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SYSTEMATIC STUDY OF CURRENT THERAPEUTIC APPROACHES OF ARRHYTHMIAS IN PATIENTS WITH HEART FAILURE

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Η Γραμματέας του Τμήματος

ΜΑΡΙΑ ΚΑΠΙΤΟΠΟΥΛΟΥ

Dedications

For my family, my wife Paschalia and my son Ioannis

Prologue

Heart failure is a public health problem associated with significant morbidity and mortality, while it also has a negative impact on the quality of life of the affected patients. The prevalence of heart failure continues to rise over time with the aging of the population. Specifically, an estimated 6.5 million American adults ≥20 years of age had heart failure between 2011 and 2014 compared with an estimated 5.7 million between 2009 and 2012. The aim of this thesis was to investigate important clinical questions related with heart failure patients with reduced ejection fraction and atrial and ventricular arrhythmias that consist common comorbidities in these patients; emphasis is placed on their prognostic role and the effect of various treatment modalities.

Specifically, we performed a meta-analysis to investigate the impact of atrial fibrillation history in patients with heart failure and an implantable cardioverter defibrillator implanted either for primary or for secondary prevention of sudden cardiac death. Furthermore, another meta-analysis was performed to investigate the possible association between appropriate and inappropriate implantable cardioverter defibrillator therapies with all-cause mortality in heart failure patients. Catheter ablation is a new approach in treating atrial fibrillation. Recent studies have shown the beneficial role of this technique in patients with heart failure. However, approximately 30% of patients undergoing catheter ablation procedure sustain an arrhythmia recurrence. We performed a retrospective analysis to investigate whether baseline characteristics may be significantly associated with atrial fibrillation recurrence in heart failure patients undergoing an atrial fibrillation catheter ablation procedure. Cardiac resynchronization therapy is another treatment modality that was found to improve major clinical outcomes in appropriately selected heart failure patients. However, a significant proportion of these patients receiving a cardiac resynchronization therapy do not seem to respond to the treatment. As a result, we performed a retrospective analysis to investigate possible associations of simple hematological laboratory indices with the response to cardiac resynchronization therapy. Finally, we performed a meta-analysis of observational studies to investigate the association of QRS narrowing after cardiac resynchronization therapy implantation with response to cardiac resynchronization therapy.

All this work could not be performed by only one person. Specifically, I want to thank my supervisor Prof Katerina K Naka for her full support and for the time that

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Table of Contents

General Part

1. Heart failure (HF)

1.1 Definition of HF

Heart failure (HF) is a clinical syndrome characterized by typical symptoms and signs caused by a structural and/or functional cardiac abnormality, resulting in impairment of ventricular filling or ejection of blood (1, 2).

1.2 Epidemiology

HF is a major public health issue and the worldwide prevalence has been increasing over the last decades. The reasons of this increase can be attributed to a combination of growing awareness and diagnosis of HF, aging population, increasing incidence of HF, improvement in the treatment and management of cardiovascular disease (3) and especially acute myocardial infarction and HF. The prevalence of HF continues to rise over time with the aging of the population. Specifically in the USA, an estimated 6.5 million American adults ≥20 years of age had HF between 2011 and 2014 compared with an estimated 5.7 million between 2009 and 2012 (4).

Additionally, hospital discharges for HF remained stable from 2000 to 2010, with first-listed discharges of 1,008,000 and 1,023,000, respectively (5). Overall, at age 45 years through age 95 years, lifetime risks for HF were high (20%–45%) while lifetime risks for HF were 30% to 42% in white males, 20% to 29% in black males, 32% to 39% in white females, and 24% to 46% in black females (4, 6). Interestingly, the lifetime risk for HF appeared to increase with higher blood pressure (BP) and body mass index (BMI) at all ages (4). Specifically, the lifetime risk of HF occurring for people with BMI ≥30 kg/m2 was double that of those with BMI <25 kg/m2, while the lifetime risk of HF occurring for people with BP >160/90 mm Hg was 1.6 times that of those with BP <120/90 mm Hg (4, 6).

1.3 Prognosis

The implementation of the evidence-based new treatment strategies (life-saving HF medications, cardiac resynchronization therapy (CRT) has led in an improvement in the long-term prognosis of HF patients (7). Among Medicare beneficiaries, the overall 1-year HF mortality rate declined slightly from 1998 to 2008 but remained high at 29.6% (8). The improvement in HF survival led to an increase in the incidence and prevalence of HF as well in the number of deaths associated with HF. Specifically, 1 in 8 deaths

has HF mentioned on the death certificate (NCHS, NHLBI unpublished tabulation) while the number of underlying cause of deaths attributable to HF was 27.7% higher in 2015 (75,251) than it was in 2005 (58,933) (4).

1.4 Symptoms and Signs

The typical clinical manifestations of HF consist of breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness and ankle swelling while the most specific signs are: elevated jugular venous pressure, hepatojugular reflux, third heart sound (gallop rhythm), and laterally displaced apical impulse (1, 2). However, less typical symptoms such as nocturnal cough, wheezing, bloated feeling, loss of appetite, confusion (especially in the elderly), depression, palpitations, dizziness, syncope, bendopnea and less typical signs such as weight gain (>2 kg/week), weight loss (in advanced HF), tissue wasting, cardiac murmur, peripheral oedema (ankle, sacral, scrotal), pulmonary crepitations, reduced air entry and dullness to percussion at lung bases (pleural effusion), tachycardia, irregular pulse, tachypnoea, Cheyne Stokes respiration, hepatomegaly, ascites, cold extremities, oliguria, and narrow pulse pressure can be present (1, 2).

1.5 Aetiology - risk factors

There is a broad spectrum of etiologic factors that can lead to HF. These factors can be divided in factors that cause myocardial damage (ischemic heart disease, toxic damage, immune mediated and inflammatory damage, infiltrative diseases, metabolic derangements, genetic abnormalities), abnormal loading conditions (hypertension, valve and myocardium structural defects, pericardial and endomyocardial pathologies, high output states, volume overload) and arrhythmias (1, 9). The NHANES study found that the traditional risk factors for HF are: coronary artery disease, cigarette smoking, hypertension, obesity, diabetes mellitus, dietary sodium intake and valvular heart disease (5, 10) while nontraditional risk factors have also been described: brain natriuretic peptide (BNP), urinary albumin-to-creatinine ratio, elevated serum γ-glutamyl transferase, and higher levels of hematocrit, increased circulating concentrations of resistin, adiponectin, inflammatory markers (interleukin-6 and tumor necrosis factor-α, C-reactive protein (CRP), white blood cells count), HBA1c, cardiac troponin, ventricular premature complexes and socioeconomic position (5).

1.6 Classification of HF

The main classification of HF is historically based on left ventricular ejection fraction (LVEF). According to the latest 2016 HF guidelines from the European Society of Cardiology (ESC), patients are classified in the following categories on the basis of LVEF: a) HF with preserved ejection fraction (HFpEF) which includes patients with LVEF ≥ 50%, b) HF with reduced ejection fraction (HFrEF) which includes patients with LVEF <40% and c) HF with mid-range ejection fraction (HFmrEF) which includes patients with LVEF in the grey zone of 40-49% (1). In the American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) 2013 HF guidelines, HFpEF is further divided into "HFpEF, borderline" including patients with persistently LVEF in the grey zone (41-49%) and "HFpEF, improved" including patients with improvement or recovery in LVEF and previously belonged in HFrEF (2). Of incident hospitalized HF events, approximately half are characterized by reduced LVEF and the other half by preserved LVEF. Black males had the highest proportion of presentations with reduced LVEF (≈70%); white females had the highest proportion of HF hospitalizations with preserved LVEF (≈60%) (4).

1.7 Diagnosis

The diagnosis of HF is mainly clinical especially in patients with preserved LVEF. According to the latest 2016 HF guidelines from the ESC, for the diagnosis of HF the following criteria should be fulfield: A) HFrEF: The presence of symptoms and/or signs of HF and LVEF<40%, B) HFpEF and HFmrEF: i) The presence of symptoms and/or signs of HF, ii) a 'preserved' EF (defined as LVEF ≥50% or 40–49% for HFmrEF), iii) elevated levels of natriuretic peptides (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL), iv) at least one of the following: a) relevant structural heart disease (left ventrcular hypertrophy and/or left atrial enlargement), b) left ventricular diastolic dysfunction (1).

1.7.1 HF with preserved Ejection Fraction (HFpEF)

Epidemiological studies have shown that up to 15-25% of HF patients have preserved LVEF (11, 12). All patients with typical or atypical symptoms and signs of HF should be further examined for objective evidence of abnormal cardiac structure and function with echocardiography, electrocardiography, chest radiography, and measurement of natriuretic peptide levels (13). However, the levels of natiuretic peptides which is a major diagnostic criterion are influenced by a number of factors: age, sex, renal

function, obesity, flash pulmonary edema (14). Regarding the aetiology, hypertension, is the most frequent primary cause of HFpEF and is followed mainly by ischemic heart disease, valve disease, idiopathic dilated cardiomyopathy and tachycardia-related cardiomyopathy (15). A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejection fraction (APOLLON) trial showed that the basic characteristics and etiology of HFpEF are significantly different from HFmrEF (16). A recent study evaluated the prevalence of the following risk factors in HF patients: diabetes mellitus, thyroid dysfunction, obesity, anaemia, chronic kidney disease, chronic obstructive pulmonary disease (COPD), stroke and peripheral arterial disease (17). The authors found that all comorbidities showed the highest prevalence in HFpEF, except for stroke. In women, older age, white race, obesity, hypertension, diabetes mellitus, atrial fibrillation (AF), coronary artery disease, anemia, chronic lung disease, radiation exposure, renal dysfunction and lesser exposure to estrogen have been associated with HFpEF (18).

Regarding the pathophysiology of HFpEF, risk factors (obesity, diabetes mellitus, hyperlipidemia, hypertension) can cause microvascular dysfunction and contribute to a proinflammatory state that can lead to LV hypertrophy, interstitial fibrosis, LV stiffness with impaired relaxation and diastolic dysfunction that finally cause the clinical syndrome of HFpEF (18). Myocardial ischemia secondary to coronary microvascular dysfunction may also have an important role in the pathogenesis of the disease (19).

Several studies have evaluated the prognostic role of different risk factors in HFpEF. Specifically, age, body mass index, New York Heart Association (NYHA) III/IV, pulmonary congestion, aortic stenosis, AF, peripheral artery disease and chronic kidney disease were found to significantly associated with all-cause mortality within 1 year (15). Another study showed that chronic kidney disease and obesity were associated with reduced quality of life in HFpEF while only chronic kidney disease, anaemia and COPD were associated with higher mortality risks (17). On the other hand, almost all comorbidities were significantly associated with reduced quality of life and higher mortality risks in HFrEF patients (17). The presence of AF and higher heart rate in patients with sinus rhythm were significantly associated with all-cause mortality in HFpEF patients (20). Dyskalemia is a common complication in HF and is associated with increased mortality. A recent study showed that the risk of moderate or severe hyperkalemia was highest in HFpEF and HFmrEF, whereas risk of hypokalemia was

highest in HFpEF (21). Independent predictors of dyskalemia in HF patients were HF severity, low hemoglobin, COPD, baseline high and low potassium, and low estimated glomerular filtration rate (eGFR) while hypokalemia was associated with increased cardiovascular disease hospitalizations (HF-related excluded) but no with HF hospitalization risk (21). Furthermore, hyponatremia at discharge was found to be associated with adverse prognosis in hospitalised patients with HFpEF (22). Albuminuria has also been associated with adverse cardiovascular outcomes (23). Results from the Health ABC study showed that in patients with HF and diabetes mellitus, patients with HFrEF tended to have lower mortality but not hospitalization risk compared to HFpEF patients regrardless of the presence of coronary artery disease (24). Furthermore, higher hs-cTnI levels were found to independently associated with risk for cardiovascular death and HF hospitalization (25).

1.7.1.1 Management

As already mentioned, patients with HFpEF have a high prevalence of comorbidities that play a key role in the pathogenesis of the disease (17, 18). Consequently, the treatment of these comorbidities is the cornerstone for the management of HFpEF patients. Nonpharmacologic strategies such as aerobic exercise and caloric restricition have been found to have beneficial resutls especially in obese patients with hypertension (26). Furthermore, in hypertensive patients with HFpEF, the sodium-restricted DASH diet was associated with favorable changes in ventricular diastolic function, arterial elastance, and ventricular–arterial coupling (27).

Regarding pharmacologic treatment, diuretics have a beneficial role in symptomatic improvement of patients acting in lowering of left ventricular filling pressures, reduce pulmonary artery pressures, and improve right ventricular loading (28). While beta-blockers, angiotensin-converting enzyme inhibitors and mineralocorticoid antagonists provide a clear survival benefit in HFrEF patients, the evidence for their role in HFpEF is not so clear. Specifically, in the Swedish Heart Failure Registry, beta-blockers reduced all-cause mortality (HR 0.93, 95% CI 0.86–0.996) but showed no difference when mortality was combined with HF hospitalizations (29). Similarly, the existing data on angiotensin-converting enzyme inhibitor (ACEi)/ angiotensin II receptor blockers (ARBs) did not show improvement in clinical outcomes in HFpEF but these trials were limited by high crossover rates (30-32). Additionally, the Treatment of Preserved Cardiac Function Heart Failure With an

Aldosterone Antagonist (TOPCAT) Trial assigned to spironolactone did not achieve a significant reduction in the primary composite outcome (time to cardiovascular death, aborted cardiac arrest, or hospitalization for management of heart failure) compared with patients receiving placebo (33). However, in TOPCAT, spironolactone significantly reduced albuminuria compared with placebo while reducing albuminuria was independently associated with improved outcomes (23). Furthermore, a recent meta-analysis of randomized controlled trials showed that mineralocorticoid antagonists significantly decreased left ventricular filling pressure and reverse cardiac remodeling although a small decrease in 6-min-walk distance was also noted (34). The role of other therapeutic approaches (neprilysin inhibitors, phosphodiesterase 5 inhibitors, relaxin-2) that can have pleiotropic beneficial effects (reduce cardiomyocyte hypertrophy and stiffness, interstitial fibrosis, endothelial dysfunction) through the myocardial cGMP pathway need further research (35-37). HFpEF accounts for an increasing portion of HF in the developed world, and therefore further research in the management of these patients is needed and on-going (38).

Conserning prognosis, this appears to be relatively similar to HFrEF; a long term registry showed that the 1-year mortality rates of HFpEF patients were 6.3%, all cause hospitalizations rates were 23.5% and HF hospitalization rates 9.7% (15).

1.7.2 HF with reduced Ejection Fraction (HFrEF)

Approximately 60% of HF patients are classified as HFrEF (15). The most common cause of HFrEF is ischemic heart disease and is followed mainly by idiopathic dilated cardiomyopathy, hypertension, valve disease and tacycardia-related cardiomyopathy (15).

Concerning the pathophysiology of the disease, the major problem in HFrEF is the abnormal ventricular contractility. In patients with HFrEF, there is a shift in Frank-Starling curves downward and to the right; this change is associated with a reduction in stroke volume and, consequently, cardiac output (39). The decrease in cardiac output leads to increased sympathetic activity and subsequent increase in cardiac contractility and heart rate while neurohumoral adaptation leads to renal salt and water retention and subsequent expansion of the blood volume (40, 41). Left ventricular hypertrophy is also part of the adaptive response to systolic dysfunction and is characterized by an increase in cardiomyocyte size and thickening of ventricular walls (42). Cardiac remodeling occurs as the response of the heart to the hemodynamic changes and the direct

myocardial injury and includes structural, functional, cellular, and molecular changes involving cardiac myocytes and the interstitial collagen matrix. While cardiac remodeling aims to maintain the cardiac function in the acute setting, progressive remodeling is deleterious and associated with a poor prognosis (43, 44). The beneficial role of ACEi/ARBs and beta-blockers in morbidity and mortality can be attributed to the role of these agents in the remodeling process (45). Furthermore, especially in severe HF, small changes in afterload can produce large changes in stroke volume and cardiac output and therefore the administration of ACEi/ARBs or other vasodilators is beneficial (46).

Electrocardiographic markers that have been associated with the future risk of HFrEF are: prolonged QRS duration, delayed intrinsicoid deflection, left-axis deviation, right-axis deviation, prolonged QT interval, abnormal QRS-T axis, left ventricular hypertrophy, ST/T-wave abnormalities, and left bundle-branch block (47). Regarding prognostic markers in patients with HFrEF, age, body mass index, systolic blood pressure, heart rate, NYHA III/IV, S3 gallop, aortic stenosis, diabetes mellitus, peripheral artery disease, chronic kidney disease, and depression have been found to be significantly associated with all-cause mortality at 1 year follow-up (15). Left atrial reservoir function measured by peak atrial longitudinal strain is independently associated with all cause death/HF hospitalization and can also be a useful marker of prognosis in these patients (48). In women, tricuspid annular plane systolic excursion and left ventricular isovolumetric relaxation time were significant predictors of mortality while LVEF and global longitudinal strain were significant predictors in men (49). Diabetes mellitus was associated with adverse outcomes in women than in men with HFrEF (50). The geographic region and environmental factors seem to influence the outcomes of patients with HFrEF (51). Regarding sex differences in major outcomes of patients with HFrEF, women with HFrEF have been found to have lower risk of all-cause mortality and risk of hospitalization but also reported lower quality of life and more phycological and physical disability (52); this could be partially explained from the suboptimal treatment of HFrEF in women (52).

1.7.2.1 Management

Interestingly, the management of HFrEF patients in community-based, dedicated HF clinics compared with routine management has been associated with augmented guideline-recommended treatment and improved survival (53).

The goals of treatment in patients with HF are; 1) to improve their clinical status, functional capacity and quality of life, 2) to prevent hospital admission and 3) to reduce mortality. Pharmacological treatment that improves survival in patients with HFrEF include neuro-hormonal antagonists [angiotensin converting enzyme inhibitors (ACEIs), mineralocorticoid antagonists (MRAs) and beta-blockers] and therefore are recommended essentially in all patients with HFrEF unless contraindications exist (1, 2). A new therapeutic class of agents acting on the renin-angiotensin-aldosterone system and the neutral endopeptidase system has been developed [valsartan and sacubitril (neprilysin inhibitor) combined in a single substance]. By inhibiting neprilysin, the degradation of natriuretic peptides (NPs), bradykinin and other peptides is slowed. Thus, higher levels of circulating atrial natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodeling (1). ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy. Sacubitril-valsartan reduced all end-points including all-cause mortality in HFrEF patients with a LVEF <40% who remained symptomatic after receiving all HF-saving medications (54). Another pharmacologic treatment with evidenced improvement in outcomes in HFrEF patients is ivabradine. Specifically, ivabradine slows the heart rate through inhibition of the If channel in the sinus node and therefore should only be used for patients in sinus rhythm. Ivabradine reduced the combined endpoint of mortality or hospitalization for HF in patients with symptomatic HFrEF or LVEF ≤35%, in sinus rhythm and with a heart rate ≥70 beats per minute (bpm) who had been hospitalized for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an MRA (55). Symptomatic improvement can be achieved with diuretics which can lead to improvement of symptoms and exercise capacity in patients with signs and/or symptoms of congestion. Correction of iron deficiency has also been shown to improve symptoms and quality of life in HFrEF patients (56). A large HF registry showed a relatively high use of evidence-based treatment, particularly in younger patients although the average dose of evidence-based medication was still lower than recommended by guidelines (57).

Regarding devices in the treatment of HFrEF patients, implantable cardioverter defibrillators (ICDs) can be used for primary or secondary prevention of sudden cardiac

death (SCD) while CRT is an effective treatment modality for therapy-refractory mild to severe HF patients with reduced LVEF and significant left ventricular conduction delay according to current guidelines (1, 2). In real-world experience, cardiac contractility modulation was recently found to have a beneficial role in patients with $25\% \leq \text{LVEF} \leq 45\%$ and $\text{QRS} < 130\,\text{ms}$ (58). Specifically, cardiovascular and HF hospitalizations were reduced and Minnesota Living with Heart Failure Questionnaire and NYHA class were improved (58).

However, despite the use of evidence-based medications, older patients experience frequent hospitalizations because of decompensated HF mainly because of higher rates of frailty, impaired cognition, depression and lower quality of life; a holistic approach to improve clinical outcomes is needed in these patients (59). Furthermore, a variety of drugs are under preclinical and early clinical development in the treatment of HF and promising results are awaited (60).

Concerning the prognosis of HFrEF patients, a large registry showed that at 1-year, mortality rates were 8.8%, all cause hospitalizations rates were 31.9% and HF hospitalization rates 14.6% (15). Results from an individual patient data meta-analysis showed that patients with HFrEF have a higher risk of death than patients with HFpEF, and this difference is seen regardless of age, gender, and aetiology of HF (61).

1.7.3 HF with mid-range Ejection Fraction (HFmrEF)

Based on recent studies, the percentage of the HF population that falls into the HFmrEF ranges between 13% and 24% (62). In a large population study, significant predictors for HFmrEF have been described: age, male sex, systolic blood pressure, diabetes mellitus, prior myocardial infarction, natriuretic peptides, cystatin-C, and high-sensitivity troponin (63). While patients with HFrEF have mainly systolic dysfunction and patients with HFpEF have mainly diastolic dysfunction, the pathophysiology of HFmrEF is not clear. This category of patients have mild systolic and diastolic dysfunction and it is a question whether they are in transition between HFrEF or HFpEF (62).

Age, female sex, systolic blood pressure, heart rate, NYHA III/IV functional status, ischemic heart disease, mitral regurgitation, chronic kidney disease and hepatic dysfunction were found to significantly associated with all-cause mortality at 1-year of follow-up (15). Regarding the outcomes of HFmrEF patients, mortality rates were 7.6%, all cause hospitalizations rates were 22% and HF hospitalization rates 8.7% (15).

A recent study found that patients with HFmrEF have a similar prognosis with HFrEF patients. Specifically, all-cause mortality following the onset of HFmrEF was worse than that of HFpEF (50 vs. 39 events per 1000 person-years, P= 0.02), but comparable to that of HFrEF (46 events per 1000 person-years, P= 0.78) (63).

Patients with HFmrEF seem to benefit from therapies that have shown to improve outcome in HFrEF (64). Furthermore, the management of co-morbidities is of great importance. However, the management of this new category of patients, needs to be further explored.

1.8 Severity classification

There are three main tools for severity classification of patients with HF. The NYHA classification is based on exercise capacity and the symptomatic status of the disease (65) while the ACCF/AHA classification emphasizes the development and progression of the disease (66). Finally, the Killip classification may be used to describe the severity of the patient's condition in the acute setting after myocardial infarction (67); Killip class I includes individuals with no clinical signs of HF, Killip class II includes individuals with rales or crackles in the lungs, an S3 gallop, and elevated jugular venous pressure, Killip class III describes individuals with acute pulmonary edema, and Killip class IV describes individuals in cardiogenic shock or hypotension (systolic BP <90 mmHg), and evidence of low cardiac output (oliguria, cyanosis, or impaired mental status) (67).

2. Arrhythmias in HF patients

2.1 Atrial fibrillation

2.1.1 Epidemiology

Estimates of the prevalence of AF in the United States ranged from ≈2.7 million to 6.1 million in 2010 (68, 69), and AF prevalence is estimated to rise to 12.1 million in 2030 (70). In the European Union, the prevalence of AF in adults >55 years of age was estimated to be 8.8 million (95% CI, 6.5–12.3 million) in 2010 and was projected to rise to 17.9 million in 2060 (95% CI, 13.6–23.7 million) (4, 70). AF is the most common arrhythmia in HF patients. Specifically, these two conditions (HF and AF) share common pathophysiological mechanisms that contribute to the initiation, progression and maintenance of each condition. Both entities share the same risk factors like hypertension, ischemic heart disease, diabetes, obesity, arteriosclerosis, valvular heart

disease and aging (71, 72). Approximately 40% of people with either AF or HF will develop the other condition (73). In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3 to 4.4 per 100 person-years of follow-up (4, 73, 74). A prospective registry from 47 countries reported substantial variability in annual AF mortality by region. Annual AF mortality in South America (17%) and Africa (20%) was double the mortality rate in North America, Western Europe, and Australia (10%; P<0.001). In individuals with AF, HF deaths (30%) exceeded deaths caused by stroke (8%) (4). Interestingly, results from a community-based study showed that AF burden seems to be associated with HF (74). In particular, chronic AF predicted that the onset of HF would increase 11-fold at one year and 28-fold at five years compared with incident paroxysmal AF (7-fold at one year and 18-fold at five years), while lone AF was not associated with HF (74). Per 1000 person-years, the incidence rate of systolic HF was 12.75 versus 1.99 for those with versus those without AF, with a multivariable-adjusted hazard ratio (HR) of AF of 5.79 (95% CI, 2.40–13.98). Corresponding numbers for preserved EF were 4.90 versus 0.85 for those with and without AF, with a multivariable-adjusted HR of AF of 4.80 (95% CI, 1.30–17.70) (4, 75).

2.1.2 Pathophysiology

Regarding the pathophysiological association of these two modalities, the presence of AF can lead to left ventricular dysfunction or further decline in an already affected left ventricular function via the loss of atrial contraction, the tachycardia and the ventricular irregularity (tachycardia mediated cardiomyopathy), while preexisting HF can lead to AF due to volume overload and increased filling pressures, alterations in calcium handling, alterations to the neurohormonal state, atrial inflammation and fibrosis that finally lead to atrial remodeling and atrial cardiomyopathy which contributes to alterations in the electrical properties of the atrial tissue (71, 76). The electrical remodeling in the atria that takes place in patients with HF has been studied with electrophysiological and electroanatomical mapping in humans (77). In this study, patients with congestive HF demonstrated an increase in atrial effective refractory period, an increase of atrial conduction time, prolongation of the P-wave duration and corrected sinus node recovery times, and greater number and duration of double potentials along the crista terminalis while electroanatomic mapping demonstrated regional conduction slowing with a greater number of fractionated electrograms associated with low-voltage areas (77). These abnormalities consist a pathological

substrate that seems to contribute in the increased incidence of AF in HF patients. The incomplete penetrance of AF phenotypes to cause left ventricular dysfunction highlights the possible role of other contributing factors and especially genetic mutations (for example angiotensin converting enzyme gene polymorphism) in the susceptibility to left ventricular dysfunction (78, 79). As a result, a circuitous 'cause and effect' relationship characterizes the complex interaction between these two conditions.

2.1.3 Complications of AF

The most common complications related to the presence of AF are: extracranial embolism to the aorta, renal, mesenteric, pelvic and peripheral arteries (4-fold in males and 5.7-fold in females) (80), stroke (4 to 5- fold increase risk) (81), dementia (1.4-fold increase risk) (82), diminished quality of life (83), falls (1.2 fold higher risk) (84), HF (4.5-fold increase risk) (75), myocardial infarction (2-fold increased risk) (85), kidney dysfunction (1.8-fold increased risk) (86), ventricular fibrillation and SCD (3-fold increased risk) (87) and all-cause mortality (3-fold increase risk) (75). A recent meta-analysis showed that the presence of AF resulted in a 5-fold increased risk of HF, while it is associated with an increased risk of death and an increased risk of other cardiovascular diseases (88, 89). Furthermore, another study showed that both pre-existing and new-onset AF were associated with greater long-term mortality among older patients with HF, while pre-existing AF was associated with greater risk of readmission (90). Additionally, results of the Women's Health Study, showed that a new-onset AF was associated with 9-fold increased risk of HF while once women with AF developed HF, all-cause and cardiovascular mortality significantly increased (91). Another interesting finding of the same study was the impact of obesity, hypertension, smoking, and diabetes in the risk of HF in women with new-onset AF (91). Indeed, there are important sex-related differences in the incidence, prevalence, pathophysiology, treatment, and outcomes of these patients. Women with HF are at greater risk of developing AF than men while more women with AF develop HF and die of AF related complication such as strokes (92).

2.1.4 Impact of AF in HF patients

There are a lot of conflicting data regarding the prognostic significance of AF in HF patients. An observational study of 390 patients with advanced HF (mean LVEF 19%) showed that AF was significantly associated with increased risk of death especially in

those patients with lower filling pressures on vasodilator and diuretic therapy (93). A retrospective analysis of the Studies of Left Ventricular Dysfunction Prevention and Treatment (SOLVD) Trials compared patients with AF to those in sinus rhythm (SR) at baseline for the risk of all-cause mortality, progressive pump-failure death and arrhythmic death. The multivariate analysis showed that AF was significantly associated with all-cause mortality (relative risk [RR] 1.34, 95% confidence interval [CI] 1.12 to 1.62, p=0.002), progressive pump-failure death (RR 1.42, 95% CI 1.09 to 1.85, p=0.01) and the composite end point of death or hospitalization for HF (RR 1.26, 95% CI 1.03 to 1.42, p=0.02), but not with arrhythmic death (RR 1.13; 95% CI 0.75 to 1.71; p=0.55) (94). Furthermore, data from 409 patients with moderate to severe chronic HF showed that the presence or the development of AF was not significantly associated with mortality (95). In Carvedilol Or Metoprolol European (COMET) Trial, 3029 patients with chronic HF were randomized to carvedilol or metoprolol tartrate and followed for a mean of 58 months. AF was associated with significantly increased mortality [relative risk (RR) 1.29: 95% CI 1.12-1.48; P<0.0001], higher all-cause death or hospitalization (RR 1.25: CI 1.13-1.38), and cardiovascular death or hospitalization for worsening HF (RR 1.34: CI 1.20-1.52), both P<0.0001 but multivariate analysis no longer independently predicted mortality (96). The negative impact of AF was also confirmed from the results of a post hoc analysis of African American Heart Failure Trial (A-HeFT) (97) and heart failure survey in Israel (HFSIS) study (98) while data from a post-hoc analysis of the Muerte Subita en Insufficiencia Cardiaca (MUSIC) study showed that reduced irregularity of RR intervals during AF was an independent predictor of all-cause mortality and sudden death and HF progression in patients with mild-to-moderate HF (99). The Veterans Affairs Vasodilator-Heart Failure Trial (V-HeFT) I and II trials assessed the relation of AF on first Holter monitor to morbidity and mortality in 632 and 795 patients with mild to moderate HF respectively (100). All-cause mortality, hospitalization and embolic event rates were not significantly increased in AF patients compared to patients in SR on all Holter recordings (100). Similar results were found from another observational study of 234 patients with advanced HF (mean LVEF 24%) who were referred for heart transplantation evaluation. Specifically, multivariate analysis showed that AF in patients with advanced HF was not associated with decreased event-free survival (101). Results from an individual patient data meta-analysis showed that AF was significantly associated with both all-cause mortality [HR: 1.10 (1.05, 1.16)] and cardiovascular mortality [HR: 1.28 (1.16, 1.41)] (61) while

subgroup analysis of another meta-analysis that aimed to explore the association of AF with SCD in the general population showed a significant association of AF with SCD in congestive HF patients [RR: 1.75 (1.40-2.19)] (102).

Regarding the prognostic significance of different AF types, VALsartan In Acute myocardial iNfarcTion (VALIANT) trial included 14,703 individuals with acute myocardial infarction complicated by HF and/or left ventricular systolic dysfunction (103). The results of this study showed that prior and current AF were significantly associated with death [HR: 1.25 (1.03-1.52; p=0.03) and 1.32 (1.20-1.45; p<0.0001) respectively] (103). Another study analyzed 15,415 patients from the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) and Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) trials regarding the impact of the type of AF in major outcomes (104). The study showed that the different types of AF have different impact on major HF patients' outcomes. Specifically, patients with paroxysmal AF at randomization had increased risk of HF hospitalization, stroke and composite endpoint of cardiovascular death or HF hospitalization while patients with persistent and permanent AF did not show significantly increased risk. Neither type of AF was associated with higher mortality (104). On the other hand, new-onset AF was associated with increased risk of all outcomes (104). Similarly, data from the United Kingdom ACALM registry showed that patients with HF in AF are at a greater risk of mortality and longer hospital stay compared to patients without this combination, while new-onset AF or HF is associated with significantly worse prognosis than long-standing disease (105). An analysis of outcomes of Medicare beneficiaries with HF shows that pre-existing AF was associated with greater risks of all-cause mortality, all-cause readmission, HF readmission, and stroke readmission compared with no AF patients (90). On the other hand, new-onset AF was associated with increased risk of mortality but not with a greater risk of the readmission outcomes (90) while another study showed a significant association of new-onset AF with HF hospitalization (106). The prognostic significance of new-onset AF is highlighted from another observational study of 944 hospitalized HF patients (107). Specifically, patients with new onset AF had higher risk of death than those with no, past or chronic AF (107). The prognostic impact of the timing of AF was also confirmed from a community-based cohort of 1664 individuals with HF. This study showed that compared to those without AF, AF after

HF conferred the highest risk of death, with more than a doubling of risk over a median follow-up of 4.0 years while those with AF prior to HF exhibited a 29% increased risk of death (108). Results from the EuroHeart Failure Survey in hospitalized patients with HF showed that new-onset AF is an independent predictor of in-hospital mortality and a longer ICU and hospital stay (109). Furthermore, analysis of 99,810 patients admitted with HF showed that patients with particularly new diagnosed AF were more likely to be hospitalized >4 days, discharged to a facility other than home and had higher hospital mortality rate (110).

Beta-blockers were known to have a beneficial role in reducing mortality in HF patients with AF independently of the pattern (persistent Vs permanent) or burden of AF (111). However, the results of a recent individual patient data meta-analysis did not show a beneficial effect of beta-blockers on all-cause mortality in HF patients with AF (112). Furthermore, another meta-analysis also showed that beta-blockers did not reduce mortality and HF hospitalizations in patients with HF and AF compared to patients in SR (113), introducing many questions in the appropriate management of patients with both conditions in everyday clinical practice.

Regarding the prognostic significance of AF in the different categories of HF (HFrEF, HFmrEF, HFpEF), data from the Swedish Heart Failure Registry (SwedeHF) showed that AF was associated with similarly increased risk of death, HF hospitalization, and stroke or TIA in all ejection fraction groups (114). Interestingly, a subgroup analysis of an observational study which included 66,357 patients showed that AF was associated with a higher risk of 30-day mortality among patients with HFpEF but not among patients with HFrEF (115). On the contrary, an observational study of 23,644 patients with HF showed that AF had higher adjusted rates of ischemic stroke, HF hospitalization, all-cause hospitalization and death while the associations of AF with these outcomes were similar for HFpEF and HFrEF, with the exception of ischemic stroke (116). Furthermore, another study that included 1,744 patients with HFpEF, showed that AF was significantly associated with exercise intolerance, impaired contractile reserve and increased mortality (117). Data from KaRen, a prospective and multicenter study, showed that AF was not associated with a worse prognosis in an elderly HF population with HFpEF (118). Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) showed that in AF patients, the presence of HF was associated with increased risk of death and

hospitalization and worse quality of life, but similar rates of thromboembolism regardless of LVEF (119). Additionally, AF patients who developed incident HF (LVEF >40%) had significantly higher risk of mortality, all-cause hospitalization, and bleeding events (120). A meta-analysis showed that the pooled HR values of AF for mortality were 1.20 (95% CI 1.12–1.28) in HFpEF and 1.07 (95% CI 1.01–1.12) in HFrEF while mortality rates were significantly higher in AF patients with HFpEF (121). In contrast, another more recent meta-analysis, showed that all-cause mortality is significantly higher in AF patients with HFrEF compared to HFpEF, although stroke risk and HF hospitalization were similar (122). On the other hand, an older meta-analysis showed that that the presence of AF was associated with an adverse prognosis in both HFrEF and HFpEF patients (123). Another recent meta-analysis involving 114,204 adults (43,549 with AF) showed that AF was associated with an increased risk of mortality and this risk varied between incident and prevalent AF, while the risk of mortality associated with incident AF was not significantly different in patients with reduced and preserved LVEF (124). Furthermore, the relative risk of mortality did not vary between paroxysmal and chronic AF patients (124).

Finally, the presence of AF in HF patients has been found to play an adverse role in other major outcomes beyond the cardiovascular system. For example, a recent meta-analysis showed that AF is significantly associated with increased risk of cognitive impairment in HF patients (125).

2.1.5 Management of AF patients with HF

The management of patients should focus on stroke prevention, rhythm and rate control. Regarding stroke prevention, recent guidelines recommend the use of CHA_2DS_2-VASc risk score for the estimation of the thromboembolic risk and the decision making regarding the need of anticoagulants (126). Catheter ablation of AF is an effective approach for restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent and probably long-standing persistent AF (127).

2.1.5.1 Catheter ablation of AF - technique

Complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter ablation (CA) and it consists of a point-by-point radiofrequency (RF) ablation, linear lesions encircling the pulmonary veins, or cryoballoon ablation, with similar outcomes (128-130). In patients with persistent AF or with recurrent AF, after the initial ablation procedure, additional ablation on top of complete PVI (complex

fractionated electrograms, ablation of rotors, or routine deployment of linear lesions or other additional ablations) may be considered (126). Regarding the procedure, a series of point-by-point radiofrequency lesions, by using more frequently irrigating RF catheters, are created to encircle the two left and two right PVs. The anatomical targets are visualized using electroanatomic mapping systems, while a computed tomography (CT) or magnetic resonance imaging (MRI) scan and endocardial ultrasound images can be merged with the electroanatomic map. Ablation is carried out under conscious sedation or general anaesthesia (131). The electrical isolation of the PVs is usually confirmed by use of a circular mapping electrode (entrance block), while pacing from within, or near, the PV can also be used to confirm electrical isolation (exit block) (132). In non-paroxysmal AF patients, the ablation procedure after PVI can focus in targeting atrial areas displaying high degrees of fractionated atrial electrograms (known as Complex Fractionated Atrial Electrograms, CFAEs) (133). CFAEs are thought to represent areas of slow conduction and pivot points of re-entrant wavelets, which could act to sustain AF. Two main strategies for CFAEs ablation have been used in patients with non-paroxysmal AF; the CFAE-guided focal ablation and the CFAE-guided linear ablation (134). A randomized study revealed that CFAE-guided linear ablation showed a trend of decreased 1-year freedom from AF/AT recurrence (134). Usually, a stepwise approach in which the procedure begins with PVI and continues using additional lesion sets until AF terminates, can be used. Newer ablation techniques using robotic magnetic navigation system have been found to be effective and safe both in patients with paroxysmal and persistent AF (135). Furthermore, while AF ablations with magnetic navigation take longer to perform, these expose patients to significantly shorter fluoroscopy times (136). The success rates of CA for AF differ between published studies. In a small registry, 356 patients (68.5%) underwent CA for paroxysmal AF and 164 (31.5%) for non-paroxysmal AF (137). After a mean follow-up period of 39.05 ± 20.83 months (range from 19 to 60 months), 254 (71.3%) and 101 (61.6%) patients with paroxysmal AF and non-paroxysmal AF respectively, were free from arrhythmia recurrence (137). Similar results were reported by Bhargava et al. where SR maintenance was found in 72.6% of patients (77.6% in paroxysmal AF and 67.2% in non-paroxysmal AF) after a single ablation procedure during a mean follow-up of 57 ± 17 months (138). Similarly, Hussein et al. reported 23.8% atrial arrhythmia recurrence in the first year after CA and 8.9% thereafter, for a median follow-up period of 55 months (139). However, lower success rates have been demonstrated in other studies.

Weerasooriya et al. studied the arrhythmia-free outcome after a single procedure in a mixed population (paroxysmal AF and non-paroxysmal AF) (140). Notably, the authors reported 40%, 37% and 29% freedom of arrhythmia at 1, 2 and 5 years of follow-up respectively. Similarly, Scherr et al. demonstrated 35.3%, 28% and 16.8% freedom of arrhythmia at 1, 2 and 5 years of follow-up respectively in a non-paroxysmal AF population (141). A systematic review and meta-analysis on long-term outcome of CA revealed 54.1% success rates after a single procedure in paroxysmal AF patients, 41.8% in non-paroxysmal AF and 53.1% in the overall population (142). These different results can be attributed to different procedure techniques used and the differences in the follow-up duration and study population.

Regarding HF patients, CA when compared to direct current synchronized cardioversion followed by amiodarone, has been associated with significantly higher one-year rates of SR maintenance and with improved cardiac function (143). Additionally, patients who underwent CA were found to have significantly lower mortality, stroke/transient ischemic attacks, and HF hospitalizations compared with patients who underwent cardioversion (144). Another interesting finding is that patients with poorer cardiac function at baseline appear to benefit most from ablation in terms of cardiac function improvement at 1 year (143). A number of observational studies have demonstrated the superiority of CA procedure of AF in LVEF improvement and other important outcomes (quality of life) compared to conventional care (145). The Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) trial included HF patients (LVEF $\leq$35%) who underwent CA or conventional care. The authors showed that CA led to significant improvement in the primary composite end point of all-cause mortality and worsening HF with a relative risk reduction of 38% while LVEF increased by 8% at 5 years of follow-up in the CA group (146). Furthermore, data from the AATAC Multicenter Randomized Trial showed that CA of AF was superior to amiodarone in achieving freedom from AF at long-term follow-up and reducing unplanned hospitalization and mortality in patients with HFrEF and persistent AF (147). A number of meta-analyses showed that CA in HF patients, resulted in improved LVEF, cardiac function, exercise capacity, and quality of life in HF patients with AF compared with the medical rate control strategy (148-153), while a recent meta-analysis showed that CA was associated with a significant reduction in mortality (risk ratio 0.50; 95% confidence interval [CI]: 0.34 to 0.74; P = 0.0005), heart failure-related hospitalizations (risk ratio 0.56; 95% CI: 0.44 to 0.71; P < 0.0001), while

CA also led to significant improvements in LVEF in patients with HFrEF (weighted mean difference, 7.48; 95% CI: 3.71 to 11.26; P < 0.0001) compared to medical therapy including the use of antiarrhythmic drugs (154). Furthermore, another meta-analysis found that CA for AF in patients with HFrEF decreased mortality and AF recurrence and improved left ventricular function, functional capacity, and quality of life compared to conventional management, without increasing complications (127).

PVI has been found to improve cardiac function in patients with paroxysmal AF and impaired LVEF (155). Furthermore, in patients with HF undergoing AF ablation, it was found that an initial short-term LVEF improvement was related to the baseline heart rate, while a long-term LVEF improvement was related to the rhythm outcome (those who maintained SR, improved) (156). The efficacy of CA in patients with impaired LVEF is better when this is performed early in the natural history of AF and HF (150). An interesting finding is that patients with and without left ventricular systolic dysfunction had similar risk for recurrent AF or atrial tachycardia (AT) after CA, but repeat procedures were required more often in those with left ventricular systolic dysfunction (157). Another study showed that PVI in HF patients was associated with improved quality of life scores at 6 months, a longer 6-minute-walk distance and a higher ejection fraction compared to patients who underwent atrioventricular node ablation and biventricular pacing (158).

The efficacy of CA has been found to be similar in patients with HFrEF and HFpEF (159). Specifically, a recent study, showed that median procedure times (233 minutes [192, 290] vs 233.5 minutes [193.0, 297.5]; P = .780) and adverse events such as acute HF (3.8% vs 6.2%; P = .395) were similar between HFpEF and HFrEF patients. Freedom from recurrent atrial arrhythmia was not significantly different in HFpEF vs HFrEF patients (33.9% vs 32.6%; adjusted hazard ratio 1.47; 95% confidence interval 0.72-3.01), with similar improvements in NYHA functional class (-0.32 vs -0.19; P = .135) and symptom severity (-0.23 vs -0.09; P = .116) after ablation (159). A randomized multicenter study showed that amiodarone therapy was found to be significantly more likely to fail (hazard ratio, 2.5; 95% confidence interval, 1.5-4.3; P<0.001) than CA in congestive HF patients (147). Additionally, over the 2-year follow-up, the unplanned hospitalization rate was lower in the CA compared to the amiodarone group (32 [31%] and 58 [57%] respectively; P<0.001, with a 45% relative risk reduction). A significantly lower mortality was observed in the CA versus the amiodarone group (8 [8%] vs 18 [18%], P=0.037) (147). Another multicenter study

showed that CA in HF patients was significantly associated with a much lower risk of major adverse cardiovascular events, defined as all-cause mortality, stroke, and unplanned hospitalization (HR 0.486, 95% CI: 0.253-0.933, P=.030) (160).

As already mentioned, a proportion of patients who undergo CA for AF, sustain early or late arrhythmia recurrence. Early arrhythmia recurrence is defined as any atrial arrhythmia recurrence during the first 3 months (blanking period) after the ablation procedure, while late arrhythmia recurrence is defined as any atrial arrhythmia recurrence after the 3 months blanking period (137). It is of great importance to identify prognostic baseline markers that can predict arrhythmia recurrence after a successful AF ablation procedure. Several groups have published results on various cohorts, aiming to identify baseline predictors of AF recurrence in different clinical settings (137, 161-164). Factors that have been proposed to be associated with arrhythmia recurrence include: persistent AF (161, 163, 165), valvular heart disease (161, 165), left atrial emptying fraction (162), body mass index (162), AF duration (162), left atrial linear ablation (162), female sex (165), in-hospital AF relapse (165), renal failure (165), left atrial appendage volume (163), left atrial enlargement (137, 164), early arrhythmia recurrence (137, 164). Three predictors of late AF recurrence were revealed from a meta-analysis (166). Specifically, the authors found that valvular AF, a left atrium diameter longer than 50mm and recurrence within 30 days after ablation procedure were the most reliable predictors of AF recurrence after CA procedure (166). Another systematic review showed with a high level of evidence that age in the range of 40-70 years old, sex, the presence of structural heart disease and duration of symptoms are not associated with AF recurrence, while the quantitative synthesis showed that non-paroxysmal AF was significantly associated with AF recurrence (167). Of note, there are not enough data regarding the predictors of AF recurrence in specific populations such as HF patients.

2.1.5.2 Implantable Cardioverter Defibrillator (ICD) Vs conventional treatment in AF patients with HFrEF

Several studies provide data regarding the role of ICD in AF patients with HFrEF. A prospective cohort of 965 patients with ischemic and nonischemic cardiomyopathies and no prior ventricular arrhythmias showed non-significant results in the subgroup of AF patients regarding the role of ICD in all-cause mortality reduction (168). Furthermore, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment

Evaluation (DEFINITE) trial enrolled 458 patients with nonischemic dilated cardiomyopathy. A sub-analysis showed that in AF patients, ICD was not significantly better compared to standard medical therapy alone in all-cause death reduction (169). On the other hand, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) enrolled 674 myocardial infarction patients (170). In this study, ICD was not associated with significantly better outcomes compared to conventional treatment alone in AF patients. However, the results of this analysis were limited because of the small number of AF patients. Similarly, the results of a sub-analysis of Sudden Cardiac Death in Heart Failure (SCD-HeFT) Trial which enrolled 2521 patients, showed no survival benefit of ICD in AF patients compared either with placebo or with amiodarone treatment (171), while the results of the Multicenter Automatic Defibrillator Implantation II (MADIT II) Trial showed that ICD in AF patients did not have a significantly beneficial role in all-cause death or in combined endpoint of death or HF hospitalizations compared to conventional treatment (172).

2.2 Ventricular arrhythmias in HF patients

Despite appropriate pharmacologic treatment, the mortality rate of HF patients remains extremely high, with up to 50% of the patients dying suddenly (173) while in a study with advanced chronic HF patients, pump failure (44.4%) was the most common mode of death followed by SCD (26.5%) (173). SCD is mainly due to malignant ventricular arrhythmias that include ventricular tachycardia (VT) and ventricular fibrillation (VF).

2.2.1 Pathophysiology of ventricular arrhythmogenesis in HF patients

The potential substrates that have been proposed for ventricular arrhythmias in HF patients are: i) ventricular structure and mechanics (ventricular scar, ventricular hypertrophy, high ventricular filling pressures, increases in cardiac preload and afterload), ii) ventricular metabolism (increase or decreases of extracellular potassium levels, increases of calcium, magnesium, sodium and cyclic adenosin monophosphate in the intracellular fluid, acidosis and increase of lysophosphoglycerides, adenosine, lactate and carbon dioxide in the extracellular fluid, iii) ventricular electrophysiology (prolongation of action potential duration, QT prolongation and dispersion, iv) neurohumoral substances (elevation of plasma epinephrine and norepinephrine, cardiac sympathetic overactivation) (174).

Regarding structural abnormalities and mechanics, increased afterload and preload conditions can lead to shortening of repolarization and refractoriness and therefore to

increased risk of ventricular tachyarrhythmias and SCD while myocardial hypertrophy lead to reduced cell-cell coupling, reduction of membrane potentials and sub-endocardial ischemia (175, 176). On the other hand, ventricular scars consist of dense fibrotic regions that create conduction block that can result in reentry circuits (177). HF also results in intracellular and extracellular metabolic and ionic changes that influence major electrophysiological properties creating a vulnerable substrate for ventricular arrhythmogenesis (174). Regarding the electrophysiological changes in HF patients, delayed afterdepolarizations play a crucial role in ventricular arrhythmogenesis inducing triggered activity. The following factors have been found to contribute in the occurrence of delayed afterdepolarizations: (1) increased Na/Ca exchanger, providing more transient inward current for any given sarcoplasmic reticulum calcium release; (2) a reduced inward rectifier Ik1, allowing more depolarization for any given transient inward current; (3) residual β-adrenergic responsiveness required to raise the low sarcoplasmic reticulum calcium content to the point at which more spontaneous calcium release occurs (178). Although the role of delayed afterdepolarizations in the ventricular arrhythmogenesis is well known, the role of early afterdepolarizations in HF is unclear (178). Early afterdepolarizations have been observed in unphysiological long cycle lengths or in shorter cycle lengths during beta-adrenergic stimulation (179). QT prolongation and dispersion is another substrate of arrhythmias especially in patients with impairment of left ventricular systolic function (180, 181). Interestingly, the presence of abnormal QT prolongation has been found to consist an independent risk factor for SCD (182). Furthermore, beta-blockers have been found to be associated with a reduction in both QT and QTc dispersion while this beneficial action may constitute the main antiarrhythmic mechanism of this drug category (181). HF results in an increased sympathetic activity as reflected by the increased levels of epinephrine and norepinephrine (183-185). High plasma levels of both catecholamines have been associated with electrical instability in the setting of ischemic heart disease (186).

2.2.2 Antiarrhythmic medications

Antiarrhythmic medications are divided into four main categories regarding their mechanism of action: Class I (sodium channel blockers), class II (beta-adrenergic receptor blockers), Class III (potassium channel blockers), and Class IV antiarrhythmics (L-type calcium channel blockers). However, the side effects and

especially the negative inotropic effects of many antiarrhythmic agents consist a barrier in their use in HF patients (174, 187).

Class I sodium-channel–blocking drugs have been associated with increased mortality in patients with structural heart disease, and should be avoided in patients with HF, given the significant negative inotropic effects and potential for proarrhythmia (187-189). Pooled analysis of eight clinical trials has shown a 34% reduction in recurrent ventricular arrhythmias in patients on antiarrhythmic therapy, a benefit driven primarily by amiodarone. However, this reduction did not translate in a mortality benefit (190). Regarding sotalol which is a class III antiarrhythmic with beta-blockade effects, its use was not found to increase the risk of mortality but given the negative inotropic properties and proarrhythmic effects, this should be used with cautious in HF patients (190, 191). In the acute setting of a hemodynamic stable VT, amiodarone is the first option, especially in patients not on chronic therapy with this antiarrhythmic drug (187). Intravenous lidocaine has been found to be a safe treatment option with short half-life and overall good safety profile (192), while procainamide, despite its negative inotropic effects, can be used with caution, considering the new data about its efficacy in the immediate termination of hemodynamically stable VT compared to amiodarone (193). Treatment with beta-blocker, mineralocorticoid antagonists and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (1).

2.2.3 Catheter ablation of ventricular arrhythmias in HF patients

CA of ventricular arrhythmias may be used as an adjunct therapy to prevent or reduce appropriate ICD interventions when antiarrhythmic medications are ineffective or not well tolerated. The mechanism of arrhythmia is of great importance for the appropriate management during CA. In post myocardial infarction HF patients, the main mechanism of VT is a re-entrant circuit through the impaired electrical conduction of the border zone tissue (177, 194) while myocardial infarction-related alterations in the afferent and efferent neural signals may contribute to the arrhythmogenic substrate (195). The areas of border zone tissue can be identified during electrophysiologic study as areas of fractionation, late potentials or local abnormal ventricular activity and consist the target of ablation (194). However, in the acute myocardial ischemia setting, focal VT originating from the Purkinje system is another arrhythmia mechanism

attributed to triggered activity and delayed afterdepolarizations that have been described earlier (194). CA is an effective treatment option in this setting (196).

Regarding dilated cardiomyopathy patients, magnetic resonance and histological findings revealed focal or more diffuse tissue fibrosis (197, 198). The mechanisms of VT in these patients is mainly scar related re-entry followed by focal automaticity or triggered activity and His-Purkinje re-entry (bundle branch re-entry VT) (199). CA is an effective approach in these cases (199).

In specific clinical conditions (arrhythmogenic cardiomyopathy, basolateral phenotype of nonischemic idiopathic dilated cardiomyopathy, Brugada phenotypes, and in some situations in ischemic cardiomyopathy), the modest efficacy of CA for VT is improved with epicardial mapping and ablation (200, 201). A recent meta-analysis was conducted to determine whether combined endocardial-epicardial ablation was superior to endocardial only ablation in patients with scar-related VT (202). The study showed that the endocardial-epicardial approach is more effective in reducing VT recurrence and all-cause mortality compared to the endocardial approach alone, while patients who underwent the combined approach showed higher rates of acute procedural complications (202). Sensitivity analysis showed the superiority of the combined approach regarding VT recurrence in ischemic cardiomyopathy and arrhythmogenic cardiomyopathy but not in nonischemic cardiomyopathy patients (202).

2.2.4 Implantable cardioverter defibrillators (ICDs)

ICDs are implantable medical devices that can terminate potentially lethal arrhythmias. The first idea for the development of the ICDs belongs to Dr Mirowski after the sudden death of his mentor Dr Harry Heller in 1966 (203, 204). At that time, Dr Mirowski dedicated his career to design and develop the ICD. As a result, the first ICD was implanted in a human in 1980 (205).

An ICD is made up of two parts: a pulse generator which includes the battery and several electronic circuits and the leads. Depending on the number of ICD leads, ICDs are classified in single-chamber ICDs (one ventricular lead in the right ventricle) and dual-chamber ICDs (one lead in the right ventricle and one lead in the ight atrium). Indications for having a dual-chamber ICD include the presence of sinus node dysfunction and of second- or third-degree atrioventricular (AV) block, while possible indications include paroxysmal AF or flutter and first-degree AV block (206).

The basic principles of ICD function are: i) sensing which consists of the recording of the electrical signal of myocardium depolarization between the tip and ring electrodes – nonintegrated– or the tip and high-voltage coil – integrated (204), ii) sensing circuit where the presenting electrogram is passed through an amplifier, low- and high-band filters and finally the signal is rectified, summing positive and negative components into a single positive electrogram, iii) detection that classifies the rhythm on the basis of a set of algorithms to determine whether therapy should be delivered (204).

2.2.4.1 ICD therapies

The therapies that an ICD delivers can be classified into anti-tachycardia pacing (ATP) and defibrillation (shocks).

ATP consists of short pacing sequences (usually 8 impulses for each train) delivered as bursts – same cycle length within a sequence – or ramps – cycle length shortens within a sequence – to terminate ventricular tachyarrhythmias without the need for shocks (Figure 1) (204). Regarding the mechanism of arrhythmia termination, these pacing sequences are delivered at very short coupling intervals (usually 69–88% of the tachycardia cycle length) in order to enter the re-entrant circuit and terminate the arrhythmia (204, 207). ATP is an effective therapy that can terminate up to 95% of tachycardia events with up to 80% with the first ATP attempt (204). Compared to ramps, burst pacing have been found to be more effective at terminating fast VT with less chance of accelerating the tachycardia cycle length or to lead in syncopal events (208). A study that compared 8 impulses burst versus 15 impulses burst on fast VT (209) found no significant differences in VT termination between them (209). Additionally, 15 pulses proved significantly better in patients without a previous history of HF and in patients with LVEF $\geq$ 40% while no significant differences between groups were observed with regard to syncope/near-syncope occurrence (209). In order to prevent syncope or tachycardia acceleration, ATP should be programmed for only one to two sequences for fast VT (>188 bpm), as data have shown that 90% are terminated within the first two ATP bursts (88% cycle length, eight pulses) (210). In conclusion, ATP is a safe, effective and painless therapy for VTs with large clinical evidence supporting its routine use in primary and secondary ICD patients contributing

in the reduction of unnecessary shocks and an improvement of clinical outcome, patients' quality of life and device longevity (211, 212).

Regarding defibrillation (shocks), current ICD systems can deliver 25–36 J/shock and up to 8 shocks/sequence. This therapy is >98% effective in terminating VF.

2.2.4.2 Appropriate and inappropriate ICD therapies

Ideally, ICD therapies (ATP and shocks) should be administered only in cases of potentially lethal ventricular arrhythmias. However, in practice, ICD patients can sustain ICD therapies for reasons other than ventricular arrhythmias. As a result, ICD therapies can be divided into appropriate and inappropriate depending on the causal arrhythmia substrate. Specifically, appropriate ICD therapies are those that occur because of a potentially lethal ventricular arrhythmia (VT/VF), while inappropriate ICD therapies are those occurring because of reasons other than ventricular arrhythmias. The main reasons are: AF, electromagnetic interference, sinus tachycardia, supraventricular tachycardia, abnormal sensing, noise etc. (213-215). Unfortunately, many patients with an ICD —as many as 1 in 3 in some studies— receive inappropriate shocks (216).

2.2.4.3 Negative impact of ICD therapies

Studies have shown that ICD shocks have a negative impact in ICD patients. Specifically, both appropriate and inappropriate ICD shocks have been associated with increased risk of all-cause mortality (216, 217). Another study found that only appropriate shocks and not inappropriate shocks are related with reduced survival and specifically only in ischemic cardiomyopathy patients as compared to dilated cardiomyopathy patients (218). This association can be attributed to the direct negative impact of ICD shocks on the myocardium. This association has been proved by serum cardiac troponin I elevation after ICD discharges (219, 220). This consists an indirect marker of myocardial damage induced by ICD shocks. Furthermore, this myocardium damage has been evaluated microscopically in patients who received recent ICD shocks (221). Possible mechanisms that can explain this negative impact of ICD shocks in the myocardium are: transient enhancement of permeability of the cellular membrane on exposure to high-intensity electric fields (electroporation phenomenon) which may cause calcium influx to produce calcium overload with subsequent hypercontraction and necrosis (222), reversible permeabilization of myocardial cell membranes, and catecholamine surges provoked by the shocks (219, 223).

On the other hand, the increased risk of mortality in patients who received ICD shocks can be attributed to the poorer functional status of these patients and as a result the ICD shocks are markers of worse prognosis. In this context, the ALTITUDE Survival by Rhythm Study showed no increased mortality risk after ICD shocks due to sinus tachycardia or noise/artifact (OR: 0.97; p=0.76) (224). Of course, the finding that appropriate ICD interventions increase the risk of mortality is not clinically important because of the potentially lethal causal arrhythmia without the presence of the ICD. Apart from the negative impact of ICD shocks on hard outcomes, ICD shocks have also been associated with a negative impact on various other health outcomes. Patients have described an ICD shock as "an earthquake," "being hit by a truck," or "being kicked by a mule" (225). In the MADIT Randomized Trial to Reduce Inappropriate Therapy (MADIT-RIT), ≥2 appropriate or inappropriate ICD shocks and ≥2 appropriate ATPs were found to be associated with more anxiety at 9-month follow-up while the same study did not find any association between appropriate/inappropriate ATP or shocks and quality of life (226). Furthermore, data from the US patients from the MADIT-II trial showed that ICD firing was significantly associated with a reduced health-related quality of life (227). Additionally, female ICD-recipients have been found to have a higher probability of shock and general related anxiety (228, 229) while the probability of anxiety and depression symptoms were associated with younger age, living alone, and a previous history of myocardial infarction or HF (228). A higher level of ICD-related concerns was most prominently related to symptoms of anxiety, depressive symptoms and poorer quality of life, while number of shocks, ICD-indication and time since implantation were not independently related (228). Some predictors of inappropriate ICD shocks have also been proposed: age younger than 70 years, history of AF, no statin use, and interim appropriate shocks (230).

2.2.4.4 ICD Discriminators

Due to the negative impact of ICD therapies on different health outcomes of ICD recipients, it is of great importance to reduce the number of inappropriate ICD therapies and especially inappropriate ICD shocks due to their possibly greater negative impact compared to the ATPs. Discriminators have been implemented in this detection process in a view to withhold VT therapy delivery on sinus tachycardia and supraventricular arrhythmias. There are two main approaches for arrhythmia discrimination: analysis of the interval patterns (onset, stability, atrium to ventricle relationship) and morphologic

analysis of the electrogram entering the arrhythmia zones (231). A slightly superior accuracy in arrhythmia classification and a reduction in the number of inappropriate treated episodes has been reported with dual chamber ICDs (232). However, dual chamber ICDs showed no benefit in reducing the incidence of death or HF admissions (233).

2.2.4.5 ICD programming

ICD programming has a great role in eliminating inappropriate ICD therapies. To achieve this target, modern ICD programming utilizes higher detection rates, longer detection durations, ATP, algorithms that discriminate supraventricular tachycardia from VT, and specific electrocardiographic features to minimize the sensing of noise. A number of clinical trials have been conducted to assess the impact of therapy reduction programming strategies and conventional programming with ICD shocks and all-cause mortality (210, 234-238). The quantitative synthesis of the main clinical trials showed that compared to conventional programming, there was no significant difference in the rate of syncope between the two programming strategies, no significant difference in the risk of appropriate ICD shocks, but a significant 50% relative reduction in the risk of inappropriate ICD shocks with therapy reduction ICD programming (239). Taking into consideration the most recent guidelines, the tachyarrhythmia detection duration should be programmed for at least 6 to 12 seconds (or for 30 intervals). In cases of unknown VT rates, a slowest tachycardia therapy zone should be programmed between 185 and 200 beats per minute, while for secondary prevention ICD patients for whom the clinical VT rate is known, the slowest tachycardia therapy zone should be at least 10 beats per minute below the documented tachycardia rate but not faster than 200 beats per minute (240).

2.2.5 Clinical trials for primary and secondary prophylaxis of Sudden Cardiac Death (SCD)

2.2.5.1 Primary prevention of SCD in ischemic cardiomyopathy patients

Several studies have been conducted to examine the potential role of ICDs compared to conventional medical therapy in primary prevention of SCD in high risk, asymptomatic patients with ischemic cardiomyopathy, while most of them enrolled patients late post-myocardial infarction. The MADIT I is the first trial that studied the role of ICDs in primary prevention of SCD in ischemic cardiomyopathy patients (241).

This study enrolled 196 patients with a history of myocardial infarction, non-sustained VT on monitoring, reduced LVEF ≤35% and inducible sustained monomorphic VT during electrophysiological study that was also induced after administration of intravenous procainamide. During an average of 27 months, patients assigned to ICD therapy had significant reductions in overall mortality, cardiac mortality, and arrhythmic deaths compared with patients assigned to medical therapy (241). Despite the significant results of the study, the small sample size and the limitations that arise especially from the strict and complex inclusion criteria, led to subsequent clinical studies. As a result, the MADIT II trial enrolled 1232 patients with prior myocardial infarction more than 30 days prior to enrollment (and more than three months if bypass surgery was performed) and reduced LVEF ≤30% (242). This study was stopped early after an average follow-up of 20 months due to the benefit of ICD therapy compared to conventional therapy. Specifically, patients in the ICD group had significantly reduced all-cause mortality (14.2% versus 19.8% for conventional therapy, HR: 0.65, 95% CI 0.51-0.93) (242). The Coronary Artery Bypass Graft (CABG) Patch trial evaluated the efficacy of an epicardial ICD implanted at the time of coronary artery bypass graft surgery (243). The trial enrolled 900 patients with severe coronary artery disease requiring surgical revascularization, reduced LVEF <36%, abnormal signal-averaged electrocardiogram and no history of sustained VT or syncope (243). The investigators found that there was no significant difference in overall or cardiovascular mortality among patients with an ICD compared with standard medical therapy (243). The Multicenter Unsustained Tachycardia Trial (MUSTT) trial enrolled 704 patients with prior myocardial infarction (ranging from at least four days to more than three years previously), asymptomatic non-sustained VT at least four days post-myocardial infarction or post-revascularization but within six months of enrollment), reduced LVEF ≤40%, inducible sustained VT during electrophysiological study and no history of sustained ventricular tachyarrhythmia or syncope (244). The patients were randomly assigned to either standard medical therapy or electrophysiological study-guided antiarrhythmic therapy which included either an antiarrhythmic agent or an ICD if at least one antiarrhythmic agent was ineffective (244). After a median follow-up of 39 months, the relative risk for the primary endpoint (arrhythmic death or resuscitated SCD) was significantly lower for electrophysiological study-guided therapy compared with standard medical therapy, while the reduction in the primary endpoint in the electrophysiological study-guided group was attributed mainly to ICD therapy (244).

However, a limitation of this study regarding the superiority of ICD therapy is that the trial was designed to assess the usefulness of electrophysiologic testing to guide antiarrhythmic therapy and not to compare different types of antiarrhythmic therapy. Furthermore, the patients who received ICDs were not assigned randomly. Another study, the SCD-HeFT trial, compared the effectiveness of ICD and amiodarone therapies in patients with ischemic or nonischemic cardiomyopathy (245). This study enrolled 2521 patients in NYHA class II-III HF, reduced LVEF ≤35%, congestive HF present for at least three months prior to randomization and treated with ACEi and beta-blocker, if tolerated. As compared with placebo, amiodarone was associated with a similar risk of death while ICD therapy was associated with a decreased risk of death and an absolute decrease in mortality (245). These results did not vary according to either ischemic or nonischemic causes of congestive HF, but varied according to the NYHA class (245).

Regarding studies that enrolled patients early after myocardial infarction, the DINAMIT trial evaluated the role of prophylactic ICD implantation compared with standard medical therapy and enrolled patients with myocardial infarction in the preceding 6 to 40 days, reduced LVEF ≤35%, reduced heart rate variability or elevated resting heart rate (≥80 beats/minute) (170). The investigators found no statistically significant difference between the two groups regarding overall mortality in high risk patients with a recent myocardial infarction (170). Similar results were found in the Immediate Risk Stratification Improves Survival (IRIS) trial that enrolled 898 patients with a myocardial infarction in the preceding 5 to 31 days and at least one of the following characteristics: i) reduced LVEF ≤40% and a resting heart rate ≥90 beats/minute and/or ii) non-sustained VT at a rate of ≥150 beats/minute (246). The investigators found no difference in all-cause mortality between patients randomly assigned to ICD therapy and those assigned to medical therapy. Similarly to DINAMIT trial, the rate of SCD was higher in the medical therapy group, but the number of non-SCDs was higher in the ICD group (246).

2.2.5.2 Primary prevention of SCD in non-ischemic cardiomyopathy patients

The Cardiomyopathy Trial (CAT) enrolled 104 patients with recent onset (≤9 months) nonischemic dilated cardiomyopathy (DCM) and a LVEF ≤30%. This trial did not provide evidence in favor of prophylactic ICD implantation compared to control group

in patients with DCM of recent onset and impaired LVEF (247). Similar results were revealed from the Amiodarone versus implantable cardioverter-defibrillator trial (AMIOVIRT) that enrolled 103 patients with non-ischemic DCM, LVEF ≤35%, class I-III HF, and asymptomatic non-sustained VT, randomized to ICD versus amiodarone therapy (248). The investigators found that mortality and quality of life in patients with non-ischemic DCM and non-sustained VT treated with amiodarone or an ICD were not statistically different (248). However, the small sample size is the major limitation of these two trials. The DEFINITE trial enrolled 458 patients with non-ischemic DCM, reduced LVEF ≤35%, ventricular premature beats or non-sustained VT (169). The patients were randomly assigned to ICD and medical therapy versus medical therapy alone. It was shown that there was a trend toward reduction in the primary endpoint of all-cause mortality in patients treated with ACEi, beta-blockers and received an ICD, with a significant reduction in the risk of sudden death from arrhythmia. However, the trial was underpowered for its primary endpoint (169). The Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH) randomly assigned 1116 patients with symptomatic systolic HF (LVEF ≤35%) to an ICD with guideline-directed optimal medical therapy or medical therapy alone (249). In both groups, 58% of patients received a CRT. Over a median follow-up of 5.6 years, there was no significant difference in the primary outcome of total mortality while a significant reduction of SCD in the group receiving ICDs was found. However, because the overall mortality rates in this study was low, the study was underpowered to show a mortality benefit for ICD therapy (249). On the other hand, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, evaluated optimal medical therapy versus CRT with or without an ICD (250). Specifically, the trial enrolled 682 patients with non-ischemic DCM, reduced LVEF ≤35%, NYHA class III or IV HF symptoms requiring hospitalization within the prior year. There was a significant reduction in the incidence of the combined endpoint of all-cause mortality and all-cause hospitalization in the two arms receiving CRT compared with the medical therapy only arm (250). The cardiac resynchronization therapy defibrillator (CRT-D) arm, but not the cardiac resynchronization therapy pacemaker (CRT-P) arm, experienced a significant improvement in the secondary endpoint of all-cause mortality alone (250). In conclusion, trials on the above subjects have yielded conflicting results and a definite conclusion cannot be made.

2.2.5.3 Secondary prevention of SCD

The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial enrolled 1016 patients who presented with resuscitated VF, sustained VT with syncope, or sustained VT with BP <80 mmHg or significant symptoms (near-syncope, congestive HF, or angina) suggesting hemodynamic compromise and LVEF ≤40% (251). Patients were randomized to treatment with either an ICD or antiarrhythmic drugs. The trial was stopped early as a significant survival benefit was observed in patients receiving the ICD compared with those treated with antiarrhythmic agents (251). Interestingly, a sub-analysis of AVID trial showed that in patients with an LVEF ≥35%, there was no significant difference in survival between ICD and antiarrhythmic drugs while in those with an LVEF between 20 and 34%, survival was significantly better with the ICD (252). Among the relatively small number of patients with an LVEF <20%, survival tended to be better with the ICD (252). In addition, the Cardiac Arrest Survival in Hamburg (CASH) trial, 349 survivors of cardiac arrest due to documented VT or VF were randomly assigned to treatment with an ICD or antiarrhythmic drugs (amiodarone, propafenone, metoprolol) (253). After a mean follow-up of 57 months, there was a non-significant reduction in total mortality in patients receiving an ICD compared with those treated with amiodarone or metoprolol, while the secondary endpoint of SCD was significantly reduced by the ICD compared with drug therapy. Interestingly, assignment to propafenone was discontinued prematurely when interim analysis revealed a 61% higher mortality than that seen in patients randomized to ICD therapy (253). The Canadian Implantable Defibrillator Study (CIDS) enrolled 659 patients with resuscitated VT/VF or syncope deemed to be secondary to VT/VF (254). The patients were randomly assigned to amiodarone or ICD therapy and was showed that there were non-significant reductions in total mortality and SCD between the two groups (254).

2.2.5.4 Meta-analyses regarding the effectiveness of ICD compared to medical therapy

The quantitative synthesis of the primary prevention trials (MADIT I, CABG Patch, MUSTT, CAT and MADIT II) showed a significant benefit in favor of the ICD in prevention of SCD [RR: 0.66, 95% CI (0.46-0.96)] (255). In another meta-analysis, the quantitative synthesis of five primary prevention, non-ischemic cardiomyopathy trials (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION) showed a significant

favoring of ICD in all-cause mortality prevention (256). Regarding secondary prevention of SCD, a significant favoring of ICD [RR: 0.75, (95% CI 0.64 -0.87)] was revealed by the quantitative synthesis of AVID, CASH, CIDS and Wever et al (257) studies (255). On the other hand, a quantitative synthesis of two secondary prevention trials (AVID, CIDS) showed a non-significant trend of superiority of ICD in prevention of all-cause mortality (256).

2.2.6 Indications of ICD implantation

According to recent guidelines, an ICD can be implanted in HF patients either for secondary or for primary prevention of SCD (1). Regarding secondary prevention, ICD implantation is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for >1 year with good functional status (Class I) (1). Regarding primary prevention of SCD, an ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of optimal medical therapy, provided they are expected to survive substantially longer than one year with good functional status, and they have either ischemic heart disease (unless they have had a myocardial infarction in the prior 40 days) or DCM (Class I) (1).

2.2.7 Cardiac resynchronization therapy (CRT)

CRT is an effective treatment modality for therapy-refractory mild to severe HF patients with reduced ejection fraction and left ventricular conduction delay. CRT is a modality of cardiac pacing used in patients with left ventricular systolic dysfunction and dyssynchronous ventricular activation that aims to provide synchronous electrical activation of the left and right ventricle via stimulation of both the left ventricle and right ventricle (biventricular pacing) or left ventricle alone (258). This is performed by either a CRT-P or by a combined CRT-D. CRT devices usually include a transvenous pacing lead placed in a branch of the coronary sinus for left ventricular pacing, in addition to leads in the right ventricle and right atrium (259).

The beneficial effect of CRT can be divided in the acute mechanical effects and long-term benefits. Regarding the mechanisms of acute beneficial effects, electrical resynchronization can: reduce both the mechanical interventricular dyssynchrony (between the two ventricle) and the intraventricular dyssynchrony within the left

ventricle, increase left ventricular filling time (through optimization of the time delay between atrial sensed event and ventricular pacing), reduce mitral regurgitation and increase the stroke volume (259). Regarding the mechanisms of long-term beneficial effects, these include improvement of neurohormonal derangement and reverse of left ventricular remodeling (reduced end-systolic and end-diastolic volumes) caused by chronic HF leading in improvement of LVEF and myocardial performance index (259). Multiple clinical trials and meta-analyses have shown that CRT improves quality of life, reduces HF hospitalizations, reduces cost, decreases mortality, and improves cardiac function (260-265).

The Multisite Stimulation in Cardiomyopathies (MUSTIC) trial enrolled 67 patients with severe HF (NYHA III) with normal SR and QRS prolongation. The study showed that multisite biventricular pacing led to an improvement in the six-min walk distance, the quality-of-life, increase of peak oxygen uptake, decrease of hospitalizations (266). The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study enrolled 453 patients with moderate to severe symptoms of HF with LVEF ≤35% and QRS prolongation (267). As compared with the control group, patients assigned to CRT experienced an improvement in the distance walked in six minutes, functional class, quality of life, time on the treadmill during exercise testing, and LVEF, while they experienced lower risk of hospitalizations or intravenous medications due to HF (267). Similarly, the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) study showed that CRT improved quality of life, functional status, and exercise capacity in patients with moderate to severe HF, a wide QRS interval, and life-threatening arrhythmias (268). The beneficial role of CRT in improving the functional status of HF patients as measured by 6-min walk test and oxygen uptake during bicycle exercise was revealed in the Pacing Therapies in Congestive Heart Failure (PATH-CHF) study (269). The Cardiac Resynchronization-Heart Failure (CARE-HF) Study enrolled patients with LVEF ≤35%, QRS prolongation, and NYHA class III-IV HF (nearly all class III) almost exclusively employed CRT-P. The study showed that compared to medical therapy, CRT group showed a significant reduction in the risk of death, improved quality of life and symptoms. In addition, CRT reduced the interventricular mechanical delay, the end-systolic volume index, the area of the mitral regurgitant jet and increased the LVEF (270). These beneficial effects of CRT persisted at follow-up periods longer than the main trial (271). The COMPANION trial enrolled 1520 patients who had advanced HF (NYHA III or IV) due to ischemic or nonischemic

cardiomyopathies and a prolonged QRS (250). As compared with optimal pharmacologic therapy alone, CRT-P/D decreased the risk of the primary end point (time to death from or hospitalization for any cause) and the risk of combined end point of death from or hospitalization for heart failure as well the risk of death from any cause (250).

2.2.7.1 Response to CRT

Despite over 20 years of history of CRT, there remains no consensus definition for CRT response or non-response (272). Notably, the reported response rates in the literature vary depending mainly on the response criteria (273). However, approximately 30% of CRT recipients do not respond to the treatment (267). Regarding the definitions of CRT response that have been used in the literature, these can be divided into clinical response criteria (quality of life, VO2 max, 6-min walk test, NYHA functional class, HF hospitalization, deaths) and echocardiographic response criteria [improvement in LVEF, left ventricular end-systolic volume (LVESV), and end-diastolic volume (LVEDV)] (272). The importance of response to CRT therapy is enhanced by the fact that it is well-established that responders to CRT therapy have lower incidence of adverse outcomes (mortality, ventricular tachycardias, hospitalizations) (274, 275).

The knowledge of baseline characteristics that can predict CRT non-response is of great importance. As a result, a number of studies have investigated possible associations between baseline characteristics and response to CRT (276). Baseline QRS duration is considered a major predictor of CRT response and is an important element of CRT indication according to recent guidelines (1). A meta-analysis of five major clinical trials COMPANION, CARE-HF, RAFT, MADIT-CRT, and REVERSE found no statistically significant reduction in death and HF hospitalization in patients with a QRS duration of <150ms compared to patients with a QRS duration ≥150ms (277). In addition to QRS duration, QRS morphology is another important parameter for predicting CRT response and consists a criterion for CRT indication (1). Data from Medicare patients showed that RBBB, ischemic cardiomyopathy, NYHA IV status and advanced age are predictors of poor outcome after CRT (278). Furthermore, data from MADIT-CRT showed that LBBB patients had a reduction in HF progression and a reduction in the risk of ventricular tachyarrhythmias compared to non-LBBB QRS pattern (RBBB or intraventricular conduction disturbances) (279). Among electrocardiographic predictors of CRT response, patients with prolonged PR interval

had higher mortality and decreased echocardiographic response rates (280). However, prolonged PR interval cannot participate in the decision-making process regarding CRT implantation as data from COMPANION trial showed that CRT patients with both prolonged and normal PR intervals did better than patients in the control group with a normal PR interval (281). As we have already mentioned, AF is a common arrhythmia in HF patients. A meta-analysis of 23 observational studies showed that AF was associated with an increased risk of non-response to CRT and all-cause mortality, less improvement in quality of life, 6-minute walk distance, and LVESV but not LVEF (282). Furthermore, the atrioventricular nodal ablation procedure appeared to improve the outcomes of AF patients and specifically reduced the risk of clinical nonresponse and the risk of death (282).

In the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, female sex, non-ischemic cardiomyopathy, LBBB, baseline QRS ≥150 ms, prior hospitalization for HF, LVEDV ≥125 mL/m2, and left atrial volume <40 mL/m2 were found to be associated with echocardiographic CRT response (283). Similarly, another study found that LBBB, non-ischemic cardiomyopathy and female gender were generally associated with improved outcomes following CRT (276) while in a recent individual patient meta-analysis of three double-blind, randomized trials (MIRACLE, MIRACLE ICD, and REVERSE trials), clinical composite score at 6 months was compared in patients assigned to CRT programmed on or off (284). The multivariable modelling identified QRS duration and LVEF as predictors of CRT clinical response (284). A systematic review of the current evidence about extracellular cardiac matrix biomarkers for predicting CRT response showed that collagen synthesis biomarkers offer the most potential for predicting CRT response (285). Regarding gender differences in CRT response and major outcomes, several studies have shown a superiority of female gender (260, 268, 286). These differences can be attributed possibly to the wider QRS of the women enrolled in the studies or in gender differences in branching patterns of the coronary venous tree that have an impact on left ventricular lead location (287).

Regarding the role of echocardiography in patient selection to CRT, interventricular and mechanical dyssynchrony has been found to be associated with CRT response (287-289). Tissue doppler imaging with measurement of the differences of the time to peak longitudinal velocities at the basal segments of opposing walls (septal–lateral, anterior–inferior, and anteroseptal–posterior) have been shown to

predict response and outcome after CRT (290, 291). A prospective, multicenter study, the Predictors of Response to CRT (PROSPECT) study, tested the performance of different echocardiographic parameters of mechanical dyssynchrony based on both conventional and tissue Doppler-based methods to predict CRT response (improved clinical composite score and ≥15% reduction in LVESV at 6 months) (292). The investigators found that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT (292). Nevertheless, variability arising from technical and interpretative factors represents a severe limitation in that study. A single-center study showed the importance of right ventricular function for CRT response. Specifically, the authors found that Tricuspid annular plane systolic excursion (TAPSE) ≥15 mm was strongly associated with response, and TAPSE <15 mm with non-response (293). A recent study found a significant association of right atrial enlargement with long-term mortality in patients with HFrEF receiving CRT (294).

Recently, speckle tracking echocardiography is widely used to assess both timing and amplitude of myocardial contraction and has been proved to be superior to tissue doppler imaging in ultrasonic angle dependency, signal-to-noise ratio, and its ability to detect viable versus scarred myocardium (295, 296). Different speckle tracking echocardiography parameters have been found to be significantly associated with CRT response. Specifically, a study found that amplitude of efficient contraction and maximum longitudinal strain were independent predictors for CRT response (297). New speckle-tracking-based quantitative assessment of mechanical dyssynchrony by start systolic index and peak longitudinal displacement was found to be an important objective tool to identify potential CRT responders (298). Another study aimed to assess the predictive value of longitudinal strain and radial strain speckle tracking measurements on echocardiographic and clinical response to CRT (299). The investigators found that only maximal delay between six segments in 4-chamber view as assessed with longitudinal strain was associated with clinical response to CRT while none of the speckle tracking indices was different between echocardiographic responders and non-responders to CRT (299). Additionally, another prospective single center study was designed to assess the relationship between septal deformation patterns obtained by two-dimensional speckle-tracking echocardiography and response to CRT (300). Particularly, longitudinal two-dimensional speckle-tracking strain

analysis in the apical 4-chamber view identified three patterns: double-peaked systolic shortening (pattern 1), early pre-ejection shortening peak followed by prominent systolic stretch (pattern 2), and pseudonormal shortening with a late systolic shortening peak and less pronounced end-systolic stretch (pattern 3). The authors found that septal deformation strain pattern 1 or 2 was highly predictive of CRT response (300). Additionally, the Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC study) suggests that strain delay index may identify responders to CRT in ischemic and non-ischemic patients. Specifically, a strain delay index > 25% identified responders to CRT (positive and negative predictive value of 80 and 84%, respectively) with low (6%) inter-observer variability (301).

The position of left and right ventricular leads seems to play an important role in the CRT response. In general, patients with lateral left ventricular wall stimulation has been found to be associated with better outcomes (302). Furthermore, a study showed that an anterior versus a nonanterior left ventricular lead position was independently associated with an increased likelihood of nonresponse to CRT and a higher risk of serious outcomes (303). On the other hand, COMPANION and PROSPECT trials did not show a significant associated between lead position and CRT outcomes (304, 305). Furthermore, in the MADIT-CRT trial, the location of the lead in anterior, lateral or posterior wall did not affect outcomes while an apical location of the lead was associated with increased risk of HF and death (306). The same trial showed that CRT with posterior or lateral LV lead position was associated with a decreased risk of arrhythmic events in comparison with anterior lead location (307). However, the electrical location has also been proposed to play a role in CRT response (308). Specifically, baseline electrical dyssynchrony, as measured by the QLV (the time from the onset of QRS to the LV electrogram peak) interval, was found to predict CRT response (308). The presence of scars is of great importance in the choice of lead position placement (309). As a result, preimplantation estimation of left ventricular scars especially in ischemic cardiomyopathy patients with previous myocardial infarction should be considered. However, a recent small study about the impact of cardiac magnetic resonance-guided left ventricular lead placement on clinical outcomes and left ventricular reverse remodeling in CRT recipients did not show significant results (310).

2.2.7.2 Indications of CRT implantation

According to recent guidelines, a CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite optimal medical therapy in order to improve symptoms and reduce morbidity and mortality (Class I), for symptomatic patients with HF in SR with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite optimal medical therapy in order to improve symptoms and reduce morbidity and mortality (Class I). Furthermore, CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity (Class I) (1).

3. Gaps in evidence and aims of our research

This PhD thesis was designed to answer important clinical questions that are related to the broad field of arrhythmia management in HF patients. Regarding our methodology, we used meta-analytic methods to quantitatively synthesize outcomes across studies to obtain information on statistical significance and relevance. Furthermore, we performed original research (observational studies) by collecting original patient data from a single cardiology center. The following five topics/clinical questions are at the core of this research:

1. The existing data are not clear regarding the prognostic significance of AF in patients with HF (94, 100). There are several observational studies with conflicting results regarding the prognostic significance of AF in major outcomes in patients with HFrEF with an ICD implanted either for primary or for secondary prevention of SCD. As a result, we proceeded in the quantitative synthesis of the existing data in order to elucidate what is the impact of AF history in patients with HFrEF and an ICD implanted either for primary or for secondary prevention of SCD.
2. There are several observational studies with conflicting results regarding the association and prognostic role of ICD therapies (appropriate/ inappropriate ATP/shocks) in HF patients (216, 218, 230, 311-324). Thus, we proceeded in the quantitative synthesis of the existing data to elucidate the association of ICD therapies with all-cause mortality in HFrEF patients.

3. Several observational studies have described the possible predictors of AF recurrence in patients undergoing AF ablation procedure (325). However, there are not enough data regarding predictors of AF recurrence in HF patients. As a result, we retrospectively analyzed the data from a large clinical center in order to find any potential association between baseline patient characteristics with AF recurrence in HF patients undergoing AF catheter ablation procedure.
4. The presence of the high proportion of non-responders to CRT highlights the need to establish simple baseline characteristics that may predict response to CRT. Existing data have demonstrated a possible association of hematological markers (neutrophil-to-lymphocyte ratio, red cell distribution width (RDW) (326, 327). We retrospectively analyzed data from a large clinical center to find any potential association between simple hematological indices with the response to CRT.
5. Some studies have indicated that QRS shortening after CRT predicts a favorable response to CRT (328-330). However, the existing data about the association of QRS narrowing after biventricular pacing with CRT response rates are not clear (331, 332). Therefore, we aimed to clarify the association between QRS narrowing and CRT response by performing a systematic review and quantitative synthesis of studies separately for clinical and echocardiographic CRT response.

Second Part

1. Clinical question 1: Patients with HFrEF and an ICD implanted either for primary or for secondary prevention; what is the impact of AF history on patient outcomes?

1.1 Methods

In order to answer the above clinical question we used the methodology of meta-analysis (333).

1.1.1 Search strategy

Two investigators searched independently MEDLINE from inception to November 2016. Due to the lack of a specific targeted study design and opting for maximum sensitivity, the search term that we used was "defibrillator". To validate our approach, we pilot-tested different algorithms that would yield the benefit of added specificity; in the produced results we observed a substantial loss in sensitivity and we thus confirmed the sole use of the broad term "defibrillator". Furthermore, the references' lists of all included studies and relevant review studies were also manually searched.

1.1.2 Eligibility criteria

We considered randomized controlled trials or observational studies in patients with HFrEF and an ICD implanted, that assessed the association between AF history or prevalent AF (paroxysmal, persistent, or permanent) at the time of ICD implantation and clinical outcomes. We included studies that fulfilled the following: i) studies were written in English, ii) patients were ≥18 years old, iii) studies included mainly HFrEF patients (to ensure that, both of the following two criteria had to be met: mean LVEF was ≤40% and the underlying heart disease was ischemic or dilated cardiomyopathy in ≥ 85% of the entire study population), iv) study populations had an ICD implanted for either primary or secondary prevention of SCD according to current guidelines and v) the authors provided quantitative data [crude or adjusted risk estimates] on the association between AF history and any of the following outcomes: all-cause mortality, appropriate (shocks and/or ATP) and inappropriate therapies (shocks and/or ATP). We excluded case-reports, case-series and review articles, studies that investigated exclusively patients with CRT, i.e. the whole study population had a CRT-D implanted, studies that investigated exclusively patients on hemodialysis. In cases of studies reporting data on the same cohort, the study with adjusted data was included in the

analysis, while if both studies provided adjusted data, the study with the longer follow-up was included.

1.1.3 Data extraction

The information extracted for each study was: i) publication details (first author's last name, journal, year of publication, PMID), ii) general characteristics of the study (country of origin, study design, single or multi-center, enrollment period, follow-up duration, number of patients included), iii) characteristics of the study population [age, gender, type of cardiomyopathy, LVEF, history of AF at the time of ICD implantation, type of AF (paroxysmal, persistent or permanent) where reported, indication of ICD implantation (primary or secondary prevention of SCD), type of ICD (single-, dual-chamber or CRT-D)], and iv) the results reported by the study: HR or RR (including adjusted values when these were reported) with confidence intervals (CI), as well as the number of events in each group (AF vs no AF) for the three outcomes (all-cause mortality, appropriate and inappropriate ICD therapies) in order to calculate the RR in case no other measure was provided by the authors. When data on AF, atrial flutter, atrial tachyarrhythmias and non-sinus rhythm were presented in combination, these were analyzed together as AF. ICD shocks and ATP therapies either reported alone or in combination, were analyzed together as ICD therapies. Two authors extracted data in duplicate and any discrepancy was resolved by both authors referring to the original study.

1.1.4 Evidence Synthesis

We performed data synthesis based on three predefined clinical outcomes: all-cause mortality, appropriate ICD therapies, and inappropriate ICD therapies. We performed the evidence synthesis using HR, RR, or OR estimates based on data availability. Due to the observational nature of the assessed evidence, we preferred adjusted estimates over unadjusted ones. For the studies where data were not available, we calculated the crude RR estimates and corresponding 95% CIs for the assessed outcomes.

We assessed the presence of statistically significant heterogeneity by the Q statistic (significant at $P<0.10$) and the extent of the observed heterogeneity by the I^2 (ranging from 0% to 100%) (334). Random-effects models were used to summarize association estimates (335). Fixed-effects models lie on the assumption that there is a common underlying association and that the observed variability observed is due to chance alone; random-effects models acknowledge the existence of true between-study

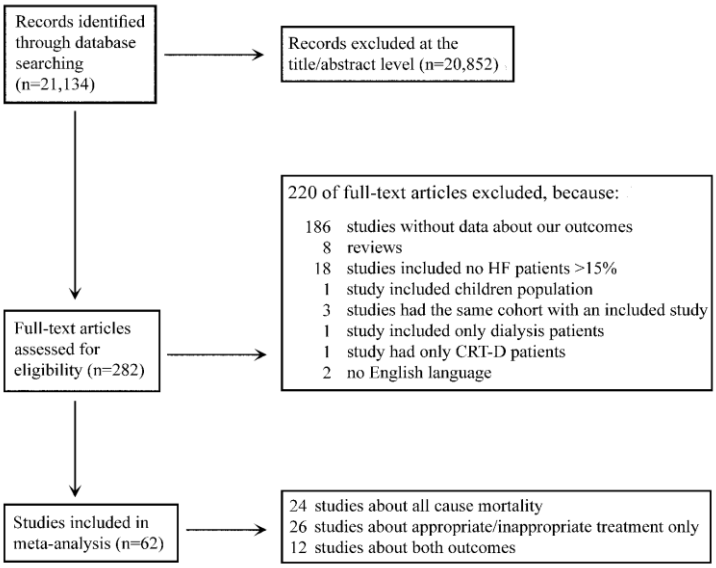
heterogeneity and incorporate heterogeneity into their calculations. In the absence of heterogeneity, fixed- and random-effects models yield the same results.

Subgroup analyses were performed according to AF type, indication for the ICD (primary vs. secondary prevention at >70% of the study population) and the presence of >15% patients with CRT-D. A sensitivity analysis was also performed by the type of the reported estimate (HR vs RR), the presence of adjustment and the study type (nested Randomised Controlled Trial, prospective cohort, retrospective cohort, registry data). We examined whether the subgroup-specific effects were significantly different beyond chance by using a z score (336). To detect publication bias, we visually examined funnel plots per assessed outcome and further assessed asymmetry by using the Begg-Mazumbar test (337). In addition, the trim-and-fill approach was used to obtain an adjusted effect size that takes into account publication bias. Finally, we performed a cumulative meta-analysis to assess the evolution of the observed effects over time (338) as well as meta-regression analyses using the baseline risk, age, and follow-up duration as covariates.

Data analysis was performed by using STATA (StataCorp. 2015. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and RevMan (Review Manager, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All P values are 2-tailed. The study is reported according to the PRISMA checklist (339).

1.2 Results

Figure 1 Meta-analysis flowchart



1.2.1 Search results

As shown in the study flowchart, 21,134 citations were screened at the title and abstract level and 20,852 items were excluded leaving 282 publications for full-text scrutiny (Figure 1). Sixty-two publications were further deemed eligible and were included in the final analysis (Table 1). In 2 of the included studies (321, 340), the study population was separated in two cohorts based on age (321) and indication for ICD (340). In both studies, the data on outcomes were provided separately for the two groups and thus each study was considered individually.

Table 1. Study Characteristics and Main Results

	Country of origin	No	Age (y)	Males (%)	Mean F/U (months)	All-cause mortality[a]	Appropriate treatment[a]	Inappropriate treatment[a]
Agarwal (2007)	US	80	64.4	80	56.4	1.56 (1.03-2.35)[b]	N/A	N/A
Alsheikh (2008)	US	525	67	81	24	N/A	1.15 (0.82-1.61)[b]	N/A
Bhavnani (2010)	US	1245	65	76.7	26.9	N/A	1.04 (0.73-1.49)[b]	1.61 (1.11-2.33)[b]
Bhavnani (2013)	US	1062	65	79	38.3	1.23 (0.85-1.79)[b]	N/A	N/A
Bilchich (2012)	US	1799	N/A	77.5	52.8	1.17 (1.10-1.25)[c,d]	N/A	N/A
Borleffs (2010) [1] [e]	N	747	61.3	77.5	27.8	1.2 (0.6-2.3)[c,d]	1.0 (0.6-1.6)[c,d]	2.9 (1.7-4.8)[c,d]
Borleffs (2010) [2] [e]	N	727	63	78.1	27.8	1.2 (0.6-2.2)[c,d]	0.9 (0.5-1.6)[c,d]	2.5 (1.4-4.4)[c,d]
Borleffs (2010) [3] [e]	N	765	61.8	79.1	27.7	1.7 (1.0-2.7)[c,d]	2.2 (1.6-3.2)[c,d]	2.7 (1.7-4.4)[c,d]
Bruch (2007)	G	146	61	80	22.1	0.99 (0.32-3.06)[b]	N/A	N/A
Brullmann (2012) [1][f]	A-S	863	62	84	43	1.50 (1.12-2.00)[c]	1.34 (1.09-1.65)[c]	N/A
Brullmann (2012) [2][f]	A-S	73	77	88	43	0.93 (0.44-1.97)[c]	1.06 (0.50-2.26)[c]	N/A
Buber (2014)	Isr	300	64.5	89.3	24 (med)	N/A	N/A	1.90 (1.05-3.20)[c,d]
Budeus (2008)	G	93	67.6	89.2	32.9	N/A	0.97 (0.61-1.55)[b]	N/A
Chemello (2010)	B	73	57	74	16.1	N/A	0.52 (0.20-1.35)[b]	N/A
Chen (2013)	UK	185	68.4	84	21	N/A	N/A	3.53 (1.23-10.10)[c,d]
Chichareon (2015)	Th	115	63.4	75.7	N/R	N/A	1.70 (0.72-3.98)[b]	N/A
Cygankiewicz (2009)	US	655	64	84	63	1.53 (1.12-2.09)[c,d]	N/A	N/A
Darma (2015)	G	330	65	81	19	N/A	1.90 (1.14-3.17)[g,d]	N/A

Daubert (2008)	G-US	719	64	84.4	20	N/A	N/A	2.90 (1.65–5.09)[c,d]
Deneke (2004)	G-N	359	61.5	81.6	9.5	2.01 (0.91-4.47)[b]	N/A	N/A
Deneke (2011)	G	400	65	80.3	15	N/A	2.90 (1.74-4.76)[c,d]	N/A
Desai (2010)	US	549	74	79.1	41.4	4.12 (2.38-7.12)[c,d]	N/A	2.50 (1.86-3.35)[g,d]
Duray (2009)	G	822	63	80	43	1.30 (1.04-1.63)[b]	N/A	N/A
Ertel (2010)	US	225	83.3	79.6	39.6	0.76 (0.39-1.48)[b]	N/A	N/A
Francia (2010)	I	83	64	87	17	N/A	0.74 (0.25- 2.22)[b]	N/A
Fumagalli (2014)	I	6,311	66	82.4	27 (med)	1.67 (1.35-2.07)[c]	N/A	N/A
Grimm (2002)	G	101	51	81	36	N/A	2.76 (1.28- 5.97)[b,d]	N/A
Gronefeld (2000)	G	229	60.7	81.2	20	1.77 (0.75-4.21)[b]	1.80 (1.20-2.70)[b,d]	2.30 (1.20-4.50)[b,d]
Hage (2013) [1][h]	US	409	58.1	70.2	50	1.49 (0.92-2.41)[c,d]	0.96 (0.42-2.19)[c,d]	N/A
Hage (2013) [2][h]	US	287	59.4	73.2	50	1.46 (0.92-2.32)[c,d]	1.83 (1.03-3.25)[c,d]	N/A
Heidenreich (2015)	US	172,9	67	73	12	1.66 (1.61-1.71)[b]	N/A	N/A
Kim (2012)	K	275	61	64	40	1.05 (0.56-1.95)[c,d]	N/A	N/A
Klein (2006)	G	250	63	76.8	18.3	N/A	1.65 (1.02-2.66)[c,d]	N/A
Kobe (2013)	G	2,613	N/A	N/A	14.5 (med)	1.39 (1.02 – 1.89)[c,d]	N/A	N/A
Kraaier (2014)	N	861	62.7	79	12	2.17 (1.11 - 4.22)[c,d]	N/A	N/A
Kreuz (2010)	G	94	66.5	N/R	34	N/A	1.02 (0.65-1.59)[b]	1.42 (0.58-3.52)[b]
Kreuz J (2011)	G	99	64.1	69.7	89 (med)	0.70 (0.36 - 2.07)[c]	0.86 (0.45- 1.63)[b]	N/A
Kreuz J (2012)	G	94	67.8	N/A	36 (med)	1.35 (0.71 - 2.55)[b]	N/A	N/A
Lee (2015)	C	3445	66 (med)	79.7	24 (med)	1.57 (1.22 - 2.01)[c]	1.61 (1.17-2.21)[c,d]	N/A
Lelakowski (2012)	P	376	66.1	85.1	14.9	0.57 (0.27 - 1.17)[b]	N/A	N/A
Levine (2014)	US	322	64.7	76.4	N/R	N/A	1.65 (0.87-3.15)[c,d]	N/A

Mitrani (2014)	US	109	71.6	88	21.2	1.02 (0.33 - 3.23)[c,d]	N/A	N/A
Nagai (2010)	J	232	58	79	29	N/A	N/A	3.70 (1.52-9.02)[g,d]
Nageh (2014)	US	93	68.4	88.2	56.5	1.52 (0.73 - 3.15)[c,d]	N/A	N/A
Pedersen (2010)	N	371	57.7	79.5	20.4	1.29 (0.56 - 2.98)[b]	N/A	N/A
Poole JE, (2008)	US-UK-	811	61	77.2	45.5 (med)	N/A	1.23 (0.90-1.68)[b]	1.72 (1.24-2.39)[b]
Providencia (2016)	F	5539	62.5	84.9	33.1 (med)	1.41 (1.13 - 1.77)[c,d]	N/A	N/A
Rienstra (2007)	N	290	59.9	79.7	31.2	N/A	1.90 (1.20-3.20)[c,d]	6.36 (2.21-18.30)[b]
Robin (2006)	US	585	63	79	26.4	N/A	1.24 (0.83-1.84)[b]	N/A
Sandgren (2015)	Sw	259	64.7	78	N/R	N/A	N/A	3.40 (1.32-8.75)[b]
Schernthaner (2007)	A	77	66	82	24.5	5.58 (1.20 - 25.99)[c,d]	N/A	N/A
Schukro (2013)	A	1170	59.7	81	63.6	0.94 (0.73 - 1.22)[c,d]	N/A	N/A
Seegers (2016)	G	1151	64.4	81.2	58.8	1.55 (1.24 - 1.93)[c]	1.34 (1.05–1.70)[c]	N/A
Sesselberg (2007)	US	719	64	84.4	20.6	N/A	3.11 (2.29-4.21)[b]	N/A
Sjoblom (2015)	Sw	865	64	82	35	N/A	1.13 (0.80-1.58)[b]	N/A
Smit (2006)	N	80	61	79	8 (med)	1.76 (0.48 - 6.51)[b]	6.90 (1.70-27.50)[c]	3.52 (0.33-37.13)[b]
Smith (2011)	N	427	58	79	31 (med)	1.41 (0.68 - 2.91)[b]	1.50 (1.04-2.17)[b]	N/A
Sood (2014)	US-D	1790	64.4	75.2	39.6	N/A	1.39 (1.00-1.94)[b]	1.22 (0.75-1.99)[b]
Stein (2009)	US	1655	66.8	82	12.6 (med)	1.89 (1.33 - 2.69)[c,d]	N/A	N/A
Tenma (2015)	J	316	58	78.5	43	N/A	N/A	1.61 (1.06-2.45)[b]
Theuns (2012)	N	100	60	79	24	N/A	5.70 (1.80-18.10)[g,d]	N/A
Van Gelder (2011)	US-N	537	68	77.5	11.1	0.35 (0.08 - 1.59)[c]	0.96 (0.43-2.14)[c]	0.69 (0.25-1.90)[c]
Van Rees (2011)	N	1544	61	79	41	1.4 (1.0 - 1.7)[c,d]	N/A	2.00 (1.50-2.70)[c,d]
Verma (2010)	C	421	68	82	25	N/A	1.31 (0.87-1.97)[b]	N/A

Williams (2011)	US	199	67.8	66.8	31.1	1.22 (0.73 - 2.04)[c]	N/A	N/A
Zhang (2015)	US	1189	60.6	72.9	12	2.51 (1.43 - 4.38)[g,d]	N/A	N/A

Abbreviations A: Austria, AF: atrial fibrillation, B: Brazil, C: Canada, CI: confidence intervals, D: Denmark, F: France, F/U: follow-up, G: Germany, Hx: History, I: Italy, Isr: Israel, J: Japan, K: Korea, med: median, N: Netherland, No: number of patients, N/A: not applicable, P: Poland, S: Switzerland, Sw: Sweeden, Th: Thailand, UK: United Kingdom, US : United States, y: years, y.o: years old.

[a] HR, RR or OR (95% CI), [b] RR, [c] HR, [d] adjusted, [e] Borleffs (2010): [1] paroxysmal AF patients, [2] persistent AF patients, [3] permanent AF patients, [f] Brullmann (2012): [1] only patients under 75 years old, [2] only patients over 75 years old, [g] OR, [h] Hage (2013): [1] only patients in primary prevention, [2] only patients in secondary prevention.

1.2.2 Overview of the evidence base

Overall, we assessed 36 unique studies that reported data on all-cause mortality, 30 unique studies on appropriate ICD therapies and 17 studies on inappropriate ICD therapies (Table 2).

Table 2. Overview of the evidence base.

	Eligible studies
Number of studies	62
Total number of participants	227,998
Number of participants per study, median (min-max)	388 (73-172,985)
Publication year, median (min-max)	2011 (2000-2016)
Age, median[a] (min-max), years	64 (51.0-83.3)
Males[b] number (%)	177,290 (74.8%)
History of coronary artery disease, number (%)	151,191 (63.8%)
Follow-up months, median (min-max)	27 (8-89)
Prevalence of AF %, median (min-max)	26.0 (0.3-50.3)
Indication of ICD[c] (number of studies)	
Primary prevention only	26
Secondary prevention only	3
Mixed (primary/secondary)	32
Outcome, number of studies/cohorts (Total number of participants)	
All-cause mortality	36/38[d] (225,863)
Appropriate ICD therapies	30/32[d] (17,725)
Inappropriate ICD therapies	17/17 (10,093)

[a] We used the mean age provided from each study except four studies which provided median age and in one study in which we had no data about age

[b] We had no data about gender in two studies

[c] We have no data about indication of ICD in one study

[d] Two studies were divided into two different subgroups [Brullmann S, Hage FG]

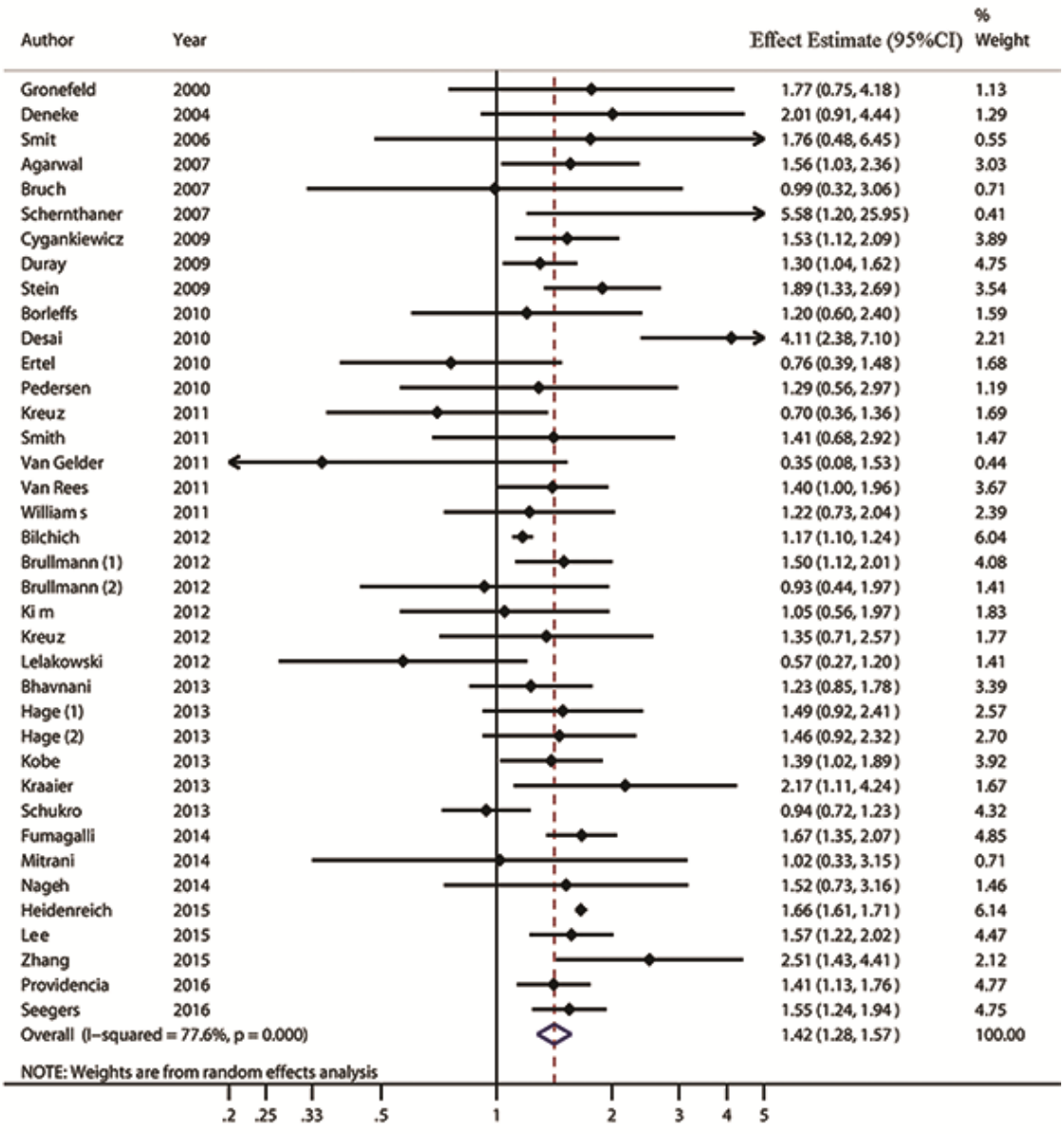
The summary characteristics of the assessed evidence base are shown in Table 2. The included studies were published from 2000-2016 (median publication year 2011) with a median follow-up of 27 months. The cumulative sample size was 227,998 patients (min-max, 73-172,985) of predominantly European ancestry with a median AF prevalence of 26% and with reported more than 17,000 deaths, more than 2,000 appropriate shocks, and more than 800 inappropriate shocks (data on absolute number of events missing from 2 studies). The median participant age was 64 years (min-max 51.0-83.3), and the majority of the included participants were males (74.8%). The most common underlying heart disease was ischemic cardiomyopathy (63.8%). Half of the studies included a mixed population regarding the indication of ICD (32 studies, 52%) while 26 studies included primary prevention patients and 3 studies secondary prevention patients only. No data on the indication of ICD were available in one study.

1.2.3 Overall impact of AF in ICD patients

1.2.3.1 Mortality

Thirty-eight study populations (Table 2) assessed the association between AF and mortality with a cumulative sample size of 225,863 patients. Two-thirds of the studies calculated HR estimates and the remaining reported RR. Overall, history of AF was statistically significantly associated with all-cause mortality [combined effect 1.42 (95% CI 1.28-1.57), $p<0.001$, I^2 78%; Figure 2].

Figure 2. Forest plot on the association of prevalent AF with all-cause mortality in all studies in patients with HFrEF and ICD. Effect estimates and 95% confidence intervals are presented for individual studies and summary data.



Sensitivity analyses performed based on the type of reported estimate, the presence of adjusted estimates and the study type yielded similar results (Figures 3-5).

Figure 3. Sensitivity analyses for all-cause mortality performed based on the type of reported estimate

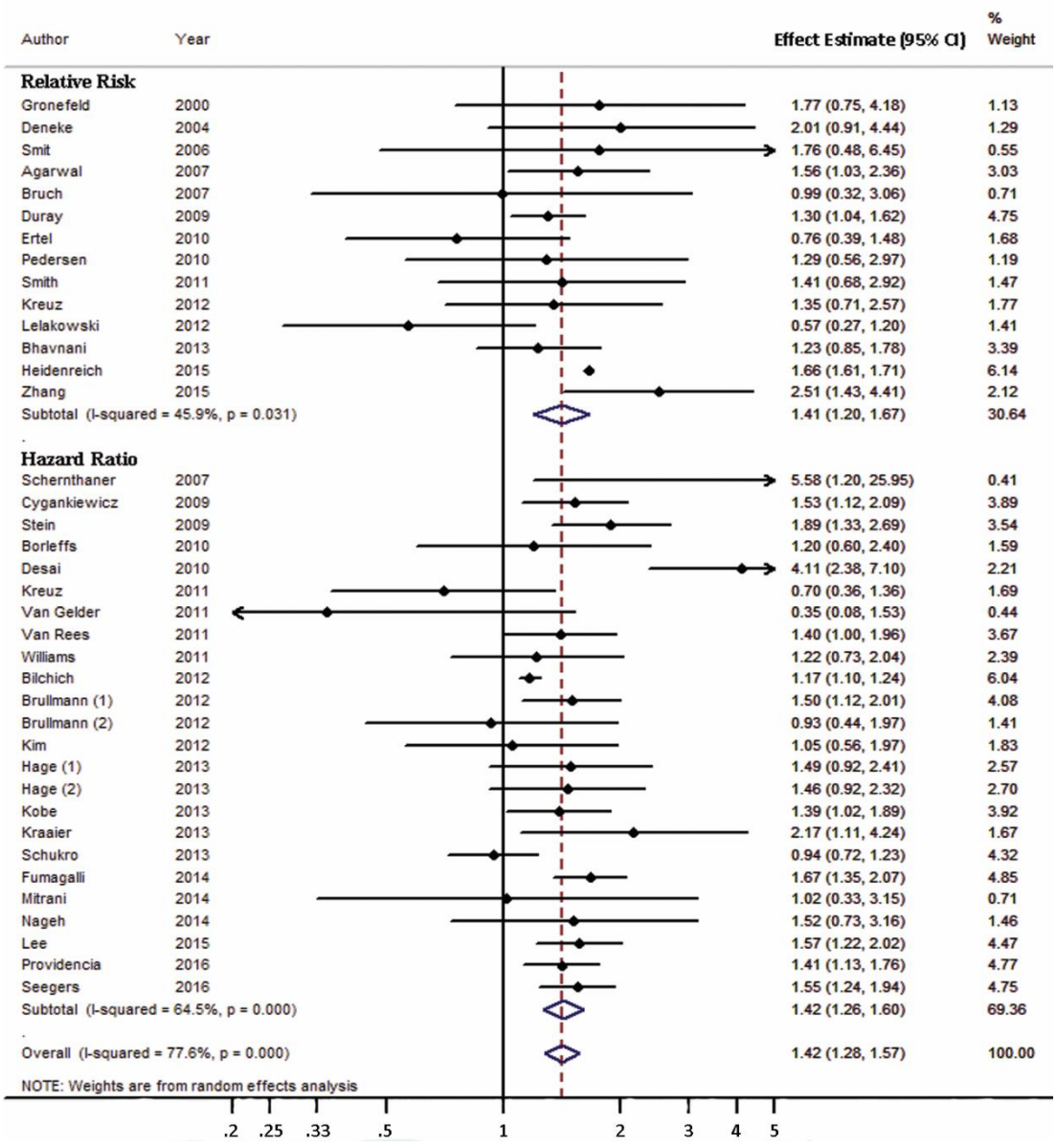


Figure 4. Sensitivity analyses for all-cause mortality performed based on the presence of adjusted estimates

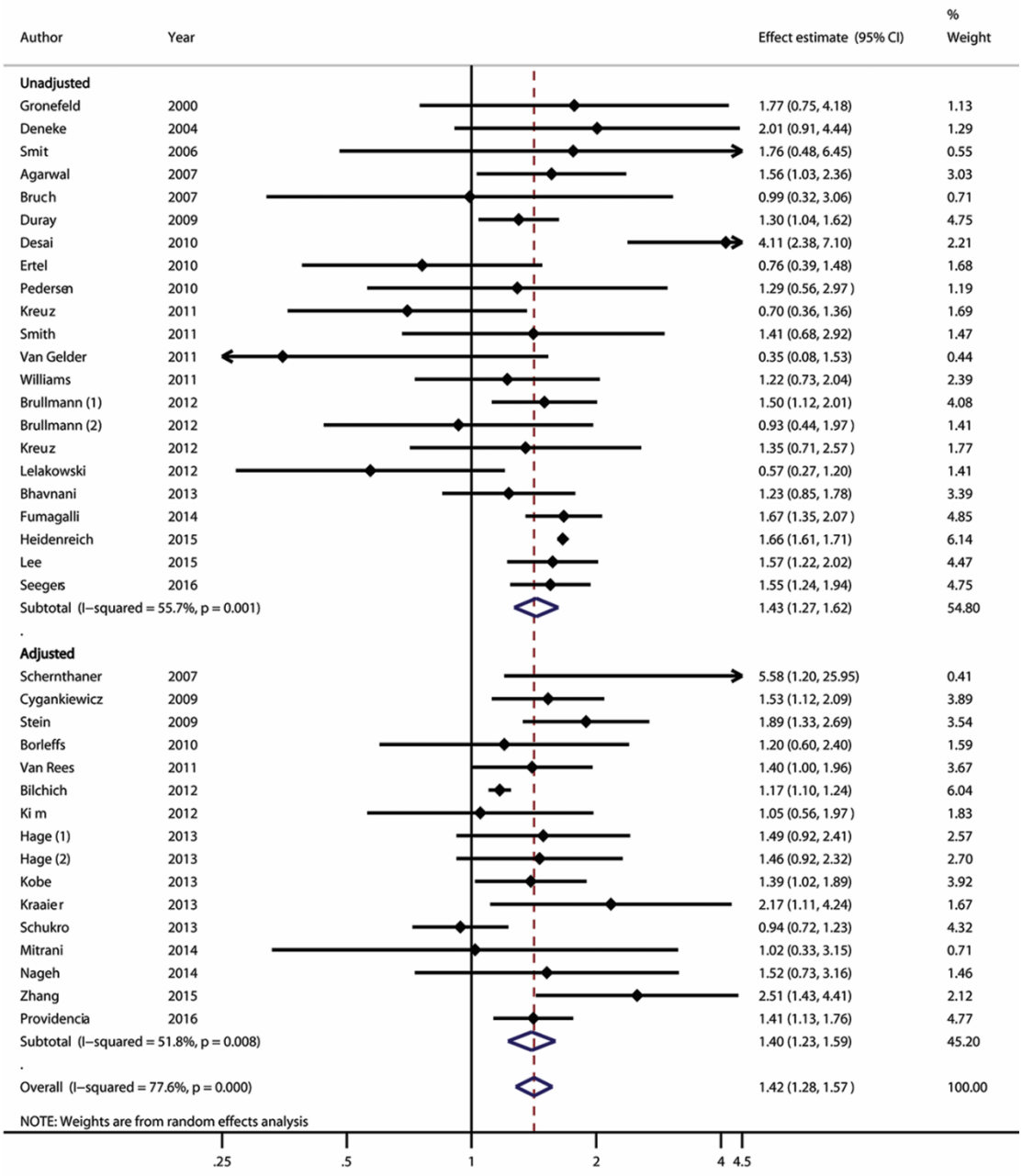
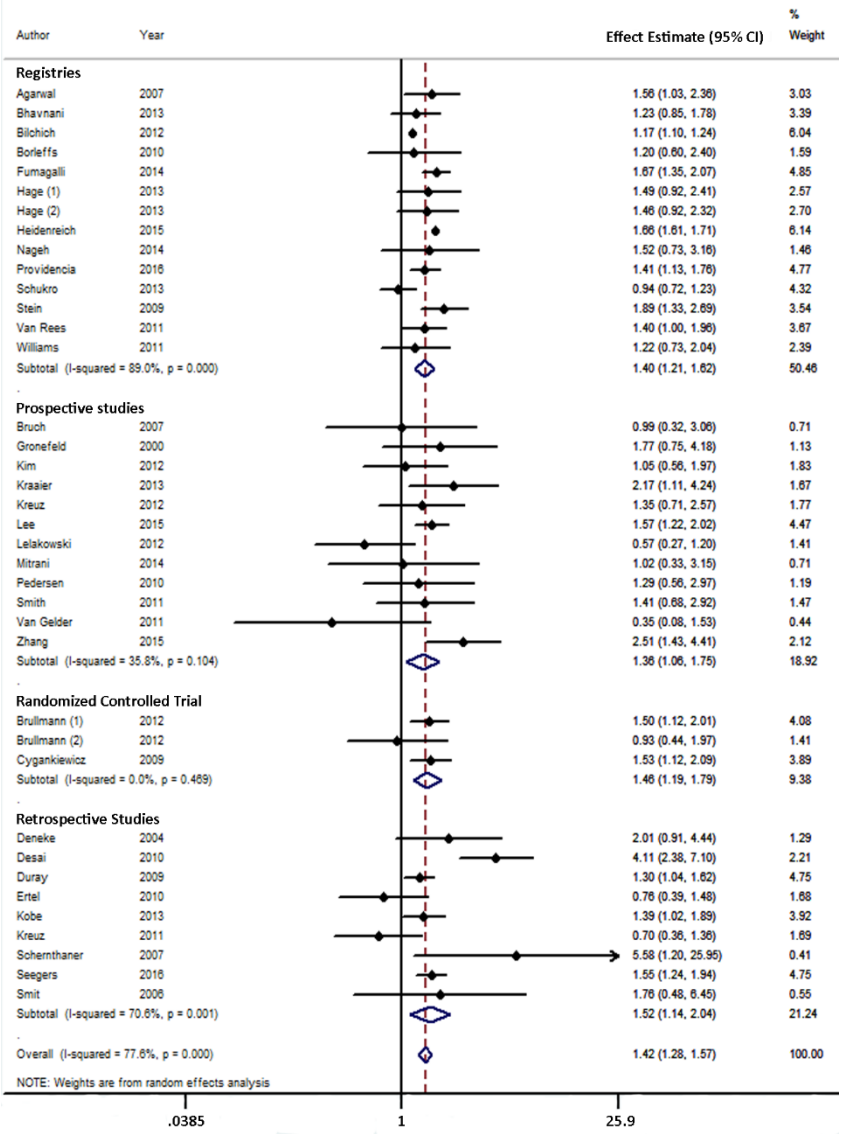


Figure 5. Sensitivity analyses for all-cause mortality performed based on the study type.



Although visual inspection of the funnel plot including all studies showed mild asymmetry (Figures 6,7), the Begg-Mazumbar test was not statistically significant and the trim-and-fill approach gave an identical imputed estimate indicating a low risk of small study effects.

Figure 6. Funnel plot for all-cause mortality

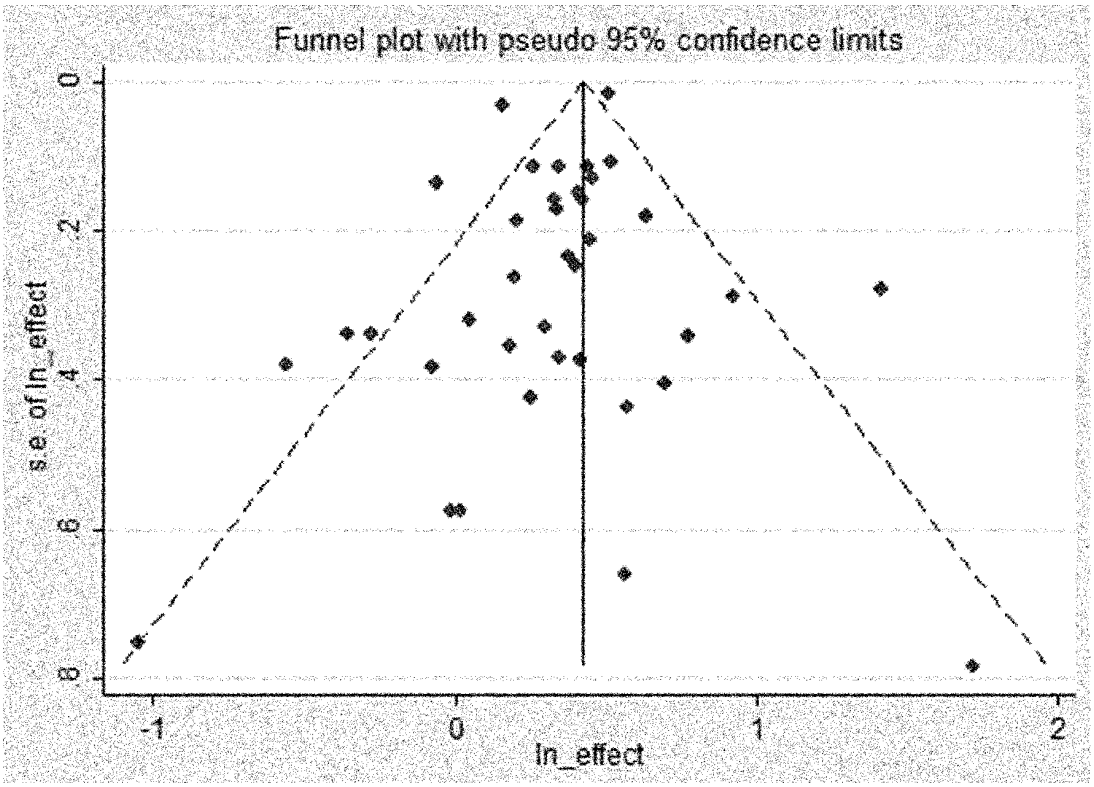
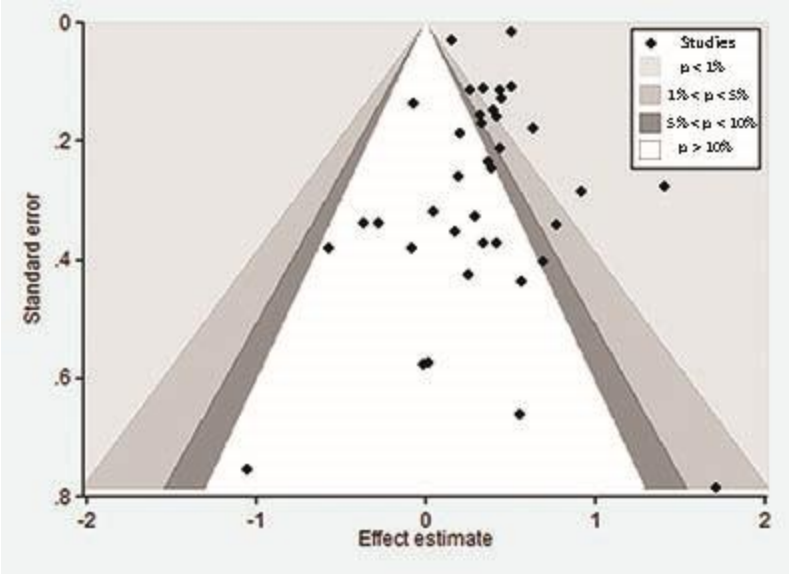
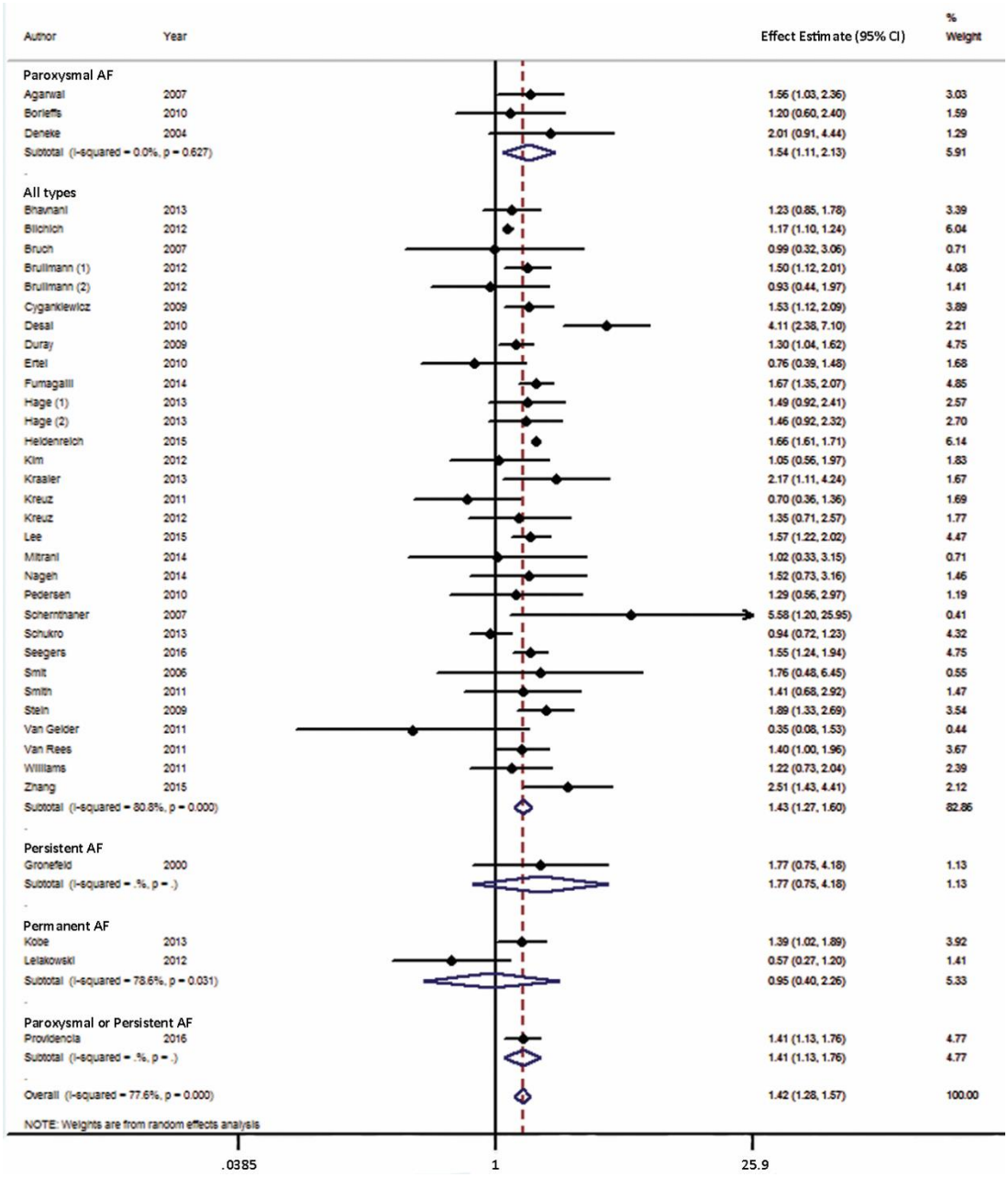


Figure 7. Contour-enhanced Funnel plot for all-cause mortality



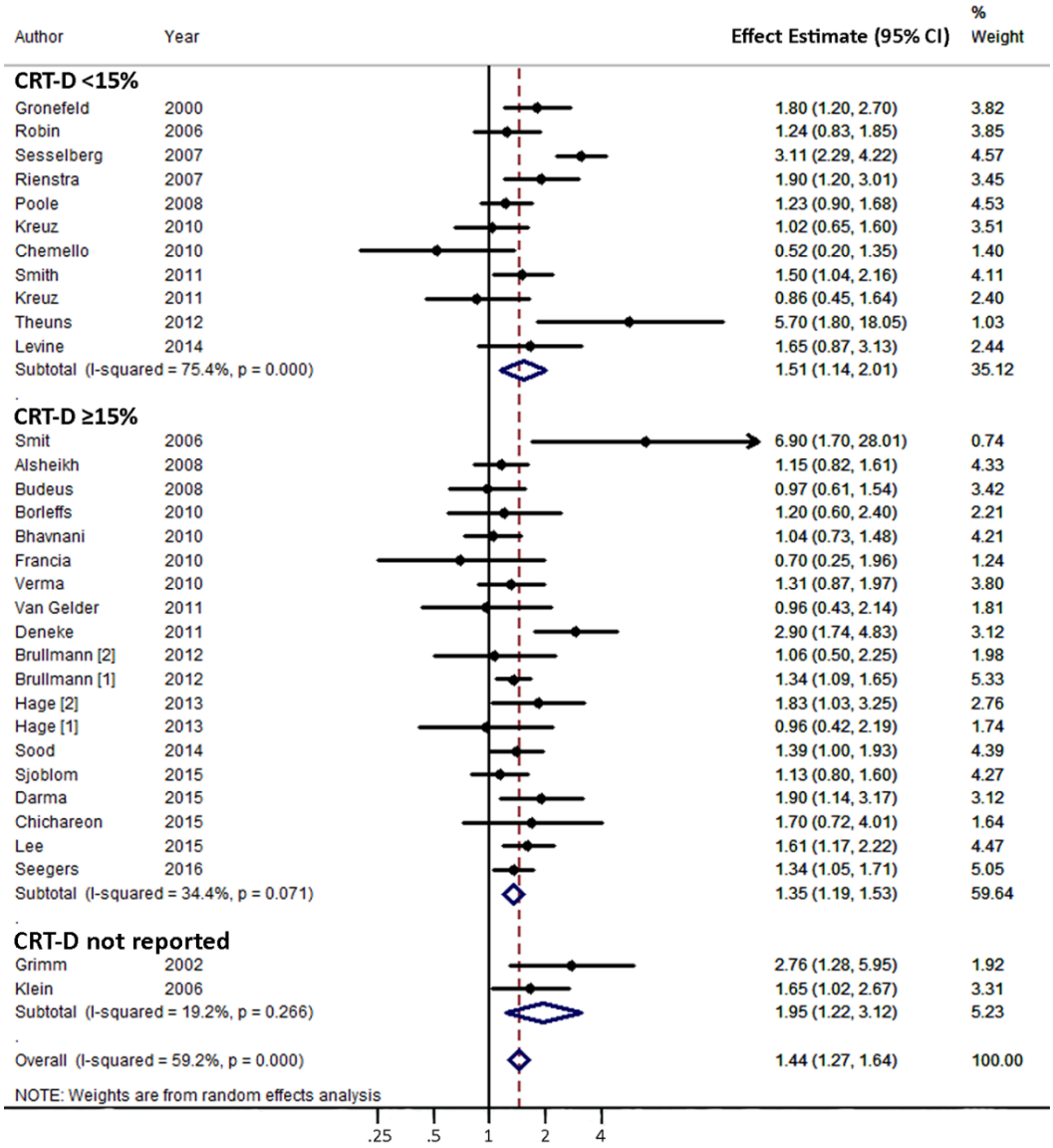
In 31 studies (82%), the type of AF was not reported. Due to the small number of the remaining studies with available AF study information, a quantitative synthesis was not deemed informative (Figure 8).

Figure 8. Subgroup analysis for all-cause mortality performed based on AF type



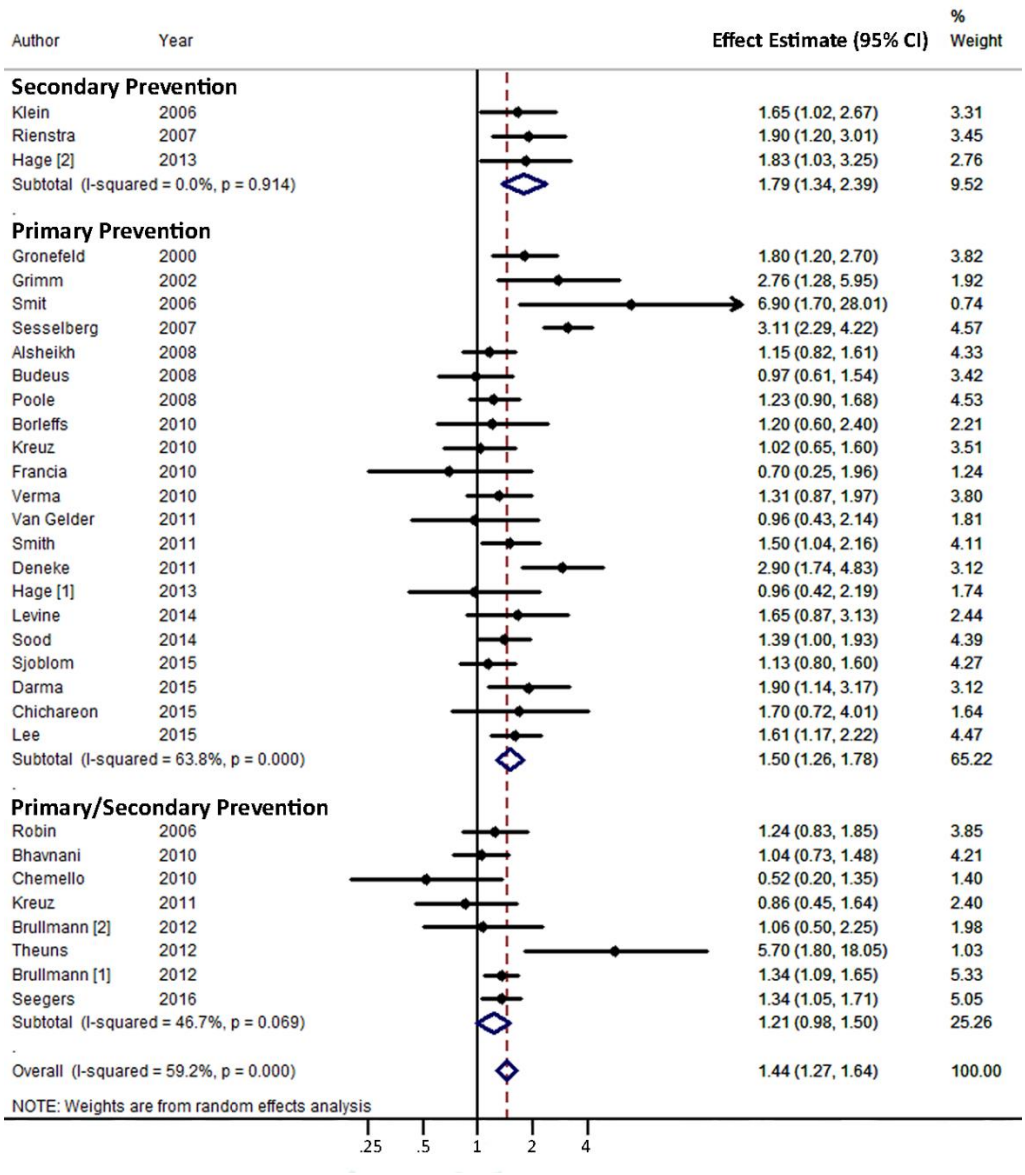
The presence of >15% of patients with an implanted CRT-D at the individual study level seemed to convey a greater mortality risk for AF patients [1.55 (95% CI 1.41 – 1.71) vs. 1.27 (95% CI 1.11 – 1.45); meta-regression p-value, 0.007] (Figure 9),

Figure 9. Subgroup analysis for all-cause mortality performed based on presence of CRT-D patients (15% cut-off point).



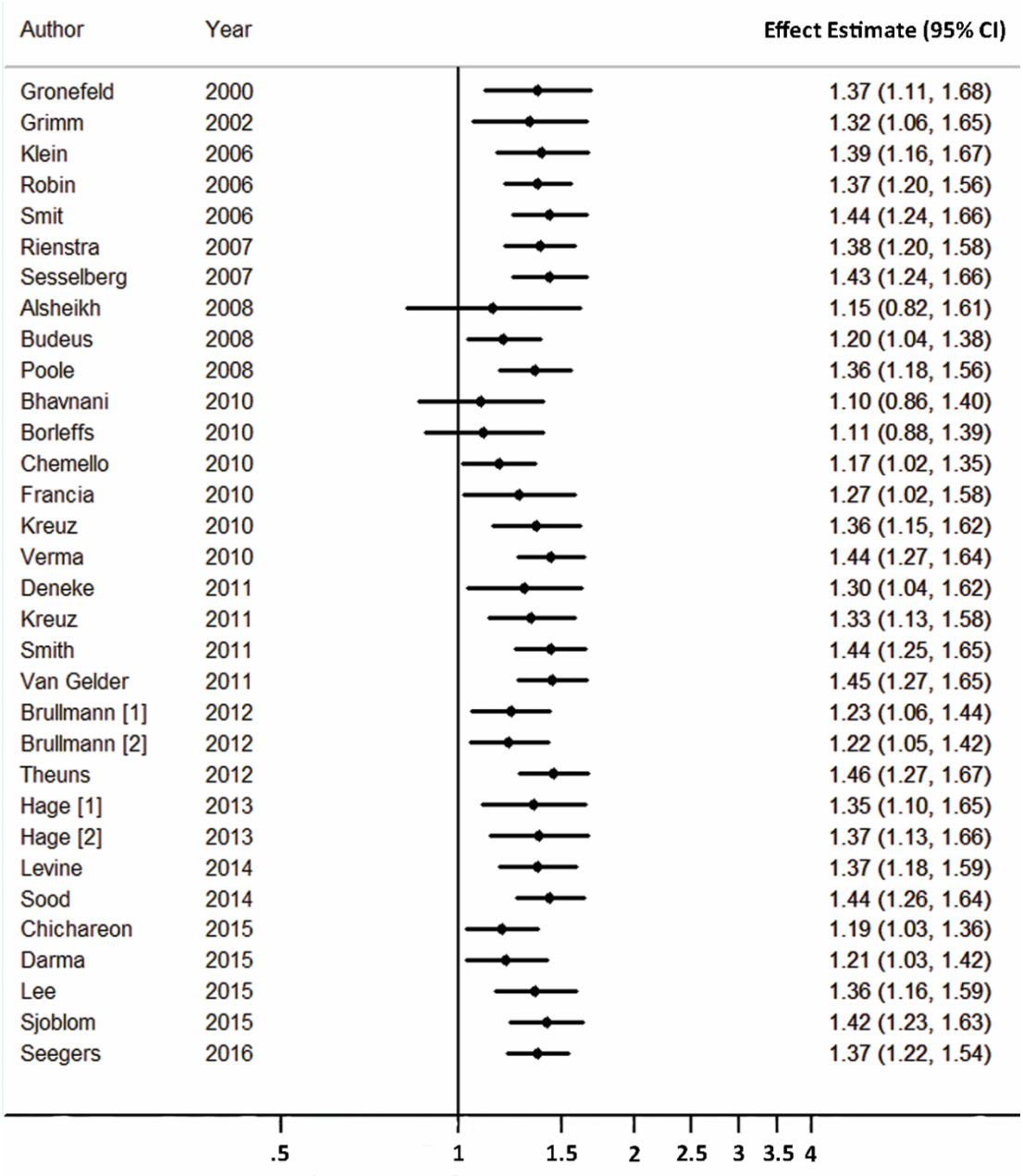
while there was no statistically significant observed difference between studies of predominantly primary and predominantly secondary prevention (Figure 10).

Figure 10. Subgroup analysis for all-cause mortality performed based on prevention type.



Cumulative meta-analysis for the year of publication showed an apparent effect consistency over time (Figure 11). Meta-regression analyses using the baseline risk, age, and follow-up duration as covariates showed no statically significant results.

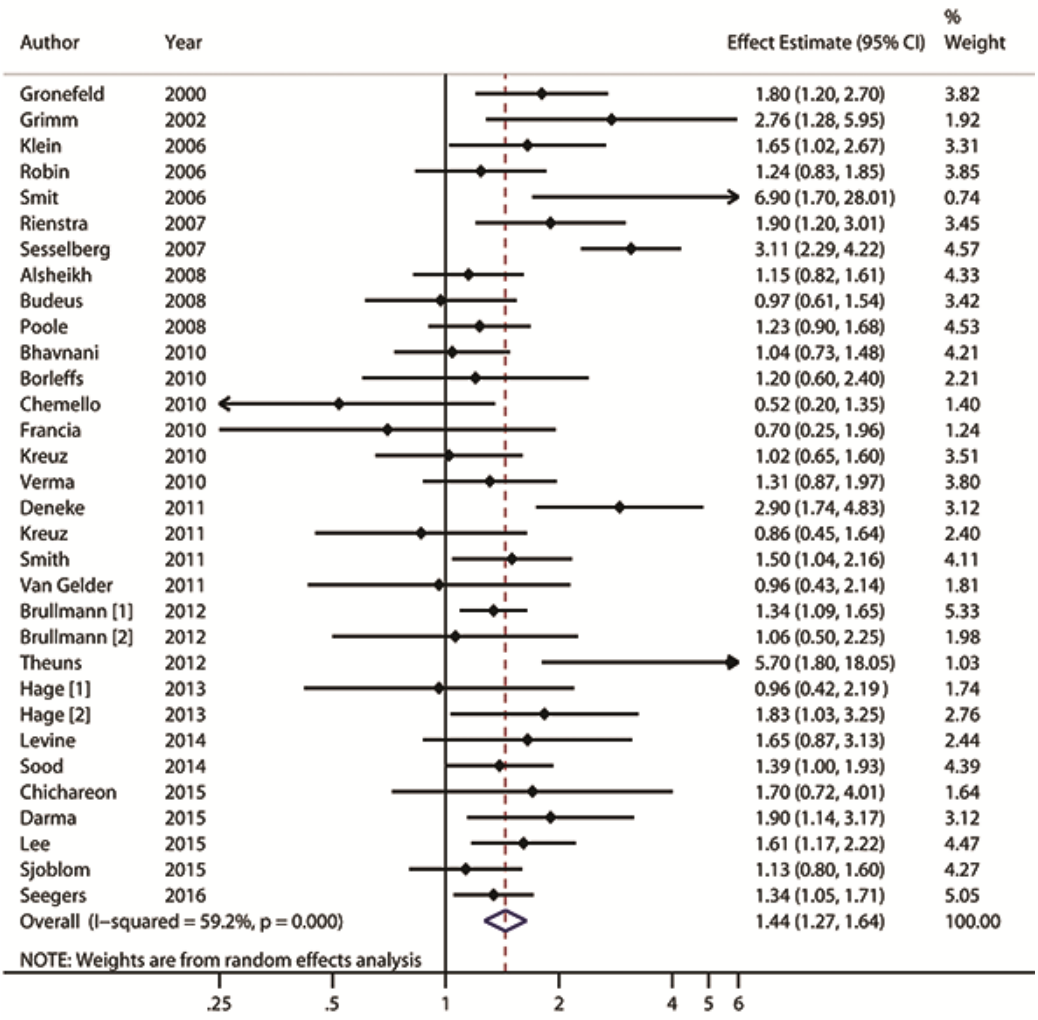
Figure 11. Cumulative meta-analysis for all-cause mortality (year of publication, betas presented).



1.2.3.2 Appropriate ICD therapies and Inappropriate ICD shocks

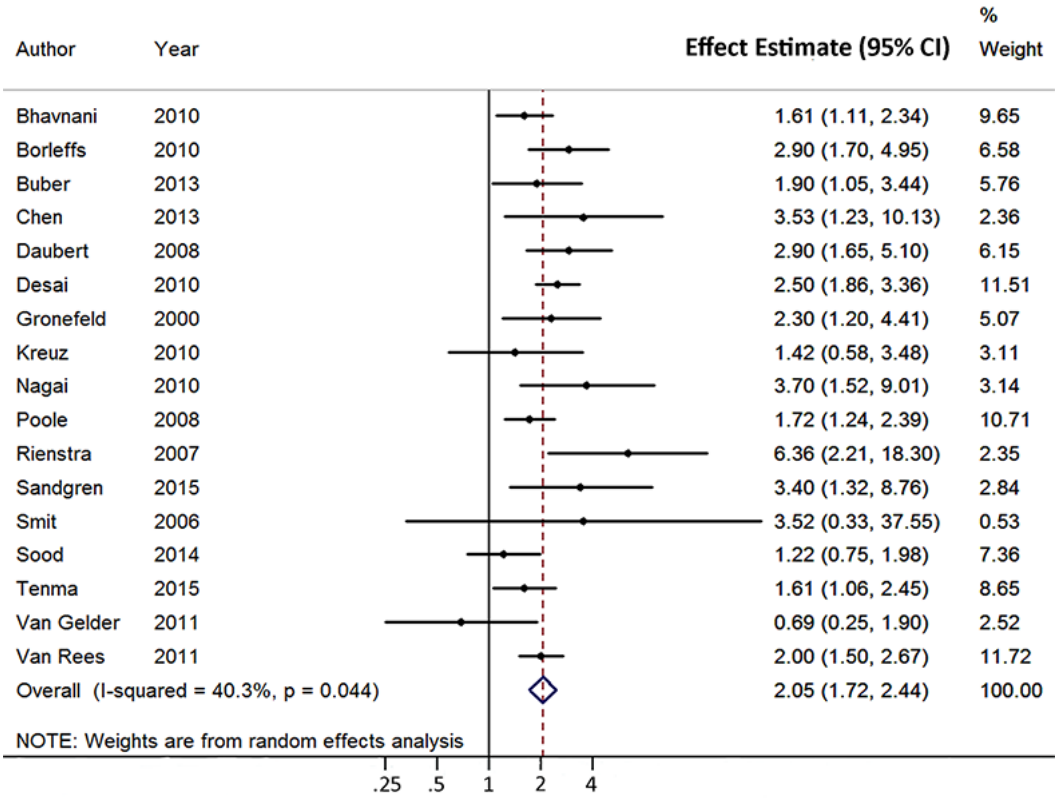
Thirty-two study populations (Table 2) assessed the association between AF and appropriate ICD therapies with a cumulative sample size of 17,725 patients. Thirteen studies produced HR estimates, 17 studies RR and 2 studies odds ratios (OR). Overall, AF history was statistically significantly associated with appropriate ICD therapies [combined effect 1.44 (95% CI 1.27-1.64), $p<0.001$, I^2 59%; Figure 12].

Figure 12. Forest plot on the association of prevalent AF with appropriate ICD therapies in all studies in patients with HFrEF and ICD. Effect estimates and 95% confidence intervals are presented for individual studies and summary data.



Seventeen study populations (Table 2) assessed the association between AF and inappropriate ICD shocks with a cumulative sample size of 10,093 patients. Six studies produced HR estimates, 9 studies RR and 2 studies OR. Overall, AF history was statistically significantly associated with inappropriate ICD shocks [combined effect 2.05 (95% CI 1.75 – 2.44), p<0.001, I2 40%; Figure 13].

Figure 13. Forest plot on the association of prevalent AF with inappropriate ICD shocks in all studies in patients with HFrEF and ICD. Effect estimates and 95% confidence intervals are presented for individual studies and summary data.



Sensitivity analyses performed based on the type of reported estimate and study type yielded similar results for both outcomes (Figures 14-16).

Figure 14. Sensitivity analyses for appropriate therapies based on the type of reported estimate

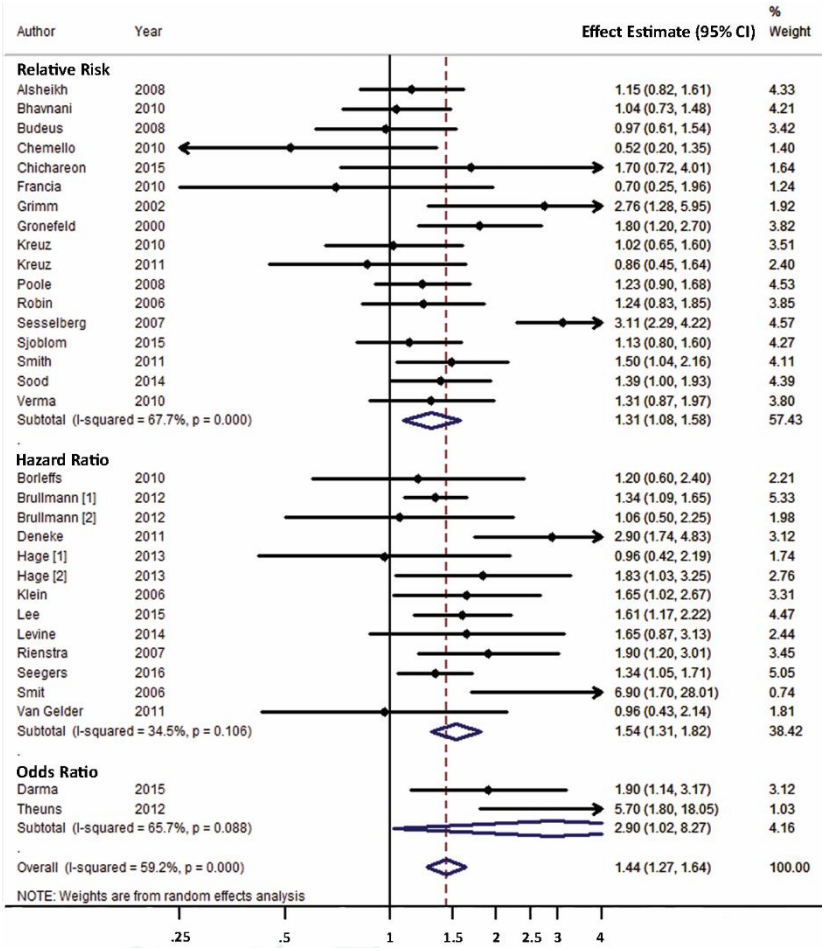


Figure 15. Sensitivity analyses for appropriate therapies performed based on the study type

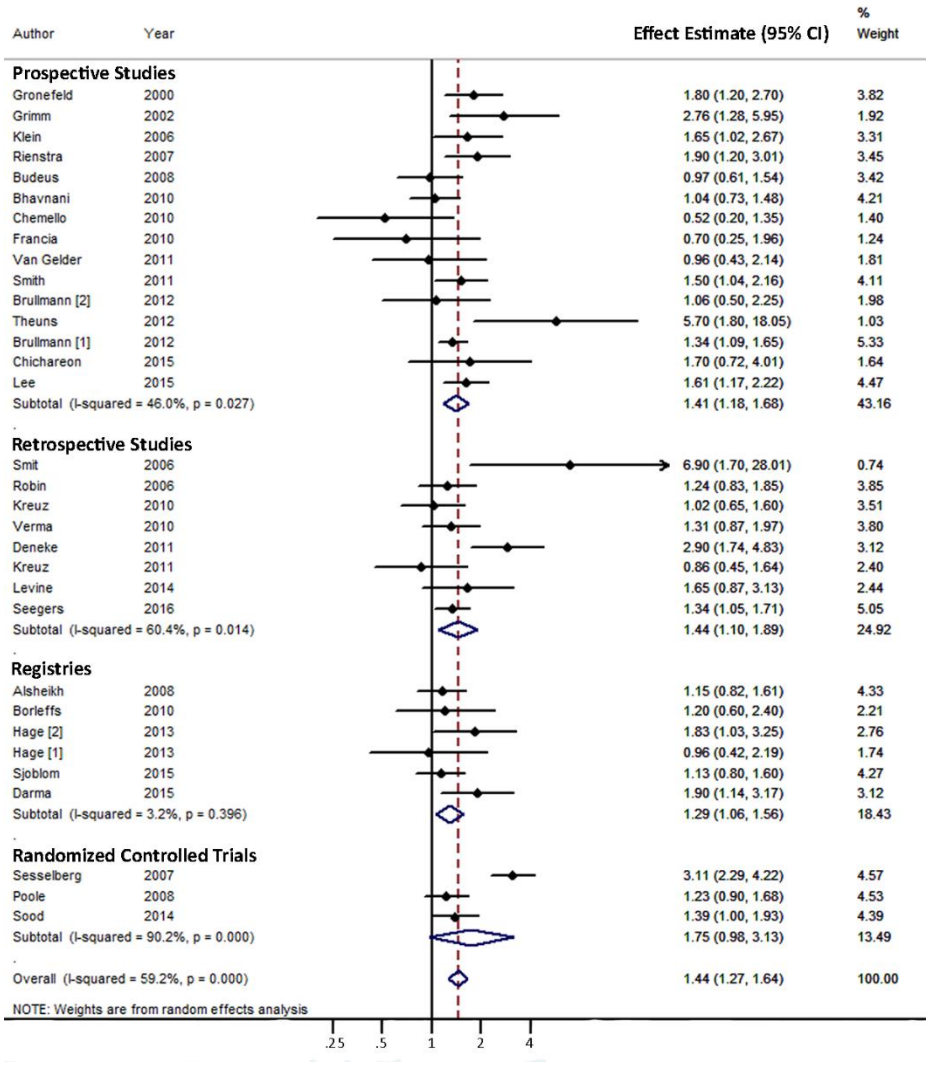
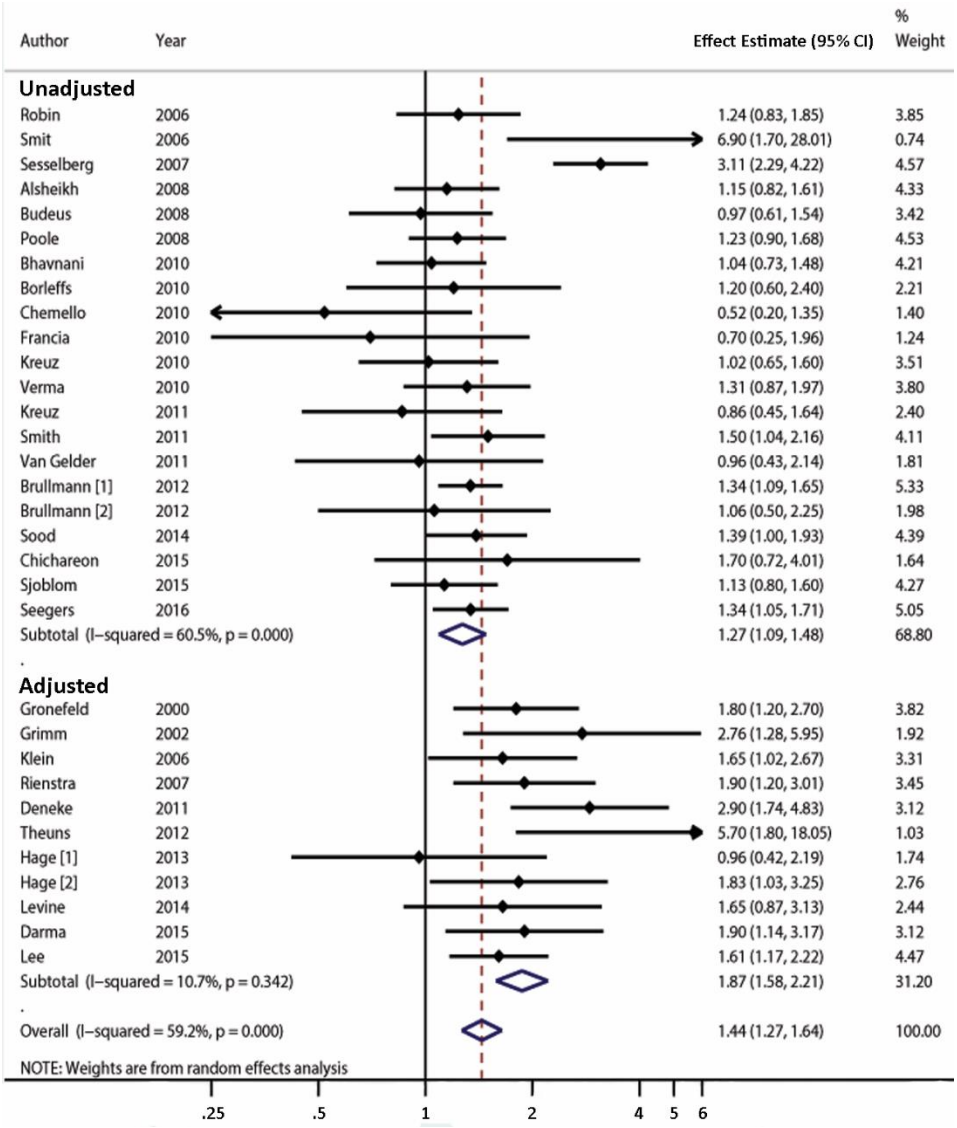
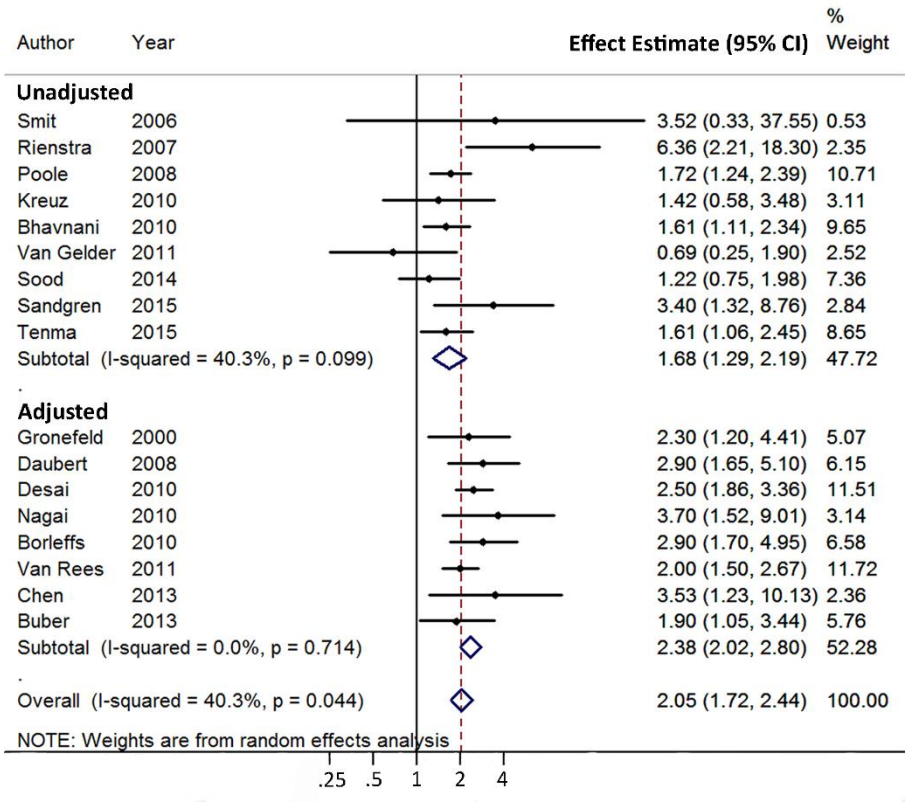


Figure 16. Sensitivity analyses for inappropriate shocks based on the type of reported estimate



Sensitivity analyses performed based on the presence of adjusted estimates showed that the adjusted risk associated with AF was statistically significantly greater than the risk derived from unadjusted data for appropriate ICD therapies (Figure 16); no significant difference between the risk derived from adjusted and unadjusted risk was observed for inappropriate ICD shocks (Figure 17).

Figure 17. Sensitivity analyses for inappropriate shocks performed based on the presence of adjusted estimates



Although visual inspection of the funnel plot including all studies for each outcome showed mild asymmetry, the Begg-Mazumbar test was not statistically significant and the trim-and-fill approach gave an identical imputed estimate indicating a low risk of small study effects (Figures 18-21).

Figure 18. *Funnel plot for appropriate therapies*

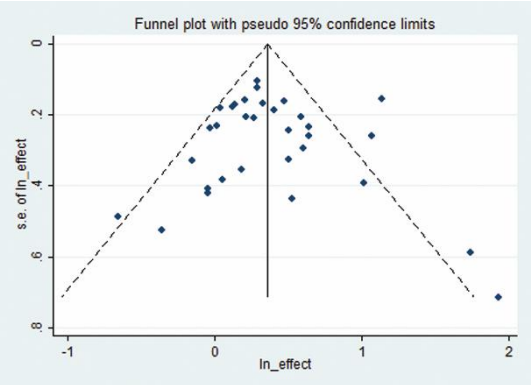


Figure 19. *Contour-enhanced Funnel plot for appropriate therapies*

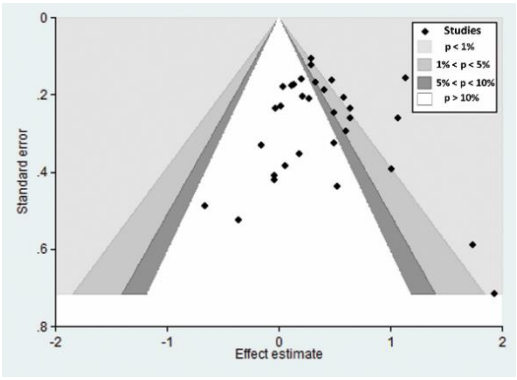


Figure 20. *Funnel plot for inappropriate shocks*

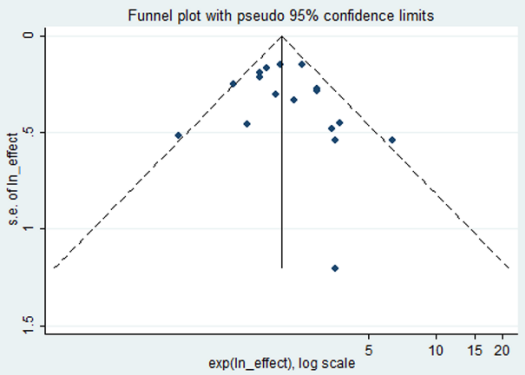
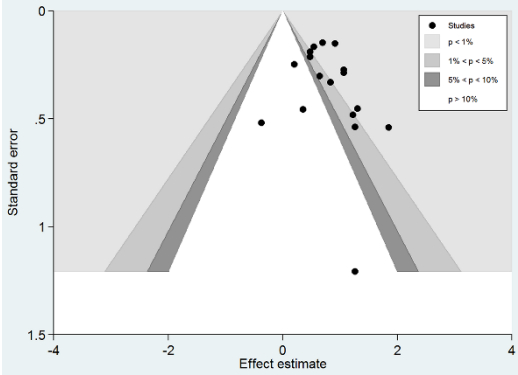


Figure 21. *Contour-enhanced Funnel plot for inappropriate shocks*



In >60% of the populations, the type of AF was not reported. Due to the small number of studies with available information on AF, a quantitative synthesis was not deemed informative (Figures 22-23).

Figure 22. Subgroup analysis for appropriate therapies performed based on AF type

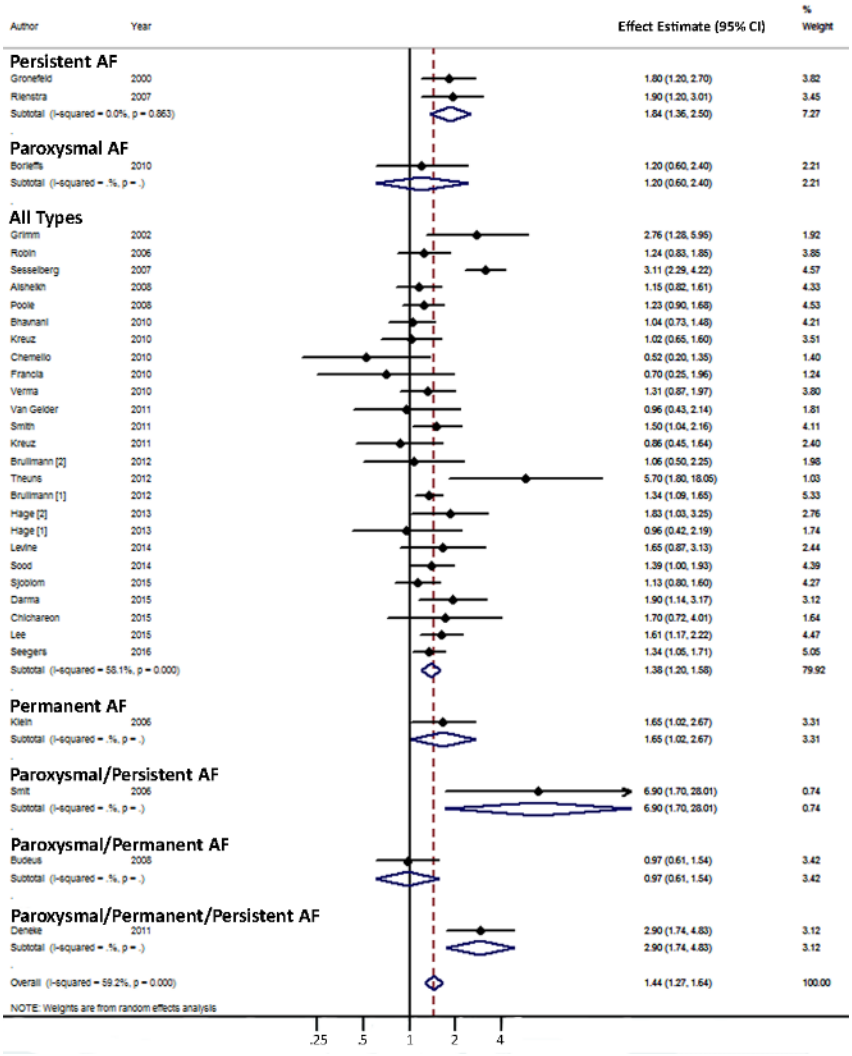
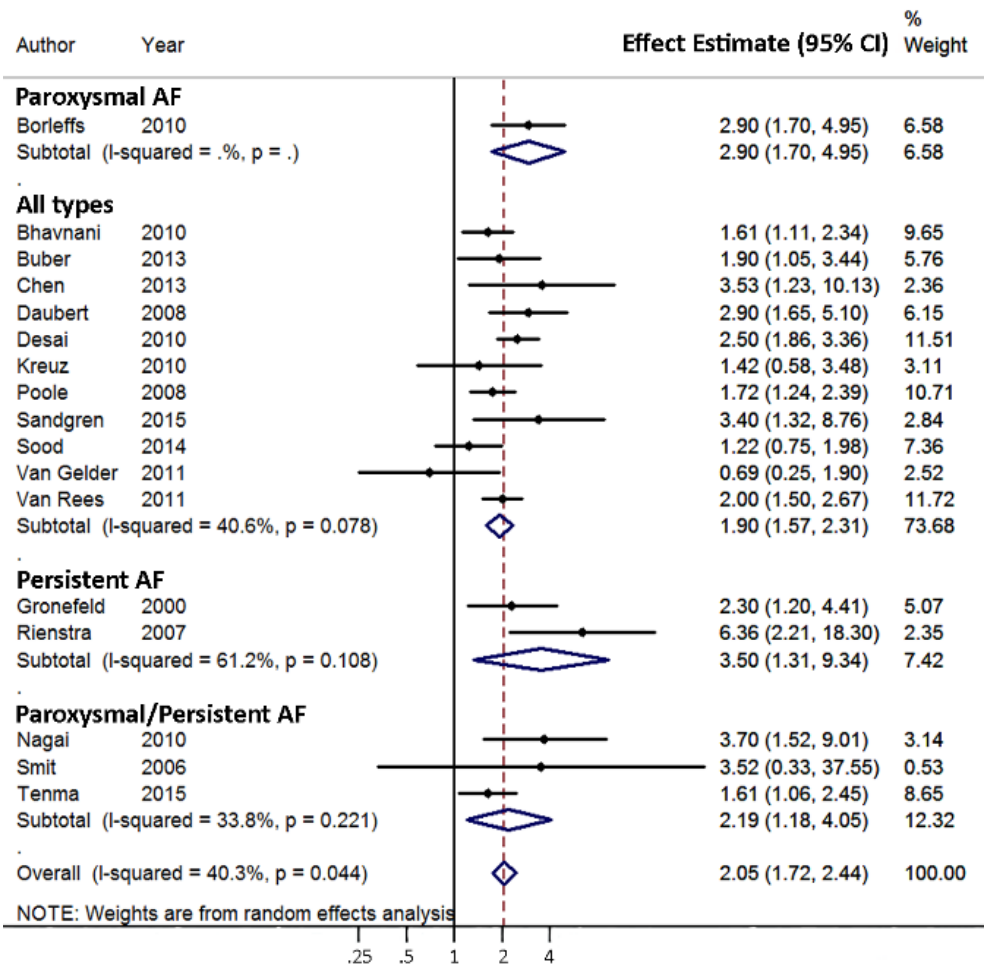


Figure 23. Subgroup analysis for inappropriate shocks performed based on AF type



The presence of >15% of patients with an implanted CRT-D at the individual study level did not seem to convey a greater risk for appropriate therapies [1.35 (95% CI 1.19 – 1.53) vs. 1.51 (95% CI 1.14 – 2.01)] (Figure 24) or inappropriate shocks [1.93 (95% CI 1.57 – 2.37) vs. 2.42 (95% CI 1.68 – 3.49)] (Figure 25) based on the presence of AF history.

Figure 24. Subgroup analysis for appropriate therapies performed based on presence of CRTD patients (15% cut-off point)

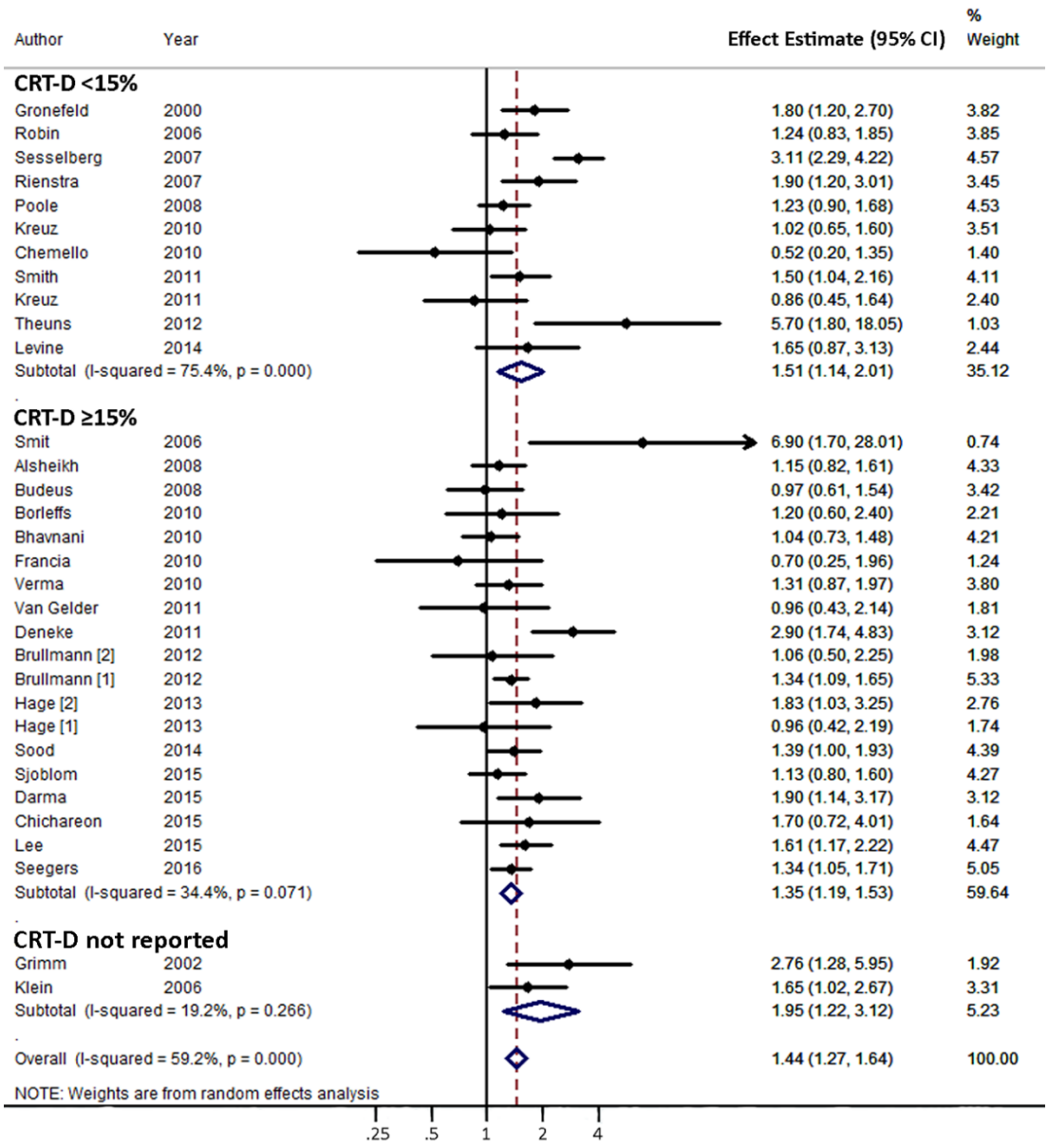
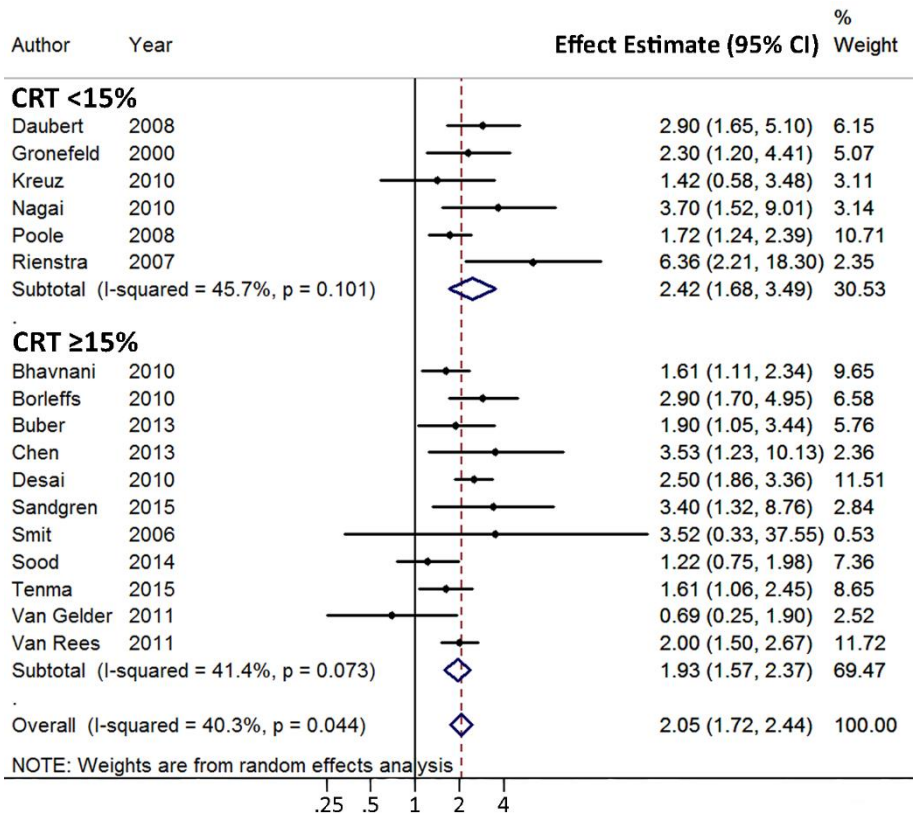


Figure 25. Subgroup analysis for inappropriate shocks performed based on presence of CRT-D patients (15% cut-off point)



There were no statistically significant observed differences between studies of predominantly primary and predominantly secondary prevention for both outcomes (Figures 26-27).

Figure 26. Subgroup analysis for appropriate therapies performed based on prevention type

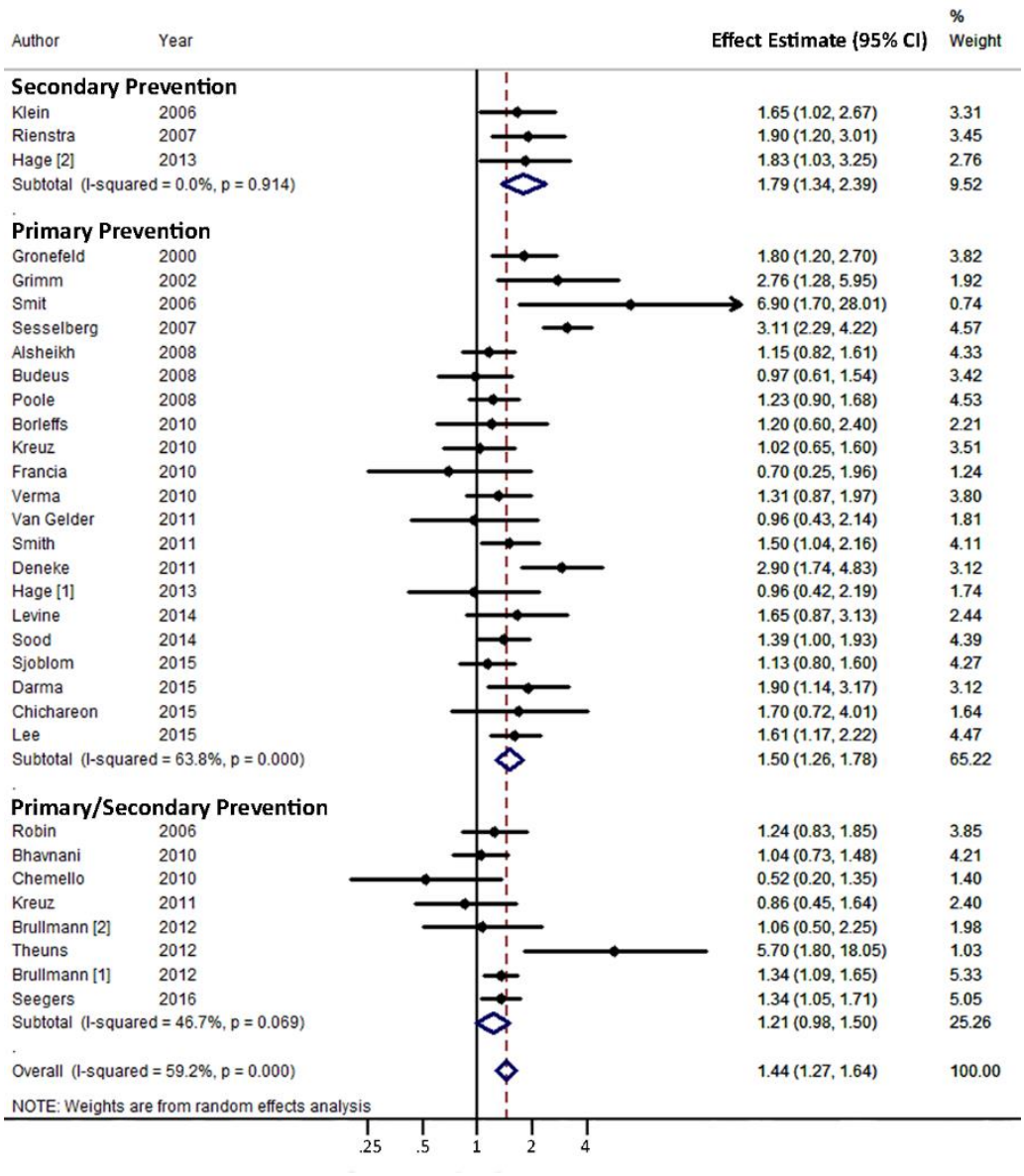
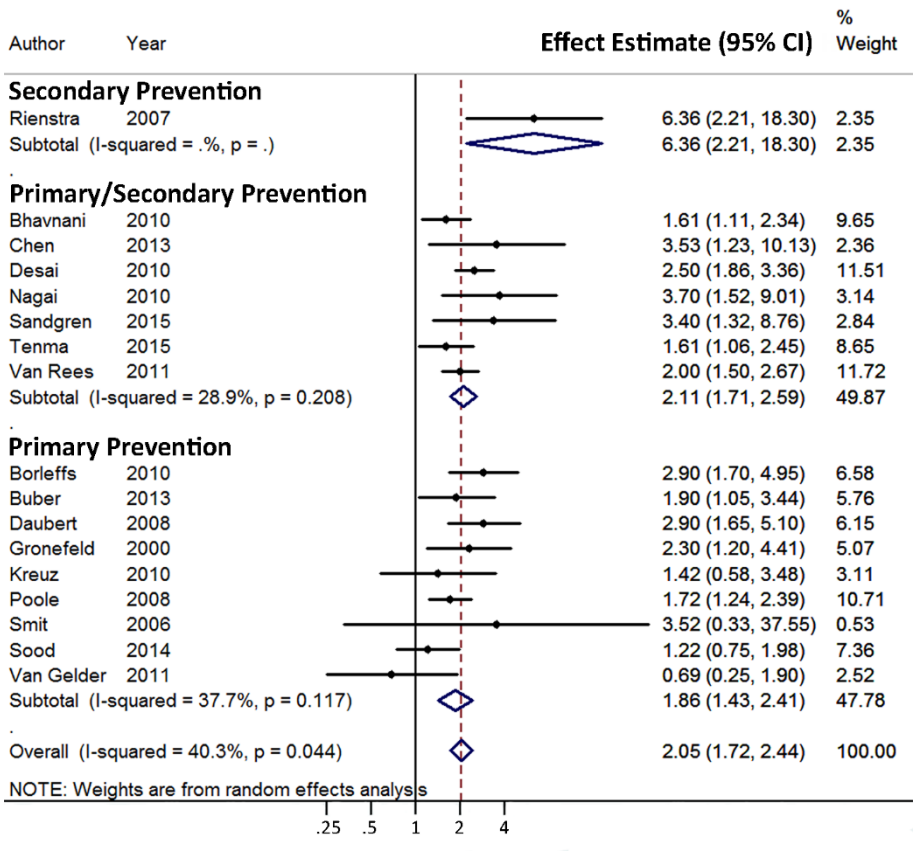


Figure 27. Subgroup analysis for inappropriate shocks performed based on prevention type



Cumulative meta-analysis for the year of publication showed an apparent effect consistency over time (Figures 28-29); meta-regression analyses using the baseline risk, age, and follow-up duration as covariates showed no statically significant results.

Figure 28. Cumulative meta-analysis for appropriate therapies (year of publication, betas presented)

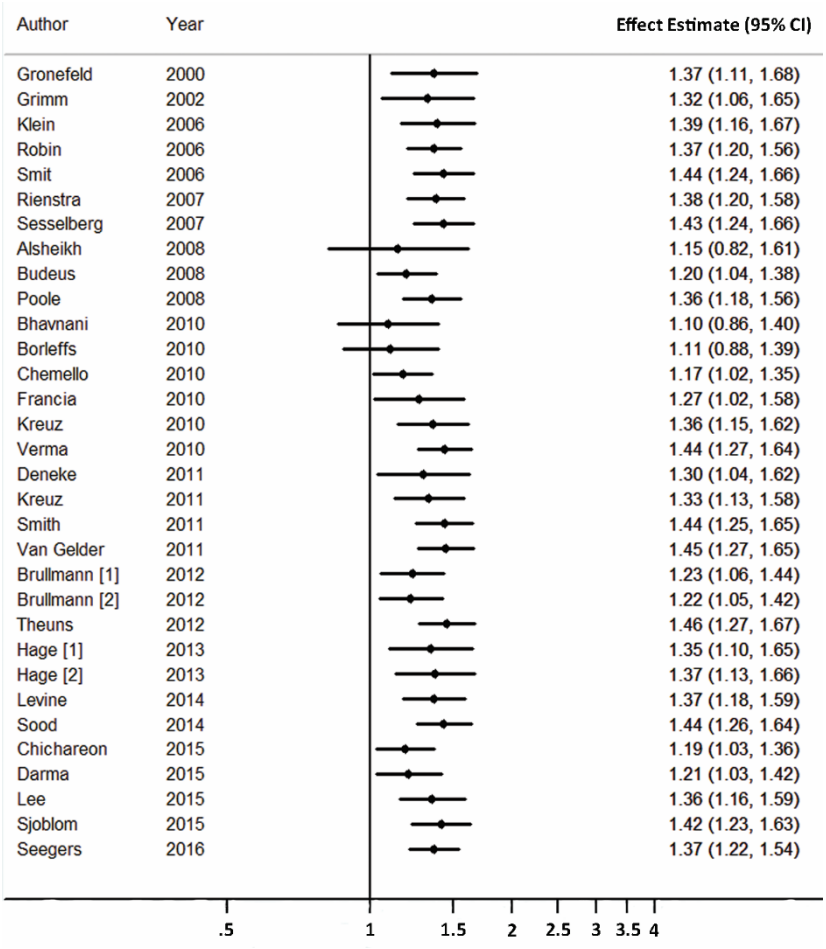
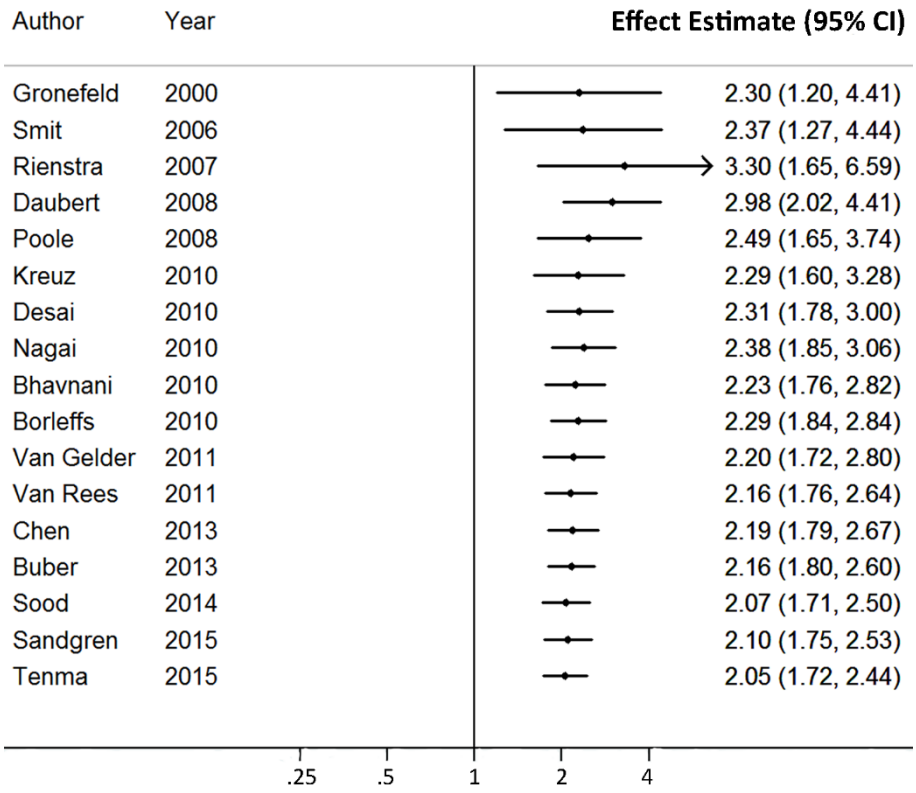


Figure 29. Cumulative meta-analysis for inappropriate shocks (year of publication, betas presented)



1.3 Discussion

In the present systematic review and meta-analysis of the currently available evidence base, we comprehensively assessed in a structured and unbiased fashion the putative association between prevalent AF and the three most important clinical outcomes (all-cause mortality, appropriate and inappropriate ICD interventions) in HF patients with an ICD implanted either for primary or for secondary prevention of SCD. We assessed 62 published study reports on 63 populations with 2011 as the median publication year, a median sample size of 388 participants per study, and almost half of the included studies assessing the association prospectively or within a nested RCT framework. The assessed studies included populations with HFrEF of diverse underlying HF etiology, and an ICD, while studies with exclusive use of CRT-D were excluded. Overall, across >200,000 study participants and at least 17,000 deaths, 2,000 appropriate ICD therapies, and 800 inappropriate shocks, we observed that AF, with a median prevalence of 26% in the scrutinized populations, was significantly associated with all studied patient-important clinical outcomes. No statistically significant moderators or modifiers were identified among the clinical attributes considered or study-level

characteristics, apart from a contribution of CRT-D to all-cause mortality in relation to AF. The negative impact of prevalent AF on all-cause mortality has been demonstrated in previous meta-analyses assessing either the general population (88) or HF patients (123, 341); an increase of about 40-50% and 30-40% in mortality in the general population and HF patients respectively has been previously reported (88, 102, 123, 341). These findings are consistent with the present meta-analysis which is the only available so far focusing exclusively on HFrEF patients with an ICD. At the individual study level, studies that assessed the independent effect of AF on mortality in HF patients yielded controversial results; some studies showed an independent deleterious effect of AF on mortality (94, 342) while others reported that AF was not independently associated with mortality but was merely a marker of HF severity (343). These controversies may be attributed to differences in population characteristics, medications used and HF disease phenotypes in these studies. Our subgroup and sensitivity analyses could not contribute to the robust identification of effect modifiers. Thus, only a meta-analysis of individual patient data could further alleviate this knowledge gap. Although we postulate that our population of HFrEF patients with ICD would be at higher risk for SCD than other HFrEF patients, cause-specific mortality could not be assessed due to data unavailability. A recent wider-scope meta-analysis demonstrated a significantly increased risk of SCD in AF patients with various types of cardiovascular disease and in the general AF population (102). A recent meta-analysis analyzed the all-cause mortality and appropriate shock therapy among AF and sinus rhythm patients who received ICD for either primary or secondary prevention and all-cause mortality among AF patients with ICD versus guideline directed medical therapy (344). Specifically, the authors showed that AF patients with ICD had significantly higher risk of all-cause mortality compared to sinus rhythm patients with ICD [OR: 1.89 (1.65–2.15), $p<0.001$] (344). However, the most interesting finding of the study was that all-cause mortality rates of AF patients that were treated with guideline directed medical therapy (while they had an indication for ICD implantation) was comparable with AF patients with an ICD implanted [OR: 0.70 (0.46–1.07), $P=0.10$] (344). Furthermore, the presence of AF was found to significantly associated with higher risk of appropriate ICD interventions [OR: 1.77 (1.47–2.13), $p<0.001$] (344). Analysis of patients in the AVID trial showed that AF/ atrial flutter is a significant independent risk factor for increased mortality in patients presenting with ventricular tachyarrhythmias (345). The possible reasons of the adverse impact of AF could be: development and progression of HF, treatment with

antiarrhythmic drugs (proarrhythmic effect), thromboembolic events while the increased incidence of ventricular arrhythmias in AF patients can be attributed to shared risk factors, increased sympathetic tone, and hemodynamic changes (344).

Incident ICD therapies (appropriate and inappropriate) in HF patients have been associated with worse prognosis (216, 346, 347). The present meta-analysis is the first to propose that AF confers an increased risk for both appropriate (i.e. 45%) and inappropriate (i.e. 113%) ICD therapies in HFrEF patients. The available evidence on the association of AF and appropriate ICD therapies is characterized by controversy; half of the studies included in this meta-analysis had demonstrated a lack of association, while the remaining half had shown a statistically significant association. This was even further accentuated in an analysis including studies with adjusted data on appropriate ICD therapies. Whether AF may be related to a ventricular pro-arrhythmic effect or to a worse HF patient profile that may be accompanied by increased incidence of ventricular arrhythmias and ICD interventions has not been clarified. It has been suggested that AF may facilitate the induction of ventricular arrhythmias through various mechanisms including a reduced ventricular refractoriness due to rapid ventricular rate (348), the presence of short-long-short sequences caused by the inherent irregularity of the cardiac rhythm (349), other hemodynamic changes or increased sympathetic tone. Also, irregular ventricular depolarization increases heterogeneity of repolarization and susceptibility to ventricular arrhythmias. More importantly, the effect magnitude of the association between mortality and AF in HFrEF patients with ICD is similar to that of the association between appropriate ICD interventions and AF. Despite the similar numbers in relative risk reduction for these two outcomes, the absolute rates of mortality and appropriate ICD therapies in populations in whom both outcomes were studied, were quite different (73, 323, 350). Whether this may partly explain the increased mortality rate associated with AF in this population is not known due to lack of available data.

In the assessed evidence base, there appears to be consistency among studies assessing the association of AF with an increased risk of inappropriate ICD shocks. This increased risk of inappropriate interventions associated with AF appears to be greater compared to the mortality risk associated with AF both in the pooled analysis and at the individual study level. This is also reflected on the absolute rates of mortality and inappropriate ICD therapies reported in previous studies (230, 351-353). Inappropriate therapies, irrespectively of the cause, have been previously shown to be

related to increased mortality (216, 217, 230, 354). Repetitive cardiac injuries following therapies especially in patients with very low cardiac function could be detrimental (355, 356) and may be a pathophysiological substrate underlying the suggested association of inappropriate therapies and mortality in AF patients. However, there has been no evidence of a direct link between the increasing inappropriate ICD therapies due to AF and the increased mortality in AF patients; only a single study has demonstrated that inappropriate shocks triggered by AF were significantly associated with a worse prognosis compared with shocks caused by lead failure (323).

During the current effort, we examined various parameters defined a priori as potential effect modifiers. No statistically significant differences between subgroups or statistically significant results in the performed meta-regression analyses were observed, apart from the CRT-D. The effect of AF on mortality appeared to be significantly lower in studies that included fewer patients with CRT-D (27% vs 55% relative effect reduction). Differences in population, such as a lower risk profile in non-CRT patients may explain these differences. Furthermore, the presence of AF in patients with CRT may cause less efficient biventricular pacing, reduce the expected benefit and increase the relative mortality risk. Separate consideration of ATP and ICD shocks, as well as, the identification of incident AF, are only a few of the various other important clinical parameters that were not included in the assessed studies and could play an important role in unraveling effect differences based on patient characteristics.

Assuming that the observed effect related to the history of AF is true, AF prevention rises as a strategy of importance in HFrEF patients with ICD. Antiarrhythmic medications and CA of AF could assist the effort to maintain SR in ICD recipients and thus prevent the occurrence of ICD interventions (357). Most recently, in a randomized controlled trial assessing a population of HFrEF with an ICD, treatment of AF with CA vs. amiodarone achieved a lower rate of AF occurrence and a significant decrease in mortality (358). On the other hand, strategic ICD programming in patients with a history of AF may reduce appropriate and inappropriate ICD shocks (359). Modern ICD devices have implemented enhanced discrimination algorithms and new strategies for arrhythmia detection and management that have been shown to reduce the incidence of inappropriate shocks (235, 236, 318, 347, 360).

1.4 Limitations

We acknowledge that due to the nature of the clinical research question posed and the assessment of AF as the exposure under study, randomized evidence could not be included in our evidence base. However, of the available observational evidence, a substantial proportion pertained to either prospective cohort studies or RCT-nested studies; moreover, we detected no inconsistencies among various study types. Exposure definition was not clearly reported in the included studies; the process of AF ascertainment was frequently omitted from the published reports and information of the type of AF was missing from the majority of the studies. Data unavailability was also an important limitation regarding our subgroup, sensitivity and meta-regression analysis. The main reason of the data unavailability can be attributed to the fact that most of the included studies were designed to answer a different clinical question than the measured outcome. However, this shortcoming is common in all evidence synthesis approaches and can only be tackled through a meta-analysis of individual participant data. Information bias, including publication bias and selective reporting bias, is another concern when dealing with clinical data. Despite the fact that selective reporting can never be excluded, funnel plots and selective reporting diagnostics did not raise substantial concerns.

1.5 Conclusions

In the present systematic review and meta-analysis of the currently available evidence base, history of AF was associated with a worse prognosis in HFrEF patients with an ICD implanted either for primary or secondary prevention. Patients with a history of AF had a higher risk of all-cause mortality, appropriate ICD interventions and inappropriate ICD shocks. These findings appeared to be consistent irrespective of study- or patient-related characteristics, except for the use of CRT-D; the effect of AF on mortality appeared to be significantly lower in studies that included fewer patients with CRT-D. Further research is needed to prove whether AF may have an independent harmful effect on HF prognosis or may simply be a marker of advanced HF. Towards that end, better characterization and detailed phenotyping of HF patients with an ICD is needed; this approach would allow identification of HF patients who would benefit from close surveillance of AF prevention and probably also aggressive rhythm control.

2. Clinical question 2: Patients with HFrEF and an ICD implanted either for primary or for secondary prevention; is there an association between appropriate/inappropriate ICD therapies with all-cause mortality?

2.1 Methods

In order to answer the above clinical question we used the methodology of meta-analysis (333).

2.1.1 Search Strategy

We systematically searched MEDLINE (by using PubMed Web-based search engine) until 30 September 2017, without year or language restriction or any other limit. We used the keyword "defibrillators". Furthermore, the reference lists of all included studies were searched to trace more relevant articles, and the relevant review articles and their references were checked.

2.1.2 Study Selection

We included studies of HF patients who received an ICD either for primary or secondary prevention, and also provided adjusted data about the association between ICD interventions and all-cause mortality. ICD interventions were defined as ATP or shocks. An appropriate ICD intervention was defined as an ICD discharge which occurred because of a fatal arrhythmia (VF or VT); an inappropriate ICD intervention was defined as an ICD discharge occurring for a reason other than VT or VF. Two criteria were used to classify HF patients: mean EF <40% and cardiomyopathy (the presence of ischemic cardiomyopathy, DCM or valvular heart disease was present in more than 85% of the total population).

Exclusion criteria included: i) patients <18 years old; ii) no HF patients meeting the above criteria; iii) only CRT or CRT device patients; iv) electrical storm; v) unacceptable definition of appropriateness of the ICD treatments; vi) studies which provided unadjusted data only.

2.1.3 Data Extraction

The information extracted from each study included: i) publication details (first author's last name, journal, year of publication); ii) general characteristics of the study (country of origin, study design, single or multi-center, enrollment period, follow-up duration, number of patients included); iii) characteristics of the study population (age, gender, type of cardiomyopathy, LVEF, NYHA HF classification, history of AF, QRS

duration, type of CRT device, mean GFR, mean creatinine level); and iv) the results reported in the study (adjusted HR or RR with 95% CI) regarding the impact of ICD interventions on all-cause mortality in HF patients.

2.1.4 Statistical Analysis

Data were analyzed using Review Manager software (RevMan, version 5.3; Oxford, UK). An adjusted HR or RR for the impact of ICD interventions on all-cause mortality was used in the analysis. Moreover, we performed a separate analysis for the impact of ATP on all-cause mortality in HF patients.

The statistical heterogeneity of the study was assessed using the I^2 index. We considered low, medium, and high heterogeneity to have approximate values: 25% (I^2= 25), 50% (I^2= 50), and 75% (I^2= 75), respectively (361). Funnel plots were constructed using RevMan software to assess publication bias. Random effect models were utilized in the analysis because they provide a more conservative estimate of the overall results. Funnel plots showed no significant publication bias.

2.1.5 Quality Assessment

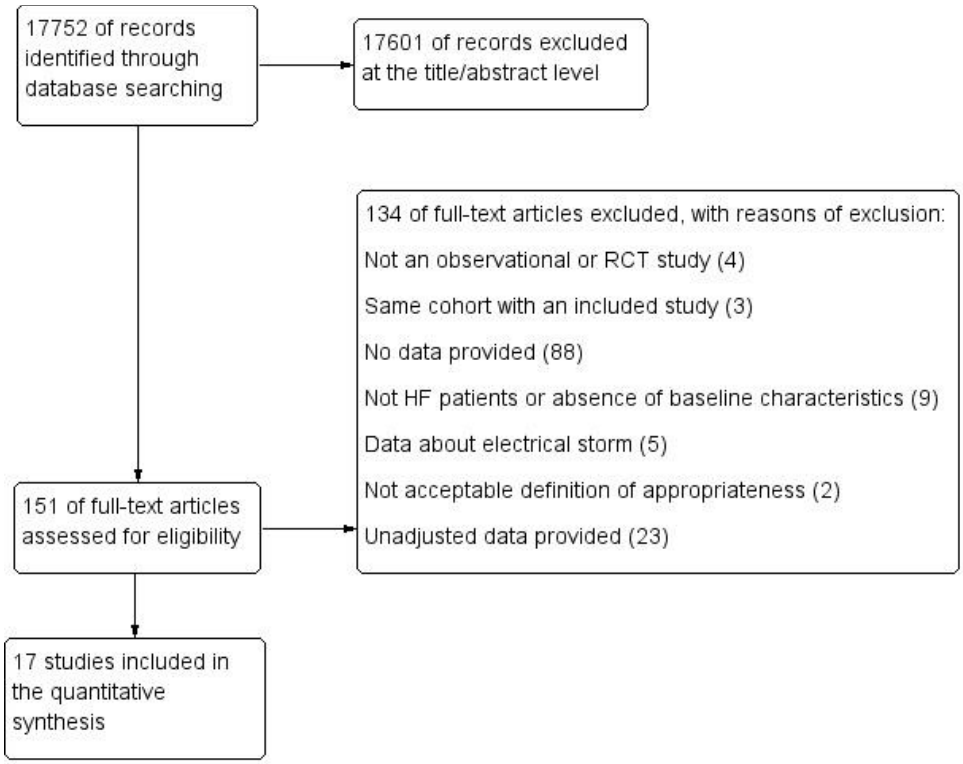
The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the included studies (362). The NOS point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: a) representation of the exposed cohort; b) selection of the non-exposed cohort; c) ascertainment of exposure; d) demonstration that outcome of interest was not present at the start of study; e) comparability of cohorts based on study design or analysis; f) assessment of outcomes; g) follow-up periods that were sufficiently long for outcomes to occur; and h) adequacy of follow-up of cohorts. This scale ranged from 0 to 9 stars, which indicated that studies were graded as poor quality if the score was < 5, fair if the score was 5 to 7, and good if the score was > 8. All included studies were graded with a score > 5.

2.2 Results

2.2.1 Search Results

Our search strategy returned 17,752 potentially relevant items (Figure 30). Of these, 17 studies (21,764 patients, mean age: 64.1 years old, 80.1% males) were included for further analysis (216, 218, 230, 311-324).

Figure 30. Flowchart of the study



The characteristics of each included study are presented in Table 3.

Table 3. Baseline characteristics of the included studies and point estimate about the impact of ICD interventions on all-cause mortality in HFrEF patients.

Author/year/ref	No. of participants	Age (yrs, mean)	Males (%)	F/U (months, mean)	# of intervention pts (appropriate/ inappropriate)	# of deaths
Almehmadi F, 2017[3]	7020	65	79.7	60.2	1767/N/A	N/A
Bhavnani SP, 2010[17]	1245	65	76.7	26.9	128/ 104	324
Denollet J, 2013[18]	589	62.6	81	38.4 med	61/ 28	94
Kleemann T, 2012[32]	1411	66 med	80.8	36 med	N/A/ 297	144
Pedersen SS, 2010[10]	371	57.7	79.5	20.4	70/ N/A	25
Poole JE, 2008[20]	811	61	77.2	45.5 med	182/ 141	173
Stabile G, 2013[21]	139	66	77	63	41/ 26	30/ 130
Tandri H, 2006[22]	1382	62	76	70	421/ N/A	792
Van Rees JB, 2011[23]	1544	61	79	41	N/A / 204	298
Van den Broek KC, 2011[24]	591	62.7	80.7	38.3	63/ 30	96
Verma A, 2010[25]	421	68	82	25	79/ N/A	46
Weeke P, 2013[26]	1609	65.2	84.2	22.8	126/ 41	194
Streitner F, 2013[27]	561	68.6	82.9	55.4	74/ 22	136
Larsen GK, 2011[28]	425	64 med	99	41 med	N/A	171
Daubert JP, 2008[29]	719	64	84.4	20	101/ 83	96
Brullmann S, 2012[30]	936	62 med	84.5	43	393/ N/A	214
Sood N, 2014[31]	1790	64.4	75.2	39.6	198/95	189

List of abbreviations: F/U: follow-up, N/A: not available, med: median, yrs: years

2.2.2 Quantitative Synthesis

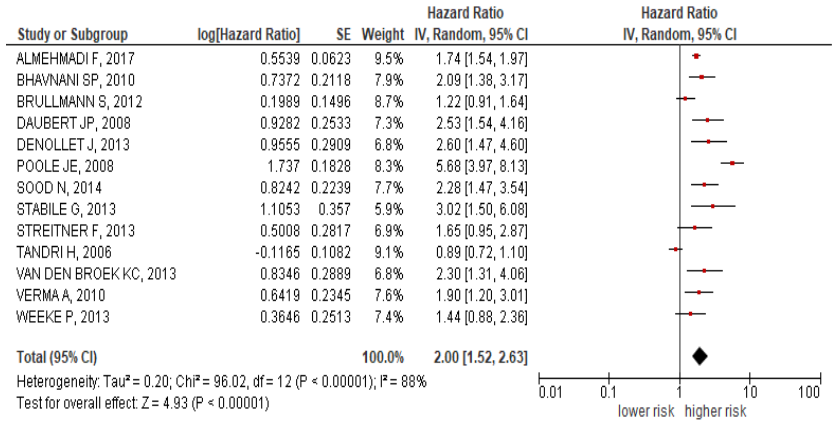
Our search retrieved 13 studies with data regarding the impact of appropriate ICD interventions on all-cause mortality. We found that appropriate ICD interventions (ATP or shocks) were significantly associated with all-cause mortality in HF patients [HR 2.00 (95% CI (1.52-2.63), p<0.01, I^2 88%] (Figure 31A). Furthermore, the quantitative synthesis of 9 studies showed a statistically significant association between inappropriate ICD interventions and increased all-cause mortality [HR 1.30 (95% CI (1.07-1.58), p<0.01, I^2 26%] (Figure 31B).

We found only 2 studies including data on any ICD intervention (appropriate or inappropriate), with a meta-analysis showing a 2-fold increase on all-cause mortality [HR 1.98 (95% CI (1.04-3.78), p=0.04, I^2 55%] (Figure 31C). Additionally, 3 studies which included data for both ICD interventions (appropriate and inappropriate) showed a significant association with all-cause mortality [HR 5.93 (95% CI (2.70-13.03), p<0.01, I^2 74%] (Figure 31D).

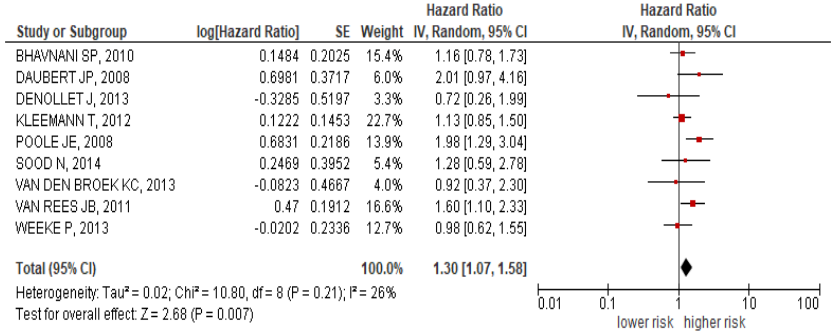
By including only studies that reported data about the impact of appropriate ICD shocks, we showed that ICD shocks were associated with a higher risk of mortality when compared to appropriate ICD interventions [HR 2.24 (95% CI (1.70-2.95), p<0.01, I^2 83%] while inappropriate ICD shocks showed similar results to inappropriate ICD interventions [HR 1.36 (95% CI (1.14-1.62), p<0.01, I^2 33%].

Interestingly, our data did not show a significant association with all-cause mortality in patients who received either appropriate ATP [HR 1.27 (95% CI (0.80-2.02), p=0.30, I^2 62%] (Figure 32A) or inappropriate ATP [HR 1.01 (95% CI (0.49-2.07), p=0.98, I^2 46%] (Figure 32B).

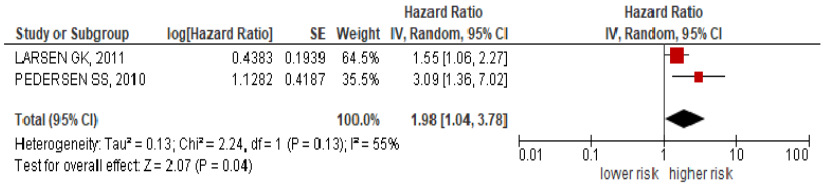
Figure 31 A. Effect of appropriate ICD interventions on all-cause mortality. B. Effect of inappropriate ICD interventions on all-cause mortality. C. Effect of any ICD interventions (appropriate or inappropriate) on all-cause mortality. D. Effect of both ICD interventions (appropriate and inappropriate) on all-cause mortality.



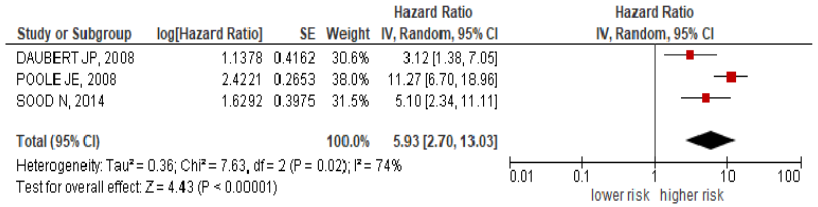
A



B

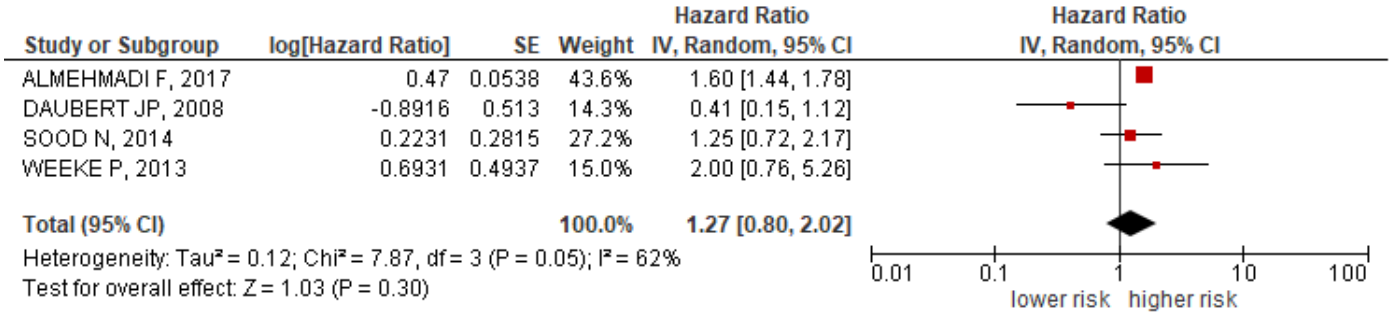


C

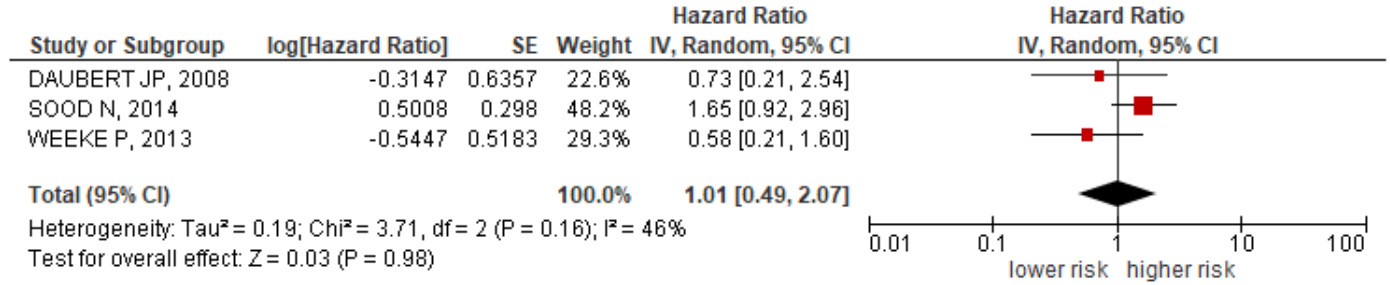


D

Figure 32. A. Effect of appropriate ATP on all-cause mortality. B. Effect of inappropriate ATP on all-cause mortality.



A



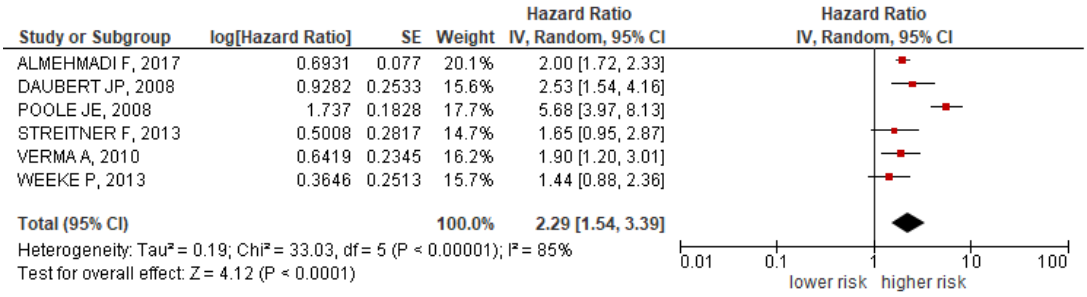
B

2.2.3 Subgroup Analysis

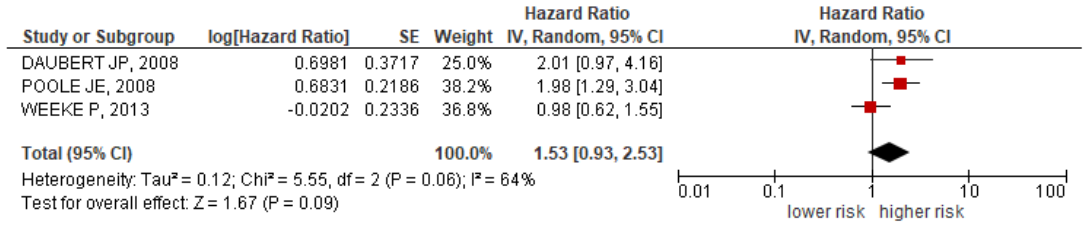
2.2.3.1 Primary Prevention Patients

Our search retrieved 6 studies with data for patients who received an ICD for primary prevention. We found that appropriate ICD interventions in that population were significantly associated with all-cause mortality [HR 2.29 (95% CI (1.54-3.39), p<0.01, I^2 85%] (Figure 33A). By contrast, patients who received inappropriate ICD interventions did not show a significant association with mortality [HR 1.53 (95% CI (0.93-2.53), p=0.09, I^2 64%] (Figure 33B). In addition, patients who received both appropriate and inappropriate ICD interventions had a 6-fold higher risk of mortality [HR 6.17 (95% CI (1.76-21.67), p=0.005, I^2 85%] (Figure 33C). Appropriate and inappropriate ATP were not significantly associated with all-cause mortality.

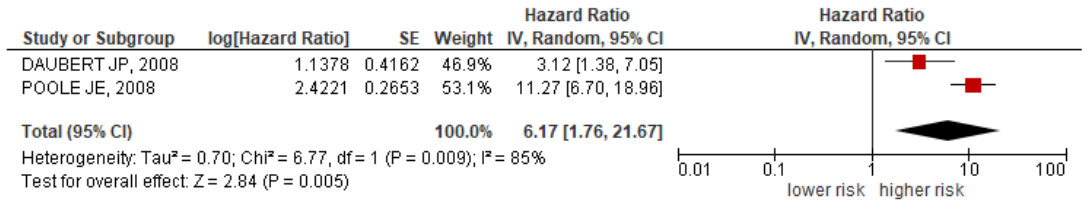
Figure 33. Primary prevention patients. A. Effect of appropriate ICD interventions on all-cause mortality. B. Effect of inappropriate ICD interventions on all-cause mortality. C. Effect of both ICD interventions (appropriate and inappropriate) on all-cause mortality.



A



B



C

2.3 Discussion

Our data showed a significant positive association between ICD interventions or shocks and all-cause mortality in patients with HFrEF. It should be noted that the association between ICD shocks and mortality does not prove causation and the results should be interpreted in this context. However, ATP, whether appropriate or inappropriate, was not a significant factor associated with all-cause mortality.

Human and experimental studies have demonstrated the causative role of ICD shocks in myocardial injury (219, 363). Moreover, ICD shocks were shown to transiently impair cardiac function and hemodynamics, especially in patients with impaired systolic function (364). Blendea *et al*. showed that troponin-T elevation after ICD discharge was an independent risk factor for all-cause mortality (223). Renal artery and coronary stent thrombosis after inappropriate shocks have also been reported (365, 366).

A recent meta-analysis which included HF patients showed a significant increase in all-cause mortality rates in patients who received inappropriate [HR 1.55 (1.29 - 1.86)] or appropriate shocks [HR 1.84 (1.43- 2.35)] compared to "no shock" patients (367). Furthermore, the mortality risk associated with appropriate shocks was not significantly different ($P > 0.20$) from the mortality risk associated with inappropriate shock (367).

A recent study including 69,000 ICD patients showed that mortality rates were higher in ICD patients who received only ATP compared to no therapy, while ICD patients who received a shock had a higher mortality compared to both groups (368). Larsen et al. showed that patients who received ATP therapy only had no significant increase in the risk of death compared with no therapy patients [HR 0.73 (0.34–1.57)] (319). However, the same study showed a significant increase in the risk of death in patients who received shocks only compared with those patients who did not receive shocks [HR 1.55 (1.07 - 2.23)] or did not receive any ICD treatment [HR 1.55 (1.06 - 2.26)] (319). Similar results were demonstrated by a MADIT II post-hoc analysis (320).

Interestingly, data from a large registry suggest that age, gender, device type, atrial fibrillation burden, and rate of arrhythmia do not change the trend of higher mortality in patients receiving ICD shock compared to ATP alone (368). However, the negative impact of shocks can be influenced from baseline characteristics. For example, Bhavnani *et al*. showed that recipients with EF ≤ 35% who received appropriate shocks had a lower all-cause mortality [HR 1.66 (1.17 - 2.30)] than those who had EF > 35%

who received appropriate shocks [HR 4.11 (1.69 - 10.03)] (311). Additionally, Streitner *et al*. showed that primary prevention patients with ischemic cardiomyopathy who received appropriate shocks had a significant increase in all-cause mortality [HR 1.99 (1.12 - 3.54)], while patients with DCM who received appropriate shocks revealed no significant association on all-cause mortality [HR 0.94 (0.32 - 2.8)] (218). However, a recent study showed that the occurrence of appropriate ICD shock or ATP in patients with secondary prevention ICDs was associated with similar magnitudes of mortality risk as those with primary prevention ICDs (324).

Furthermore, the type of causative arrhythmia (VT or VF) was shown to play a key role in the increased risk of death. ICD patients who received a shock for monomorphic VT had an increased risk of death [HR 1.35 (1.01 - 1.81)] compared to those who received a shock for polymorphic VT or VF (369). Moreover, the factor causing the inappropriate ICD intervention can influence the risk of death in patients. Kleemann *et al*. showed that inappropriate shocks resulting from AF were independently associated with a worse prognosis [HR 1.44 (1.03 - 2.03)] (323). By contrast, shock deliveries caused by lead failure were not associated with an increased mortality [HR 0.99 (0.55 - 1.80)] (323). Additionally, the ALTITUDE study showed that only shocks for AF/atrial flutter were associated with an increased risk of death [HR 1.61 (1.17 - 2.21)] since there was no significant difference in survival for patients who received a shock for sinus tachycardia/supraventricular tachycardia [HR 0.97 (0.68 - 1.37)], noise/artifact/oversensing [HR 0.91 (0.50 - 1.67)], or non-sustained arrhythmias [HR 2.17 (0.86 - 5.70)] compared to the no shock group (369). Bhavnani *et al.* also showed that shocks for induced arrhythmias at the time of noninvasive electrophysiology study have also been compared to appropriate shocks for VT/VF, and were not associated with an increased risk of mortality (311). These findings indicate that appropriate and inappropriate shocks are markers of sicker patients with more co-morbidities rather than the cause of the worse prognosis in these patients. This aspect may also be supported by the results of the Shockless Implantation Evaluation (SIMPLE) trial which showed that defibrillation testing had no impact on the measured outcomes (370).

2.4 Limitations

The included studies in this meta-analysis were observational while two of them had a retrospective design. Furthermore, we included only studies with adjusted data about the measured outcome. Studies that sought for independent predictors of mortality using multivariate analysis but provided no adjusted data for ICD interventions because of non-significant results in univariate analysis, were excluded. Therefore, our results may have overestimated the measured outcome. Moreover, most of the included studies did not provide enough data about significant clinical parameters of the studied population and therefore our results may have been influenced by unmeasured confounders. The observed heterogeneity in our analyses was not assessed with a meta-regression analysis to identify potential effect modifiers while the small number of the included studies and the mixed populations that were included did not permit a subgroup analysis based on the indication of ICD implantation (primary versus secondary prevention) or the percentage of patients with a CRT-D implanted. These factors may have significantly modified the effect estimate. Furthermore, we could not assess the impact of ICD interventions based on the cause of intervention (monomorphic/polymorphic VT, fast/slow VT or VF for appropriate ICD interventions and atrial tachyarrhythmias, artifacts, lead problems etc for inappropriate ICD interventions). Recent data suggest that the cause of intervention may have an impact on the association of ICD interventions with all-cause mortality (371). Specifically, it was found that fast ventricular arrhythmias is a marker for increased mortality rather than ICD therapy (ATP or shock) directly contributing to increased risk. Furthermore, ICD shocks or ATP were not associated with increased mortality if rendered for slow ventricular arrhythmias and supraventricular tachycardia (371). Moreover, the number of ICD interventions may modify the association between ICD interventions and mortality.(372) However, we could not proceed with subgroup analysis regarding the number of ICD interventions because of lack of data in the included studies.

As a result, our findings should be interpreted with caution mainly because the cause of ICD interventions and the number of interventions were not further examined.

2.5 Conclusions

In conclusion, appropriate and inappropriate ICD interventions or shocks were significantly associated with increased mortality in patients with HFrEF, although such an association was not found for ATP therapies. Further research is needed to

investigate whether shocks (appropriate and/or inappropriate) are the cause of the worse prognosis or only indices of greater HF severity and worse overall health in these patients.

3. Clinical question 3: HF patients undergoing AF catheter ablation procedure; could we identify predictors of AF recurrence?

3.1 Methods

Our study included HF patients with EF< 50% who underwent AF catheter ablation at our department between January 2010 and March 2017. The patients were anticoagulated using acenocoumarol with a target international normalized ratio of 2.0–3.0 or direct oral anticoagulants at least 4 weeks before and 3 months after the procedure. All patient underwent echocardiography exam before the ablation procedure. The LVEF was estimated with both visually estimation and quantitative biplane Simpsons measurements. CA was performed under intravenous sedation with midazolam and remifentanyl by two experienced operators (M.E. and K.P.L). Following a single transseptal puncture, the three-dimensional geometry of the left atrium was reconstructed using the CARTO 3 navigation system (Biosense Webster, Inc., Diamond Bar, Calif., USA). Wide circumferential lesions for isolation of large atrial areas around both ipsilateral PVs (PV antral isolation) were applied using a 3.5-mm tip ablation catheter (Thermo Cool Navi-Star, Biosense Webster, Inc., Diamond Bar, Calif., USA). Circumferential ablation was performed on the posterior wall >2 cm and on the anterior wall >5 mm away from the defined PV ostia. The endpoint of ablation was the absence or dissociation of potentials in the isolated area as documented with the circular mapping catheter (Lasso, Biosense Webster, Inc., Diamond Bar, Calif., USA). When PV conduction was still present following wide circumferential lesions around both ipsilateral veins, both PVs were mapped sequentially by the circular mapping catheter to localize the earliest PV potentials. Based on the earliest PV potentials recorded by the circular mapping catheter, RF energy was reapplied to close the conduction gap. If we could not terminate AF to SR or AT after wide circumferential PV-LA junction ablation, we ablated all the low-voltage areas (<0.4 mV) annotated during high density mapping which had at least one of the interesting aforementioned electrograms. Our goal was AF termination defined as conversion to SR or a stable AT (373) and to eliminate all these areas having fractionation, activation gradient, firing and dispersion of fractionation. We performed linear ablation only when AF converted into mitral, roof or right isthmus flutter. A bidirectional block across linear lesions was verified by established criteria (374, 375). If the mechanism of AT was localized reentry, we mapped and ablated the critical

isthmus of the reentrant tachycardia (376). At the end, if we could not terminate AT to SR, we performed electrical cardioversion.

3.1.1 Post-ablation care and follow-up

Patients were hospitalized for the next 24hrs after CA. After ablation procedure, all patients were submitted to transthoracic echocardiography in order to exclude pericardial effusion. Oral anticoagulants were administered 3 hours after CA and continued for 2 months or longer, based on CHA2DS2-VASc score. Antiarrhythmic drugs, except amiodarone, were discontinued five days before the ablation procedure and were re-initiated on the next day only in patients with non-paroxysmal AF for 3 months after the procedure. Amiodarone was discontinued for 4 weeks before the procedure to allow enough time for wash out while non-paroxysmal AF patients were reloaded after the procedure. 24hrs or 48hrs Holter recordings and 12-lead electrocardiograms were performed in all patients at 1, 3, 6, 9- and 12-months post-ablation and every 6 months thereafter. In cases of symptoms occurrence (such as palpitations), patients were instructed to perform a 12-lead electrocardiogram and 24-Holter recording. Recurrence was defined as documented symptomatic or asymptomatic AF or AT episodes lasting >30 sec following the 3-month blanking period. Recurrences were treated with anti-arrhythmic drugs and/or cardioversion if needed.

3.1.2 Statistical analysis

Continuous variables were presented as mean values ± standard deviation, while categorical ones were presented as absolute and relative frequencies (percentages). Continues variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables with and without normal distribution were compared using Student's t-test or the Mann-Whitney U test, respectively. Pearson's chi-square or Fisher's exact test were used to test for any associations between two categorical variables. We examined univariate models and multivariate models with forward selection of variables per likelihood ratio criteria. Analyses were done with SPSS (version 17.0, SPSS Inc., Chicago, IL, USA) and all reported p -values are two-tailed.

3.2 Results

The study enrolled a total of 38 patients with reduced EF (< 50%) (mean age: 54.1 ± 12.2 years old, 28 (73.7%) males, mean EF: 38.2 ± 6.3%). The baseline characteristics of patients are shown in Table 4. Of the total population, 16 patients (42.1%) underwent CA for paroxysmal AF and 22 (57.9%) for non-paroxysmal AF. There were no procedure-related complications. The mean duration of the procedure was 191.6 ± 29.3 min and the mean fluoroscopy time was 16.4 ± 4.98 min.

Table 4. Baseline characteristics of the 38 patients included in this study.

Variable	
Follow-up (months)	39.05 ± 20.83
Age (mean ± SD)	54.1 ± 12.2
Males [n (%)]	28 (73.7)
BMI (mean ± SD) (kg/m^2)	29.2 ± 5.3
Type AF	
Paroxysmal [n, (%)]	16 (42.1)
Persistent [n, (%)]	22 (57.9)
Early AF recurrence [n, (%)]	6 (15.8)
Creatinine levels (mg/dl)	0.82 ± 0.23
Hypertension [n, (%)]	20 (52.6)
Diabetes mellitus [n, (%)]	8 (21.1)
Dyslipidemia [n, (%)]	8 (21.1)
Coronary artery disease [n, (%)]	8 (21.1)
Duration of history of AF (years)	5.0 ± 4.45
MEDICATIONS	
AADs before AF ablation	
Amiodarone [n, (%)]	8 (21.1)
b-blockers [n, (%)]	36 (94.7)
AADs after AF ablation	
Amiodarone [n, (%)]	4 (10.5)
b-blockers [n, (%)]	18 (47.4)
Anticoagulation	
Acenocoumarol	20 (52.6)
Dabigatran	4 (10.5)
Apixaban	6 (15.8)
Rivaroxaban	8 (21.1)
ECHOCARDIOGRAPHY	
LAd (mm)	43.6 ± 4.5
LVEF [n, (%)]	38.2 ± 6.3
IVSd (mm)	9.1 ± 1.01
LVEDD (mm)	47.9 ± 4.82
PWD	9.32 ± 0.66
PROCEDURAL CHARACTERISTICS	
Procedure time (min)	191.6 ± 29.3
Fluoroscopy time (min)	16.4 ± 4.98
Radiation dose (mGy/m^2)	2532.8 ± 1450.9

List of abbreviations

AF: atrial fibrillation; BMI: body mass index; AADs: anti-arrhythmic drugs; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LAd: left atrial diameter; LVEF: left ventricular ejection fraction; IVSd: intraventricular septum thickness at systole; LVEDD: left ventricular end diastolic diameter; PWD: posterior wall thickness

After a mean follow-up period of 38.2 ± 33.6 months (ranged from 5 to 92 months), 28 patients (73.7%) were free from late arrhythmia recurrence (Table 5). Sinus rhythm was maintained in 12 (75%) and 16 (72.7%) patients with paroxysmal AF and non-paroxysmal AF, respectively. During the blanking period, which was defined as the 3-months period after ablation procedure, 6 (15.8%) patients presented with early arrhythmia recurrence. Univariate analysis revealed that early arrhythmia recurrence during the blanking period (p=0.027) and amiodarone medication before the procedure (p=0.002) were statistically significant predictors of late arrhythmia recurrence.

Table 5. Baseline characteristics of the included patients stratified by late AF recurrence following a single catheter ablation procedure.

Characteristics	**Late recurrence**		**P-value**
	Yes (n=10. 26.3%)	**No (n=28. 73.7%)**	
Age	55.2±7.1	53.7±13.6	0.737
Male gender	10 (35.7%)	18 (64.3%)	1.00
BMI	29.5±4.0	29.1±5.7	0.856
Paroxysmal AF	4 (25%)	12 (75%)	0.875
AF duration (years)	6.0±2.58	4.64±4.94	0.412
Early recurrence	4 (66.7%)	2 (33.3%)	**0.027**
Hypertension	6 (30%)	14 (70%)	0.588
Diabetes mellitus	2 (25%)	6 (75%)	0.924
Dyslipidemia	4 (50%)	4 (50%)	0.100
Coronary artery disease	4 (50%)	4 (50%)	0.100
Medication before the procedure			
Amiodarone	6 (75%)	2 (25%)	**0.002**
b-blockers	10 (27.8)	26 (72.2%)	1.00
Medication after the procedure			
Amiodarone	2 (50%)	2 (50%)	0.279
b-blockers	2 (11.1%)	16 (88.9%)	0.067
Echocardiographic parameters			
IVSd	9.4±1.07	8.93±0.98	0.209
LVEDD	46.2±3.43	48.5±5.15	0.199
PWD	9.4±0.52	9.29±0.71	0.636
LVEF	35.2±8.57	39.29±5.04	0.087
LAd	43.4±2.55	43.71±5.08	0.848
Procedure characteristics			
Fluoroscopy time (min)	17.71±5.42	15.86±4.82	0.312
Duration of procedure (min)	220±29.81	181.43±21.72	**0.003**

Radiation dose (mGy/m^2)	3784.6±2132.9	2085.7±761.9	**0.029**

List of abbreviations

AF: atrial fibrillation; BMI: body mass index; AAD: anti-arrhythmic drugs; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LAd: left atrial diameter; LVEF: left ventricular ejection fraction; IVSd: intraventricular septum thickness at systole; LVEDD: left ventricular end diastolic diameter; PWD: posterior wall thickness.

In multivariate analysis, early arrhythmia recurrence (p=0.03) and amiodarone anti-arrhythmic drug administration (p=0.003) remained independent predictors of late arrhythmia recurrence (Table 6).

Table 6. Predictors of AF recurrence (multivariate analysis)

	OR (95% CI)	p-value
Early recurrence	13.35 [95% CI (1.29-138)]	**0.03**
Amiodarone before the procedure	26.3 [95% CI (3.01-229.2)]	**0.003**

Moreover, we performed a separate analysis to find predictors of early arrhythmia recurrence (during the blanking period) (Table 7). Univariate analysis revealed that treatment with b-blockers before or after ablation and baseline LVEF was a significant predictor of early arrhythmia recurrence. However, none of the variables that were significant in univariate analysis remained a significant predictor following multivariate adjustment.

Table 7. Baseline characteristics of the included patients stratified by early AF recurrence following a single catheter ablation procedure.

Characteristics	Early recurrence		P-value
	Yes (6, 15.8%)	No (32, 84.2%)	
Age	50±8.2	54.9±12.7	0.375
Male gender	6 (21.4%)	22 (78.6%)	0.168
BMI	32.5±4.93	28.6±5.19	0.297
Paroxysmal AF	4 (25%)	12 (75%)	0.217
AF duration (years)	5.0±3.58	5.0±4.64	0.807
Hypertension	4 (20%)	16 (80%)	0.663
Diabetes mellitus	2 (25%)	6 (75%)	0.587
Dyslipidemia	2 (25%)	6 (75%)	0.587
Coronary artery disease	2 (25%)	6 (75%)	0.587
Medication before the procedure			
Amiodarone	2 (25%)	6 (75%)	0.587
b-blockers	4 (11.1%)	32 (88.9%)	0.021
Medication after the procedure			
Amiodarone	0 (0%)	4 (100%)	1.000
b-blockers	0 (0%)	18 (100%)	0.021
Echocardiographic parameters			
IVSd	9.33±1.37	9.0±0.95	0.614
LVEDD	45.3±3.14	48.4±4.96	0.159
PWD	9.33±0.52	9.31±0.69	0.929
LVEF	28.7±4.93	40.0±4.75	<0.001
LAd	43.7±1.03	43.6±4.92	0.572
Procedure characteristics			
Fluoroscopy time (min)	17±5.37	16.2±4.98	0.687
Duration of procedure (min)	196.7±33.86	190.6±28.84	0.870
Radiation dose (mGy/m^2)	3983±2983.6	2260.9±770.3	0.261

List of abbreviations

AF: atrial fibrillation; BMI: body mass index; AAD: anti-arrhythmic drugs; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LAd: left atrial diameter; LVEF: left ventricular ejection fraction; IVSd: intraventricular septum thickness at systole; LVEDD: left ventricular end diastolic diameter; PWD: posterior wall thickness.

Subgroup analysis according to the cause of HF (ischemic vs. non-ischemic) was also performed. In our study, eight ischemic HF patients and 30 non-ischemic HF patients (valvular heart disease, DCM and hypertrophic cardiomyopathy) were included. In those with ischemic HF (mean age: 56 years old, 75% males), 4 patients (50%) had late AF recurrence whilst 4 patients (50%) remained free from arrhythmia recurrence during the follow-up period. The patients with AF recurrence were older, had longer AF duration, higher prevalence of dyslipidemia and thicker posterior wall diameter that patients without AF recurrence. By contrast, in those with non-ischemic HF (mean age: 53.6 years old, 73.3% males), six patients (20%) had late AF recurrence while 24 patients (80%) remained free from arrhythmia recurrence. There were not significant differences in baseline characteristics between the two groups.

3.3 Discussion

The main findings of the present study are that:

a) a single AF CA procedure is an effective and safe modality in HF patients with AF;
b) after a mean 3.3 years of follow-up, 73.7% of HF patients remained in sinus rhythm; and

c) early arrhythmia recurrence and the use of amiodarone before the procedure were significant predictors of arrhythmia recurrence after the blanking period.

CA, when compared to direct current synchronized cardioversion followed by amiodarone, has been associated with significantly higher one-year rates of SR maintenance and with improved cardiac function (143). Additionally, patients who underwent CA were found to have significantly lower mortality, stroke/TIA, and heart failure hospitalizations compared with patients underwent cardioversion (144). Another interesting finding is that patients with poorer cardiac function at baseline appear to benefit most from ablation in terms of cardiac function improvement at 1 year (143).

The CASTLE-AF trial included HF patients (LVEF≤35%) who underwent AF CA or conventional care. The authors showed that CA led to significant improvement in the primary composite end point of all-cause mortality and worsening HF with a relative risk reduction of 38% while LVEF increased by 8% at 5 years of follow-up in the CA group (146). Recent meta-analyses showed that CA resulted in improved LVEF, cardiac function, exercise capacity, and quality of life in HF patients with AF compared with the medical rate control strategy (148-150). Additionally, PVI improves cardiac function in patients with paroxysmal AF and impaired LVEF (155). Furthermore, in patients with HF undergoing AF ablation was found that there is an initial short-term LVEF improvement related to baseline heart rate and a log-term LVEF improvement related to the rhythm outcome (improved in SR maintenance) (156). The efficacy of CA in patients with impaired LVEF is better when it is performed early in the natural history of AF and HF (150). An interesting finding is that patients with and without left ventricular systolic dysfunction had similar risk for recurrent AF or AT after CA, but repeat procedures were required more often in those with left ventricular systolic dysfunction (157). Another study showed that PVI in HF patients was associated with improved questionnaire score at 6 months, a longer 6-minute-walk distance and a higher EF compared to patients underwent AV node ablation and biventricular pacing (158).

The success rates of CA for AF differ between published studies. This can be attributed to different procedure techniques used and the differences in the follow-up duration. For example, Bhargava et al. reported SR maintenance in 72.6% of patients (77.6% in paroxysmal AF and 67.2% in non-paroxysmal AF) after a single ablation procedure during a mean follow-up of 57 ± 17 months (138), while Weerasooriya et al. in a mixed population (paroxysmal AF and non-paroxysmal AF) reported 40%, 37% and 29% freedom of arrhythmia at 1, 2 and 5 years of follow-up respectively (140).

Interestingly, we identified different predictors of early and late arrhythmia recurrence. For early arrhythmia recurrence, they were: the use of beta-blockers before or after ablation and LVEF. By contrast, for late recurrence, they were: use of amiodarone before the procedure and early arrhythmia recurrence. In other words, none of the factors significant for early arrhythmia recurrence remained a significant predictor for late recurrence.

Moreover, early arrhythmia recurrence is a well-known predictor of late AF recurrence in both paroxysmal AF and non-paroxysmal AF patients (166, 377-380). This finding was similarly observed in our study. Early arrhythmia recurrence events occurring in the initial 2 weeks following PV antral isolation may be related to inflammation that occurs post-ablation (379). Beyond this period, early arrhythmia recurrence events, especially when multiple, probably are provoked by PV re-conduction and other pathophysiological mechanisms of AF (379). Finally, age is a significant factor which is associated with disease progression in AF (381, 382). Bunch et al. reported that age was a significant factor in determining outcomes after CA for AF (383). Furthermore, Kosiuk et al (384) with the DR-FLASH score and Letsas et al (385) with CHA_2DS_2-VASc score highlighted the importance of age as an independent predictor of arrhythmia recurrence after CA. This is partly explicable to age-related fibrosis leading to conduction abnormalities (386, 387). However, in our study, age was not differed significantly between patients with and without arrhythmia recurrence.

Our data showed that amiodarone use before ablation is an independent predictor of late AF recurrence. This finding is attributable to the progression of AF that occurs during drug trials (388). The presence of congestive HF found to be a significant risk factor for complications after CA (389). However, the existing data showed that there is no difference in the risk of complications in patients with and without HF (157). Together, all of our findings support the notion that early intervention is needed to AF due to its progressive nature.

3.4 Limitations

The present study has several limitations. Firstly, it is a small single-center study. Due to the lack of statistical power, separate analyses in patients with mid-range and reduced EF could not be performed. Secondly, although the baseline characteristics of all participants, the procedure details and the events during follow-up period were collected prospectively, the study is retrospective in nature. Thirdly, the follow-up monitoring for the detection of arrhythmia recurrence was performed via 24hrs or 48hrs Holter recordings and 12-lead electrocardiograms. Thorough methods of monitoring (loop recorders, 7-day Holter monitoring) were not applied and the percentage of recurrence may have been underestimated. Finally, the follow-up was not sufficiently long to detect the AF recurrence.

3.5 Conclusions

The main findings of this study are that a) a single AF CA procedure is an effective and safe modality in HF patients with AF, b) after a mean 3.3 years of follow-up, 73.7% of HF patients remained in SR, c) early arrhythmia recurrence was a significant predictor of arrhythmia recurrence after the blanking period.

4. Clinical question 4: HFrEF patients undergoing CRT; Is there any association of simple hematological indices with the response to CRT?

4.1 Methods

A retrospective analysis of prospectively collected data in our institution was conducted. HF patients (ischemic or dilated cardiomyopathy) referred to our hospital for CRT implantation, between January 2013 to November 2017 were screened. The inclusion criteria were: 1) NYHA class II–IV HF despite adequate medical treatment (i.e. all HF medication classes should be administered provided there were no contraindications or serious side-effects); 2) chronic left ventricular systolic dysfunction caused by ischemic or dilated cardiomyopathy (LVEF ≤ 35%); 3) QRS duration ≥130 ms; 4) SR or AF patients if after implantation a stable paced rhythm ≥ 95% was maintained; 5) LBBB and 6) comprehensive echocardiographic evaluation at baseline and 6 months follow-up. Exclusion criteria were: 1) prior pacemaker or ICD; 2) recent (< 6 months) acute coronary syndrome and/or coronary revascularization; 3) poor echocardiographic window; 4) chronic hematologic disorders or known chronic inflammatory or autoimmune disorders that may influence the hematological indices; 5) inadequate percentage of paced rhythm (<95%), 6) life expectancy of <1 year due to non-cardiac diseases and 7) major change in any life-saving medication class during follow-up.

All patients were at least 18 years old and provided written, informed consent to be included in the prospective database of the Department for further studies. The study protocol was approved by the local hospital Ethics Committee.

4.1.1 Definitions

The response to CRT was defined an increase in LVEF ≥10% or a decrease in LVESV of ≥15% at the 6-month follow-up.

4.1.2 Data collection

The following details were extracted: demographic information [age, sex, weight, height, body mass index (BMI)], clinical (type of HF, history of hypertension, diabetes mellitus and dyslipidemia, smoking habits, NYHA class, medications), electrocardiographic parameters [(QRS duration, PR duration, QTc duration, fragmentation of QRS complex)], echocardiographic parameters (LVEF, LVESV, LVEDV, left ventricular end systolic diameter (LVESD), left ventricular end diastolic

diameter (LVEDD), interventricular septum diameter (IVS), posterior wall diameter (PWD), left atrial volume (LAV) and diameter (LAD) at end-systole, right ventricular systolic pressure (RVSP)], and laboratory data [hemoglobin (Hb), hematocrit (Hct), white blood cells (WBC), platelets (PLT), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), platelet to neutrophil ratio (PNR), red blood cell distribution width (RDW), creatinine, lactate dehydrogenase (LDH), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides] of the included patients at baseline (before CRT implantation).

4.1.3 Blood samples and echocardiography

Venous blood samples were collected in the morning on the day of CRT implantation and immediately processed. Blood samples were taken into standardized tubes containing dipotassium ethylene-dinitro-tetra-acetic acid (EDTA) for complete blood count. Echocardiographic examinations were performed with GE Vivid 7 (GE Healthcare, Chalfont St. Giles, United Kingdom) during the last week before CRT implantation in a standardized manner LVEDV, LVESV, LVEF and LAV were calculated by a modified Simpson biplane method from apical imaging planes. LAD was measured in the parasternal long-axis view.

4.1.4 Device implantation

All devices were implanted by experienced operators. All patients received a CRT device in combination with a cardioverter defibrillator. The implantation was performed transvenously by using the left subclavian route. A coronary sinus venography was routinely obtained before the introduction of the LV lead which was preferably inserted into the lateral or postero-lateral branches of the coronary sinus. The right atrial and right ventricular leads were implanted at the atrial appendage and at the apex, respectively. Optimization of AV interval was performed by an experienced cardiologist using Doppler echocardiographic measurements of transmitral flow. For patients with permanent AF, biventricular pacing was ensured by optimization of drug therapy in order to obtain permanent ventricular pacing, or by radiofrequency ablation of the AV junction.

4.1.5 Long-term follow-up

After hospital discharge, patients were regularly followed-up at 6 months post-implantation. The primary outcomes included all-cause mortality, hospitalizations for

HF, and assessment of LVEF and LVESV to establish the CRT responders. VT episodes (> 3 QRS complexes with a rate >100 beats per minute) were defined as a secondary outcome.

4.1.6 Statistical analysis

Data were analyzed on Prism (Version 6.0, GraphPad, CA, USA) and IBM SPSS Statistics (Version 24, IBM Corp., NY, USA). Continuous variables were reported as mean ± standard deviation (SD) and Boolean variables as proportions. Univariate analyses were conducted for CRT response (all patients, DCM subgroup and ischemic cardiomyopathy subgroup), VT, hospitalizations for HF, and all-cause mortality. For continuous variables, normal distribution was assessed by Shapiro-Wilk's test, and the unpaired independent samples t-test with Welch's correction or Mann-Whitney U test was applied as appropriate. Fisher's exact test (two-tailed, alpha<0.05) was used for dichotomous variables. The chi-squared test for trend (linear by linear) was used for MR at baseline. Variables that provided p-value <0.05 were further evaluated in multivariate analyses using binomial logistical regression. Linear regressions were run to understand the effects of haematological indices on change in LVESV and change in LVEF.

4.2 Results

Our cohort consisted of 48 patients (mean age: 66.2±9.5 years, 81,3% males). HF had an ischemic etiology in 29 (60.4%) while DCM was the cause in 19 (39.6%) patients. All patients were followed-up for six months. Baseline characteristics of the included patients are shown in Table 8.

Table 8. Baseline and follow-up data of the study population

		Non-responders to CRT [n=11 (22.9%)]	**Responders to CRT [n=37 (77.1%)]**	**p-value**
Characteristics				
Age (years)		59.7 ± 8.9	68.1 ± 8.9	**0,01**
Males		11 (100)	28 (75.7)	0,10
BMI (kg/m^2)		27.0 ± 3.8	26.3 ± 2.7	0,58
QRS width (ms)		155.9 ± 13.2	146.5 ± 16.9	0,07
HF type	Ischemic CMP	4 (36.4)	25 (67.6)	0,09
	Dilated CMP	7 (63.6)	12 (32.4)	
Echocardiographic parameters at baseline				
LVEF (%)		26.4 ± 4.1	26.8 ± 4.9	0,78
LVESV (mL)		181.5 ± 51.6	158.9 ± 40.2	0,20
LVEDD (mm)		69.0 ± 7.0	64.5 ± 6.2	0,07
LVESD (mm)		59.0 ± 7.9	55.5 ± 6.8	0,20
LVEDV (mL)		257.8 ± 47.6	224.3 ± 51.6	0,06
LA diameter (mm)		47.9 ± 3.9	44.7 ± 4.1	**0,03**
LA volume (mL)		94.1 ± 16.3	79.0 ± 19.1	**0,02**
PASP (mmHg)		39.2 ± 5.7	36.6 ± 13.0	0,37
MR	No MR-1+/4+	3 (27.3)	21 (56.8)	0,23
	2+/4+	7 (63.6)	12 (32.4)	
	3+/4+	1 (9.1)	4 (10.8)	
Medications				
ACEIs/ARBs		10 (90.9)	33 (89.2)	1,00
BBs		11 (100)	35 (94.6)	1,00
MRAs		10 (90.9)	34 (91.9)	1,00
Ivavradine		1 (9.1)	0 (0)	0,23
Diuretics		11 (100)	36 (97.3)	1,00

Nitrates	1 (9.1)	3 (8.1)	1,00
Digoxin	2 (18.2)	2 (5.4)	0,22
CCBs	1 (9.1)	1 (2.7)	0,41
Anticoagulants	5 (45.5)	11 (29.7)	0,47
Antiplatelets	7 (63.6)	14 (37.8)	0,17
Anti-arrhythmic drugs	6 (54.5)	17 (46.0)	0,74
Statins	8 (72.7)	18 (48.7)	0,19
Laboratory parameters at baseline			
WBCs (10^6/L)	7656 ± 1477	7374 ± 1869	0,61
Lymphocytes (10^6/L)	1675 ± 686	1911 ± 666	0,33
Platelets (10^6/L)	206455 ± 67828	226838 ± 51330	0,37
Neutrophils (10^6/L)	5231 ± 1576	4664 ± 1458	0,30
NLR	3.8 ± 2.3	2.8 ± 1.6	0,21
PLR	143.3 ± 76.1	134.9 ± 62.4	0,74
PNR	42.6 ± 19.3	52.8 ± 18.7	0,14
RDW-SD (fL)	46.0 ± 4.1	44.9 ± 5.1	0,45
RDW-CV (%)	14.9 ± 1.9	14.9 ± 1.9	0,99
Hemoglobin (g/dL)	13.2 ± 1.5	12.9 ± 1.4	0,50
Hematocit (%)	40.0 ± 4.6	38.3 ± 3.9	0,27
Creatinine (mg/dL)	1.55 ± 0.56	1.06 ± 0.21	**0,02**
LDH (U/L)	241.1 ± 95.0	220.1 ± 50.4	0,50
Total cholesterol (mg/dL)	177.9 ± 47.6	165.2 ± 44.9	0,45
HDL (mg/dL)	44.2 ± 22.4	43.3 ± 20.5	0,91
LDL (mg/dL)	110.6 ± 49.7	100.4 ± 42.9	0,55
Triglycerides (mg/dL)	114.8 ± 41.2	114.7 ± 38.1	0,99
Follow-Up			
VT	6 (54.6)	4 (10.8)	**<0.01**
AF	1 (9.1)	7 (18.9)	0,66
Rehospitalizations	10 (90.9)	14 (37.8)	**<0.01**

Death of any cause	2 (18.2)	0 (0)	**0,05**
LVEF (%)	26.3 ± 5.2	41.1 ± 8.6	**<0.01**
LVESV (mL)	175.7 ± 46.1	97.1 ± 28.5	**<0.01**
ΔLVEF (%)	- 0.1 ± 2.8	14.3 ± 7.8	**<0.01**
ΔLVESV (mL)	- 5.7 ± 16.9	- 61.7 ± 39.6	**<0.01**

Continuous data are presented as mean values ± SD while categorical variables as absolute and relative frequencies (percentages).

Abbreviations: ACEIs/ARBs, angiotensin-converting-enzyme inhibitor/ Angiotensin II receptor blockers; AF, atrial fibrillation; BB, b-blockers; BMI, body mass index; CCB, calcium channel blockers; CMP: cardiomyopathy; CRT, cardiac resynchronization therapy; HDL, high density lipoprotein; HF, heart failure; LA, left atrium; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LVEDD, left ventricular end systolic diameter; LVEDV, left ventricular end diastolic volume; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MRAs, mineralocorticoid receptor antagonists; NLR, neutrophil to lymphocyte ratio; PASP, pulmonary artery systolic pressure; PLR, platelet to lymphocyte ratio; PNR, platelet to neutrophil ratio; RDW-CV, red blood cells distribution width-coefficient variation; RDW-SD, red blood cells distribution width-standard deviation; VT, ventricular tachycardia; WBC, white blood cells; ΔLVEF, left ventricular ejection fraction difference; ΔLVESV, left ventricular end systolic volume difference

4.2.1 Predictors of CRT response

At 6-months follow-up, 37 patients (77.1%) responded to CRT while 11 patients (22.9%) were non-responders. Univariate analysis showed that age (p=0.01), LAD (p=0.03), LAV (p=0.02) and creatinine levels (p=0.02) were significantly associated with response to CRT. On the other hand, a significant association was not found between hematological markers (WBC, neutrophils, lymphocytes, platelets, NLR, RDW) and CRT response (Table 8). Multivariate analysis that included the significant factors from the univariate analysis revealed that age (p=0.03) and creatinine levels (p=0.02) were the only independent predictors of the response to CRT. Linear regression analysis showed that creatinine (p=0.03) and LDH (p=0.03) levels were significantly associated with a LVEF increase during follow-up while no significant association was found between laboratory markers and LVESV decrease.

4.2.2 Adverse outcomes during follow-up

VT occurred in 10 (20.8%) patients while 24 (50%) patients reported rehospitalization and 2 (4.2%) patients died during follow-up period. Univariate analysis showed that a

smaller LVEF increase and LVESV decrease during follow-up were significant predictors ($p<0.001$) for hospitalizations and VT occurrence. Regarding laboratory indices, patients with VT had significantly lower levels of red distribution width-coefficient variation (RDW-CV) ($p=0.005$) while patients with hospitalizations had higher LDH levels ($p=0.01$) and paradoxically lower WBC and lymphocyte levels ($p=0.04$). No significant associations were found for all-cause mortality, probably due to the small number of events.

4.2.3 Subgroup analysis according to HF type

4.2.3.1 Dilated cardiomyopathy

The DCM group consisted of 19 patients (mean age: 67.4±8.8 years, 94,7% males). During the 6-month follow-up, 12 (63.2%) patients were found to be responders while 7 (36.8%) patients did not respond to CRT. Univariate analysis showed that age ($p=0.01$) and PNR ($p=0.04$) were significantly associated with CRT response (Table 9). However, multivariate analysis did not show any independent predictors of CRT response.

4.2.3.2 Ischemic cardiomyopathy

The ischemic cardiomyopathy group consisted of 29 patients (mean age: 65.4±10 years, 72,4% males). During the 6-month follow-up, 25 (86.2%) patients were found to be responders while 4 (13.8%) patients did not respond to CRT. Univariate analysis did not reveal any significant predictor of CRT response (Table 10).

Table 9. Baseline characteristics of dilated cardiomyopathy patients

Characteristics	Response to CRT therapy		p-value
	Non-responders to CRT (7, 36.8%)	**Responders to CRT (12, 63.2%)**	
Age (years)	60.4 ± 7.8	71.5 ± 6.6	**0,01**
Males	7 (100)	11 (91.7)	1,00
Laboratory parameters at baseline			
Hemoglobin (g/dl)	13.6 ± 1.2	12.6 ± 1.4	0,12
Hematocrit (%)	41.5 ± 3.5	37.6 ± 4.2	0,05
Platelets (10^6/L)	195857 ± 35709	231083 ± 51156	0,10
RDW-SD (fl)	47.7 ± 4.2	45.4 ± 6.2	0,34
RDW-CV (%)	15.6 ± 2.2	15.2 ± 2.1	0,68
WBC (10^6/L)	8034 ± 1539	7158 ± 1718	0,27
Lymphocytes (10^6/L)	1602 ± 771	1818 ± 660	0,55
Neutrophils (10^6/L)	5651 ± 1853	4667 ± 1552	0,26
NLR	4.4 ± 2.7	2.9 ± 1.7	0,22
PLR	142.8 ± 55.8	145.3 ± 72.2	0,94
PNR	37.7 ± 12.1	55.2 ± 22.3	**0,04**
LDH (U/L)	215.9 ± 62.7	208 ± 44.7	0,79

Continuous data are presented as mean values ± SD while categorical variables as absolute and relative frequencies (percentages).

Abbreviations: LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNR, platelet to neutrophil ratio; RDW-CV, red blood cells distribution width-coefficient variation; RDW-SD, red blood cells distribution width-standard deviation; WBC, white blood cells

Table 10. Baseline characteristics of ischemic cardiomyopathy patients

	Non-responders to CRT (4, 13.8%)	**Responders to CRT (25, 86.2%)**	**p-value**
Age (years)	58.5 ± 11.7	66.5 ± 9.5	0,27
Males	4 (100)	17 (68)	0,55
Laboratory parameters at baseline			
Hemoglobin (g/dl)	12.6 ± 2.1	13.0 ± 1.4	0,70
Hematocrit (%)	37.5 ± 5.7	38.6 ± 3.7	0,74
Platelets (10^6/L)	225000 ± 109839	224800 ± 52339	0,10
RDW-SD (fl)	43.0 ± 1.8	44.6 ± 4.6	0,24
RDW-CV (%)	13.8 ± 0.7	14.8 ± 1.8	0,07
WBC (10^6/L)	6996 ± 1275	7478 ± 1963	0,54
Lymphocytes (10^6/L)	1804 ± 589	1959 ± 678	0,66
Neutrophils (10^6/L)	4498 ± 542	4662 ± 1444	0,69
NLR	2.7 ± 0.8	2.8 ± 1.5	0,88
PLR	144.2 ± 114.2	129.9 ± 58.1	0,82
PNR	51.1 ± 28.3	51.7 ± 17.2	0,97
LDH (U/L)	285.3 ± 134.7	224.9 ± 52.5	0,44

Continuous data are presented as mean values ± SD while categorical variables as absolute and relative frequencies (percentages).

Abbreviations: LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNR, platelet to neutrophil ratio; RDW-CV, red blood cells distribution width-coefficient variation; RDW-SD, red blood cells distribution width-standard deviation; WBC, white blood cells

4.3 Discussion

The main findings of our study are: 1) older age and lower creatinine levels were significant predictors of CRT response, 2) a smaller increase and a smaller decrease in LVEF and LVESV respectively were significantly correlated with VT and hospitalization rates during follow-up, and 3) there was no significant association between hematological markers and CRT response.

It is well-established that responders to CRT therapy a have lower incidence of adverse outcomes (mortality, VT, hospitalizations) (274, 275). Simple echocardiographic markers and laboratory indices have been studied regarding their potential predictive value for CRT response and cardiovascular outcomes in CRT patients. LAD and LAV are easily measured echocardiographic indices that have been previously associated with response to CRT therapy. In particular, a single-center study found that LAD and LAV were significantly associated with CRT response defined as a reduction in LVESV of ≥10% (390). The same study showed that responders to CRT had improved left atrium ejection fraction, a significant reduction in LAD and LAV in addition to significant improvement of positive and negative longitudinal strain compared to baseline (390). Moreover, CRT has been found to significantly reduce LAV compared with defibrillator-only therapy (391). Furthermore, the reduction in LAV with CRT therapy has been associated with a significant reduction in the risk of subsequent atrial tachyarrhythmias (392). By using an improvement in LVEF >10% at 6 months as definition of CRT response, LBBB and a smaller LAV index were found to be significant predictors of response in patients with advanced HF (393). Interestingly, a smaller LAD has also been associated with CRT super-response (394, 395). Apart from the role of left atrial dimensions, the possible association of left atrial function with CRT response has also been studied. Specifically, left atrial systolic peak of strain rate has been shown to be a good predictor of CRT response in terms of left ventricular reverse remodeling (396). A post-hoc analysis of the MADIT-CRT trial showed that a higher baseline LAV was independently associated with a higher risk of adverse outcomes (HF or death and all-cause mortality) while each 1% reduction in LAV during follow-up was associated with a 4% reduction in the hazard of subsequent HF or death (391). In an observational study, LAV >59.4 ml/m^2 was associated with a near 5-fold increase in mortality during follow-up (397). However, data from a prospective study which evaluated the impact of baseline LAV and left atrial function,

as assessed by computed tomography, on CRT response showed no significant association between these two parameters with either the clinical or echocardiographic response, while the reverse left atrial remodeling was modest despite a pronounced reduction in left ventricular volume during follow-up (398).

Regarding hematological markers, the RDW is a measure of variability in size of circulating erythrocytes and is generally used as an indicator of the differential diagnosis of anemia. RDW has been found to consist a strong predictor of prognosis in HF patients (399). There are few observational studies which propose the RDW as a predictor of response to CRT. Specifically, a prospective study showed that baseline RDW levels did not predict left ventricular reverse remodeling defined as a reduction of LVESV ≥15% at 6-months follow-up, while RDW levels ≥14.5% independently predicted the composite endpoint of death and HF hospitalization (400). These authors also investigated the impact of RDW variation between baseline and 3-months follow up on left ventricular remodeling and the composite endpoint. They found that stable-high levels of RDW ≥ 14.5% and the increase of RDW from <14.5% to ≥14.5% were associated with lower likelihood of left ventricular reverse remodeling and independently predicted the composite outcome (400). Moreover, a retrospective study showed that for every 1% rise in RDW, there was a 19% rise in all-cause mortality while patients with elevated RDW levels demonstrated significantly less improvement in LVEF and reductions in LVEDV and LVESV than patients with normal levels (401). In addition, results from another study showed that non-responders to CRT had higher baseline RDW levels and had a significantly higher increase of RDW at 6 months follow-up compared to responders (327). In multivariate analysis, baseline RDW levels were found to be the only predictor of echocardiographic response defined as ≥15 % relative increase in LVEF after 6 months (327).

The exact pathophysiologic relationship between RDW and cardiovascular outcomes is unknown. However, it has been proposed that an inflammatory environment with increased levels of cytokines, such as in HF patients, can inhibit erythropoietin-induced erythrocyte maturation and decreased erythrocyte maturation may result in elevated RDW (327).

Anemia is another factor that may influence the outcomes of patients who undergo a CRT device implantation. Specifically, it was found that anemia at baseline (defined as Hb ≤12g/dl in women and ≤13 g/dl in men) and a larger decrease in Hb levels during follow-up were significantly associated with the composite endpoint (HF

hospitalization, left ventricular assist device placement, heart transplantation, and all-cause mortality) (402). However, anemia did not influence echocardiographic response to CRT (402).

Inflammation has been recognized as a significant player in the pathogenesis of HF, AF and other cardiovascular diseases. Data from a post-hoc analysis of the SOLVD trial showed that subclinical inflammation as indicated by an increase in WBC count and neutrophils count has been associated with increased risk of death and cardiovascular events in HF patients (403) while a pilot study showed that a neutrophil count increase is associated with higher incidence of sudden unexpected death in HF patients (404). The NLR, PLR and WBC counts are simple hematological indices that reflect the inflammatory status. A retrospective analysis found that non-responders to CRT had higher NLR and PLR levels while the relative lymphocyte count was significantly lower compared to responders (405). Furthermore, the authors showed a significant correlation of NRL and relative lymphocyte count with NYHA functional class (405). The predictive role of NLR was demonstrated in the multivariate analysis of another single center study with a small sample size (326). Additionally, high sensitivity C-reactive protein serum levels have been found to predict both non-responders and patients at higher risk for cardiac death (406). CRT seems to have an anti-inflammatory role, and this may contribute to its beneficial action in reverse remodeling. Indeed a decrease in inflammatory markers (NLR, c-reactive protein, interleukins) has been shown in CRT responders (326).

Renal dysfunction is a common comorbidity in patients with HF. The results of a meta-analysis showed that baseline renal dysfunction had an adverse effect on-all cause mortality in patients who underwent CRT (407). There are controversial data about the role of renal dysfunction on CRT response. Some authors found that renal dysfunction did not influence the clinical or echocardiographic response following CRT implantation (408, 409), while a large observational study showed that impaired renal function was associated with a lack of echocardiographic response during 6-month follow-up (410). On the other hand, responding to CRT therapy seems to have a beneficial role in the improvement of renal function (408), while renal responders were shown to have favorable long-term outcomes (411). Interestingly, in MADIT-CRT, patients with an elevated ratio of blood urea nitrogen to serum creatinine experienced a significantly greater reduction in the risk of HF or death following CRT-D therapy compared to those with a low ratio (412). Data from the sub analysis of the MIRACLE

trial showed that patients in the CRT group independently of its renal function had superior benefit compared to the control group with regard to decrease in left ventricular volumes and increase in LVEF although impaired renal function led to less response (413). In addition, data from the CARE-HF trial showed that CRT reduced the risk of composite end point of death or HF hospitalization independently of baseline renal function compared to medical therapy alone (270).

4.4 Limitations

The main limitation of our study is that the study population is relatively small, while this was a single-center retrospective study. The small statistical power of the study is reflected to the non-significant difference in CRT response regarding the type of HF. It is well established by the sub analysis of the prospective randomized studies including MIRACLE (414), CARE-HF (415), REVERSE (416) and MADIT-CRT (417) that non-ischemic cardiomyopathy patients had more favorable reverse remodeling compared to ischemic cardiomyopathy. Echocardiographic measures were performed by a single operator that may introduce some bias. No laboratory investigations were performed at 6-month follow-up, and thus an analysis on the changes of hematological indices over time cannot be done. A universal definition of CRT response does not exist, making difficult a direct comparison of our results with the existing data from the literature.

4.5 Conclusions

In conclusion, our study showed that older age and lower creatinine levels were significant predictors of CRT response while a smaller increase and a smaller decrease in LVEF and LVESV respectively at 6 months follow-up, were significantly correlated with VT and hospitalization rates during follow-up. Finally, there was no significant association between the CRT response and simple hematological markers.

5. Clinical question 5: HFrEF patients undergoing CRT; Is there any association between QRS narrowing after CRT implantation with response to CRT?

In order to answer the above clinical question we used the methodology of meta-analysis (333).

5.1 Methods

This meta-analysis was performed in accordance with both the Meta-Analysis of Observational Studies in Epidemiology and Strengthening the Reporting of Observational Studies in Epidemiology guidelines (418).

5.1.1 Search strategy and eligibility criteria

Two independent investigators performed a comprehensive systematic search in MedLine and EMBASE databases through July 2018 without any limitations. Furthermore, the reference lists of the relevant research studies as well as the relevant review studies and meta-analyses were manually searched. The following keywords were used to retrieve all relevant studies: “cardiac resynchronization therapy”, “biventricular pacing”, “response”. We first screened the titles and abstracts of each study and in case of considering a study as relevant then we went through the full text. In case of duplicate cohorts, we kept the study with the longest follow-up and if it was similar, the cohort with the greater sample size. Disagreements were resolved by a third investigator.

5.1.2 Data extraction

The following data were extracted: First author, Journal of publication, Year of publication, study design (prospective-retrospective), inclusion/exclusion criteria, duration of follow-up, number of patients, gender, age, type of cardiomyopathy (ischemic, non-ischemic), chronic AF, LBBB, definition of CRT response, number of responders/non-responders, mean ± SD QRS pre and post CRT implantation (or mean ± SD delta QRS) for each group and timing for post-CRT implantation QRS measurements.

5.1.3 Statistical analysis

Data analysis was performed by using the Review Manager software (RevMan), version 5.3 (available from the website of the Cochrane Collaboration) and STATA 13.0. We performed separate analyses according to the definitions of CRT response. Furthermore, we performed separate analyses regarding delta QRS (post QRS minus

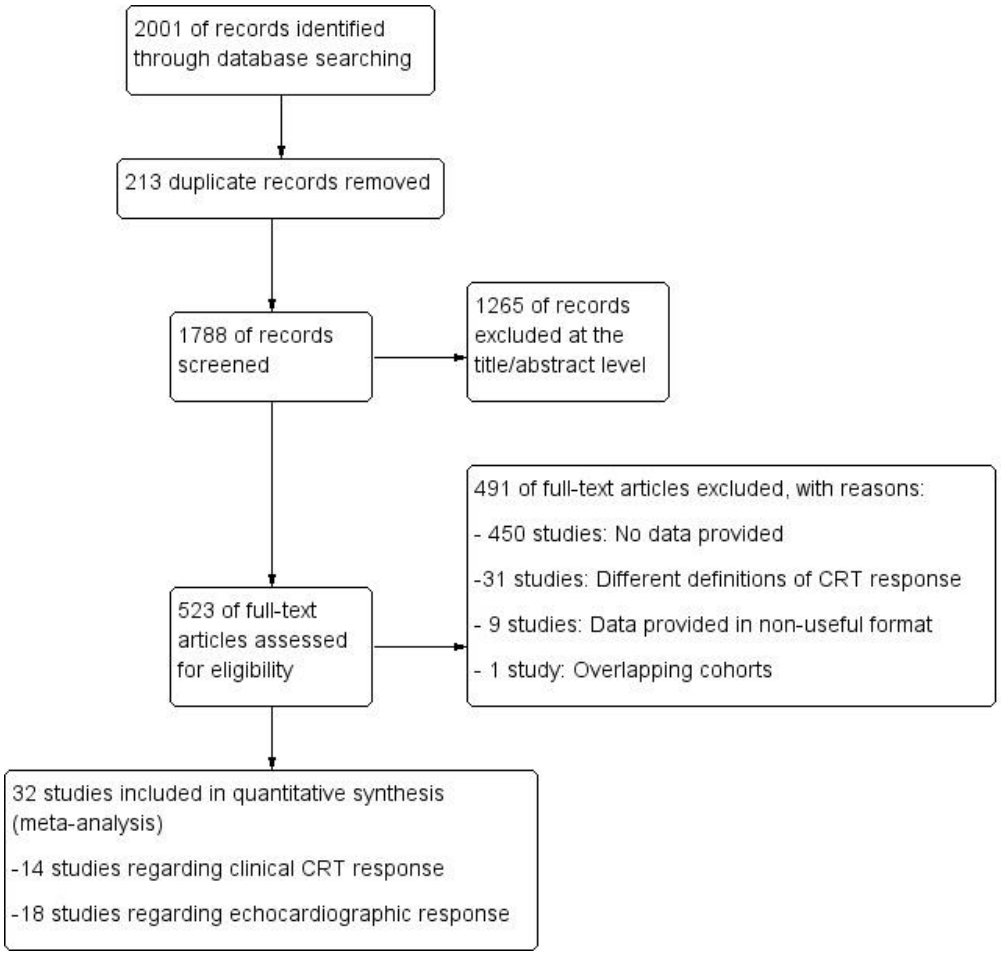
pre QRS) and attained post CRT implantation QRS duration difference between responders and non-responders. Continuous outcome variables were pooled as mean difference with 95% CI. The proportion of heterogeneity across studies not explained by chance was assessed by the I-squared index. A random effects model was used for the analyses. Funnel plots were constructed using RevMan software to assess publication bias. The NOS was used for quality assessment of the included studies (362). The NOS point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. This scale ranged from zero to nine stars, which indicated that studies were graded as poor quality if the score was < 5, fair if the score was 5 to 7, and good if the score was > 8. The rating of the evidence was performed according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework (419-424). A sensitivity analysis was performed by estimating the pooled effect size after removing each study one by one. A separate sensitivity analysis was performed by estimating the pooled effect size after removing the lower quality studies. Subgroup analysis was performed according to the timing of post-CRT implantation QRS measurement (immediately after CRT implantation or at the follow-up). Potential variables to account for observed heterogeneity were explored using meta-regression. Furthermore, we assessed how robust our findings are to potential unmeasured or uncontrolled confounding by calculating the E-value of each observational study included in our analyses (https://www.evalue-calculator.com/) (425). A P-value of less than 0.05 (two-tailed) was considered statistically significant.

5.2 Results

5.2.1 Search results

Our search strategy returned 2001 possible relevant studies (Figure 34).

Figure 34. Flowchart of the study



Of those, 213 studies excluded as duplicate records, 1265 studies were excluded at the title/abstract level while 460 studies were excluded at the full text level, yielding 63 studies which were included for further analysis. Of those, 31 studies were excluded because of the different definitions of CRT response, that did not permit quantitative synthesis. Finally, we included 32 studies that used the same definition of CRT response and were analyzed in two major groups: 14 studies (1274 patients, mean age: 64 years, males: 79.3%) using clinical CRT response (defined as improvement in NYHA functional classification of ≥ 1 class) (328, 332, 426-437) (Table 11) and 18 studies (1270 patients, mean age: 64 years, males: 69.1%) using echocardiographic CRT response [defined as a reduction of LVESV ≥ 15%] (301, 329-331, 438-451) (Table 12).

Table 11. Characteristics of the included studies reporting clinical response to cardiac resynchronization therapy

First author	Year	Country	Cohort design	Enrollment Period	De novo CRT implantation	Subjects	Males (n, %)	Mean age (years)	Ischemic Cardiomyopathy (n, %)	LVEF (%)	Follow-up (months)	Responders (n, %)	Mean baseline QRS width in responders (ms)	Mean QRS width in responders at follow-up (ms)	Mean baseline QRS width in non-responders (ms)	Mean QRS width in non-responders at follow-up (ms)	Mean attained QRS difference (95%CI) (ms)	Time to post-CRT QRS width measurement
Lunati M	2002	Italy	R	1999-2000	52	52	46, 88.5	52	18, 34.6	26,4	11,6	42, 80.8	194	158	197	164	-6.0 (-19.1, 7.1)	at follow-up
Oguz E	2002	Turkey	R	n/a	16	16	16, 100	16	10, 62.5	25,8	7,6	5, 31.3	149	131	176	156	-24.7 (-40.83, -8.57)	6 months
Molhoek SG	2005	Netherlands	R	n/a	109	125	93, 74.4	125	67, 53.6	23	23	91, 72.8	178	147	168	158	-11.0 (-21.11, -0.89)	6 months
Duncan AM	2006	UK	R	2003-2004	39	39	30, 76.9	39	23, 59	21	6	29, 74.4	153	135	157	152	-17.0 (-69.96, 35.96)	immediately after CRT
Kubanek M	2006	Czech republic	P	2001-2002	39	43	37, 86.1	43	18, 41.9	22	25,8	30, 69.8	193	138	200	154	-16.0 (-30.06, -1.94)	immediately after CRT

Buch E	2007	US	R	2003-2005	83	83	73, 88	83	83, 100	23	6	39, 47	159	150	159	167	-17.0 (-26.07, -7.93)	6 months
Lellouche N	2007	US	R	2003-2005	164	164	125, 76.2	164	77, 47	22,1	6	107, 65.2	159	157	155	164	-7.0 (-15.25, 1.25)	6 months
Mollema SA	2007	Netherlands	P	n/a	242	242	197, 81.4	242	154, 63.6	23	6	164, 67.8	165	151	164	153	-2.0 (-8.3, 4.3)	immediately after CRT
Yeim S	2007	France	P	2005-	100	100	78, 78	100	46, 46	26,7	6	69, 69	162	152	148	153	-0.9 (-15.31, 13.51)	6 months
Cazeau SJ	2008	France, Italy, Germany, UK	P	n/a	64	64	54, 84.4	64	27, 42.2	27	12	33, 51.6	123	135	118	149	-13.5 (-29.68, 2.68)	6 months
Lipoldova J	2009	Czech republic	R	2000-2009	194	194	146, 75.3	194	60, 30.9	21,3	3	119, 61.3	166	155	157	165	-10.0 (-16.07, -3.93)	Immediately after CRT
Xu GJ	2013	China	P	2003-2008	65	65	51, 78.5	65	23, 35.4	25	12	42, 64.6	181	152	184	165	-13.0 (-26.67, 0.67)	immediately after CRT
Davoodi G	2014	Iran	P	n/a	21	21	13, 61.9	21	n/a	n/a	6	16, 76.2	162	132	137	136	-3.9 (-19.22, 11.42)	6 months

Badhwar N	2016	US	P	2004-2011	66	66	51, 77.3	66	36, 54.5	32,1	6	47, 71.2	167	n/a	158	n/a		n/a	6 months

List of abbreviations: LVEF, Left ventricular ejection fraction; Ms, milliseconds; CRT, Cardiac resynchronization therapy; US, United States; UK, United Kingdom

Table 12. Characteristics of the included studies reporting echocardiographic response to cardiac resynchronization therapy

First author	Year	Country	Cohort design	Enrollment Period	De novo CRT implantation	Subjects	Males (n, %)	Mean age (years)	Ischemic Cardiomyopathy (n, %)	LVEF (%)	Follow-up (months)	Responders (n, %)	Mean baseline QRS width in responders (ms)	Mean QRS width in responders at follow-up (ms)	Mean baseline QRS width in non-responders (ms)	Mean QRS width in non-responders at follow-up (ms)	Mean attained QRS difference (95%CI) (ms)	Time to post-CRT QRS width measurement
Yu CM	2002	China	P	n/a	30	30	21, 70	62	12, 40	25,1	3	17, 56.7	166	142	150	131	11.0 (-2.32, 24.32)	3 months
Boriani G	2006	Italy	P	2002-2004	20	20	15, 75	62	8, 40	27,5	3	13, 65	116	n/a	166	n/a	n/a	3 months
Sassone B	2007	Italy	P	n/a	48	48	32, 66.7	67	26, 54.2	26,0	6	31, 64.6	152	n/a	151	n/a	n/a	6 months
Soliman O	2007	Netherlands	P	n/a	60	60	43, 71.7	59	26, 43.3	18,6	6	47, 78.3	170	139	172	145	-6.0 (-26.21, 14.21)	12 months
De Boeck BW	2009	Netherlands	P	n/a	62	62	41, 66.1	64	27, 43.5	18,4	6,5	31, 50	180	163	165	156	7.0 (-4.96, 18.96)	6 months
Lim P	2011	France	P	2008-2009	189	189	132, 69.8	65	63, 33.3	26,0	6	114, 60.3	157	n/a	143	n/a	n/a	6 months
Chen Z	2013	UK	P	n/a	13	13	10, 76.9	70	5, 38.5	25,2	6	7, 53.8	150	134	166	161	-27.0 (-46.03, -7.97)	immediately after
Rickard J	2013	US	R	2003-2008	0	112	79, 70.5	69	62, 55.4	n/a	9,9 median	72, 64.3	189	n/a	186	n/a	n/a	immediately after
Chang PC	2014	Taiwan	R	n/a	0	25	16, 64	71	n/a	29,7	6	18, 72	174	149	183	144	5.0 (-7.32, 17.32)	6 months

Ma CY	2014	China	P	2007-2011	42	42	25, 59.5	57	42, 100	25,1	12	29, 69	183	118	153	146	-27.1 (-42.18, -12.02)	12 months
Zhang H	2014	China	P	2009-2012	45	45	38, 84.4	63	9, 20	23,5	6	27, 60	175	n/a	170	n/a	n/a	immediately after
Celikyurt U	2015	Turkey	R	2008-2011	67	67	38, 56.7	65	22, 32.8	22,6	6	39, 58.2	139	107	131	125	-18.0 (-28.48, -7.52)	6 months
Karaca O	2016	Turkey	R	n/a	125	125	80, 64	64	57, 45.6	26,3	6	81, 64.8	163	140	145	158	-18.5 (-27.37, -9.63)	immediately after
Kaypakli O	2016	Turkey	P	n/a	156	156	100, 64.1	66	64, 41	25,8	>3 months	84, 53.8	148	n/a	140	n/a	n/a	>3 months
Walid A	2016	Egypt	P	n/a	30	30	24, 80	59	21, 70	n/a	6	19, 63.3	144	131	147	146	-14.4 (-27.04, -1.76)	immediately after
Mele D	2017	Italy	R	2010-2016	128	128	105, 82	68	63, 49.2	29,5	6	79, 61.7	155	131	153	152	-21.7 (-27.87, -15.53)	6 months
Modi S	2017	Canada	P	n/a	42	42	30, 71.4	64	19, 45.2	25,2	6	35, 83.3	165	150	164	161	-11.2 (-24.32, 1.92)	immediately after
Ruan ZB	2018	China	R	2013-2016	76	76	49, 64.5	58	20, 26.3	26,7	29,4	52, 68.4	159	123	159	157	-34.1 (-48.56, -19.64)	6 months

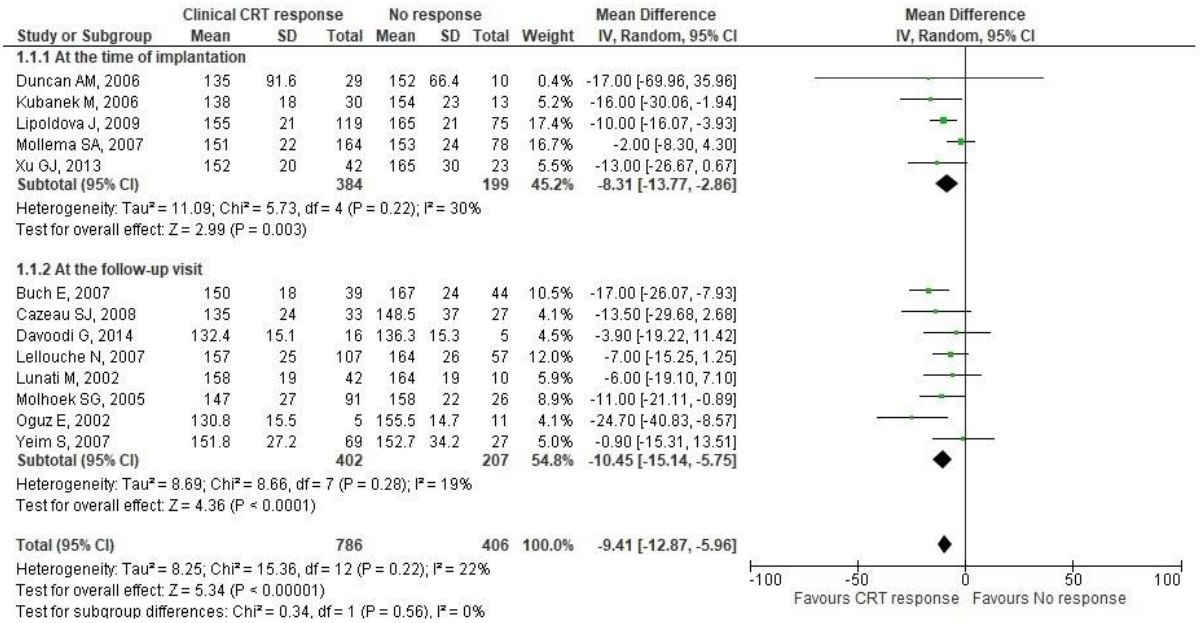
List of abbreviations: LVEF, Left ventricular ejection fraction; Ms, milliseconds; CRT, Cardiac resynchronization therapy; US, United States; UK, United Kingdom; n/a, not applicable

5.2.2 Clinical response

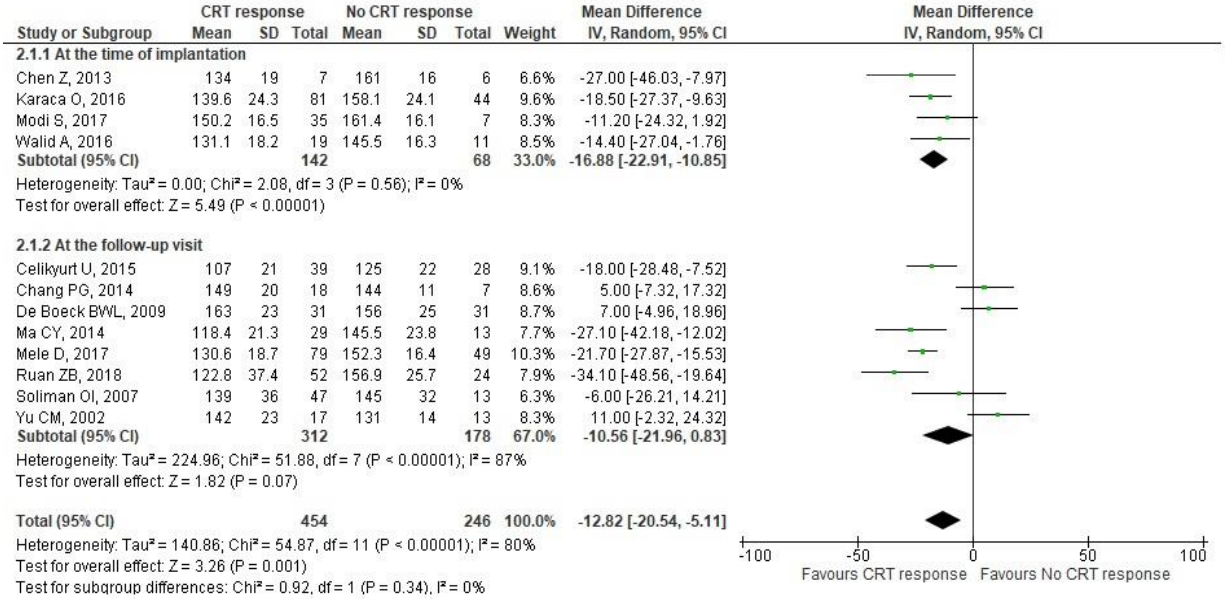
5.2.2.1 Attained QRS difference

Regarding the clinical response analyses, we analyzed 13 studies (1192 patients, 7 retrospective studies, 6 prospective studies) (332, 426-437) that provided data about attained QRS duration in each subgroup after CRT implantation. The quantitative synthesis showed that patients with clinical response to CRT had significantly shorter attained QRS duration following CRT implantation compared to patients without clinical response [-9.41 ms (-12.87, -5.96), I2 22%, $p<0.001$] (Figure 35a). Findings were consistent whether the studies provided post-CRT QRS width immediately post-implant or at follow-up (Figure 35a). Separate analyses of prospective or retrospective studies yielded similar results (Figure 36a).

Figure 35. Forest plots about the association of attained QRS difference with a. clinical and b. echocardiographic CRT response. Data provided as subgroups regarding the timing of QRS measurement post-CRT implantation

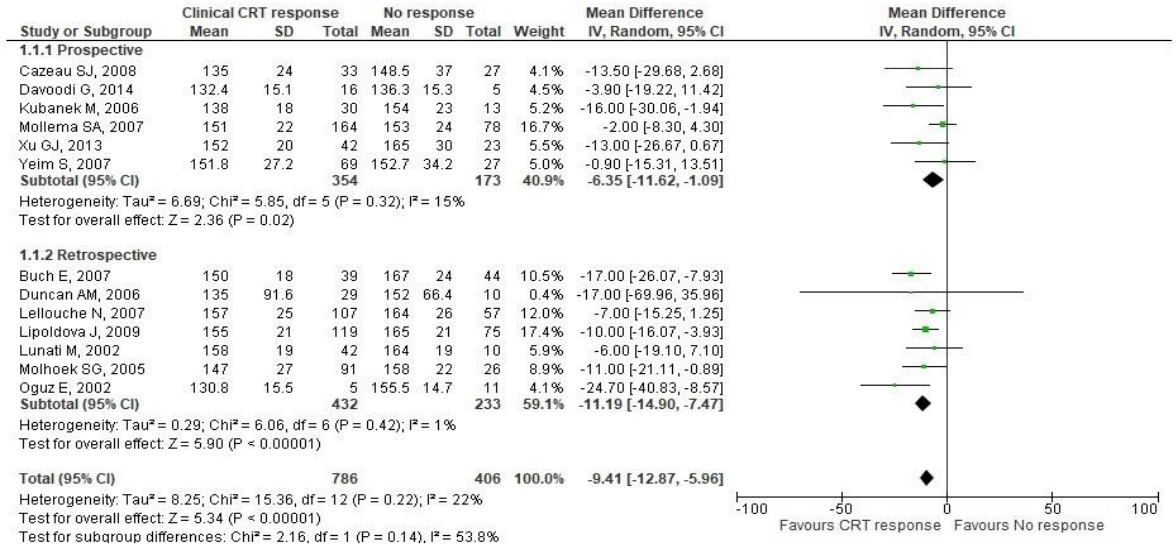


a)

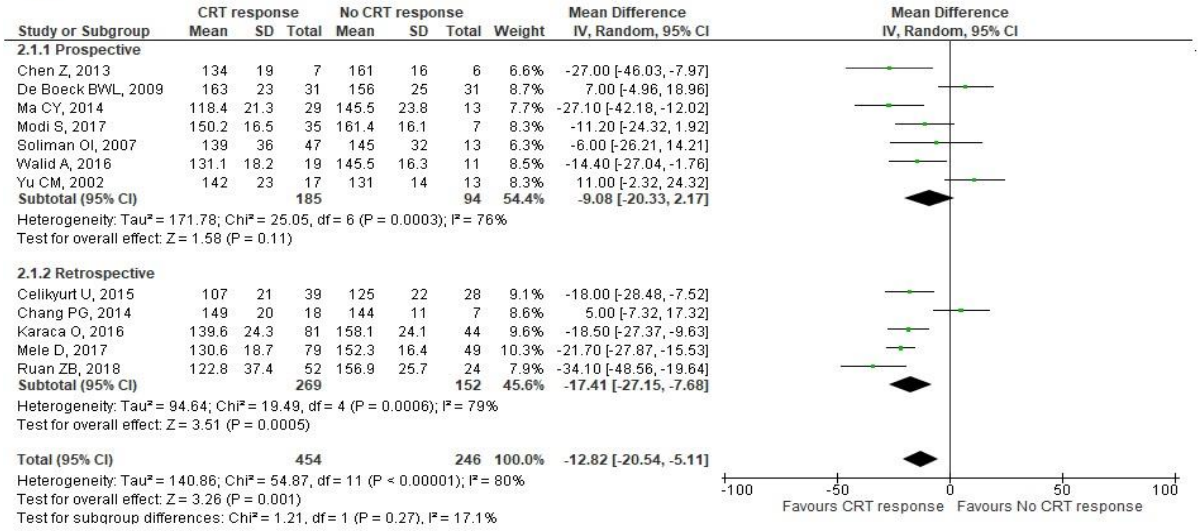


b)

Figure 36. Forest plots about the association of attained QRS difference with a. clinical and b. echocardiographic CRT response. Data provided as subgroups regarding the study design.



a)



b)

Sensitivity analysis indicated that no study had a significant impact on the pooled mean difference or on the statistical significance of the estimate. Meta-regression analysis showed no evidence of differential response rates with respect to gender, age, type of cardiomyopathy or baseline QRS duration. The E-value of each observational study is reported in Table 13.

Table 13. Quality assessment of the included studies according to the Newcastle-Ottawa Scale.

Prospective studies

	Selection				Comparability	Outcome				
STUDY	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total stars	E-value
Kubanek M	*	*	*	*	**	*	*	*	9	2.07
Mollema SA	*	*	*	*	**	*	*	*	9	1.23
Yeim S	*	*	*	*	**	*	*	*	9	1.12
Cazeau SJ	*	*	*	*	**	*	*	*	9	1.72
Xu GJ	*	*	*	*		*	*	*	7	1.77
Badhwar N	*	*	*	*	**	*	*	*	9	2.15
Davoodi G	*	*	*	*	**	*	*	*	9	1.44
Yu CM	*	*	*	*	**	*	*	*	9	1.94
Boriani G	*	*	*	*		*	*	*	7	2.15

Sassone B	*	*	*	*	**	*	*	*	9	2.49
Soliman O	*	*	*	*		*	*	*	7	1.35
De Boeck BW	*	*	*	*	**	*	*	*	9	1.54
Lim P	*	*	*	*	**	*	*	*	9	1.59
Chen Z	*	*	*	*	**	*	*	*	9	3.45
Ma CY	*	*	*	*	*	*	*	*	8	2.66
Zhang H	*	*	*	*	**	*	*	*	9	1.42
Kaypakli O	*	*	*	*	**	*	*	*	9	1.83
Walid A	*	*	*	*	**	*	*	*	9	2.26
Modi S	*	*	*	*	**	*	*	*	9	1.84

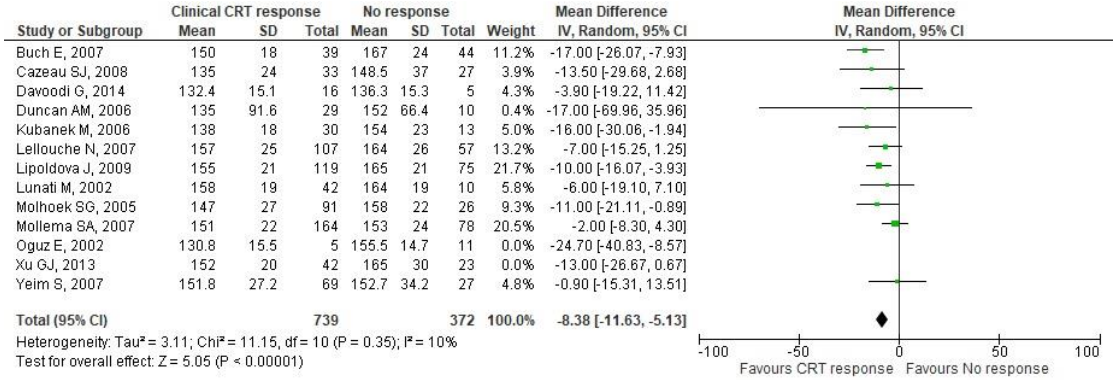
Retrospective studies

	Selection				Comparability	Outcome				
STUDY	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Total stars	
Lunati M	*	*	*	*	**	*	*	*	9	1.49

Oguz E	*	*	*	*		*	*	*	7	3.37
Molhoek SG	*	*	*	*	**	*	*	*	9	1.68
Duncan AM	*	*	*	*	**	*	*	*	9	1.42
Buch E	*	*	*	*	**	*	*	*	9	2.24
Lellouche N	*	*	*	*	**	*	*	*	9	1.5
Lipoldova J	*	*	*	*	**	*	*	*	9	1.77
Rickard J	*	*	*	*	**	*	*	*	9	1.68
Chang PC	*	*	*	*	**	*	*	*	9	1.58
Celikyurt U	*	*	*	*	**	*	*	*	9	2.27
Karaca O	*	*	*	*	**	*	*	*	9	2.14
Mele D	*	*	*	*		*	*	*	7	2.88
Ruan ZB	*	*	*	*	**	*	*	*	9	2.62

The measured E-values of the included studies indicate that little unmeasured confounding would be needed to explain away the effect estimate. Sensitivity analysis by excluding the lower quality studies (classified with <9 stars according to NOS) showed similar results (Figure 37).

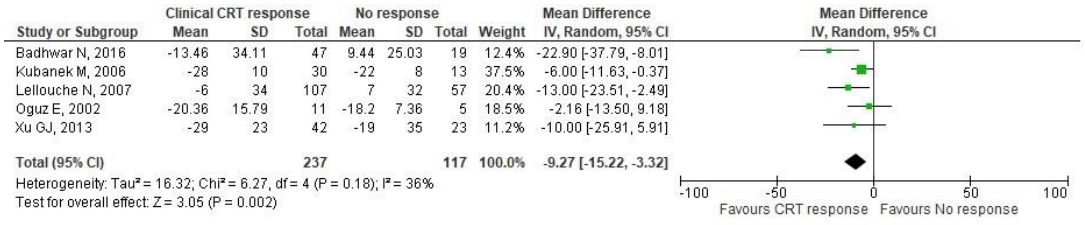
Figure 37. Sensitivity analysis by excluding the lower quality studies – clinical response.



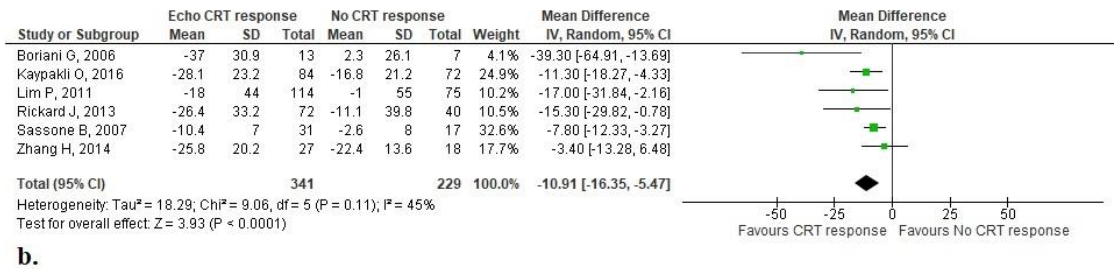
5.2.2.2 Delta QRS

We analyzed 5 studies (328, 332, 430, 431, 436) that provided data on delta QRS and clinical response to CRT. The quantitative synthesis showed that QRS narrowing was significantly associated with clinical response [-9.27 ms (-15.22, -3.32), I^2 36%, p=0.002] (Figure 38a).

Figure 38. Forest plots about the association of QRS narrowing with a. clinical and b. echocardiographic CRT response. Data provided as delta QRS pre/post implantation.



a.



b.

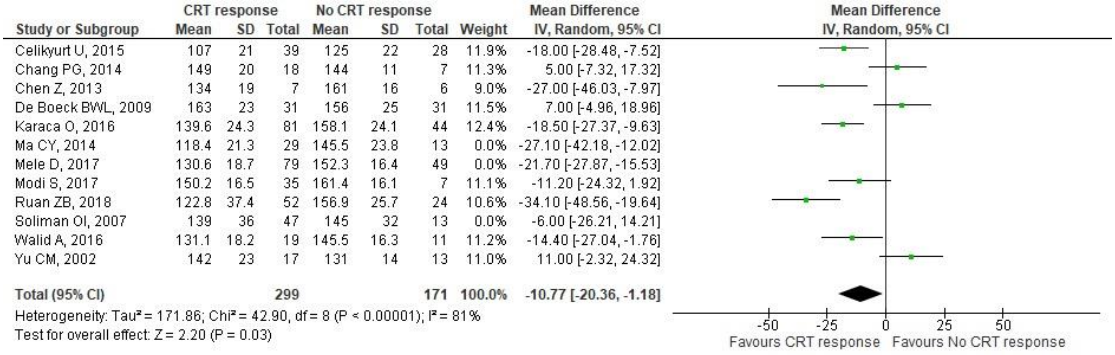
5.2.3 Echocardiographic response

5.2.3.1 Attained QRS difference

In echocardiographic response analyses, we analyzed 12 studies (700 patients, 7 prospective studies, 5 retrospective studies) (439-446, 448-451) that provided data about attained QRS duration in each subgroup after CRT implantation . The quantitative synthesis showed that patients with echocardiographic response to CRT had shorter attained QRS duration following CRT implantation compared to patients without echocardiographic response [-12.82 ms (-20.54, -5.11), I^2 80%, p=0.001] (Figure 35b). Findings were consistent whether the studies provided attained QRS width immediately post-implant or at follow-up (Figure 35b). Separate analyses of prospective or retrospective studies yielded similar results (Figure 36b). No study had a significant impact on the pooled mean difference or on the statistical significance of the estimate. Meta-regression analysis showed no evidence of differential response rates with respect to gender, age, type of cardiomyopathy or baseline QRS duration.

The E-value of each observational study is reported in Table 13. The measured E-values of the included studies indicate that little unmeasured confounding would be needed to explain away the effect estimate. Sensitivity analysis by excluding the lower quality studies (classified with <9 stars according to NOS) showed similar results (Figure 39).

Figure 18. Sensitivity analysis by excluding lower quality studies – echocardiographic response.



5.2.3.2 Delta QRS

We analyzed 6 studies (301, 329-331, 438, 447) that provided data on delta QRS duration and echocardiographic response to CRT. The quantitative synthesis showed that QRS narrowing was significantly associated with echocardiographic response [-10.91 ms (-16.35, -5.47), I^2 45%, p<0.001] (Figure 38b).

5.2.4 Quality assessment - Publication bias - Rating of evidence

There was no evidence of significant publication bias in the presented analyses as demonstrated in the funnel plots (Figures 40-45).

Figure 19. Funnel plot about attained QRS difference (subgroups: study type) - Clinical response

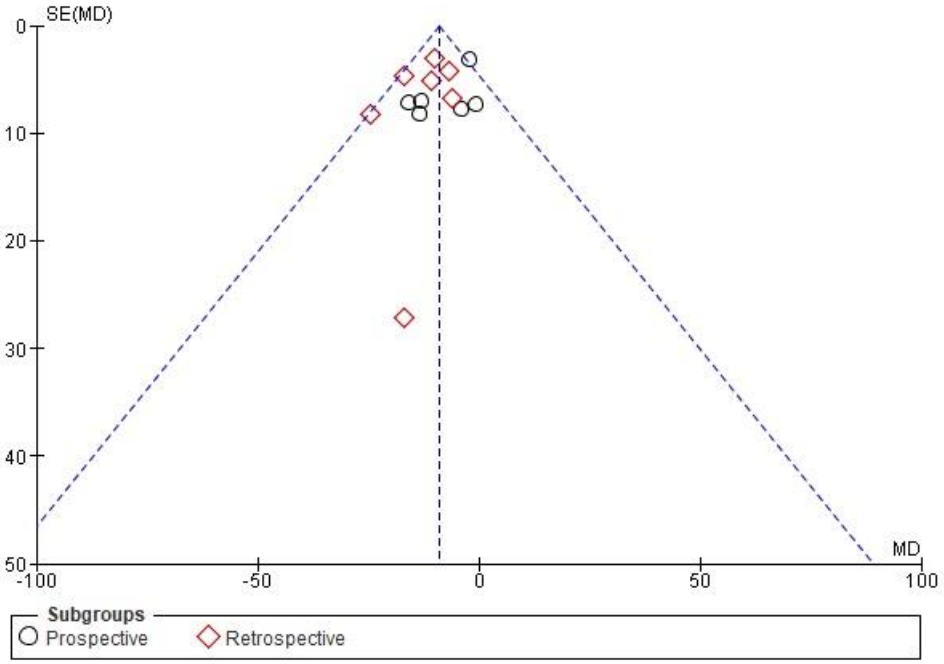


Figure 20 Funnel plot about attained QRS difference (subgroups: study type) - Echocardiographic response

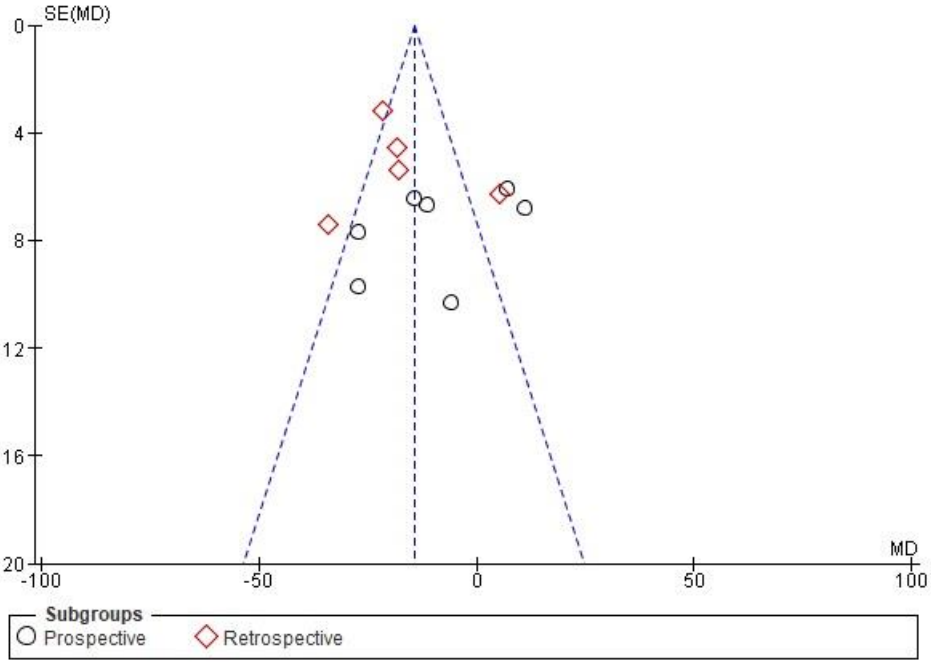


Figure 21 Funnel plot about attained QRS difference (subgroups: timing of attained QRS measurement) - Clinical response

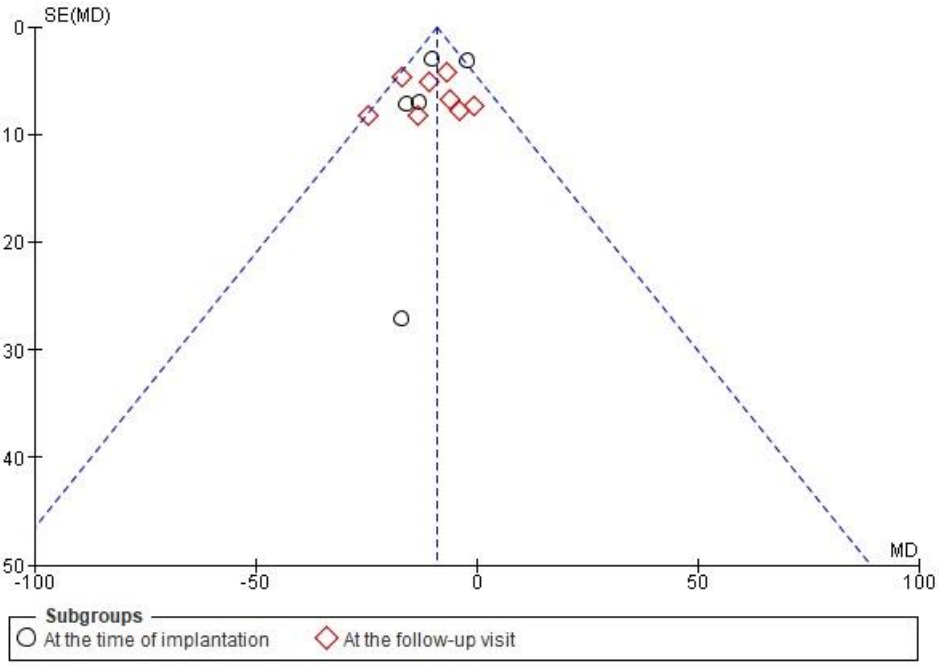


Figure 22. Funnel plot about attained QRS difference (subgroups: timing of attained QRS measurement) - Echocardiographic response.

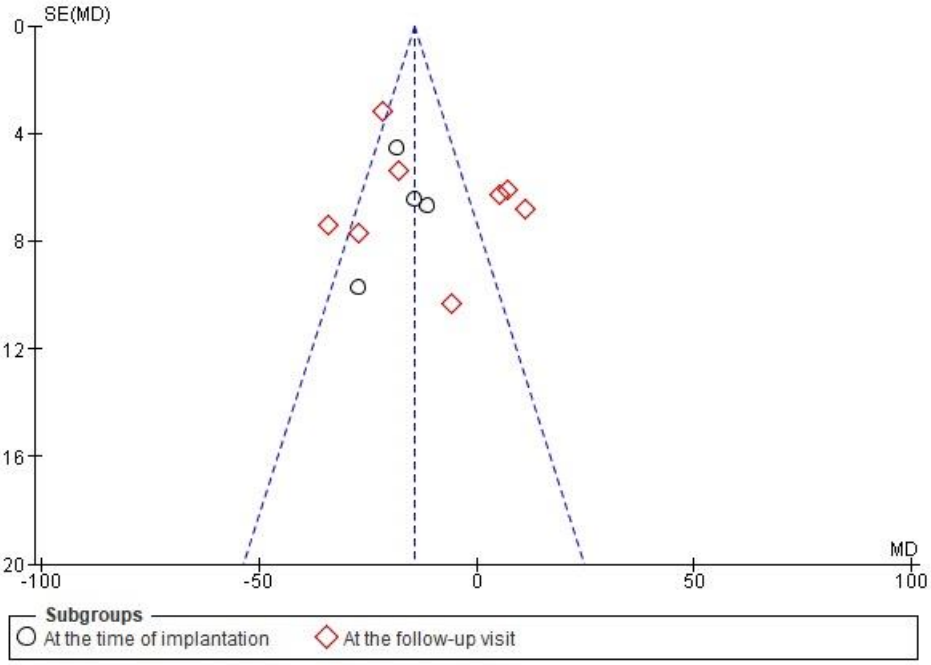


Figure 23. Funnel plot about ΔQRS analysis – Clinical response

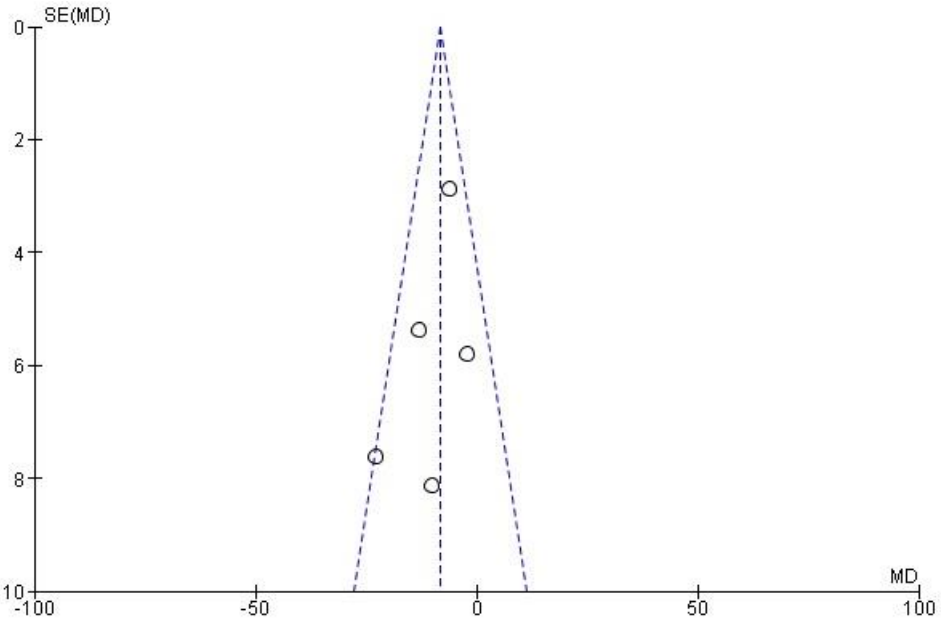
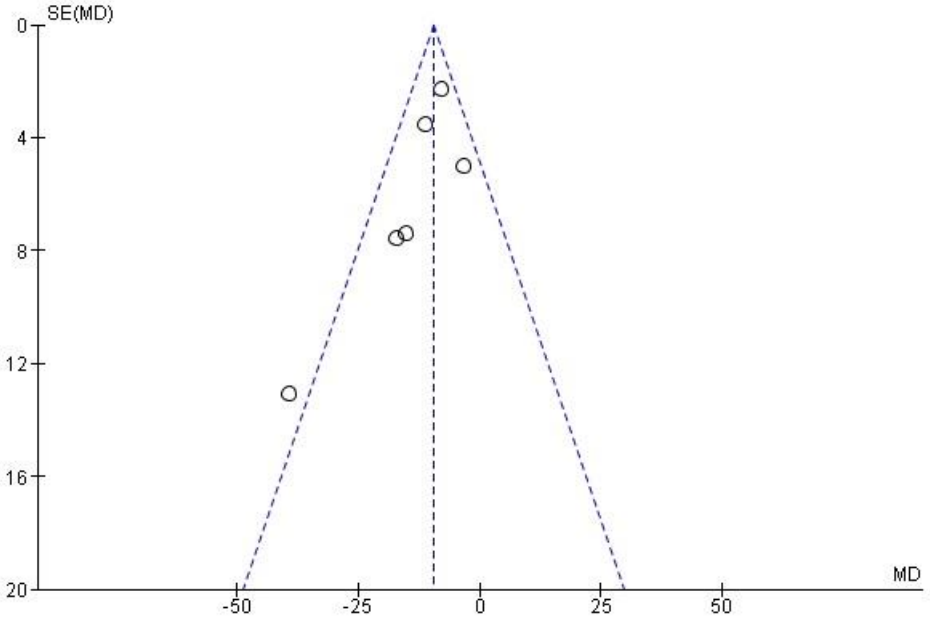


Figure 24. Funnel plot about ΔQRS analysis – Echocardiographic response



Regarding the quality assessment, all included studies were graded with a score > 5 and none of the included studies was characterized as having a poor quality (Table 13). According to GRADE framework, we classified our analyses as having moderate quality of evidence (the true effect is probably close to the estimated effect) (Table 14).

Table 14. Qualification of the overall evidence using GRADE

No. of studies	Risk of bias	In-consistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Outcome	Mean difference (95% CI)
13 studies, 1192 patients	Not serious	Serious	Not serious	Not serious	Not serious	Moderate	Clinical CRT response	-9.41 (-12.87, -5.96)
12 studies, 700 patients	Not serious	Serious	Not serious	Not serious	Not serious	Moderate	Echocardiographic CRT response	-12.82 (-20.54, -5.11)

5.3 Discussion

The main finding of our meta-analysis is that QRS narrowing and shorter attained QRS duration following biventricular pacing are significantly associated with clinical (decrease in NYHA ≥ 1) and echocardiographic (decrease in LVESV ≥ 15%) CRT response.

QRS duration is a simple electrocardiographic marker of ventricular electrical dysynchrony. The negative prognostic role of electrical desynchrony in patients with HFrEF is well established (452). QRS narrowing after biventricular pacing reflects a reduction in electrical dysynchrony. Our study showed that both acute and late reduction of the electrical dysynchrony, as measure by QRS duration, with biventricular pacing is significantly associated with both clinical and echocardiographic responses defined as a reduction of NYHA ≥ 1 or LVESV reduction ≥ 15% respectively. Interestingly, in patients with left ventricular dysfunction, short-term trial-level therapeutic effects of a drug or device on left ventricular remodeling have been found to be associated with longer-term trial-level effects on mortality (453). The present findings are in the same line with those demonstrated in previous meta-analysis (454, 455). However, as already mentioned, the methodology of our study differs significantly from the previous studies because we included only the studies with the same definition of CRT response. We believe that this strategy eliminates a significant type of bias that results from the different definitions of response and therefore lead to more reliable interpretation. This is supported from the findings of Fornwalt et al who studied the agreement of different CRT response criteria by implementing them in 426 patients from the PROSPECT study (456). They found that the agreement between different methods to define CRT response is poor which severely limits the ability to synthesize the different studies in the same analysis (456). Furthermore, the specific definitions for CRT response that we used in our analysis (decrease in LVESV ≥ 15% and NYHA ≥ 1) were found to represent the most powerful predictors of major adverse cardiac events after CRT (457). However, the prognostic role of QRS narrowing for adverse events should be studied in a prospective manner.

Another difference from previous meta-analyses is that we performed two separate analyses. Specifically, we included studies that provided data either as change in QRS or as mean attained QRS post-CRT implantation and analyzed them separately.

Previous meta-analyses included only studies providing data on change in QRS in responders and non-responders.

Mechanical dysynchrony as assessed by different indices seem to be significantly associated with CRT clinical or echocardiographic response (301, 458-460). The PROSPECT trial showed that among various echocardiographic indices of mechanical dysynchrony used, interventricular mechanical delay was significantly associated with a clinical CRT response (461). However, the electrical and mechanical desynchrony are not well correlated in HF patients (462, 463) while the type of underlying cardiomyopathy (ischemic or nonischemic) may influence the concordance of these two parameters (464). Interestingly, the combination of electrical and mechanical measurements of dysynchrony may improve the prediction of the response to CRT defined as LVESV ≥ 15% (465).

Regarding the prognostic significance of QRS narrowing in cardiac events, existing studies have shown that postoperative QRS widening after CRT implantation is associated with an increased mortality risk or cardiac transplantation during follow-up (466, 467). On the other hand, QRS narrowing has been associated with better survival rates or lower cardiac hospitalizations in CRT recipients (468-470). A recent study showed that acute QRS narrowing is significantly associated with long-term mortality and morbidity in LBBB patients only (471). However, results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Study showed that after adjustment for baseline variables, acute QRS change after CRT was not an independent predictor of death or HF hospitalization (472).

Our findings highlight the importance of aiming the greatest QRS narrowing during implantation or during device programming after implantation. Specifically, the greatest QRS narrowing can guide the optimal pacing position site while lack of QRS narrowing might lead to device programming and optimization of pacing vector and timing intervals. Specific conduction characteristics of each patient makes the implementation of a universal programming strategy impossible. However, a recent study showed that biventricular pacing with SyncAV (a device-based algorithm that automatically adjusts paced atrioventricular delay (default or programmable offset) according to intrinsic atrioventricular conduction) with offset that minimized QRSd

showed the better results regarding QRS narrowing (473). Furthermore, recent results from an Italian multicenter registry that compared conventional CRT with multipoint pacing via a quadripolar left ventricular lead showed superiority of multipoint pacing in achieving a greater QRS narrowing and therefore leading to an increase in ejection fraction and clinical composite response (474).

5.4 Limitations

The results of this study should be interpreted in the light of the following limitations. The major limitation of our study is the observational nature of the studies included in our analysis. Another major limitation is that responders and non-responders are arbitrarily separated especially regarding the clinical response definition. Furthermore, although the inclusion of the studies which share the same definition of CRT response is reasonable and strengthens the results of our study, this led to the exclusion of many studies which provided data about the association of the change in QRS width or attained QRS difference with the clinical and/or echocardiographic response. In addition, several studies that showed significant or non-significant results and did not provide data in a useful format in order to be included in the quantitative synthesis and therefore they were excluded (475). This fact may lead to an overestimation of the measured relation between QRS narrowing and attained QRS difference between responders/non-responders with CRT response in the present meta-analysis. Another limitation is the high heterogeneity that was found in the analysis regarding the association of attained QRS duration with echocardiographic response. This heterogeneity can be attributed to the absence of a same methodology of QRS width measurement between the included studies. The different methods to measure QRS width leads to different nominal values and furthermore influences the value of QRS width in predicting CRT response (476). In this context, QRS duration measured at the earliest onset of the QRS waveform in any lead till the latest offset in any lead showed lower variability in predicting CRT response and should be implemented in the future studies for achieving more reliable results (476). Furthermore, the LVESV was not measured with an objective technique, explaining a large part of the observed heterogeneity. According to GRADE framework, our analyses were classified as having moderate quality of evidence which means that the true effect size is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Furthermore, as already reported, E-value is the minimum strength of

association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to explain away a treatment–outcome association (425). Although a threshold cutoff for the E-value does not exist, the measured E-values of the included studies were small, indicating that little unmeasured confounding would be needed to explain away an effect estimate. Finally, our study did not assess the relation between QRS narrowing and major clinical outcomes (mortality, hospitalization rates) which are of great clinical importance.

5.5 Conclusions

Acute and late improvement of electrical dysynchrony following biventricular pacing assessed by QRS narrowing is associated with clinical and echocardiographic response. However, large prospective studies are needed to further examine this association as well as its impact on major adverse cardiac events in patients undergoing CRT.

6. Abstract in Greek (Περίληψη)

Η καρδιακή ανεπάρκεια είναι ένα σημαντικό πρόβλημα της δημόσιας υγείας, ο επιπολασμός του οποίου έχει αυξηθεί τις τελευταίες δεκαετίες. Αναλόγως με το κλάσμα εξώθησης, διακρίνονται δύο τύποι καρδιακής ανεπάρκειας: η καρδιακή ανεπάρκεια με χαμηλό και με διατηρημένο κλάσμα εξώθησης. Οι ασθενείς με καρδιακή ανεπάρκεια παρουσιάζουν αυξημένη συχνότητα εμφάνισης τόσο κολπικών όσο και κοιλιακών αρρυθμιών. Πέραν της φαρμακευτικής αγωγής, οι νεότερες θεραπείες αντιμετώπισης της καρδιακής ανεπάρκειας και των αρρυθμιών που εμφανίζονται στους ασθενείς αυτούς (κατάλυση, απινιδωτής, θεραπεία καρδιακού επανασυγχρονισμού) έχουν αποδεδειγμένο κλινικό όφελος σε συγκεκριμένες κατηγορίες ασθενών. Στόχος της παρούσας διατριβής είναι η απάντηση σε σημαντικά κλινικά ερωτήματα που αφορούν του ασθενείς με καρδιακή ανεπάρκεια με χαμηλό κλάσμα εξώθησης. Συγκεκριμένα, πραγματοποιήσαμε μια μετα-ανάλυση για την αναζήτηση πιθανής συσχέτισης μεταξύ του ιστορικού κολπικής μαρμαρυγής και σημαντικών κλινικών εκβάσεων. Διαπιστώσαμε ότι το ιστορικό κολπικής μαρμαρυγής στους ασθενείς αυτούς σχετίζεται με 42% αυξημένο κίνδυνο θνησιμότητας από κάθε αιτία, 44% αυξημένο κίνδυνο πρόσφορων θεραπειών και διπλάσιο κίνδυνο απρόσφορων θεραπειών σε σχέση με τους ασθενείς χωρίς ιστορικό κολπικής μαρμαρυγής. Ένα επιπλέον ερώτημα που κληθήκαμε να απαντήσουμε είναι το κατά πόσο οι πρόσφορες και απρόσφορες θεραπείες σχετίζονται με αυξημένο κίνδυνο ολικής θνησιμότητας στους ασθενείς με καρδιακή ανεπάρκεια με χαμηλό κλάσμα εξώθησης. Τα αποτελέσματα της μελέτης έδειξαν ότι οι πρόσφορες θεραπείες σχετίζονται με διπλάσιο κίνδυνο θνησιμότητας από κάθε αιτία ενώ οι απρόσφορες θεραπείες με 30% αυξημένο κίνδυνο. Τα αποτελέσματα αυτά δε θα πρέπει να ερμηνευτούν ως σχέση αιτίας-αποτελέσματος αλλά ότι οι πρόσφορες και απρόσφορες θεραπείες του απινιδωτή αποτελούν δείκτη δυσμενούς πρόγνωσης των ασθενών αυτών. Το επόμενο κλινικό ερώτημα που μελετήσαμε, αφορά τους ασθενείς με καρδιακή ανεπάρκεια και χαμηλό κλάσμα εξώθησης που υποβάλλονται σε επέμβαση κατάλυσης κολπικής μαρμαρυγής. Πραγματοποιήσαμε μια αναδρομική μελέτη παρατήρησης που περιλάμβανε 38 ασθενείς (μέση ηλικία: 54.1 ± 12.2 χρονών, 28 (73.7%) άνδρες, μέσο κλάσμα εξώθησης: 38.2 ± 6.3%) που υποβλήθηκαν σε επέμβαση κατάλυσης κολπικής μαρμαρυγής (16 ασθενείς με παροξυσμική κολπική μαρμαρυγή και 22 ασθενείς με μη παροξυσμική κολπική μαρμαρυγή). Δείξαμε ότι το 73,7% των ασθενών κατά τη διάρκεια των 38,2 μηνών παρακολούθησης παρέμειναν σε φλεβοκομβικό ρυθμό ενώ η

πολυπαραγοντική ανάλυση ανέδειξε πως η εμφάνισης πρώιμης υποτροπής κολπικής μαρμαρυγής (κατά τη διάρκεια των πρώτων 3 μηνών μετά την επέμβαση κατάλυσης) και η χορήγηση αμιωδαρόνης σχετίζονται με αυξημένη συχνότητα εμφάνισης όψιμης (πέραν των τριών μηνών) υποτροπής κολπικής μαρμαρυγής. Σχετικά με τη χορήγηση αμιωδαρόνης, η συσχέτισης της με την υποτροπή της αρρυθμίας μπορεί να εξηγηθεί μόνο στα πλαίσια εξέλιξης της νόσου που οδήγησαν στην ανάγκη χορήγησης αμιωδαρόνης. Τέλος, κληθήκαμε να απαντήσουμε δύο κλινικά ερωτήματα σχετικά με τους ασθενείς που έχουν υποβληθεί σε θεραπεία καρδιακού επανασυγχρονισμού. Η πρώτη μελέτη, αφορά μια αναδρομική μελέτη παρατήρησης που σκοπό είχε την εύρεση συσχέτισης μεταξύ απλών αιματολογικών δεικτών και της ανταπόκρισης στη θεραπεία καρδιακού επανασυγχρονισμού. Η μελέτη μας περιέλαβε 48 ασθενείς (μέση ηλικία: 66.2±9.5 χρονών, 81.3% άνδρες, 29 (60.4%) με ισχαιμική καρδιακή ανεπάρκεια). Στους 6 μήνες παρακολούθησης, 37 (77.1%) ασθενείς ανταποκρίθηκαν στη θεραπεία καρδιακού επανασυγχρονισμού. Η πολυπαραγοντική ανάλυση ανέδειξε πως η μεγαλύτερη ηλικία και τα χαμηλότερα επίπεδα κρεατινίνης σχετίζονται με την ανταπόκριση στη θεραπεία καρδιακού επανασυγχρονισμού ενώ δεν ανευρέθηκε στατιστικά σημαντική συσχέτιση με τους μελετούμενους αιματολογικούς δείκτες (λευκά αιμοσφαίρια, ουδετερόφιλα πολυμορφοπύρηνα, λεμφοκύτταρα, αιμοπετάλια, λόγος ουδετεροφίλων-λεμφοκυττάρων, εύρος κατανομής ερυθρών αιμοσφαιρίων). Η επόμενη μελέτη, αφορά την εύρεση πιθανής συσχέτισης μεταξύ της βελτίωσης του ηλεκτρικού δυσυγχρονισμού μετά την εμφύτευση συσκευής καρδιακού επανασυγχρονισμού με την ανταπόκριση στη θεραπεία εκφραζόμενη είτε με κλινικά είτε με υπερηχογραφικά κριτήρια. Πραγματοποιήσαμε μια μετα-ανάλυση μελετών παρατήρησης διεξάγοντας ξεχωριστές αναλύσεις σχετικά με τη κλινική ανταπόκριση στη θεραπεία (εκφραζόμενη ως βελτίωση του NYHA ≥1) και την υπερηχογραφική ανταπόκριση (εκφραζόμενη ως μείωση του τελοσυστολικού όγκου ≥15%). Η μελέτη μας έδειξε ότι η βελτίωση του ηλεκτρικού δυσυγχρονισμού, εκφραζόμενη είτε ως επίτευξη βραχύτερου διαστήματος QRS μετά την εμφύτευση είτε ως βράχυνση του QRS διαστήματος πριν και μετά την εμφύτευση της συσκευής επανασυγχρονισμού, σχετίζεται στατιστικά σημαντικά τόσο με την κλινική όσο και με την υπερηχογραφική ανταπόκριση στην θεραπεία. Κατά συνέπεια, η μελέτη μας έδειξε τη σημασία της επίτευξης όσο το δυνατόν βραχύτερου διαστήματος QRS είτε κατά την εμφύτευση είτε κατά τον προγραμματισμό της συσκευής.

7. Abstract

Heart failure (HF) is a major public health issue and the worldwide prevalence has been increasing over the last decades. The main classification of HF is historically based on left ventricular ejection fraction (LVEF). According to the latest 2016 HF guidelines from the European Society of Cardiology (ESC), patients are classified in the following categories: a) HF with preserved ejection fraction (HFpEF) which includes patients with LVEF ≥ 50%, b) HF with reduced ejection fraction (HFrEF) which includes patients with LVEF <40% and c) HF with mid-range ejection fraction (HFmrEF) which includes patients with LVEF in the grey zone of 40-49%. The clinical course of HF syndrome is complicated by atrial and ventricular arrhythmias. Innovative treatment strategies that include catheter ablation and cardiac resynchronization therapy have a beneficial role in the prognosis of specific HF patients. The aim of this PhD thesis was to answer important clinical questions regarding the management of HFrEF patients. More specifically, we performed a meta-analysis to assess the association between atrial fibrillation (AF) and all-cause mortality / implantable cardioverter defibrillators (ICD) therapies in HFrEF and an implanted ICD. We found that HF patients with a history of AF had a 42% [combined effect estimate (cEE) 1.42 (95% CI: 1.28-1.57)] higher risk of all-cause mortality compared to patients with no AF history. Furthermore, AF patients had a higher risk of appropriate [cEE 1.44 (95% CI: 1.27-1.64)] and inappropriate ICD interventions [cEE 2.05 (95% CI 1.75-2.44)]. Moreover, we performed a meta-analysis concerning the impact of ICD interventions on all-cause mortality in HFrEF. Our data showed that, in patients with HFrEF, appropriate [HR 2.00 (95% CI (1.52-2.63), p<0.01, I^2 88%]] and inappropriate [HR 1.30 (95% CI (1.07-1.58), p<0.01, I^2 26%] ICD interventions were significantly associated with increased all-cause mortality. However, further research is needed to investigate whether shocks (appropriate and/or inappropriate) are the cause of the worse prognosis or only indices of greater HF severity and worse overall health in these patients. Regarding the next clinical question, we aimed to evaluate the long-term results of a single radiofrequency catheter ablation procedure in HF patients with AF. We performed a retrospective study that included a total of 38 patients with EF<50% (mean age, 54.1 ± 12.2 years; 28 [73.7%] males; mean LVEF, 38.2% ± 6.3%). After a mean follow-up period of 38.2 months (range, 5–92 months), 28 patients (73.7%) were free from arrhythmia recurrence. In multivariate analysis, early arrhythmia recurrence (P = 0.03) and amiodarone antiarrhythmic drug administration (P = 0.003) remained independent

predictors of arrhythmia recurrence. The next two research studies are related with HF patients with a CRT implanted. We performed a retrospective study investigating the association between different hematological and biochemical indices and response to CRT. A total of 48 patients (mean age: 66.2 ± 9.5 years, 81.3 % males) were included; 29 (60.4 %) had ischemic cardiomyopathy, and 19 (39.6 %) had dilated cardiomyopathy. At six months of follow-up, 37 patients (77.1 %) had responded to CRT. Ten patients (20.8 %) had ventricular tachycardia (VT), 24 (50 %) patients were hospitalized, and two patients (4.2 %) died during the follow-up period. Multivariate analysis demonstrated that age (p =0.03) and creatinine levels (p =0.02) were independent predictors of the response to CRT. No significant associations between hematological markers (white blood cells, neutrophils, lymphocytes, platelets, neutrophil to lymphocyte ratio, red blood cells distribution width) and CRT response were observed. Finally, we performed a meta-analysis to investigate the association between QRS narrowing after CRT with clinical (defined as New York Heart Association (NYHA) reduction $\geq$ 1) and echocardiographic (defined as left ventricular end-systolic volume (LVESV) reduction $\geq$ 15%) response in patients with HF. We included 32 studies (14 studies (1274 patients mean age 64 years old, males 79.3%) using clinical CRT response and 18 studies (1270 patients, mean age 64 years old, males 69.1%) using echocardiographic CRT response. A significant association between QRS narrowing and shorter attained QRS duration with clinical and echocardiographic CRT response was observed. This association was independent of the timing of QRS width measurement after CRT implantation. As a result, we concluded that acute and late improvement of electrical dysynchrony as depicted by QRS narrowing following biventricular pacing is associated with clinical and echocardiographic response to CRT.

8. Abbreviations

ACCF/AHA: American College of Cardiology Foundation/ American Heart Association

ACEi: angiotensin-converting enzyme inhibitor

AF: Atrial fibrillation

A-HeFT: African American Heart Failure Trial

AMIOVIRT: Amiodarone versus implantable cardioverter-defibrillator trial

ANP: atrial natriuretic peptide

APOLLON: A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejection fraction

ARBs: angiotensin II receptor blockers

AT: atrial tachycardia

ATMOSPHERE: Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure

ATP: anti-tachycardia pacing

AV: atrioventricular

AVID: Antiarrhythmics Versus Implantable Defibrillators trial

BMI: body mass index

BNP: brain natriuretic peptide

BP: blood pressure

CA: catheter ablation

CABG: Coronary Artery Bypass Graft Patch trial

CARE-HF: Cardiac Resynchronization-Heart Failure

CASH: Cardiac Arrest Survival in Hamburg trial

CASTLE-AF: Catheter Ablation for Atrial Fibrillation with Heart Failure Trial

CAT: cardiomyopathy trial

CFAEs: Complex Fractionated Atrial Electrograms

CI: confidence intervals

CIDS: Canadian Implantable Defibrillator Study

COMET: Carvedilol Or Metoprolol European Trial

COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial

COPD: chronic obstructive pulmonary disease

CRP: C-reactive protein

CRT-D: cardiac resynchronization therapy defibrillator

CRT-P: cardiac resynchronization therapy pacemaker

DANISH: Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality

DCM: dilated cardiomyopathy

DEFINITE: Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial

DINAMIT: Defibrillator in Acute Myocardial Infarction Trial

eGFR: estimated glomerular filtration rate

FGF-23: fibroblast-growth factor-23

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

Hb: hemoglobin

Hct: hematocrit

HDL: high density lipoprotein

HF: heart failure

HFmrEF: heart failure with mid-range ejection fraction

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HFSIS: heart failure survey in Israel study

HR: hazard ration

ICD: implantable cardioverter defibrillator

IRIS: Immediate Risk Stratification Improves Survival trial

IVS: interventricular septum diameter

LAD: left atrial diameter

LAV: left atrial volume

LDH: lactate dehydrogenase

LDL: low density lipoprotein

LVEDD: left ventricular end diastolic diameter

LVEDV: left ventricular end-diastolic volume

LVEF: left ventricular ejection fraction

LVESD: left ventricular end systolic diameter

LVESV: left ventricular end-systolic volume

MADIT RIT: MADIT Randomized Trial to Reduce Inappropriate Therapy

MADIT: Multicenter Automatic Defibrillator Implantation Trial

MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

MIRACLE ICD: Multicenter InSync ICD Randomized Clinical Evaluation

MIRACLE: Multicenter InSync Randomized Clinical Evaluation

MRAs: mineralocorticoid antagonists

MUSIC: Muerte Subita en Insufficiencia Cardiaca study

MUSIC: Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy

MUSTIC: Multisite Stimulation in Cardiomyopathies

MUSTT: Multicenter Unsustained Tachycardia trial

NLR: neutrophil to lymphocyte ratio

NOS: Newcastle–Ottawa Quality Assessment Scale

NYHA: New York Heart Association

OR: odds ratio

ORBIT-AF: Outcomes Registry for Better Informed Treatment of Atrial Fibrillation

PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

PATH-CHF: Pacing Therapies in Congestive Heart Failure study

PLR: platelet to lymphocyte ratio

PLT: platelets

PNR: platelet to neutrophil ratio

PROSPECT: Predictors of Response to CRT

PVI: pulmonary vein isolation

PVs: pulmonary veins

PWD: posterior wall diameter

RDW: red blood cell distribution width

RDW: red cell distribution width

RDW-CV: Red Distribution Width-Coefficient Variation

REVERSE: Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Study

RF: radiofrequency

RR: relative risk

RVSP: right ventricular systolic pressure

SCD: sudden cardiac death

SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial

SD: standard deviation

SIMPLE: Shockless Implantation Evaluation trial

SOLVD: Studies of Left Ventricular Dysfunction Prevention and Treatment Trials

SR: sinus rhythm

SwedeHF: Swedish Heart Failure Registry

TAPSE: Tricuspid annular plane systolic excursion

TOPCAT: Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

VALIANT: VALsartan In Acute myocardial iNfarcTion trial

VF: ventricular fibrillation

V-HeFT I, II: Veterans Affairs Vasodilator-Heart Failure I, II Trials

VT: ventricular tachycardia

WBC: white blood cells

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