 8. Forest plots about the association of RER with **(a)** gender, **(b)** baseline QRS morphology (LBBB vs. non-LBBB) and **(c)** heart failure aetiology (ICMP vs. NICMP).

a. gender



b. baseline LBBB vs. non-LBBB



c. ischaemic vs. non-ischaemic heart failure

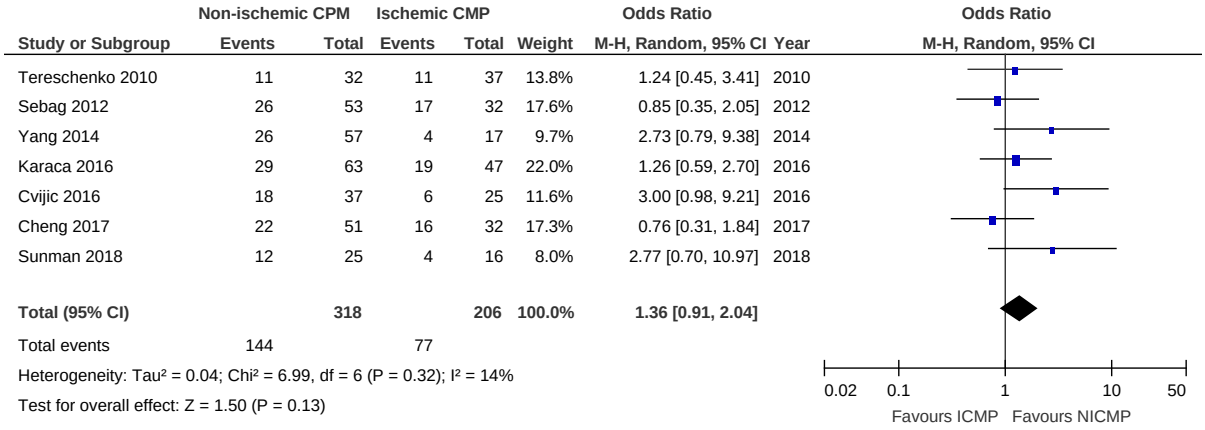
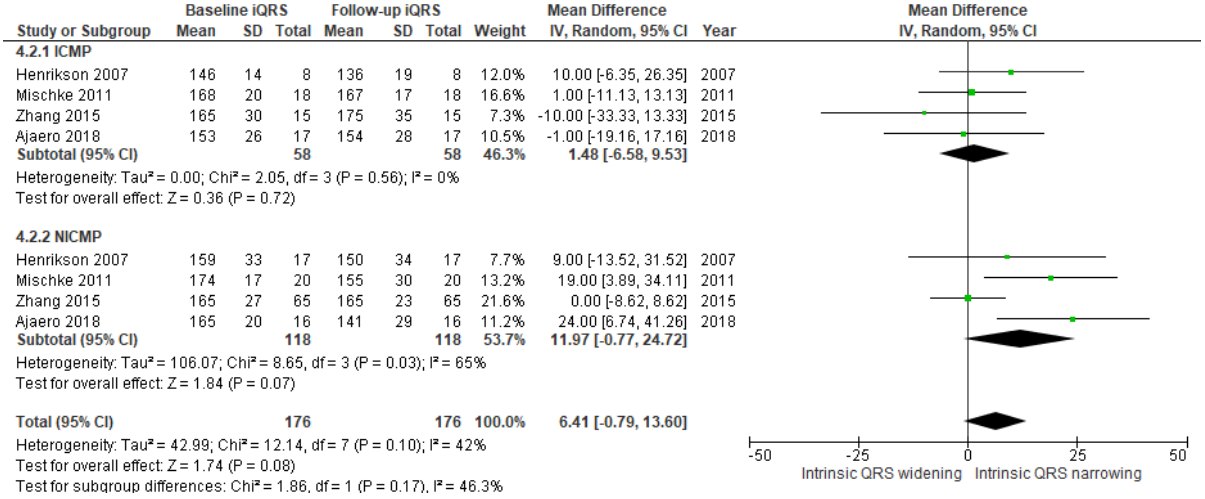
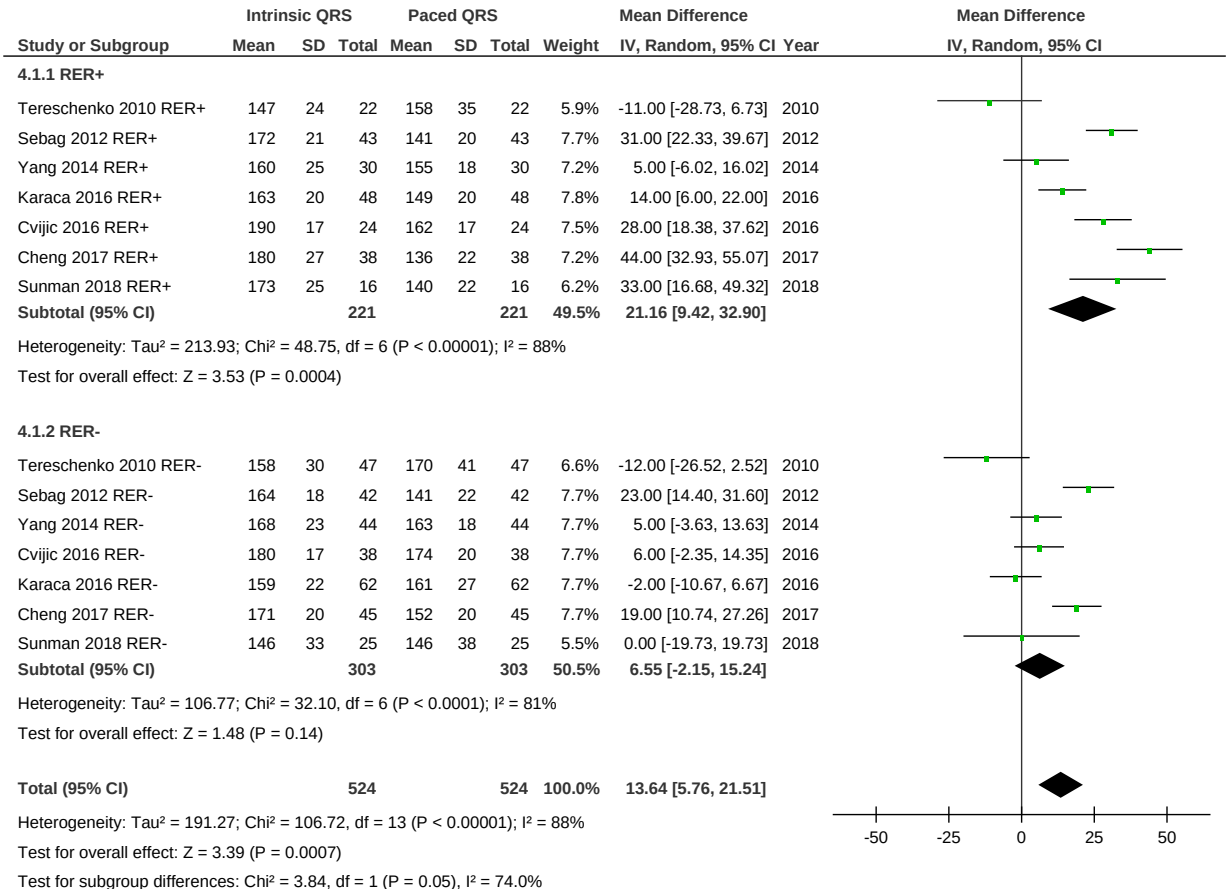


Figure 9. Intrinsic QRS narrowing (ms) in ICMP vs. NICMP subgroups



Finally, we analysed the association between acute narrowing of paced QRS (defined as baseline iQRS – post-implantation paced QRS) with later RER. Appropriate data were reported in seven studies with overall 524 participants [33,34,41,43–45,47]. Patients with later RER showed significant acute narrowing of paced QRS by 21.2ms (95% CI 9.4-32.9, $p < 0.01$) while narrowing of paced QRS was not significant in patients without later RER (6.6 ms, 95% CI -2.2-15.4, $p = 0.14$) (Figure 10). The mean difference in the narrowing of paced QRS was also significant between the two groups ($p = 0.05$). Similar results were found if only high-quality studies were included (Supplementary Figure 4).

Figure 10. Postimplantation narrowing of QRS by pacing in patients with and without later RER



4.2.6 │Publication bias

According to the rank correlation test of Begg and Mazumdar, there was no evidence of significant publication bias in any of the meta-analyses (association between electrical and mechanical response: $\tau = 0.306$, $p = 0.252$; clinical response: $\tau = 0.167$ $p = 0.734$; all-cause mortality: $\tau = -0.500$ $p = 0.308$; gender: $\tau = 0.476$, $p = 0.133$; QRS morphology: $\tau = 0{,}00$, $p = 1.0$; HF aetiology: $\tau = 0.381$, $p = 0.230$). Furthermore, corresponding to Duval and Tweedie's trim and fill input method, there was no evidence that publication bias would significantly impact the overall effect sizes observed (see Supplementary Figures 5-10).

5 │ DISCUSSION

5.1 │ Risk of arrhythmias after electrical accident

5.1.1 │ Main findings

The presented analysis is one of the largest studies published to focus on arrhythmias and cardiac biomarker changes following EA. We found that most cardiac arrhythmias in patients presenting after EA could be diagnosed by ECG on admission. Late-onset malignant arrhythmias were not observed at all, and the in-hospital and 30-day mortality were 0%. In our patient cohort, elevation of cTnI was rare and was not associated with arrhythmias. CK-MB% was also not useful in risk assessment after EA.

5.1.2 │ Arrhythmias after electrical accident

Arrhythmias caused by electric shock usually occur immediately after EA, and can directly lead to death [52]. A few cases of late-onset malignant arrhythmias after EA have been reported, but only two of them were documented with an initial ECG. In the first case, published by *Sharma et al.*, a progressive AV block was detected after electrocution of 220-240V, followed by ventricular fibrillation a few hours later [53]. The second case report describes a patient who developed pulseless ventricular tachycardia within 24 hours after hospitalization, which was terminated with DC shock. The admission ECG showed a prolonged QTc interval (500ms) while marked fragmentation of the QRS complex was also observed. At one month's follow-up, these ECG abnormalities were normalized [54].

Some previous reports have investigated the risk of arrhythmias after EA in a systematic fashion. *Pawlik et al.* retrospectively investigated 240 patients who suffered electric shock and were admitted to an ED. Sixty-two percent of patients were monitored for an average of 4.25 hours, during which no malignant arrhythmias occurred. Ninety-day mortality was 0% for all patients [55]. Similar results were found in the retrospective analysis of *Searle et al.* All 262 patients involved in the study were monitored for more than 12 hours; no life-threatening arrhythmias were observed, and in-hospital mortality was 0% [56]. The prospective multicentre study published by *Bailey et al.* involved only patients (n = 134) with one or more risk factors according to the current ERC guideline. Malignant arrhythmias did not occur in any of the patients during 24 hours of monitoring, and there were no late cardiac complications during the one-year follow-up [57].

A nationwide, Danish register-based study reviewed 11462 patients who presented at the emergency ward or were admitted to hospital after EA. The occurrence of documented cardiac

procedures was very low during the one-year follow-up period and in no case could a relationship between the cardiac event and electric accident be identified. The five-year mortality of EA survivors was similar to that of the matched patient population, regardless of whether the patient was admitted to hospital or discharged directly from ED [58].

Our high-volume retrospective analysis confirms the results of previous studies. Clinically relevant arrhythmias were rare in patients presenting after EA at the ED and could be diagnosed based on admission ECG. No new-onset arrhythmias were observed in patients who underwent cardiac monitoring, except for in one case where regular supraventricular tachycardia was detected. Some of the detected arrhythmias may be explained as physiological responses or normal variability, such as sinus tachycardia due to pain or anxiety or sinus bradycardia in young and physically fit patients. Other of the observed ECGs could be classified as borderline changes that should not necessarily be considered as pathological findings (e.g. atypical ST changes or incomplete RBBB).

In summary, if the patient's admission ECG is negative, the onset of clinically relevant arrhythmias is still unlikely. As our mortality data suggest, delayed fatal adverse events (e.g. fatal ventricular arrhythmias) did not occur regardless of whether the patient was monitored. Parameters considered to be risk factors, such as known structural heart disease, loss of consciousness, high-voltage electric shock, burn and soft tissue injuries, were also not predictive of the occurrence of arrhythmias.

5.1.3 │ Predictive value of biomarkers after electrical accident

There is insufficient evidence about the role of cardiac biomarkers in risk stratification after EA. A small prospective study found higher N-terminal pro b-type natriuretic peptide levels in patients with high-voltage electric injury and arrhythmia [59]. In the same study, CK-MB and cTnI were not found to be higher in arrhythmic patients compared to patients without arrhythmia after EA. Several other studies also suggest that CK-MB is not a reliable marker for screening arrhythmic and cardiac complications, as this can also be elevated due to skeletal muscle and soft tissue damage [60,61]. Although cTnI is a much more sensitive cardiac biomarker than CK, it does not usually increase after an EA [14,62]. Troponin elevation is only observed in some rare cases, is usually without clinical relevance, and most studies do not support the claim that cTnI elevation can predict arrhythmias after EA [14,55–57]. The arrhythmogenic effects of electric shocks are not considered to be primarily due to myocardial necrosis. This hypothesis is supported by the histopathological observation that the most common change in victims of electrocution is myofibre break-up leading to inhomogenity of the conduction system of the

heart [63]. Focal myocardial fibrosis and increased numbers of sodium-potassium pumps can also play a significant role [64].

Although CK elevation was relatively common in our patient cohort, CK-MB% was below 5% in each case. Significant elevation of cTnI was only detected in one patient who was resuscitated for 25 minutes due to ventricular fibrillation. TnI elevation was therefore considered to be due to long-term myocardial low perfusion. Sinus tachycardia was seen on the patient's admission ECG recording without repolarization abnormalities, while control laboratory tests showed no further increase in cTnI levels. To summarize, cTnI elevation appears to be sporadic and has no predictive value concerning arrhythmias after EA. Measurement of cTnI and CK-MB%, especially in stable patients with no ECG changes, may be unnecessary and increase cost and patient waiting time.

5.1.4 │ Limitations

The main limitation of our work stems from the retrospective nature of data collection, although we excluded incompletely documented cases from the dataset. It should be noted that patients were not always monitored according to the recommended monitoring protocol, and patient disposition was often influenced by the subjective decisions of clinicians. The majority of patients in the present research had suffered low-voltage electric injury, so these results can not be simply extrapolated to high-voltage electric accidents. Since no Holter recording was undertaken for the monitored patients, we were only able to detect arrhythmias that were mentioned in medical reports and for which ECG documentation was available. Another limitation is that only a small number of patients received an echocardiography. Survival data were calculated on the basis of the validity of health insurance numbers, which does not exclude the scenario that patients were admitted to another hospital because of late but non-fatal cardiac arrhythmias or other complications.

5.2 │ Reverse electrical remodeling in cardiac resynchronization therapy

5.2.1 │Main findings

We observed a significant association between RER and echocardiographic and clinical response rate to CRT. Prolonged QRS complex is an independent risk factor of mortality in heart failure patients [20]. QRS duration shows a progressive prolongation during the progression of the disease in many patients, which also correlates with increased mortality [65]. The fact that in our analysis mechanical responders experienced a significant iQRS shortening while mechanical non-responders developed a widening of iQRS correlates with these findings.

Shortening of iQRS could be therefore a rational prognostic marker, however reverse remodeling of conduction system during chronic biventricular pacing has not been studied so intensively as echocardiographic response. We found that RER could be detected in about 45% of patients. However, a relatively large variance in the incidence of RER between different studies was observed. This can be explained by the different definition of RER and the different inclusion criteria of the included studies (e.g. in the study of *Li et al.* only super-responders were included). Furthermore, there were differences in the utilized method of QRS measurement between the studies, which may also influenced the proportion of patients with RER.

5.2.2 │ Mechanism of reverse electrical remodeling

The mechanism of RER is not fully clarified. The association of RER and mechanical response suggests that RER is caused by a reduction of left ventricular volumes. However, this may also be influenced by an improvement in conduction velocity and of the impaired intramyocardial impulse transmission [66]. Major morphological changes in the native QRS or complete resolution of LBBB following CRT are seldom seen, occurring in only a few cases in the studies included here [40,66]. Furthermore, patients undergoing left bundle branch area pacing may undergo complete reverse electrical remodeling, as published in a recent case report [67]. *Suszko et al* assessed the number of leads with fragmented QRS before CRT and during follow-up with high-resolution ECG, and found a strong association between the reduction of ECG leads with fragmented QRS and the mechanical response [50]. Beside reverse remodeling of left ventricle, CRT may lead to reduction of mitral regurgitation and also to reverse remodeling of left atrium by reducing left atrial volume, which is associated with lower risk of atrial tachyarrhythmias [68]. A small observational study found that atrial remodeling can manifest as a reduction in P-wave duration [69].

5.2.3 │ Known predictors of CRT response and electrical remodeling

Based on international registry data, only about one-quarter of CRT recipients are women [70], but women obtain greater clinical and mortality benefit from CRT than men, as shown in multiple trials [71]. Several pivotal trials also indicated that women experience a greater degree of echocardiographic reverse remodeling than men [72,73], some other studies found no difference [74,75]. Our current meta-analysis found no significant association between gender and occurrence of RER. A previous meta-analysis indicated that gender differences become apparent only during follow-up periods longer than one year [76]. This fact could be one explanation for our findings; thus, the mean follow-up period was between 6 and 13 months in the included studies.

Furthermore, baseline QRS morphology is a strong predictor of CRT response: while patients with LBBB have the highest chance to benefit from biventricular pacing, positive effects are markedly lower in the case of right bundle branch block or intraventricular conduction delay[29,77]. *Perrin et al.* investigated changes of iQRS duration in different QRS morphologies during biventricular pacing. Shortening of iQRS was significantly more pronounced in complete LBBB than in the case of residual left bundle conduction or intraventricular conduction delay and patients with complete LBBB had also a greater reduction in LVEF [78]. In the current meta-analysis, three of four studies showed a higher occurrence of RER in patients with baseline LBBB [41,43,44], but the meta-analytic calculation showed a trend not reaching significance apparently ($p = 0.07$). Due to the limited number of studies, further prospective data are needed to clarify this issue.

Duration of native QRS is also strongly associated with later response to CRT and, therefore, plays a crucial role in patient selection for CRT. The REVERSE trial demonstrated greater extent of mechanical remodeling and more significant clinical benefit with increasing baseline QRS duration [79,80]. In two studies including only patients with LBBB, patients with later electrical response had significantly broader baseline QRS duration than patients without RER[34,47]. Other included studies of the meta-analysis showed no significant difference in baseline QRS duration between patients with and without RER. Further studies are needed to clarify the association of baseline QRS duration with RER.

Finally, there is clear evidence that patients with NICMP benefit more likely from CRT [81]. In our analysis two studies showed that patients with NICMP develop greater reduction of iQRS than patients with ICMP [48,82]. We found a numerically higher occurrence of RER in patients with NICMP compared to patients suffering from heart failure of ischaemic aetiology. However, the difference was not significant, possibly due to the low patient number. Regarding the extent of iQRS narrowing measured in milliseconds, a trend toward greater narrowing of iQRS in NICMP patients was also observed, suggesting a greater chance for remodeling in this patient group.

5.2.4 │ Paced QRS duration

It has been shown that shorter paced QRS and greater acute reduction of paced QRS could be associated with later clinical and echocardiographic CRT response [83]. Our results correlate with these findings, since patients with later RER had a greater acute reduction of paced QRS duration. Reverse electrical remodeling can be also detectable in shortening of paced QRS

duration during chronic CRT. *Yang et al.* assessed changes in paced QRS during long-time follow-up and found that narrowing of paced QRS was significant in responders after 6 months of biventricular pacing, and super-responders (defined as LVEF ≥ 50%) had a further reduction of paced QRS duration measured at time of generator replacement [84].

5.2.5 │Unanswered questions and further perspectives

There is very limited data about time course of reverse electrical remodeling. *Cvijic et al.* found that shortening of iQRS precedes mechanical remodeling and can be detected already 1 month after implantation [43]. This data suggest that RER may be an early marker of CRT-response. Measurement of intracardiac conduction delays with the help of quadripolar leads may be a novel and easily measurable method to assess RER. *Toner et al.* found a more significant reduction of intrinsic activation time (measured between right ventricular and left ventricular lead) in CRT responders than in non-responders [85]. An ongoing trial should further clarify the correlation between changes in interelectrode conduction times, surface electrocardiogram and echocardiographic response [86]. Finally, a recent, relatively small cohort study showed that about half of patients without CRT treated with sacubitril-valsartan experienced shortening of QRS complex duration, which strongly correlated with the improvement in LVEF and reduction of left ventricular volume [87]. This observation suggests that medical treatment may play an important role in RER, necessitating further prospective large cohort trials.

5.2.6 │ Limitations

The presented meta-analysis shows all the potential limitations of this kind of analysis. First, the number of patients was low in most studies. Second, there are some methodological bias, such as the difference in definition of RER (>0 ms, ≥10 ms or ≥20 ms shortening of intrinsic QRS); difference in definition of echocardiographic response; minor differences in measurement time and method of intrinsic QRS duration (Table 7). Third, data included in the meta-analysis were collected from the published papers and we did not have access to individual patient data. Finally, RER could be measured only in patients who were not pacemaker-dependent. Therefore, the results can not be applied to the whole CRT patient population.

6 | CONCLUSIONS

1. We found that clinically relevant arrhythmias in patients presenting to the emergency department after an electrical accident are rare and can be diagnosed by 12-lead ECG on admission. Routine continuous ECG monitoring appears to be unnecessary and should be performed only in cases with risk factors.
2. In our patient cohort, elevation of cardiac troponin I and CK-MB was only sporadically detected and was not useful in risk assessment after EA. Therefore, routine assessment of cardiac necroenzymes does not seem necessary in patients after EA.
3. Late-onset malignant arrhythmias were not observed in our patient cohort. Therefore, our data suggest that symptom-free patients without ECG abnormalities or risk factors like syncope, high-voltage injury, and severe burns can be discharged safely from the emergency department.
4. Our systematic review and meta-analysis of currently available studies found that electrical reverse remodeling of the native conduction system measured on 12-lead ECG by shortening of intrinsic QRS in patients undergoing CRT was associated with better echocardiographic and clinical response.
5. Reverse electrical remodeling could be more frequently observed in patients with baseline left bundle branch morphology than in patients without LBBB. We also found that patients with later RER had a greater post-implantation reduction of paced QRS duration.
6. Our results suggest that RER should be considered as a part of definitions of response to CRT and may be used as a predictor of clinical outcomes. Measurement of intrinsic QRS duration by 12-lead electrocardiogram during follow-up is a simple, time-sparing, and cost-effective method, but further prospective studies are needed to clarify the exact role of intrinsic QRS measurement in the clinical management of patients undergoing CRT.

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8 | FURTHER PUBLICATIONS NOT RELATED TO THE THESIS

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Deus providebit.

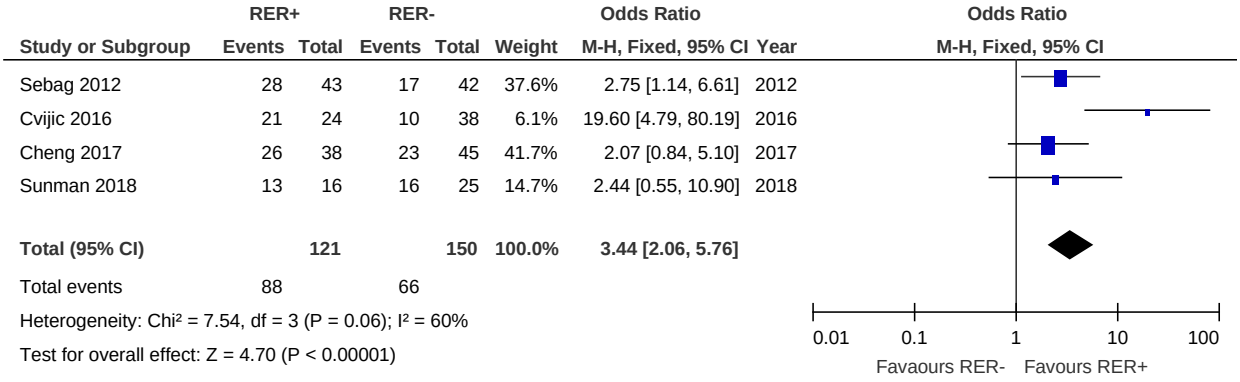
10 | SUPPLEMENT

Supplementary Table 1. MINORS criteria for quality assessment of included studies

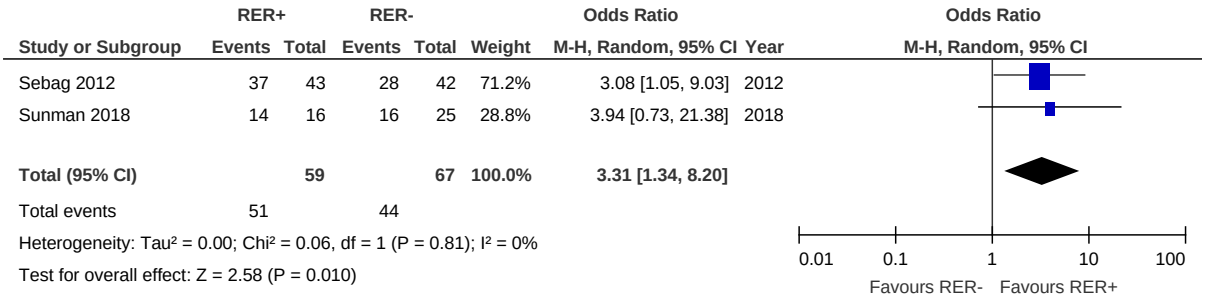
First author and year	aim of the study	inclusion of consecutive patients	prospective data collection	appropriate endpoint to the aim of the study	unibiased evaluation of endpoints	follow-up period appropriate to the endpoint	loss to follow-up no more than 5%	prospective calculation of the sample size	All	Quality
Henrikson 2007	2	0	2	2	1	2	0	0	**9**	**low**
Stockburger 2008	2	0	1	2	0	2	2	0	**13**	**low***
Tereschenko 2010	2	1	2	2	0	2	2	0	**11**	**moderate**
Mischke 2011	2	2	2	2	1	2	2	0	**14**	**high**
Sebag 2012	2	1	2	2	2	2	2	0	**13**	**high**
Yang 2014	2	1	1	2	1	2	2	0	**11**	**moderate**
Diab 2014	2	1	1	2	1	2	2	0	**11**	**moderate**
Aslani 2015	2	2	2	2	1	2	2	0	**13**	**high**
Zhang 2015	2	2	2	2	1	2	2	0	**13**	**high**
Cvijic 2016	2	1	2	2	1	2	2	0	**12**	**high**
Karaca 2016	2	1	0	2	1	2	2	0	**10**	**moderate**
Cheng 2017	2	2	2	2	1	2	2	0	**13**	**high**
Sunman 2018	2	1	2	2	1	2	2	0	**12**	**high**
Suszko 2019	2	2	2	2	1	2	2	0	**14**	**high**
Kwon 2020	2	2	2	2	1	2	2	0	**14**	**high**
Li 2020	2	2	0	2	1	2	0	0	**10**	**moderate**

*For the study of *Stockburger et al.*, all items (1-12; maximal score 24) of the MINORS criteria were applied because this study had a comparator group.

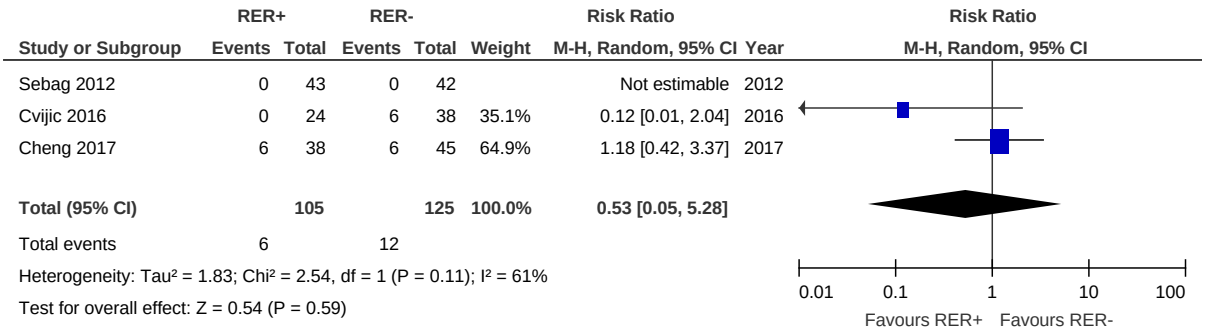
Supplementary Figure 1. Association of reverse electrical remodeling (RER) with mechanical response in high-quality studies



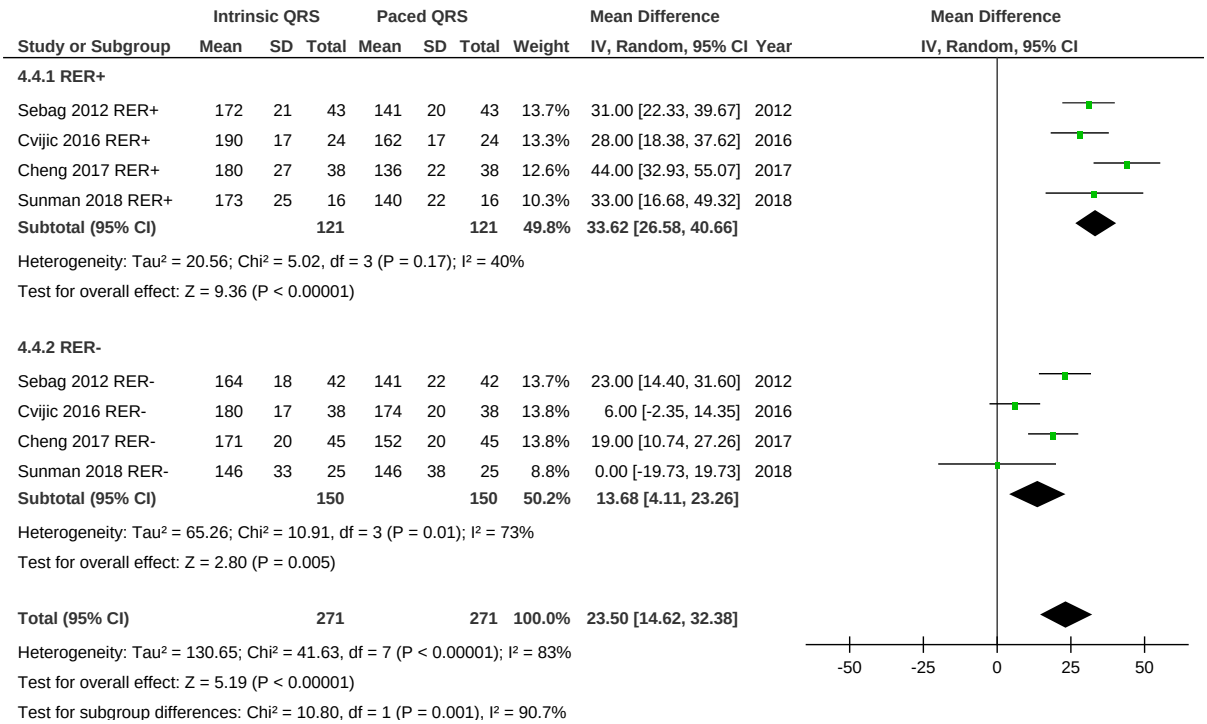
Supplementary Figure 2 Association of reverse electrical remodeling (RER) with clinical response in high-quality studies



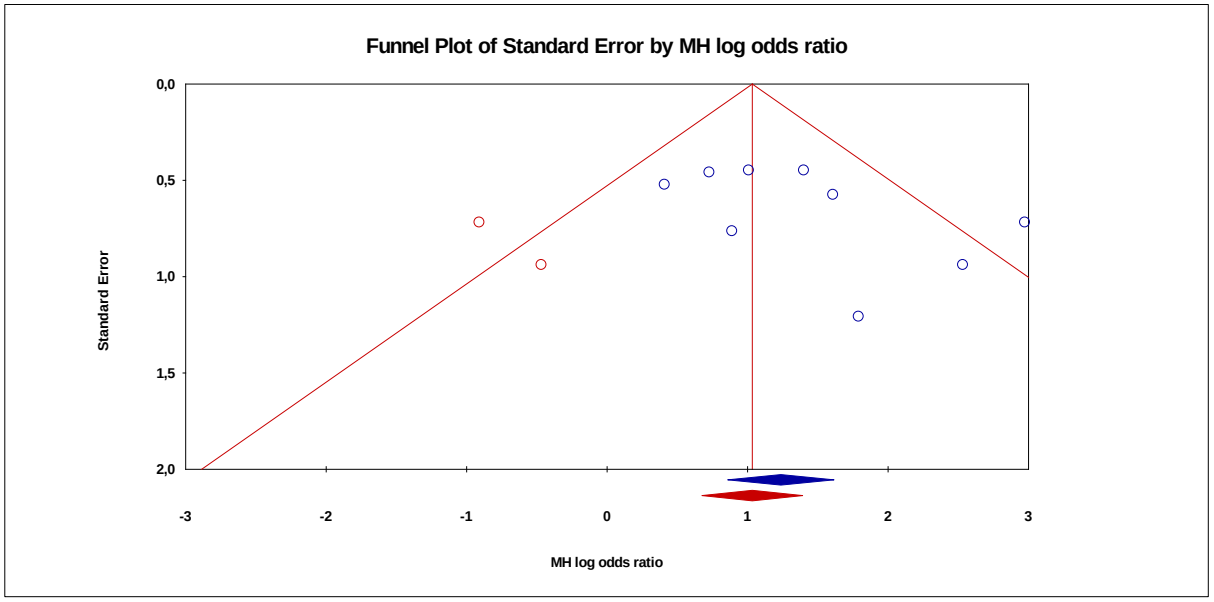
Supplementary Figure 3 Association of reverse electrical remodeling (RER) and mortality in high-quality studies



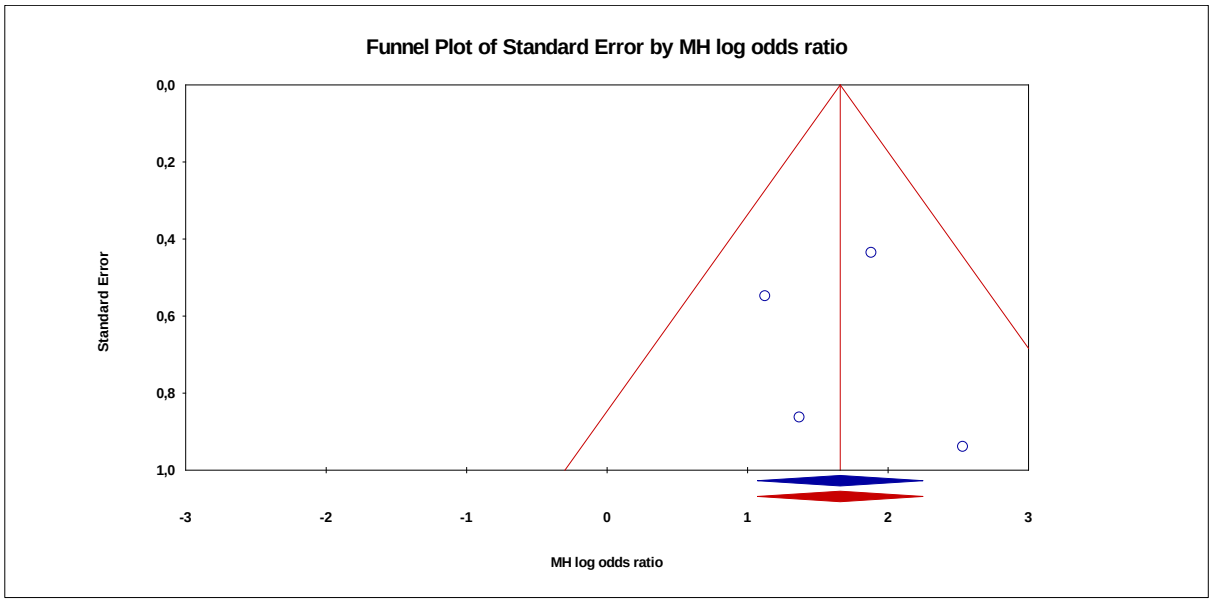
Supplementary Figure 4 Postimplantation narrowing of QRS width by pacing in patients with and without RER in high-quality studies



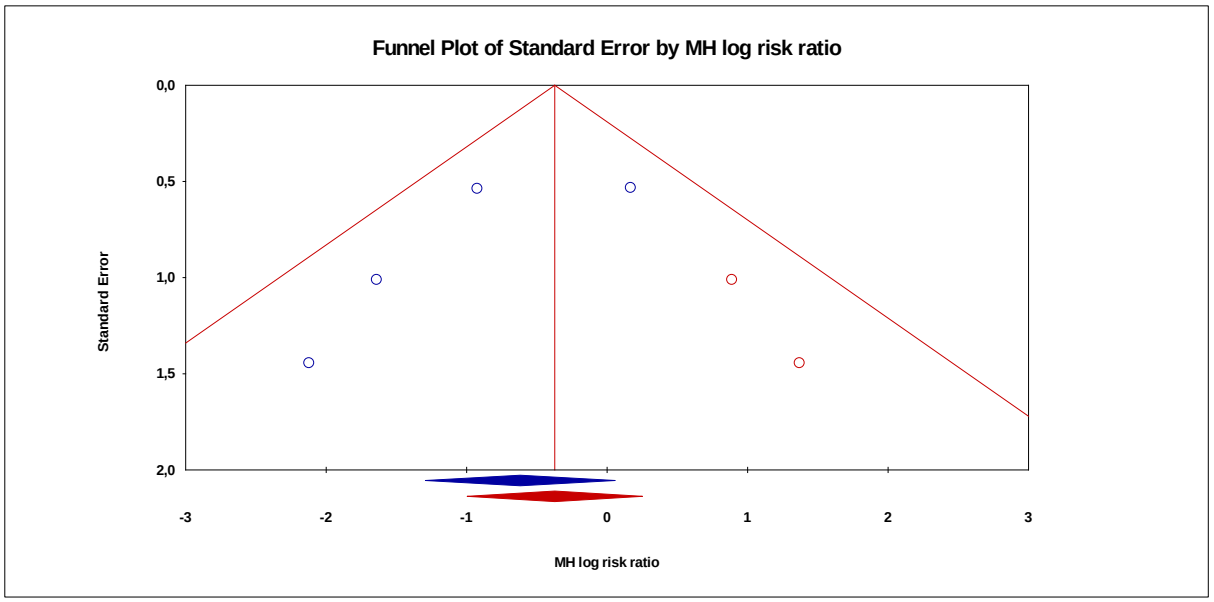
Supplementary Figure 5. Funnel plot of reverse electrical remodeling and mechanical response expressed in MH odds ratio. Two studies were trimmed to the left of the mean (red circles) according to Duval and Tweedie's trim and fill method (OR: 3.70, 95% CI, 2.24 to 6.09, vs. 2.86, 95% CI, 1.60 to 5.12).



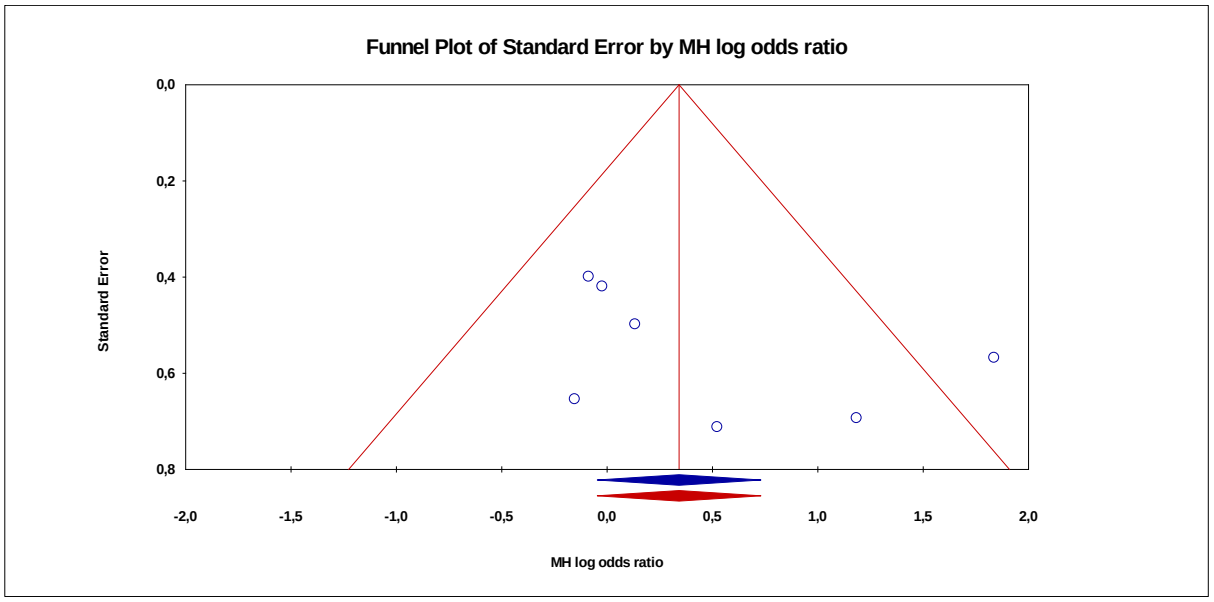
Supplementary Figure 6. Funnel plot of reverse electrical remodeling and clinical response expressed in MH odds ratio. No study should have been trimmed according to Duval and Tweedie's trim and fill method.



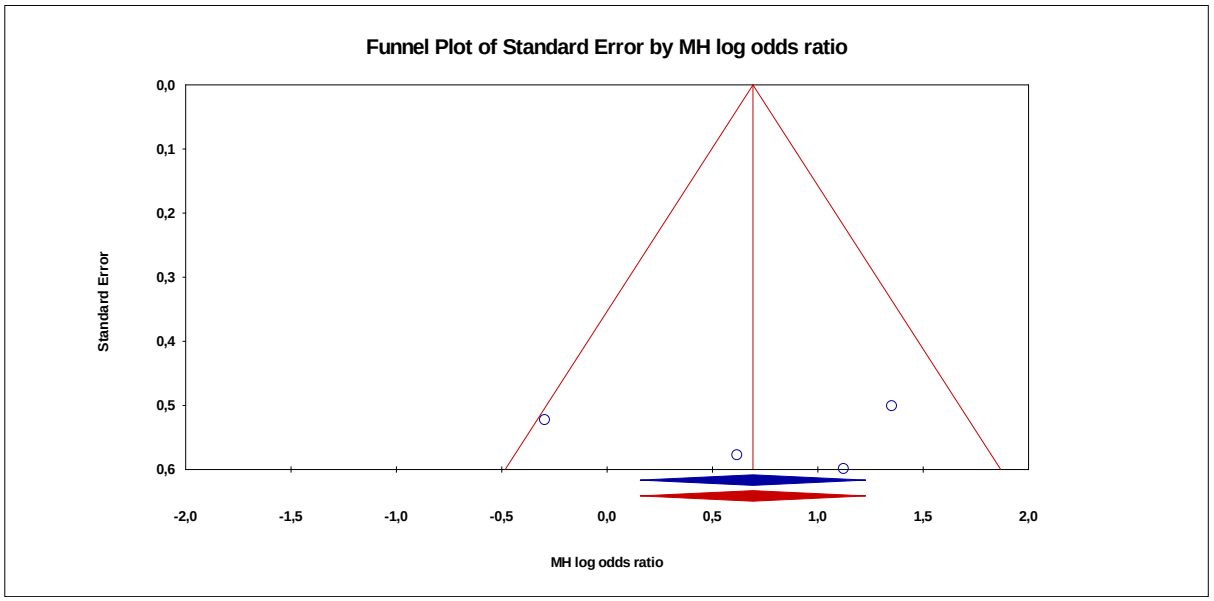
Supplementary Figure 7. Funnel plot of reverse electrical remodeling and all-cause mortality expressed in MH risk ratio. Two studies were trimmed to the right of the mean (red circles) according to Duval and Tweedie's trim and fill method (RR: 0.47, 95% CI, 0.18 to 1.21, vs. 0.69, 95% CI, 0.28 to 1.66).



Supplementary Figure 8. Funnel plot of reverse electrical remodeling and gender expressed in MH odds ratio. No study should have been trimmed according to Duval and Tweedie's trim and fill method.



Supplementary Figure 9. Funnel plot of reverse electrical remodeling and QRS morphology expressed in MH odds ratio. No study should have been trimmed according to Duval and Tweedie's trim and fill method.



Supplementary Figure 10. Funnel plot of reverse electrical remodeling and HF etiology expressed in MH risk ratio. Two study were trimmed to the left of mean (red circles) according to the Duval and Tweedie's trim and fill method (OR: 1.36, 95% CI, 0.91 to 2.04, vs. 1.14, 95% CI, 0.74 to 1.76).