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Safety and efficacy of conventional and modern therapeutic approaches of cardiac arrhythmias and heart failure

PhD Thesis

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1. ABBREVIATIONS

ACC/AHA = American College of Cardiology Foundation/American Heart Association

ACE = angiotensin converting enzyme

AF = atrial fibrillation

ARB = angiotensin II receptor blocker

ASA = acetyl-salicylic acid

ATP = anti-tachycardia pacing

AUC = Area Under the Curve

BiV = biventricular

BLOCK-HF = Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block trial

BNP = B-type natriuretic peptide

BPM = beats per minute

CABG = coronary artery bypass graft

CHF = congestive heart failure

CI = confidence intervals

CIEDs = Cardiac Implantable Electronic Devices

COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation trial

CPVT = catecholaminergic polymorphic ventricular tachycardia

CRT = cardiac resychronisation therapy

CRT-D = cardiac resychronisation therapy with defibrillator

DIG = Digitalis Investigation Group trial

DT = defibrillation testing

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio / heart rate

HRV = heart rate variability

ICD = implantable cardioverter defibrillator

ICU = intensive care unit

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

MADIT-CRT = Multicentre Automatic Defibrillator Implantation Trial - Cardiac Resynchronisation Therapy

MIRACLE = Multicentre InSync Randomised Clinical Evaluation trial

MRA = mineralocorticoid receptor antagonists

MUSTIC = Multisite Stimulation in Cardiomyopathy trial

NYHA = New York Heart Association Functional classification

PARTNERS HF = Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure trial

PCI = percutaneous coronary intervention

RBBB = right bundle branch block

REPLACE registry = Implantable Cardiac Pulse Generator Replacement registry

REVERSE = Resynchronisation Reverses Remodelling in Systolic Left Ventricular trial

ROC-analysis = Receiver Operating Characteristic method

RR = relative risk

RyR = ryanodine receptor

SD = standard deviation

TIA = transient ischemic attack

ULN = upper limit of normal

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2. INTRODUCTION

2.1. Modern therapy of heart failure

Heart failure (HF) is a clinical syndrome caused by the abnormality of cardiac function. Due to diverse underlying diseases and reasons heart fails to pump enough blood to the metabolizing tissues or is able to do but only at the cost of elevated diastolic filling pressure. Chronic systolic HF is often associated with severe comorbidities and complications, such as life-threatening cardiac arrhythmias, and has also a worse prognosis. Since, the prevalence of HF is high in developed countries (~1-2% of the adult population), and rising to ≥10% among people 70 years of age [Ponikowski et al. 2016] the importance of appropriate treatment is remarkable.

In patients with symptomatic chronic HF the first line therapy consists of the pharmacological treatment with neurohormonal antagonists (ACEIs, beta-blockers, MRAs). These drugs have a robust evidence for improving survival in HF. Scientific data supporting the use of other alternative drugs, such as ivabradine, angiotensin receptor neprilysin inhibitors or direct vasodilators are much more limited. Digitalis glycosides are also still in use. This medicine has been introduced into clinical practice more than 200 years ago. Since that time, both drug and device therapy have evolved explosively and several observational studies raised concerns in terms of the safety of digitalis when used in patients on contemporary medications.

Beside the aforementioned drug therapies implantable cardioverter defibrillators and cardiac resynchronisation therapy are the most important therapeutic modalities with reliable evidence for improving survival in HF. Since, not all HF patients benefit the same from these devices, the optimal patient selection is being studied extensively. Technical advances, for example combination with remote monitoring technics, provide further clinical directions and research goals in this field.

Although significant improvements in prognosis of arrhythmic and HF patients have been achieved, there is still substantial mortality encountered as a consequence of these conditions. Hence, continuous search for new therapeutic approaches is imperative.

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While new therapies need scrutiny, there is still much to learn about old drugs and routines and their safety and efficacy should be reassessed again and again in the era of novel therapies. This present work focuses on the safety of digitalis glycosides and novel functions and indications of cardiac resynchronisation therapy.

2.2. Digitalis glycosides

2.2.1. Pharmacology of digitalis glycosides

Cardiac glycosides are one of the oldest drugs of medicine. The use of the foxglove plant (Digitalis purpurea, Figure 1A.) for the treatment of heart failure was first described by a British physician, chemist and botanist, Sir William Withering in Birmingham, UK in 1785 [Withering 1785].

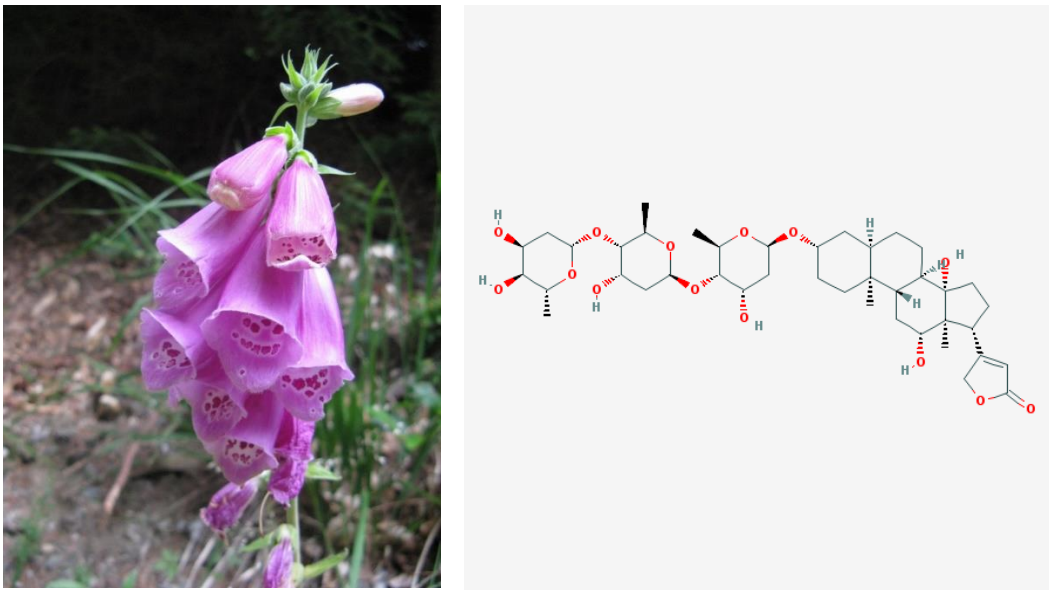

Figure 1A. Digitalis purpurea (photo: József Juhász, Kőszeg Mountains); **1B.** Chemical structure of digoxin (source: PubChem)

The leaves of the purple (Digitalis purpurea) and woolly foxglove (Digitalis lanata) contain the medically most relevant cardiac glycosides. The so-called A-, B- and C-purpurea-glycosides can be found in the leaves of the purple foxglove flower. These provide the agent digitoxin• during an enzymatic conversion while drying the leaves. Digoxin• originates from the A-, B- and C-lanata-glycosides, driven by a similar enzymatic process (Figure 1B.) [Papp et al. 2001].

The clinically most relevant difference in the pharmacokinetics of digitalis glycosides is the way of elimination. While digoxin is mainly excreted by the kidneys ($t_{1/2}$ ~36h, overall weak plasma binding), the principle route of elimination for digitoxin is hepatic/intestinal ($t_{1/2}$ 5-7 days, overall strong plasma binding). Both volume of distribution and drug clearance rate are decreased in elderly patients. Despite renal clearance, digoxin cannot effectively be removed via haemodialysis due to the drug's large volume of distribution [Papp et al. 2001; Brunton et al. 2011].

2.2.2. Mechanisms of action

Digitalis has three key pharmacological mechanisms of action: hemodynamic (positive inotropic), electrophysiological (negative dromotropic) and neurohormonal (parasympathomimetic) [Smith 1988; Brunton et al. 2011]. The main pharmacological effect is associated with the reversible inhibition of the membrane sodium-potassium ATPase. Calcium enters the myocyte during the plateau phase of the action potential and triggers further calcium release from the sarcoplasmic reticulum stores required to activate contractile proteins. These proteins convert the signal of increased intracellular calcium-ion concentration into mechanical force. Cardiac glycosides bind and inhibit the phosphorylated α-subunit of the sarcolemmal Na^+-K^+-ATPase and thereby increase cytosolic Na^+ concentration. This decreases the transmembrane Na^+ gradient that drives the Na^+-Ca^{2+} exchangers. As a consequence, less Ca^{2+} is removed from the cell and more Ca^{2+} is accumulated within the cytosol. This mechanism triggers the release of stored Ca^{2+} from the sarcoplasmic reticulum via the ryanodine receptor (RyR). The Ca^{2+}-induced Ca^{2+} release increases the level of cytosolic Ca^{2+} available for interaction with the myofilaments. Greater interaction between the contractile proteins improves the force of contraction leading to a global increase in left ventricular systolic function (Figure 2.) [Brunton et al. 2011]. Notably, there are some further hypotheses of mechanism of action besides the most accepted one described above.

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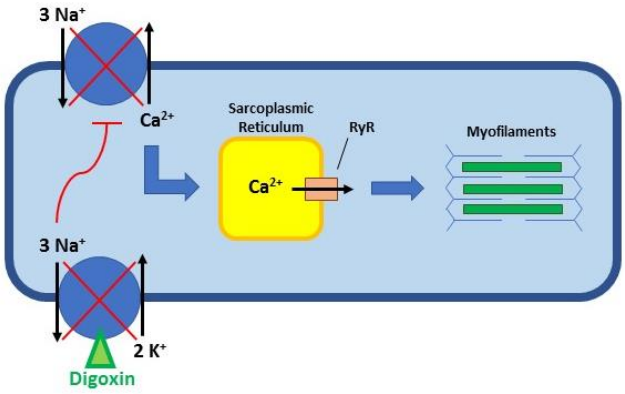

Figure 2. Mechanism of modulation of myocardial function by cardiac glycosides

The neurohormonal effect of digitalis on vagal activation is leading to a shift in autonomic balance toward parasympathetic dominance. This is thought to be beneficial in chronic heart failure (HF), since overactivation of the sympathetic nervous system is typical in HF patients. The precise mechanism for this direct antisympathetic activity has not fully been elucidated, but it most likely reflects a beneficial influence of the carotid baroreflex responsiveness to changes in carotid sinus pressure [Wang et al. 1990]. Furthermore, there are reports suggesting that digoxin reduces plasma norepinephrine, renin, and aldosterone levels and exerts effect on the central nervous system as well.

In addition, there are important indirect electrophysiological effects of digitalis. These are mediated via an increase of the vagal tone and inhibition of the sympathetic nervous system. Since atrial tissue is more exposed to cholinergic innervation than ventricular myocardium, these parasympathomimetic effects are dominating on the sinoatrial and atrioventricular nodal tissues. Collectively, this may contribute to a negative dromotropic effect and increase the refractory period [Papp et al. 2001; Brunton et al. 2011].

2.2.3. Proarrhythmic effects

Optimal binding of digitalis glycosides to the specific inhibitory site requires Na^+, Mg^+, and ATP, whereas extracellular K^+ inhibits the binding. The diastolic level of intracellular calcium rise is thought to be negligible under non-toxic conditions, however both systolic and diastolic intracellular Ca^{2+} levels appear to rise with higher concentrations of digitalis and contribute to oscillatory disturbances of the membrane potential [Kass et al. 1978]. Thus, proarrhythmic effects of digitalis are believed to be the result of Ca^{2+}-overload with consequential spontaneous release and uptake of calcium by the sarcoplasmic reticulum

followed by afterdepolarizations of the cardiac cell membrane [Smith 1988]. Non-arrhythmic toxic manifestations of digitalis excess (for example nausea, vomiting or altered colour sensations) are mediated by chemoreceptors of the brain rather than direct effects on the gastrointestinal tract. Predominantly vasoconstrictive hemodynamic side-effects are also neurally mediated.

Life-threatening digitalis intoxication can effectively be treated with digoxin-specific Fab fragments purified from antibodies raised in sheep via an immunisation process [Smith et al. 1982].

2.2.4. Scientific evidences

The early withdrawal studies, the PROVED [Uretsky et al. 1993] and the RADIANCE trial [Packer et al. 1993] led to the FDA approval of digoxin for the treatment of patients suffering from heart failure and atrial fibrillation with rapid ventricular rate in 1998. In the placebo-controlled PROVED trial, patients with HFrEF (heart failure with reduced ejection fraction) were randomised to receive either digoxin continuation (n=42) or withdrawal (n=46) on top of a background therapy of diuretics. Patients in the withdrawal group showed worsened exercise capacity (p=0,003), lower LVEF (p=0,016) and an increase in the incidence of HF exacerbations (p=0,039) [Uretsky et al. 1993]. In the RADIANCE trial, 178 patients with an LVEF≤35% and NYHA class II-III on a drug regimen of digoxin, diuretics and ACE-inhibitors (i.e. captopril or enalapril) were randomised to withdrawal or continuation of digoxin for 12 weeks. The relative risk of worsening heart failure in the placebo group as compared with the digoxin group was 5,9 (95% CI, 2,1-17,2). Furthermore, all measures of functional capacity deteriorated in patients receiving placebo as compared to patients that were still continuing to take digoxin (p=0,033 for maximal exercise tolerance, p=0,01 for submaximal exercise endurance, and p=0,019 for NYHA class). In addition, patients that switched from digoxin to placebo had lower quality-of-life scores (p=0,04), decreased left ventricular ejection fractions (p=0,001), and increased heart rate (p=0,001), and body weight (p<0,001) [Packer et al. 1993].

All these results lead to the high-volume, multicentre, placebo-controlled, randomised Digitalis Investigation Group (DIG) trial, published in 1997 in the New England Journal of Medicine [Garg et al. 1997]. Ambulatory patients with a left-ventricular ejection

fraction of ≤45% and sinus rhythm were randomly assigned to receive digoxin (n=3397) or placebo (n=3403) in addition to standard HF medication. Of note, at the time when the study was conducted, contemporary HF medication included only ACE-inhibitors (94% of patients) and diuretics (82% of patients). In the whole cohort, 70% of the patients had ischaemic cardiomyopathy and 22% were female. The median dose of digoxin was 0,25 mg/die, with a mean serum digoxin level of 0,86 and 0,80 ng/ml at 1 and 12-month follow-up, respectively. After a mean follow-up of 37 months, digoxin failed to reduce the primary endpoint of all-cause mortality in comparison to placebo (34,8 vs. 35,1%), however, the rate for hospitalization due to worsening of heart failure was significantly reduced (RR 0,72, 95% CI, 0,66-0,79; p<0,001). The significantly higher mortality from „other cardiac causes" in patients receiving digoxin including cardiac arrhythmic mortality (15,0% vs. 13,0%, RR 1,14%, 95% CI, 1,01-1,30) is often forgotten when interpreting the results of the DIG study. Furthermore, only 12% of the randomised patients had a history of atrial fibrillation questioning the power of scientific evidence for rate control therapy with digitalis.

The data set collected for the DIG trial has been utilized for a number of post hoc analyses. The most important one of these from Rathore et al. [2003] describes the association of serum digoxin concentrations and all-cause mortality. In fact, it could be demonstrated that higher serum digoxin levels (defined as ≥1.2 ng/mL) were significantly associated with increased mortality, whereas lower plasma concentrations seemed to provide clinical benefit in the trial.

Since the publication of the DIG trial, treatment of chronic heart failure has changed fundamentally. With the routine use of beta-blockers, mineralocorticoid receptor antagonists, direct vasodilators and the introduction of device therapy (i.e. ICD and CRT), mortality and morbidity of HF patients were improved significantly. In addition, a series of studies were published in the last two decades raising serious doubts on the benefit of digoxin when added to contemporary rate control or heart failure treatment. In fact, some observations indicated that digoxin might have a negative effect on mortality. These studies will be discussed in detail after the results of our meta-analysis with digoxin.

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2.3. Cardiac resynchronisation therapy

2.3.1. Principles of resynchronisation therapy

Due to the impaired systolic function during the progression of heart failure, intracardiac pressure and wall stress increase, an excessive peripheral vasoconstriction occurs and all these changes result in a complex pathological mechanism called ventricular remodelling. This term refers to an alteration in ventricular architecture, with increased volume and altered chamber configuration, driven by a combination of pathologic myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis [Konstam et al. 2011]. An important characteristic of cardiac remodelling is the dilation of atrium and ventricle with consecutive mitral valve regurgitation. In about 30-50% of patients with chronic systolic heart failure, electrocardiographic evidence of different types of conduction delays can also be found [Shamim et al. 1999; Eschalier et al. 2015]. This result in mechanical dyssynchrony, i. e. nonsynchronous contraction of the wall segments of the left ventricle (intraventricular) and between the left and right ventricles (interventricular). Mechanical dyssynchrony in turn enhances the hemodynamic consequences of chronic systolic ventricular dysfunction.

Despite important therapeutic advances in medical treatment (i.e. ACE-inhibitors or angiotensin II–receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists), the prognosis of patients with chronic systolic heart failure remains poor. This has stimulated the search for nonpharmacological therapies, such as cardiac resynchronisation therapy (CRT). CRT was developed to overcome the aforementioned pathophysiological mechanisms, particularly the haemodynamically relevant conduction delay between the left and right side of the heart. During CRT, the right as well as the left ventricle (via the coronary sinus to the basal or midventricular left ventricle regions) are stimulated in an atrial-synchronised way to improve LV contractile function and to achieve reverse remodelling (Figure 3.).

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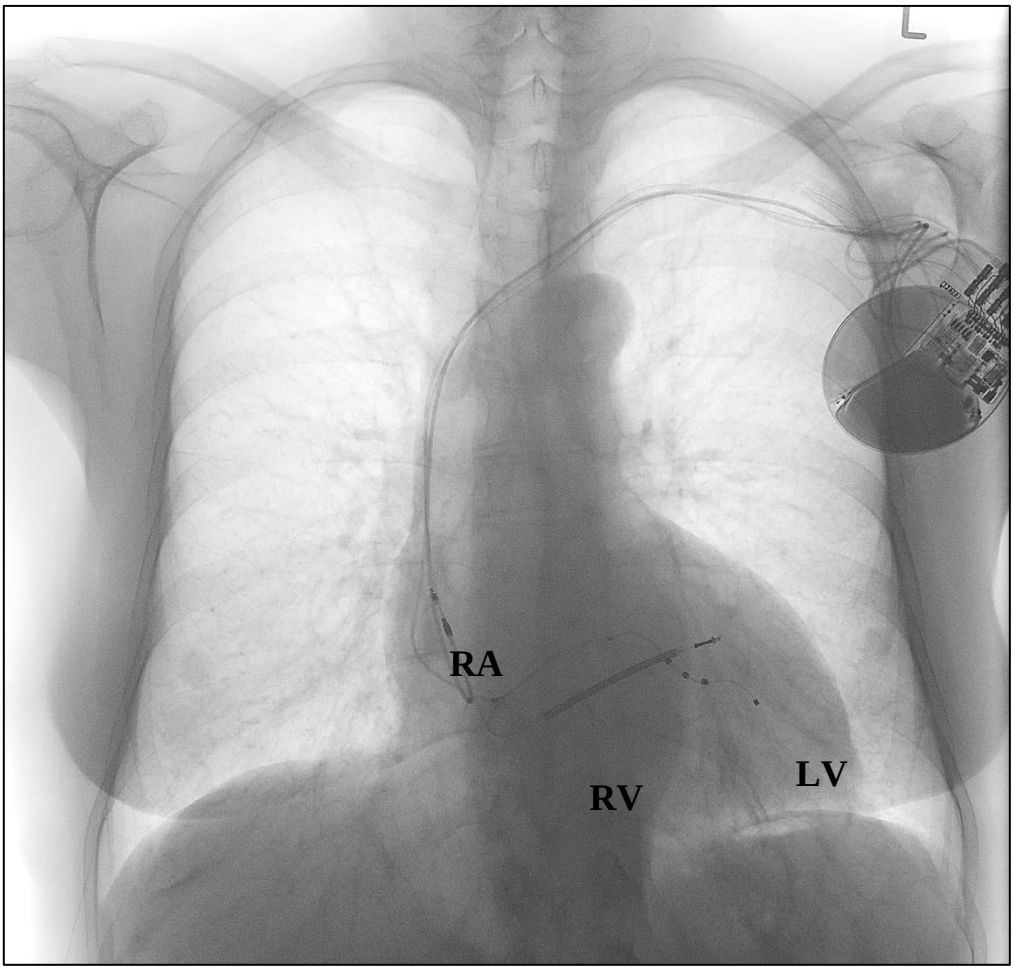

Figure 3. Antero-posterior X-ray of a patient with a CRT-D system. RA: right atrial, bipolar lead; RV: right ventricular, bipolar, single-coil ICD lead; LV: left ventricular, quadripolar lead in a lateral side branch of the coronary sinus

2.3.2. Scientific evidences

The first multi-centre, randomised trial to demonstrate clinical benefit of CRT in patients with chronic systolic heart failure and electrocardiographical evidence of ventricular dyssynchrony was the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial published in 2001 [Cazeau et al. 2001]. This trial examined 67 patients with symptomatic heart failure (LVEF ≤35 %, NYHA class III, sinus rhythm and QRS duration >150 ms) who had a biventricular pacemaker implanted. Patients were enrolled in a cross-over study design with three-month periods of either inactive (back-up VVI mode with 40 bpm) and active (atriobiventricular) pacing. CRT resulted in significant improvement in 6-minute walk distance ($p<0,001$), quality of life ($p<0,001$) and peak oxygen uptake

(p<0,03) as well as decreased hospitalisation rate (p<0,05). The Multicentre InSync Randomised Clinical Evaluation (MIRACLE) trial is another cornerstone in CRT research. It evaluated a similar but much larger patient population (n=453 patients) and demonstrated significant improvements in 6-minute walk distance, NYHA class and quality of life. Furthermore, CRT was effective in reducing the need for hospitalization or intravenous medications for the treatment of acute worsening of heart failure [Abraham et al. 2002].

The first randomised study that could demonstrate significant reduction in overall mortality by CRT was the Comparison of Medical Therapy, Pacing and Defibrillation trial (COMPANION, n=1520, LVEF ≤35 %, NYHA class III–IV, QRS duration >120 ms) which used a combined primary endpoint of first hospitalisation or death from any cause [Bristow et al. 2004]. The beneficial effect of CRT on survival in patients with optimal medical therapy was only significant with CRT-defibrillator (HR 0,64; 95% CI 0,48-0,86; p=0.003), however, there were results suggesting a mortality benefit from CRT even in the absence of defibrillator capabilities (HR 0,76; 95 % CI 0,58-1,01; p=0,059).

A series of studies have since examined the impact of cardiac resynchronisation therapy alone (i.e. CRT-P) on survival in heart failure patients. CARE-HF was the first randomised trial to demonstrate a mortality benefit with CRT even in the absence of defibrillator therapy [Cleland et al. 2005]. CRT-P was associated with a statistically significant reduction in all-cause mortality (HR 0,64; 95 % CI, 0,48 to 0,85). Beneficial effect of CRT over traditional ICD therapy was further confirmed in the randomised Resynchronisation-Defibrillation for Ambulatory Heart Failure (RAFT) trial [Tang et al. 2010]. The REVERSE study extended the earlier observations noted previously from COMPANION for patients with an LVEF <40 % and NYHA functional class of I–II [Linde et al. 2008].

The largest CRT trial to date is the Multicentre Automatic Defibrillator Implantation Trial - Cardiac Resynchronisation Therapy (MADIT-CRT) [Moss et al. 2009]. In this study, 1820 HF patients were enrolled (LVEF ≤ 30%, QRS ≥ 130ms, NYHA I-II) and randomised to receive CRT-D or an ICD alone. During a mean follow-up of 2,4 years, the primary composite end point of death or heart-failure event occurred in 17,2% of patients in the CRT-D group and 25,3% of patients in the ICD-only group (0,66; 95% CI,

0,52-0,84). However, the superiority of CRT was mainly derived from the reduction of HF events. Furthermore, this trial proved that patients with better functional classes (i.e. NYHA I–II) could also benefit from CRT.

More recently, the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial demonstrated the superiority of biventricular pacing over RV pacing in pacemaker-dependent patients with mild HF symptoms (NYHA II-III) and reduced ejection fraction (EF<50%, the baseline mean EF=45%) [Curtis et al. 2013]. Furthermore, there is evidence that CRT - especially in responders - can significantly reduce the risk of ventricular tachyarrhythmias [Saini et al. 2016].

2.3.3. Limitations of CRT

It should be noted that also important limitations of CRT have been reported. For instance, patients with non-left bundle branch block QRS morphology [Cunnington et al. 2015] or narrow QRS complex despite echocardiographic evidence of left ventricular dyssynchrony [Ruschitzka et al. 2013] seem not to benefit from this therapy. For optimal efficacy, cardiac resynchronization therapy should ensure as close to 100% biventricular stimulation [Hayes et al. 2011; Brignole et al. 2013]. Based on the results of a large, prospective single-centre study of unselected heart failure patients, a cumulative mortality rate of 16,9% is to expect under CRT-P/D therapy and this could be well predicted with the Seattle Heart Failure Model [Clemens et al. 2012].

2.3.4. Current guideline recommendations

Based on the scientific evidence mentioned above, the current European guidelines recommend CRT implantation for patients with symptomatic heart failure (New York Heart Association class of II, III or ambulatory IV), reduced left-ventricular ejection fraction ≤ 35 %, sinus rhythm, QRS duration ≥ 130 ms with underlying pattern of left bundle branch block (LBBB) and optimal medical treatment [Ponikowski et al. 2016]. There are also CRT recommendations for patients in atrial fibrillation or with non-LBBB QRS morphology; however, the evidence for these patient groups is weak. Despite some distinct differences [Kutyifa et al. 2017], the latest American guidelines for CRT [Tracy et al. 2012] are similar to the European ones.

2.3.5. Unresolved issues

Despite significant advances in CRT technique, such as stabilization of the LV electrode with stenting in coronary sinus side branches [Gellér et al. 2011], quadripolar LV leads [Vamos et al. 2013; Turkahia et al. 2016] or automatic AV- and VV-interval adjustment [Brugada et al. 2017], unresolved issues remain: a clinically relevant percentage of non-responders [Friedman et al. 2014], CRT in patients with non-LBBB and broad QRS complexes [Cunnington et al. 2015; Eschalier et al. 2015], LV-stimulation in patients with unsuitable anatomy of the coronary sinus [Duray et al. 2008], identifying patients who are more likely to benefit from CRT-D instead of CRT-P [Barra et al. 2016; Nyolczas et al. 2013], clinical role and workup of remotely transmitted information of the device in the daily practice [Ploux et al. 2017], or upgrade to CRT in patients with previously implanted pacemaker or ICD systems [Merkely et al. 2016].

2.4. Background of our studies

2.4.1. Digitalis glycosides in atrial fibrillation and heart failure

The two main indications for the use of cardiac glycosides are the treatment of symptomatic heart failure (HF) in patients with impaired left-ventricular function and rate control in patients with atrial fibrillation. The scientific evidence with respect to digoxin's effects on heart failure is mainly based on two withdrawal studies [Uretsky et al. 1993; Packer et al. 1993] and one large randomised placebo-controlled trial [Garg et al. 1997, Ahmed et al. 2006]. With regards to the second indication, rate control in atrial fibrillation (AF), there is not a randomised placebo-controlled study yielding supportive data. Nevertheless, both indications are endorsed by recent guideline recommendations [McMurray et al. 2012; Camm et al. 2012; Yancy et al. 2013]. However, it is well appreciated that digoxin has a narrow therapeutic window in part related to significant drug–drug interactions and may cause harm if not carefully administered including regular measurements of serum digoxin levels. A series of recent studies have cast serious doubt on the benefit of digoxin when added to contemporary heart failure treatment [Hallberg et al. 2007; Friberg et al. 2010; Fauchier et al. 2009; Dhaliwal et al. 2008; Butler et al. 2010; Freeman et al. 2013]. In fact, some observations have indicated that digoxin

may have a negative effect on mortality [Hallberg et al. 2007; Butler et al. 2010; Freeman et al. 2013; Gjesdal et al. 2008; Whitbeck et al. 2013; Turakhia et al. 2014; Shah at el. 2014; Gamst et al. 2014; Chao et al. 2014; Freeman et al. 2015; Pastori et al. 2015; Domanski et al. 2005].

2.4.2. Digitalis glycosides in ICD patients

Digitalis is used to treat patients with symptomatic heart failure and/or with atrial fibrillation (AF) to control their ventricular rate [Yancy et al. 2013; McMurray et al. 2012; Camm et al. 2010]. There is only one randomised trial evaluating the effects of digitalis compared with placebo in patients with heart failure and impaired left ventricular function who were in sinus rhythm, the so-called DIG trial [Garg et al. 1997]. This trial failed to show a reduction in mortality in patients allocated to active therapy, but digitalis was associated with a lower hospitalization rate compared. Based on these results, current guidelines recommend digitalis use as a Class IIb indication for the treatment of symptomatic heart failure in order to reduce hospitalisation [Yancy et al. 2013; McMurray et al. 2012]. In addition, there is a Class IIa indication for digitalis to establish rate control in patients with AF [Camm et al. 2010], although there is no randomised placebo-controlled trial supporting this recommendation. Digitalis is commonly used despite its narrow therapeutic window and its potential for drug-drug interactions [Hohnloser et al. 2014]. A post hoc analysis of the DIG trial showed that it is of paramount importance to maintain low digitalis plasma concentrations to avoid harmful effects on mortality [Rathore et al. 2003]. Since the publication of the DIG trial, many pro- and retrospective studies raised concerns in terms of the safety of digitalis when used in patients who were otherwise treated with contemporary medications [Hallberg et al. 2007; Butler et al. 2010; Freeman et al. 2013; Whitbeck et al. 2013; Gjesdal et al. 2008]. A recent comprehensive meta-analysis of 19 studies we found an increased relative risk of all-cause mortality (HR = 1.21; 95% CI 1.07-1.38; p = 0.01) in subjects treated with digitalis when compared with those not receiving this medication. There is a lack of data concerning the use of digitalis in implantable cardioverter defibrillator (ICD) patients. A recent subgroup analysis from MADIT-CRT showed an increased risk of high-rate ventricular tachycardia/ventricular fibrillation (VT/VF) episodes in patients treated with digitalis, but no difference in mortality [Lee et al. 2015].

2.4.3. Intrathoracic impedance monitoring with CRT-devices

Unfavourable prognostic impacts of recurrent hospitalizations in chronic systolic heart failure (HF) are well known [Setoguchi et al. 2007]. Accordingly, several methods have been developed aiming at early detection of worsening HF with the potential for timely intervention to prevent hospitalizations and to improve survival. Some of the cardiovascular implantable electronic devices offer extended monitoring capabilities of vital parameters which may help to predict HF events. Yu et al. developed a detection algorithm called OptiVol^{TM} to predict cardiac decompensation by applying Fluid Index derived from the changes of intrathoracic impedance, as a marker of lung fluid status [Yu et al. 2005]. However, the reliability of OptiVol remained contradictory in further clinical trials [Veldhuisen et al. 2011; Conraads et al. 2011]. In the prospective multicentre PARTNERS HF study, the clinical utility of impedance monitoring could have been improved by using a combined device diagnostic algorithm based on additional parameters such as: new onset of atrial fibrillation (AF), rapid ventricular rate during AF, low patient activity levels, high night heart rate, low heart rate variability (HRV), low percentage of biventricular pacing, and ventricular arrhythmias with ICD shocks [Whellan et al. 2010; Sharma et al. 2015]. In this trial the strongest predictor was the elevated Fluid Index (i.e. OptiVol alert). Although the applied device diagnostic algorithm could predict the following hospitalization with high probability, only in 213 of 1324 (16,1%) high-risk periods proved to be associated with true HF events. In further studies the number of false positive or unexplained OptiVol alerts also remained remarkably high despite the combination with remote monitoring techniques [Aizawa et al. 2014; Lüthje et al. 2015; Nishii et al. 2015].

2.4.4. Upgrade cardiac resynchronization therapy

The beneficial impact of newly implanted cardiac resynchronization therapy (CRT) on morbidity and mortality are well described in selected patients with heart failure [Lewis et al. 2015; Al-Majed et al. 2011; Cleland et al. 2013; Zareba et al. 2011; Sipahi et al. 2012; Cunnington et al. 2015]. Patients with heart failure already fitted with a conventional pacemaker or implantable cardioverter defibrillator (ICD) system are often considered for a CRT upgrade after the new development of CRT criteria (i.e., new left bundle branch block [LBBB]) or because of the need of frequent right ventricular pacing. The latest 2012 American College of Cardiology Foundation/American Heart

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Association/Heart Rhythm Society guidelines recommend a CRT upgrade at the time of device replacement with anticipated requirement for significant ventricular pacing as a class IIa indication for patients with a left ventricular ejection fraction (LVEF) ≤35% [Tracy et al. 2012]. In the latest European pacemaker and CRT guidelines from 2013, upgrade procedures from conventional pacemakers or ICDs to CRT are considered as a class I indication (level B) for heart failure patients with a New York Heart Association (NYHA) functional class of III to ambulatory IV, LVEF ≤35%, and a high percentage of ventricular pacing [Brignole et al. 2013]. Accordingly, the number of upgrade procedures from single- or dual-chamber devices to CRT is increasing. However, there is only weak scientific evidence about the outcomes of patients undergoing upgrade procedures compared with de novo CRT implantations [Tracy et al. 2012; Brignole et al. 2013].

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3. OBJECTIVE

3.1. In the light of such conflicting data, a systematic review of published data appears to be timely and may provide the best way to estimate the effectiveness and safety of digoxin therapy and to identify patient populations which are less likely to benefit.

3.2. We aimed to evaluate the effects of digitalis use in a large series of consecutive ICD recipients for the prevention of sudden cardiac death and who were followed for up to 10 years.

3.3. We hypothesized that the reliability of OptiVol alerts could be improved with some modifications of the original PARTNERS HF criteria considering more sensitive diagnostic values and the changes of pattern of these parameters. In our observational study, we aimed to compare the clinical applicability of the device diagnostic algorithm described in PARTNERS HF study to a newly developed algorithm applying refined diagnostic criteria.

3.4. We aimed to compare clinical response and long-term survival in a large cohort of consecutive patients receiving either de novo or upgrade CRT defibrillator (CRT-D) therapy.

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4. METHODS

4.1. Meta-analysis of digoxin associated mortality

4.1.1. Study selection

A comprehensive PubMed and Cochrane search was conducted from 1993 (the publication year of the digoxin withdrawal trials [Uretsky et al. 1993; Packer et al. 1993]) to November 2014 of the English literature dealing with the effects of digoxin on all-cause-mortality in patients with AF or congestive heart failure (CHF). In order to identify and retrieve all potentially relevant articles regarding this topic, the search was performed utilizing the terms ‘digoxin’, ‘mortality’, ‘chronic heart failure’, and ‘atrial fibrillation’. An additional search was also performed using the names of the 10 authors most frequently cited in narrative reviews on this subject and bibliographies of the most recent narrative review articles.

Potentially relevant articles were evaluated by two experienced, independent reviewers, and additional manuscripts were retrieved that either reviewer felt were potentially relevant. Any disagreement was subsequently resolved by all authors of this meta-analysis. Additional publications were identified using the reference lists of selected manuscripts. Only full-size articles of English language published in peer reviewed journals were considered for this meta-analysis. Randomised controlled trials, case-control studies, or cohort studies were eligible for this meta-analysis if the following requirements, prospectively defined by our review protocol [Liberati et al. 2009; da Costa et Jüni, 2014] were met:

(i) inclusion of AF or heart failure patient populations;

(ii) report of adjusted results of effects of digoxin on all-cause-mortality (as the primary or secondary study outcome measure);

(iii) effect sizes provided as hazard ratios (HR).

Studies reporting only composite endpoints but no specific data on all-cause mortality or dealing with different patient populations were not considered.

Methodological quality of all studies was assessed using the Methodological Index for Non-Randomised Studies (MINORS) [Slim et al. 2003]. A score system with a maximum

value of 24 points (each item to be scored from 0 to 2) was used regarding the following aspects: aim of the study, inclusion of consecutive patients, prospective data collection, appropriate endpoint to the aim of the study, unbiased evaluation of endpoints, follow-up period appropriate to the endpoint, loss to follow-up no more than 5%, comparable control group, contemporary groups, baseline equivalence of groups, prospective calculation of the sample size, use of adequate statistical analysis. After both reviewers independently scored the selected publications, the average MINORS score was used for final assessment. Studies were defined to be low-quality and high-quality studies based on their MINORS scores of <16 and ≥16 points [Slim et al. 2003; Ghanbari et al. 2012].

4.1.2. Statistical analysis

All statistical analyses were conducted utilizing Comprehensive Meta-Analysis 3.3 (Biostat, Inc., USA). Heterogeneity between individual trial estimates was assessed using the Q statistic and I^2 statistic [Higgins et al. 2002]. The principal measurement of effect size (i.e. all-cause mortality) was the HR along with the 95% upper and lower confidence intervals (CI). All selected non-randomised studies provided risk assessments which had been adjusted for important baseline clinical variables with different types of statistical methods (mostly Cox regression analysis or propensity-matched analysis). The random-effect model [Borenstein et al. 2009; Borenstein et al. 2010] was used to calculate HR for the overall effect and for the two subgroups (AF, heart failure) in this meta-analysis. A forest plot was constructed showing the individual trials with the pooled estimates. Publication bias was assessed using the funnel plot, the trim and fill method of Duval and Tweedie [Borenstein et al. 2009], and an adjusted rank-correlation test according to Begg and Mazumdar [Begg et al. 1994]. Sensitivity analyses including only publications reporting separate data for patient subsets suffering from AF or CHF, respectively, and studies providing data on the daily digoxin dose and/or the mean digoxin plasma levels were performed.

4.2. Digitalis in ICD patients

4.2.1. Patient population

Our retrospective observational study is based on the analysis of data collected in consecutive patients who received an ICD or a cardiac resynchronization device (CRT-

D) at the J.W. Goethe University Frankfurt between 1996 and 2010 and who were followed at the same institution. Devices from various manufacturers were used (Medtronic, USA; St Jude Medical/Ventritex, USA; Guidant/Boston Scientific, USA; ELA/Sorin, Italy). The study was approved by the institutional review board of the J.W. Goethe University and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

4.2.2. Data collection and outcomes

Data were prospectively collected from the index hospitalization at the time of initial ICD implantation and at each follow-up visit that took place every 6 months or at the time of unscheduled visits in the out- or inpatient clinic. Data collection included patient characteristics such as age and race, the initial indication for ICD as well as the type of device implanted (single-, dual, or triple-chamber ICD), the most recent left ventricular ejection fraction, and relevant co-morbid conditions. Pertinent medication use (beta-blockers, ACEs or ARBs, digitalis glycosides, antiarrhythmic drugs) was documented. Digitalis was used to treat heart failure and/or to control heart rate in AF, according to current guideline recommendations [Yancy et al. 2013; McMurray et al. 2012; Camm et al. 2010]. Data were also collected from device interrogations. All relevant information was entered into a customized database (Microsoft Access 5 or Microsoft Excel). For missing data, particularly in case of missed follow-up visits, family members, treating physicians, or other hospitals were contacted to retrieve the missing information.

The primary outcome measure was time to all-cause mortality. Cause-specific mortality was defined according to the Hinkle and Thaler classification [Hinkle et al. 1982].

4.2.3. Statistical analysis

Statistical analysis was performed using SPSS version 22 program (IBM, USA). Baseline characteristics were compared by the Wilcoxon Mann-Whitney U test (continuous variables) and the χ^2 test or Fisher exact test (categorical variables). Survival analysis was performed using Kaplan–Meier analysis. Survival curves were compared using the log-rank test and Wald test for the Cox proportional hazard model. Crude and adjusted hazard ratios (HR) with 95% CI for digitalis use were calculated for potential confounding factors including age, gender, primary/secondary prevention indication, ischaemic/non-ischaemic heart disease, NYHA classification, LVEF, ICD type, QRS width, documented AF, diabetes mellitus, and chronic renal disease. Independent

predictors of mortality were derived by backward stepwise variable selection using Wald test in the multivariate Cox regression model. Only two-sided tests were used, and p-values of 0,05 were considered statistically significant.

4.3. Intrathoracic impedance monitoring with CRT-devices

4.3.1. Study patients and study design

All consecutive patients implanted with an OptiVol and wireless telemetry capable CRT-D device (Medtronic Inc, Minneapolis, MN, US) in the Medical Centre of Hungarian Defence Forces and signed to be followed up via the CareLink remote monitoring system (Medtronic Inc, Minneapolis, MN, US) were prospectively recruited from April 2011 to June 2014. The optional function of intrathoracic impedance monitoring (OptiVol) was activated in all patients with an automatic remote alert, if the fluid index reaches 60 Ω-day.

Patients were followed up at our outpatient HF clinic every 3 months or if clinically indicated. In-office device control was performed half-yearly by electrophysiologists. The transmitted CareLink data were evaluated by an electrophysiologist and HF specialist team weekly and within 24 hours for clinically relevant alerts.

If an OptiVol alert occurred, all device monitored parameters were recorded and patients were interviewed by an independent HF specialist for the presence of HF symptoms via telephone calls and during additional outpatient visits, as necessary. An OptiVol alert was categorized as true positive (verified HF event) when signs and symptoms of decompensated HF required an increase in diuretic dose in an outpatient setting or hospitalization.

All patients signed an informed consent form. The study complies with the Declaration of Helsinki, and the study protocol was approved by the Institutional Ethics Committee.

4.3.2. Assessment of original PARTNERS HF criteria

The original PARTNERS HF criteria were evaluated for all OptiVol alerts (Fluid Index ≥ 60 Ω-day) using a time-frame window of 20 days prior to an alert, and the sensitivity and specificity of the original PARTNERS HF device diagnostic algorithm were determined.

4.3.3. New device diagnostic algorithm development

Our refined diagnostic algorithm was derived from an OptiVol alert (Fluid Index ≥ 60 Ω-day) and the presence of further positive parameters in a 20 days time-frame window prior to the alert. The following modified diagnostic criteria were utilized:

- **New AF episode:** ≥ 6 h on at least 1 day
- **High ventricular rate during AF:** average ventricular rate during AF ≥ 90 bpm on at least 24 h
- **Lower patient activity level for at least 5 days:**
    - -2 h/day, if the prior average was ≥ 4 h/day
    - -1 h/day, if the prior average was < 4 h/day
    - except (parameter was defined negative), if prior average was permanently under 1 h/day or activity decline was related to extracardiac reason (e.g. elective surgery, musculoskeletal disorders etc.)
- **Elevated nocturnal heart rate:** average night HR > 85 bpm or elevated with ≥20 bpm to the prior average for at least 5 consecutive days
- **Low heart rate variability:** < 60 ms every day for 1 week, except (parameter was defined negative), if permanently under 60 ms
- **Low biventricular pacing rate:** < 90% for at least 5 days, except (parameter was defined negative), if permanently <90%
- **Ventricular arrhythmias:** treated by 1 or more ICD shocks or successful anti-tachycardia pacing (ATP)

The differences between the original PARTNERS HF criteria and our refined parameters are highlighted in Table 1. The utilized modifications mainly derived from our clinical experience with the device based diagnostic.

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Table 1. Definition of the refined diagnostic criteria and differences to the original PARTNERS HF parameters

Device measured parameter	Original PARTNERS HF criteria	Refined PARTNERS HF criteria
New AF episode	AF ≥ 6 h on at least 1 day without persistent AF	AF ≥ 6 h on at least 1 day without persistent AF
Ventricular rate during AF	AF ≥ 24 h & daily average ventricular rate during AF ≥ 90 bpm, on at least 24 h	AF ≥ 24 h & daily average ventricular rate during AF ≥ 90 bpm, on at least 24 h
Patient activity level	Average activity < 1h over 7 days	Lower average activity ***over 5 days with*** ***» - 2 h/day, if the prior average was ≥ 4 h/day*** ***» - 1 h/day, if the prior average was < 4 h/day*** ***» except, if prior average was permanently < 1 h/day or activity decline for extracardiac reason (e.g. elective surgery, any musculoskeletal disorders etc.)***
Nocturnal heart rate	Average night heart rate > 85 bpm for 7 consecutive days	Average night heart rate > 85 bpm ***or elevated with ≥ 20 bpm to the prior average*** for at least ***5 consecutive days***
Heart rate variability	< 60 ms every day for 1 week	< 60 ms every day for 1 week, ***except if permanently under 60 ms***
Biventricular pacing rate	< 90% for 5 of 7 days	< 90% for 5 of 7 days, ***except if permanently < 90%***
Ventricular arrhythmias	≥ 1 shocks during the evaluation period	≥ 1 shocks ***or ATPs*** during the evaluation period

4.3.4. Statistical analysis

Statistical analyses were performed using STATISTICA version 10.0 (Tulsa, Oklahoma, USA), SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and MedCalc version 14.12.0 (Ostend, Belgium) softwares. Numerical values are presented as means ± SDs. Multivariate discriminant analysis was used to assess the association between device based parameters and the progression of HF. Parameters independently associated with true HF events (p-value < 0,05) were included in the final risk score. The predictive power of the original and refined clinical algorithms was described with sensitivity, specificity, positive and negative predictive statistics and the Receiver Operating Characteristic method (ROC-analysis). To obtain an unbiased ROC analysis (training and validation was performed on the same population) a cross-validation was performed. The cross-validation of ROC-curves and the confidence interval calculations were performed with SAS software by the "Proc Logistic" procedure.

4.4. Upgrade CRT

4.4.1. Patient population

Implantation and outcome data were prospectively collected from consecutive patients undergoing CRT-D implantation at the J.W. Goethe University (Frankfurt, Germany), at the Evangelical Hospital Bielefeld (Bielefeld, Germany), and at the Medical Centre, Hungarian Defence Forces (Budapest, Hungary). CRT was considered for patients on optimized medical treatment with heart failure of NYHA functional class from II to IV, LVEF of ≤35%, and QRS width of >120 ms (de novo group). Furthermore, patients with previously implanted pacemakers or ICDs who developed the above-mentioned criteria with or without need for continuous ventricular pacing were also considered for CRT (upgrade group). The study was approved by the institutional review board of the J.W. Goethe University and complies with the ethical guidelines of the Declaration of Helsinki.

4.4.2. Device implantation

CRT–ICDs from various manufacturers were used (Biotronik, Germany; ELA/Sorin, Italy; Guidant/Boston Scientific, Marlborough, MA; Medtronic, Minneapolis, MN; St. Jude Medical, St. Paul, MN) after standard indications for primary or secondary prophylaxis of sudden cardiac death. Left ventricular leads were implanted transvenously, preferably the lateral or posterolateral vein or a side-branch in close proximity to the posterolateral area,

avoiding apical positions as suggested in the guidelines [Brignole et al. 2013]. In case of unsuccessful attempts of coronary sinus lead implantation, an epicardial approach was used as a separate procedure. Patients were followed-up in the outpatient clinic of participating hospitals in 6 months' intervals or when clinically indicated.

4.4.3. Study endpoints

Outcome measures were clinical response to CRT and long-term mortality. Patients were considered to be responders if they survived to the 6 months follow-up visit with an improvement of at least 1 NYHA functional class. Echocardiographic data, including LVEF and left ventricular end-diastolic diameter (LVEDD), were also collected at baseline and reassessed at 6 months after the initiation of resynchronization therapy. Survival was assessed as the time from CRT implantation to all-cause mortality.

4.4.4. Statistical analysis

Statistical analysis was performed using SPSS Statistics software, version 23.0 (IBM, Armonk, NY) with the R software plug-in (The R Foundation, version 3.1.0) for propensity score matching. The Kolmogorov–Smirnov test was used to evaluate the normal distribution of continuous data. The $\chi 2$ test was used to test for categorical variables and the 2-sample t test or the Mann–Whitney U test for continuous variables among patients groups. The effects of baseline parameters on response rate were assesed by the $\chi 2$ test and by a multivarite logistic regression model. To assess the effects of procedure type (ie, de novo versus upgrade) on survival, the Cox proportional hazards regression model was used. The statistical models were adjusted for potential baseline confounders, including sex, age, primary/secondary prevention indication, aetiology of heart failure, atrial fibrillation, hypertension, dyslipidaemia, diabetes mellitus, stroke/transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, baseline NYHA class, baseline LVEF, presence of LBBB, QRS width, estimated glomerular filtration rate, and therapy with antiplatelet drugs, anticoagulants, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, diuretics, statins, amiodarone, and digitalis, respectively. The univariate mortality risk assessment was also repeated among propensity score-matched patient groups. Patients receiving upgrade CRT were matched 1:1 with de novo subjects using the nearest neighbour matching method with a calliper of 0,2 by applying baseline characteristics listed above for the multivariate Cox regression. Survival curves were constructed according to the Kaplan–Meier method

and compared with the Cox proportional hazard model and the Wald test for the multivariate analysis. In addition, survival analysis was repeated for subgroups according to NYHA functional class (NYHA II versus NYHA III–IV) and to QRS width/morphology (>150 ms, LBBB). Two-sided p values <0,05 were considered statistically significant.

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5. RESULTS

5.1. Meta-analysis of digoxin associated mortality

5.1.1. Selection of studies

From a total of 1524 studies initially identified, 25 matched our search criteria. Additional six trials were excluded because they consisted of reports based on the same original trial database (i.e. post-hoc analyses of DIG [Georghiade et al. Eur J Heart Fail 2013; Bourge et al. 2013; Rathore et al. 2002; Rathore et al. 2003] and AFFIRM [Georghiade et al. EHJ 2013; Elayi et al. 2011] studies). This yielded a total of 19 studies which were selected for the present analysis (Figure 4.).

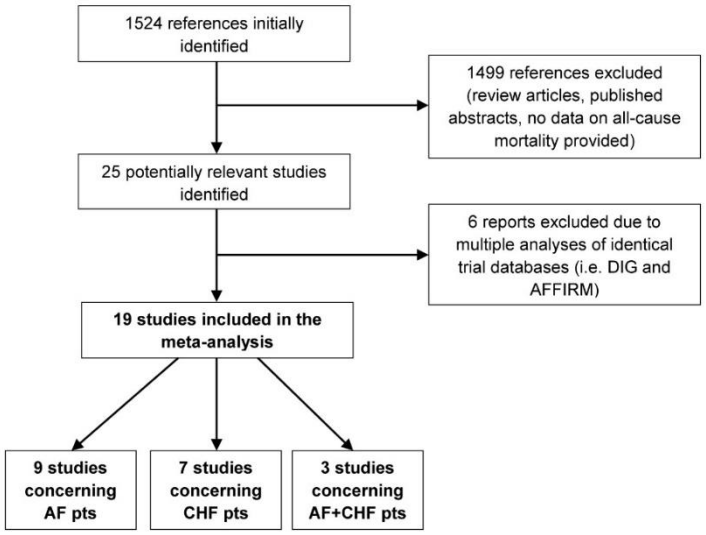

Figure 4. Flow diagram of the literature search and study selection

The individual trial characteristics are given in Table 2. Digoxin use was defined as use at baseline or as a time varying covariate [Murphy et al. 2013]. Nine studies comprised patients with AF [Fauchier et al. 2009; Gjesdal et al. 2008; Whitback et al. 2013; Turakhia et al. 2014; Gamst et al. 2014; Freeman et al. 2015; Pastori et al. 2015; Rodríguez-Mañero et al. 2014; Mulder et al. 2014] and seven comprised patients with CHF (in sinus rhythm or in AF) [Garg et al. 1997; Ahmed et al. 2006; Fauchier et al. 2009; Dhaliwal et al. 2008; Butler et al. 2010; Freeman et al. 2013; Domanski et al. 2005]. The remaining three studies reported separate data for patients suffering from both conditions [Hallberg et al. 2007; Shah et al. 2014; Chao et al. 2014]. The primary inclusion criterion for the study by Chao et al. [Chao et al. 2014] consisted of the diagnosis of AF. Hence, this study was initially included in the meta-analysis as an AF study although endpoint results were available for the overall patient group as well as for the patient subset with AF only and heart failure only.

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Table 2. Publications included in meta-analysis

Study, Year	Subgroup	Patient cohort	Design	Digoxin use defined as	Subjects		Follow-Up (years)	Quality (MINORS score)
					Total	Digoxin		
Hallberg (RIKS-HIA), 2007	AF	AF	Prospective registry study	baseline use	21459	4872	1	high (17.5)
Gjesdal (SPORTIF III, V), 2008		AF	Post-hoc analysis of RCT	baseline use	7329	3911	1.55 - 1.64	high (20)
Friberg (SCAF), 2010		AF	Prospective registry study	baseline use	2824	802	4.7	high (19)
Whitback (AFFIRM), 2012		AF	Post-hoc analysis of RCT	time-varying covariate	4060	2816	3.5	high (20.5)
Turakhia (TREAT-AF), 2014		AF	Analysis of administrative database	baseline use & time-varying covariate	122465	28679	2.9	high (19)
Shah, 2014	AF	AF	Retrospective population-based cohort study	baseline use	46262	23131	3.0 - 4.2	high (18.5)
Gamst, 2014		AF	Retrospective population-based cohort study	baseline use	8880	3622	1	high (18)
Chao, 2014		AF	Analysis of administrative database	baseline use	4781	829	4.26	high (18)
Rodriguez-Manero (AFBAR), 2014		AF	Prospective registry study	baseline use	777	270	2.9	high (19.5)
Mulder (RACE II), 2014		AF	Post-hoc analysis of RCT	baseline use	608	284	2.9	high (21)
Freeman (ATRIA-CVRN), 2014		AF	Retrospective population-based cohort study	baseline use & time-varying covariate	14787	4231	1.17	high (20)
Pastori, 2015		AF	Prospective observational study	baseline use	815	171	2.73	high (19.5)
Garg (DIG), 1997		CHF (SR)	RCT	baseline use	6800	3397	3.04	high (23.5)
Domanski (SOLVD), 2005	Men	CHF (SR/AF)	Post-hoc analysis of RCT	baseline use	6797	2244	3.4	high (20)
Domanski (SOLVD), 2005	Women	CHF (SR/AF)		baseline use				
Ahmed (DIG Ancillary), 2006		CHF (SR)	RCT	baseline use	988	492	3.0	high (23)
Hallberg (RIKS-HIA), 2007	CHF - SR	CHF (SR)	Prospective registry study	baseline use	22345	3796	1	high (17.5)
Hallberg (RIKS-HIA), 2007	CHF - AF	CHF (AF)		baseline use	16960	7758		
Fauchier, 2008		CHF (AF)	Prospective registry study	baseline use	1269	591	2.4	high (19)
Dhaliwal, 2008		CHF (SR/AF)	Retrospective population-based cohort study	baseline use	347	155	0.83	high (17)
Butler (Val-HeFT), 2010		CHF (SR/AF)	Post-hoc analysis of RCT	baseline use	5010	3374	1.9	high (20.5)
Freeman, 2013		CHF (SR/AF)	Analysis of administrative database	baseline use & time-varying covariate	2891	529	2.5	high (18.5)
Shah, 2014	CHF	CHF (AF)	Retrospective population-based cohort study	baseline use	27972	13986	3.0 - 4.3	high (18.5)

Accordingly, this meta-analysis comprises data from 235 047 AF patients and 91 379 patients with heart failure. Patients were followed between 0.83 and 4.7 years (average observation period 2,57±1.13 years) in the individual studies. Of all identified studies, only one (and its ancillary publication) was a randomised controlled clinical trial [Garg et al. 1997; Ahmed et al. 2006], whereas the remainder of studies were retrospective or prospective observational studies (Table 2.). All included reports were assessed as high-quality publications (average MINORS score: 19,7±1,6).

There were significant differences in treatment effects between individual studies indicated by the statistical test for heterogeneity (Q = 153,5, p < 0,01, T^2 = 0,008, I^2 = 85,7%) [Higgins et al. 2002]. According to the rank correlation test of Begg and Mazumdar [Begg et al. 1994], there was no evidence of significant publication bias (Tau = 0,087, p = 0,28). Furthermore, corresponding to the Duval and Tweedie's trim and fill input method [Borensetin et al. 2009], there was no evidence that publication bias would impact on the overall effect size observed (HR 1,214 vs. HR 1,208) (Figure 5.).

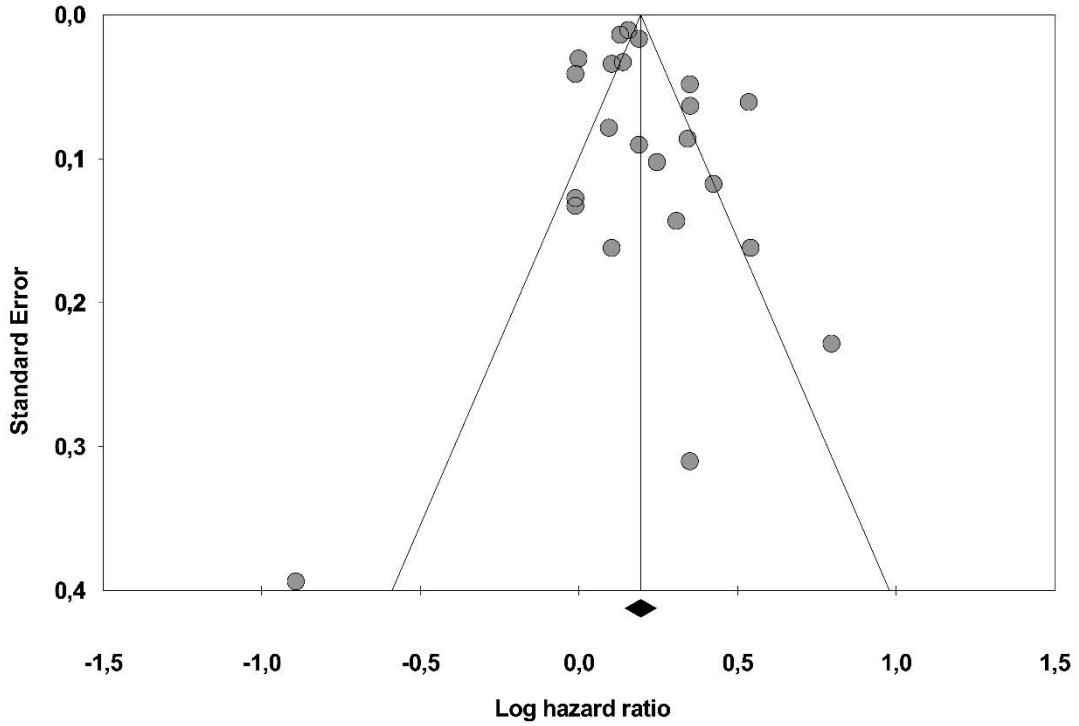

Figure 5. Funnel plot of publications included in the meta-analysis

5.1.2. Effects of digoxin on all-cause mortality

Mortality risks were reported in all selected studies after adjustment for important baseline variables for a total of 326.426 patients. Based on the analysis of all 19 trials, digoxin use was associated with an overall 21% increased relative risk of all-cause mortality compared with patients not receiving this medication (HR 1,21, 95% CI, 1,07 to 1,38, p < 0,01) (Figure 6.).

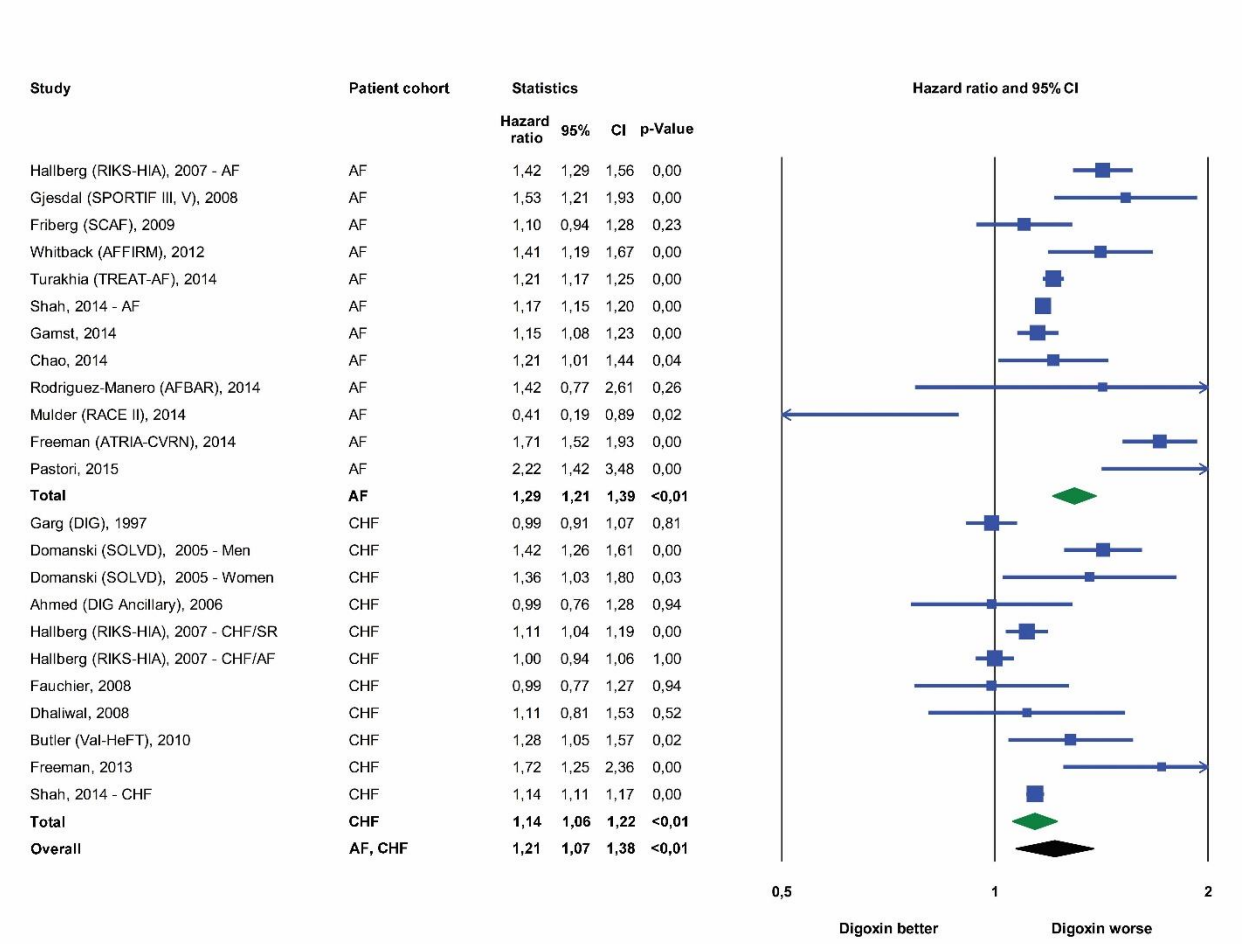

Figure 6. Forest plot of studies describing the effects of digoxin on mortality, both for studies in atrial fibrillation and congestive heart failure. Data had been adjusted for potential confounders in the various studies.

A total of 235.047 AF patients were included in 12 studies with a range between 608 and 122.465 patients per study. For this subgroup of patients, treatment with digoxin was associated with an increased mortality risk of 29% when compared with AF patients not receiving digoxin (HR 1,29, 95% CI, 1.21 to 1.39, p < 0.01) (Figure 6). We included the AFFIRM post-hoc analysis by Whitback [Whitback et al. 2013] in this set of studies;

however, we repeated the analysis after substituting this study by the one of Gheorgiade et al. [Gheorgiade et al. EHJ 2013] which used the same database but a different analysis methodology [Murphy 2013]. The HR for digoxin-associated mortality risk remained similarly elevated (HR 1,27, 95% CI 1,18 to 1,36, $p < 0,01$).

Nine studies comprised 91 379 subjects with heart failure. In this patient population, digoxin use was again associated with a higher risk for all-cause mortality compared with individuals not treated by cardiac glycosides (HR 1,14, 95% CI, 1,06 to 1,22, $p < 0,01$) (Figure 6).

5.1.3. Analysis of studies comprising subsets of patients with atrial fibrillation and congestive heart failure

Three large studies comprising a total of 117.434 patients reported all-cause mortality data for subsets of patients with AF and with CHF [Hallberg et al. 2007; Shah et al. 2014; Chao et al. 2014]. In the respective studies, data sources were identical for the two patient subsets and the same analysis methodology was applied. As shown in Figure 7., there was a substantial increase in the digoxin-associated risk of death in all three studies for patients with AF (HR 1,28, 95% CI, 1,12 to 1,46, $p < 0,01$). The estimated pooled mortality risk for all three patient samples with CHF revealed no significant increase in those subjects who were receiving digoxin (HR 1,05, 95% CI, 0,91 to 1,20, $p=0,52$).

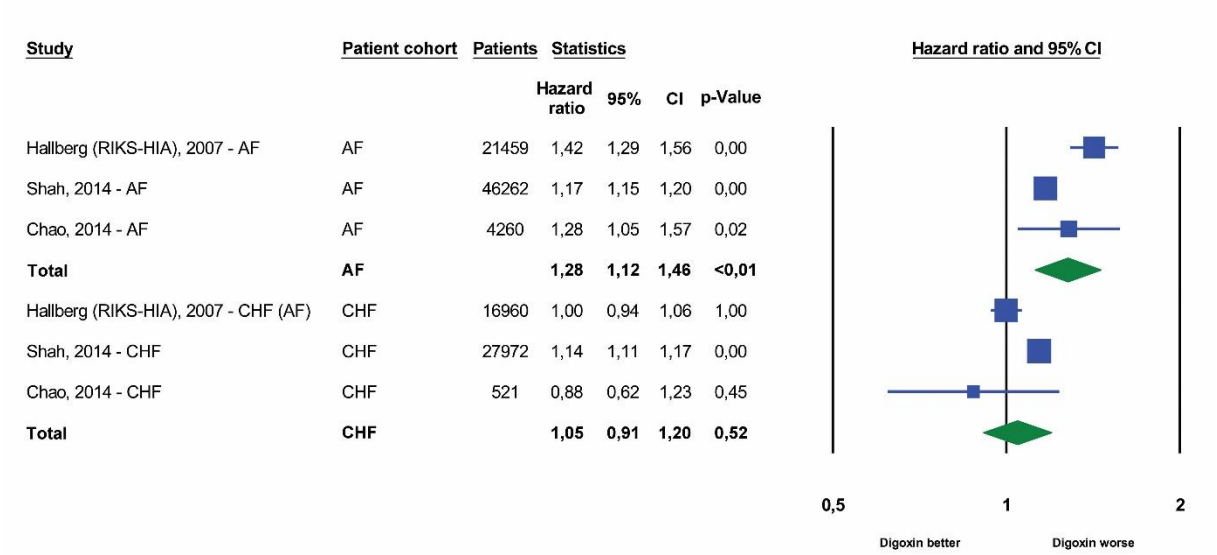

Figure 7. Forest plot of 3 large studies reporting data on patient populations with atrial fibrillation (upper half) and congestive heart failure (lower half) relying on the same databases and applying identical analytic methodology.

5.1.4. Analysis of studies providing data on digoxin dosing and/or plasma levels

Six of the 19 studies [Garg et al. 1997; Ahmed et al. 2006; Freeman et al. 2013; Freeman et al. 2015; Mulder et al. 2014; Pastori et al. 2015] reported data on the daily digoxin dose and/or the mean digoxin plasma levels (Table 3.). A sensitivity analysis of these studies revealed a similar HR (1,26, 95% CI, 0,91 to 1,74) (Figure 8.) as the analysis of all 19 studies, although this was no more statistically significant despite the inclusion of almost 27.000 patients. Only three studies [Garg et al 1997; Freeman et al. 2013; Freeman et al. 2015] reported data on digoxin plasma levels (Table 3.).

Table 3. Publications with data on digoxin doses or serum concentrations

Study, Year	Patient cohort	Patient number	Mean digoxin dose (mg)	Mean serum digoxin concentration (ng/ml)
Mulder (RACE II), 2014	AF	608	0,25	no data
Freeman (ATRIA-CVRN), 2014	AF	14787	0,164	0.96 (available for 69% of all pts)
Pastori, 2015	AF	815	0,126	no data
Garg (DIG), 1997	CHF (SR)	6800	0,244	0.8
Ahmed (DIG Ancillary), 2006	CHF (SR)	988	0,235	no data
Freeman, 2013	CHF (SR/AF)	2891	0,15	1.02 (available for 70% of all pts)

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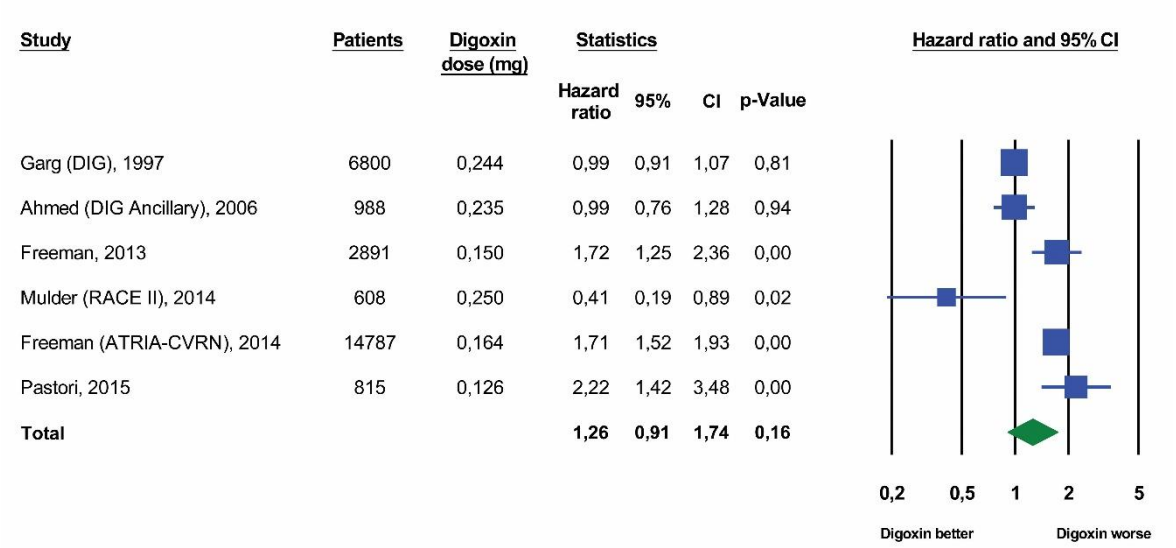

Figure 8. Sensitivity analysis of 6 studies which provided data on digoxin dosing.

5.2. Digitalis in ICD patients

5.2.1. Patient population

A total of 1448 patients underwent ICD implantation at the University Hospital Frankfurt from 1996 to 2010 for primary or secondary prevention of sudden cardiac death. Of those, 1020 were regularly followed-up in the ICD outpatient clinic and form the basis of this report. Of these, 561 (55%) received a single-chamber ICD, 295 (29%) a dual-chamber device, and 159 (16%) a CRT-D. The follow-up period ranged between 10 and 209 months (median 37 months).

Baseline characteristics and pertinent medications of the included patients are summarized in Table 4. and Table 5. Our patient cohort consisted of a typical ICD population with a mean age of 63 years, male preponderance (79%), and ischaemic heart disease (68%) as the predominant underlying structural heart disease (Table 4.).

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Table 4. Patient characteristics at ICD implantation

Variables	All Patients n = 1020	Patients on digitalis n = 438	Patients not on digitalis n = 582	p-value
Age mean (SD) [years]	63 (12)	63 (11)	62 (13)	n. s.
Male gender, n (%)	809 (79)	345 (79)	464 (80)	n. s.
Primary prevention, n (%)	585 (58)	251 (57)	334 (57)	n. s.
Secondary prevention, n (%)	430 (42)	182 (43)	248 (43)	
Ischaemic heart disease, n (%)	690 (68)	288 (66)	402 (69)	0,02
Non-ischaemic heart disease, n (%)	430 (32)	150 (34)	248 (43)	
NYHA-classification, n (%)				< 0,001
0 + I	256 (25)	52 (12)	204 (35)	
II	348 (34)	156 (36)	192 (33)	
III	257 (25)	167 (38)	90 (15)	
IV	23 (2)	16 (4)	7 (1)	
LVEF mean, % (SD)	33 (13)	26 (8)	38 (14)	<0,001
ICD type, n (%)				0,01
Single chamber	561 (55)	233 (53)	328 (56)	
Dual chamber	295 (29)	106 (24)	189 (32)	
CRT-D	159 (16)	94 (21)	65 (11)	
QRS ≥ 120 ms, n (%)	397 (39)	206 (47)	191 (33)	<0,001
Documented AF, n (%)	150 (15)	94 (21)	56 (10)	<0,001
Diabetes mellitus, n (%)	311 (30)	169 (39)	142 (24)	<0,001
Chronic kidney disease, n (%)	258 (25)	150 (34)	108 (19)	<0,001

Table 5. Medication at ICD Implantation

Variables	All Patients n=1020	Patients on Digitalis n=438	Patients not on Digitalis n=582	p-value
ACE inhibitor, n (%)	761 (75)	338 (77)	423 (73)	n. s.
Amiodarone, n (%)	196 (19)	95 (22)	101 (17)	n.s.
ARB, n (%)	94 (9)	48 (11)	46 (8)	n. s.
ASA, n (%)	604 (59)	243 (55)	361 (62)	0,01
Calcium antagonist, n (%)	121 (12)	40 (9)	81 (14)	n. s.
Class 1c antiarrhythmic, n (%)	7 (1)	2 (0)	5 (1)	n. s.
Clopidogrel, n (%)	245 (24)	120 (27)	125 (21)	0,01
Diuretics, n (%)	700 (69)	374 (85)	326 (56)	0,06
Sotalol, n (%)	58 (6)	14 (3)	44 (8)	n. s.
Vitamin K antagonist, n (%)	336 (33)	193 (44)	143 (26)	0,03
β-blocker, n (%)	873 (86)	391 (89)	482 (83)	0,02

At ICD implantation, 438 patients (43%) were receiving digitalis glycosides. Digitalis medication was prescribed either for the treatment of congestive heart failure or for the control of ventricular rate in AF, or for both conditions. Patients treated with digitalis were older (median 63 years), were more often in AF (21 vs. 10%; p<0,001), and had worse left ventricular function (mean LVEF 26%) than patients not treated with digitalis (mean LVEF 38%; p<0,001). Intraventricular conduction disturbances with a QRS duration of ≥120 ms were present in 47% of digitalis patients and in 33% of those without this medication. Patients on digitalis had significantly more co-morbidities such as diabetes mellitus and chronic kidney failure (p<0.001) (Table 4.).

5.2.2. All-cause mortality

During the observation period, 213 patients died, 128 treated with digitalis at baseline, and 85 not receiving this medication. Crude Kaplan-Meier survival analysis demonstrated a significantly higher mortality in patients who received digitalis at the time of ICD implantation compared with those not on this medication (HR 2,47; 95% CI 1,87-3,25; p=0,001) (Figure 9A). To correct for potential confounders, Kaplan–Meier analysis was repeated with data adjusted for all variables found significantly different between both

patient groups. Significant predictors of mortality on univariate analysis were age, male gender, NYHA, LVEF, prolonged QRS duration, AF, and diabetes mellitus. In the multivariate analysis age, male gender, NYHA classification, and prolonged QRS duration remained as independent predictors. After adjustment, the risk for death continued to be higher among patients on digitalis compared with subjects not receiving digitalis (HR 1,65; 95% CI 1,14-2,39; p=0,01) (Figure 9B). We performed a subgroup analysis of patients with ischaemic heart disease and of patients with non-ischaemic heart disease and the effects of digitalis on mortality. In patients with ischaemic heart disease, the HR was 1,67 (95% CI 1,09-2,54; p=0,02) compared with a HR of 2.15 (95% CI 0,90-5,16; p=0,09) in patients with non-ischaemic heart disease.

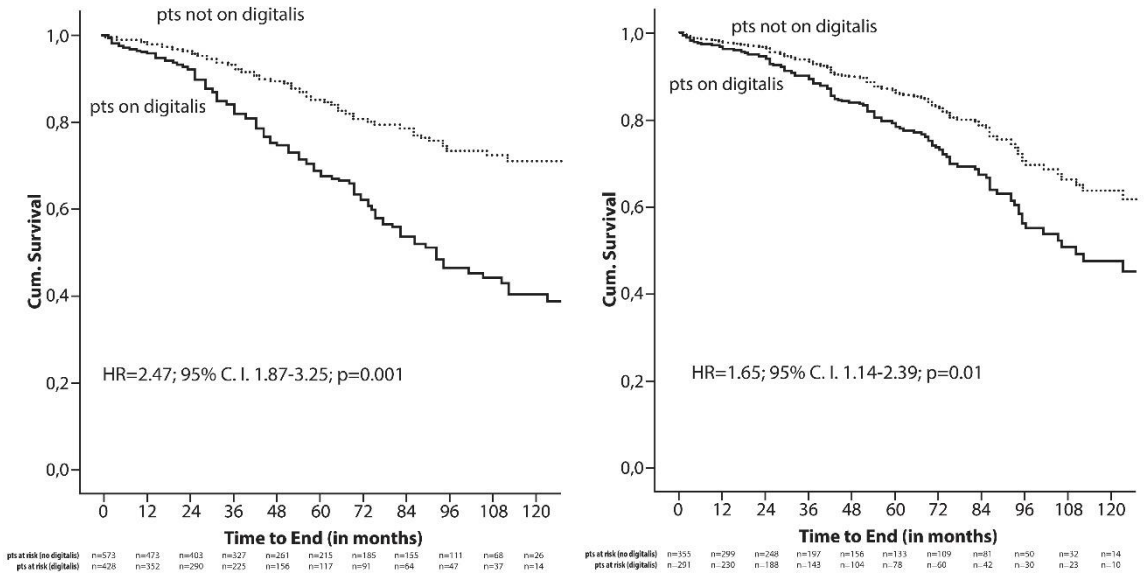

Figure 9. Crude (A) and adjusted (B) Kaplan–Meier analysis of all-cause mortality in relationship to the use of digitalis.

5.2.3. Cause-specific mortality

In 69 of 213 patients, cause-specific mortality according to the Hinkle and Thaler classification [Hinkle et al. 1982] could not be assessed due to missing detailed information surrounding circumstances of death. Among patients receiving digitalis, 37% suffered from cardiac arrhythmic, 24% from cardiac non-arrhythmic, and 11% from non-cardiac death. Respective numbers for patients not on digitalis were 32% (p=0,044), 19% (p = 0,036), and

12% (p = n.s.) (Table 6.). Subsequently, more ICD shocks occurred in patients on digitalis compared with patients not on digitalis (HR = 1,30; 95% CI 0,93-1,80). For appropriate shocks, the HR was 1,74 (95% CI 1,14-2,65), and for inappropriate shocks, a HR of 0,92 (95% CI 0,56-1,51) was found.

Table 6. Cause-specific mortality in relation to digitalis use

Variables	Patients on Digitalis n=438	Patients not on Digitalis n=582	p-value
Cardiac arrhythmic death, n (%)	44 (37)	27 (32)	0,044
Cardiac non-arrhythmic death, n (%)	32 (24)	16 (19)	0,036
Non-cardiovascular death, n (%)	15 (11)	10 (12)	n. s.
Unknown, n (%)	37 (28)	32 (37)	n. s.

5.2.4. Digoxin/digitoxin

Two different digitalis preparations were used in our patient population and could be retrieved in most of the patients (96% of digitalis patients; Table 7.). The majority of the patients received digitoxin (n = 306). Digoxin was prescribed to 105 patients. The median prescribed daily dosages were in the recommended range (digitoxin: 0.035-0.10 mg/day; digoxin 0,05-0,20 mg/day). Plasma concentrations of digoxin (normal range at our institution: 0,8-2,0 mg/l) or digitoxin (normal range at our institution: 10,0-30,0 mg/l) at any time during follow-up could be retrieved by chart review in 220 patients (50%). In these patients, mean digoxin plasma concentration was 0,8 mg/L, and mean digitoxin plasma concentration was 21,6 mg/l. Concerning all-cause mortality, there was no difference between patients treated with digitoxin and patients treated with digoxin (HR = 1,55; 95% CI 0,74-3,25; p = 0,25) (Figure 10.).

Table 7. Digoxin/Digitoxin dosages and serum concentrations

Variables	Patients on Digoxin	Patients on Digitoxin	Missing values, n (%)
Number, n (%)	105 (24)	306 (70)	27 (6)
Dose mean [mg] (min-max)	0,2 (0,05 – 0,2)	0,07 (0,035 – 0,1)	42 (10)
Serum concentration median [ug/L]	0,8	21,6	218 (50)

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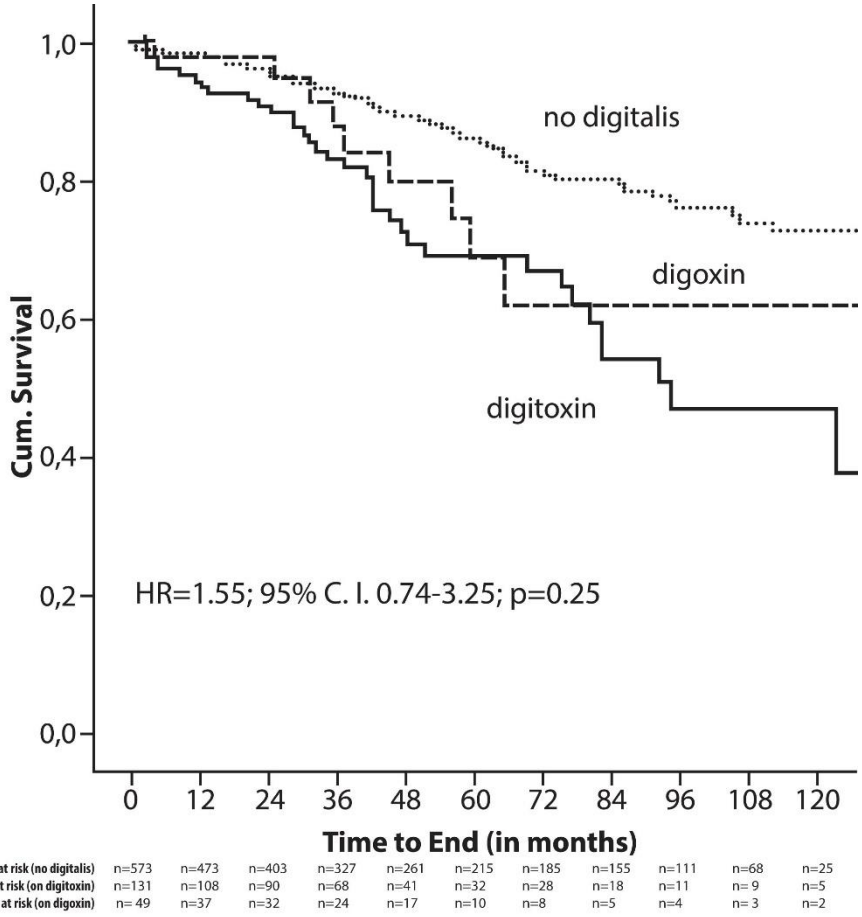

Figure 10. Kaplan-Meier analysis for all-cause mortality in relationship to the digitalis preparation used.

5.3. Intrathoracic impedance monitoring with CRT-devices

5.3.1. Patient cohort and clinical characteristics

The average follow-up of the 42 enrolled patients was 38,0 ± 23,6 months. Detailed patient baseline data are summarized in Table 8. It should be highlighted that all patients (100 %) were on beta-receptor blockers and 45,2 % of them received the maximum recommended dose.

Five patients died, two underwent heart transplantation, one required an assist device implantation and in one case the CRT-D system had to be explanted due to infection.

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Table 8. Baseline characteristics (C)

Total (N)	42
Demographics	
Age (years)	64,0 ± 11,7
Gender (male, %)	81,0
Heart failure aetiology (%)	
Ischaemic	57,1
Non-ischaemic	42,9
Valvular	4,8
Non-compaction cardiomyopathy	2,4
Toxic	2,4
Myocarditis	9,5
DCM/Genetic/Unknown	23,8
Indication for defibrillator implantation (%)	
Primary prevention	78,6
Secondary prevention	21,4
Characteristics	
LVEF (%)	26,9 ± 6,1
NYHA class	2,42 ± 0,78
LBBB (%)	76,2
QRS duration (ms)	151 ± 24
Comorbidities (%)	
Atrial fibrillation paroxysmal	40,5
Atrial fibrillation permanent	23,8
Diabetes mellitus	38,1
Hypertension	85,7
Hyperlipidaemia	26,2
Chronic pulmonary disease	16,7
History of chronic kidney disease*	59,5
Laboratory values at baseline	
Creatinine (µmol/L)	124,8 ± 52,7
Haemoglobin (g/L)	128,8 ± 17,0
Cardiovascular medication (%)	
Beta blockers	100
ACE inhibitors/ARBs	92,9
Diuretics	83,3
Mineralocorticoid receptor antagonists	78,6
Nitrates & Dihydralazine	81,0
Antiplatelet therapy	59,5
Oral anticoagulants	64,3
Statins	76,2
Amiodarone	19,0
Digoxin	11,9

*GFR<60ml/min

5.3.2. OptiVol alerts and heart failure events

Altogether 722 remote transmissions were received during the follow-up period. After exclusion of eight transmissions due to the unavailability of HF specialist´s adjudication 128 of all transmissions with OptiVol alerts (Fluid Index ≥ 60 Ω-day) were included in this analysis. Verified heart failure events were observed in 32 cases (25%) (Figure 11.) with need for hospitalization in eight cases. For the remaining cases no clinical events were identified or clear extracardiac causes were found in the background of OptiVol alerts (typically infection of the upper/lower respiratory tract, acute exacerbation of chronic obstructive pulmonary disease, surgery for any reason).

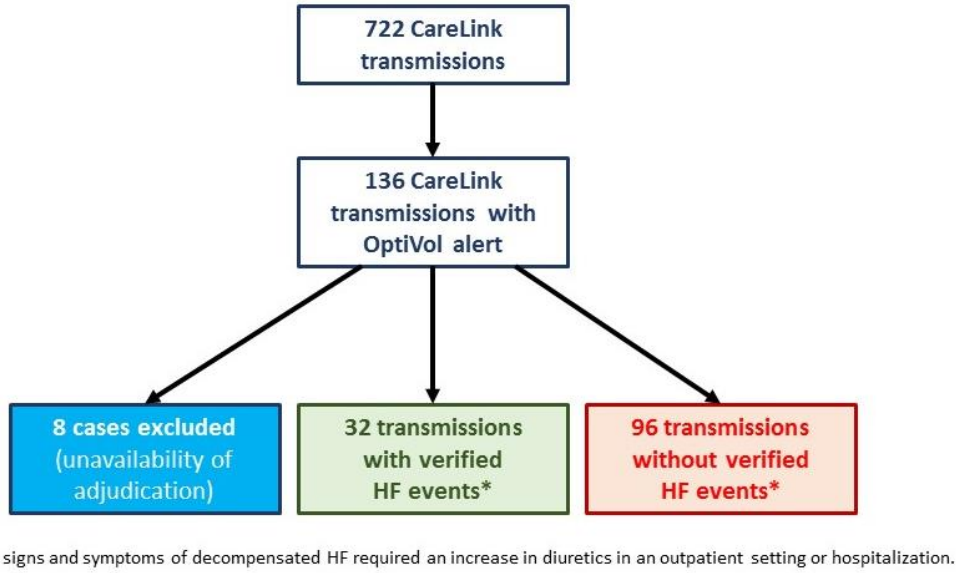

Figure 11. Flowchart of CareLink transmissions during the study period

5.3.3. Assessment of original PARTNERS HF criteria in our patient population

The classic PARTNERS HF diagnostic algorithm was positive in 31 of 32 cases with true deterioration of HF (sensitivity 96,9 %, CI 95% 83,8-99,9; negative predictive value 97,3 %, CI 95% 85,8-99,9), however, the specificity remained very low with 60 false positive events (specificity 37,5 %, CI 95% 27,8-48,0%; positive predictive value 34,1 %, CI 95% 24,5-44,7) (Table 9).

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Table 9. Prognostic characteristics of the original and the refined diagnostic criteria

	PARTNERS HF classic (without OptiVol ≥ 100)	OptiVol + 1 modified criteria
Sensitivity (95% CI)	96,9 % (83,8-99,9)	93,8 % (79,2-99,2)
Specificity (95% CI)	37,5 % (27,8-48,0)	86,5 % (78,0-92,6)
Positive predictive value (95% CI)	34,1 % (24,5-44,7)	69,8 % (53,9-82,8)
Negative predictive value (95% CI)	97,3 % (85,8-99,9)	97,6 % (91,8-99,7)
ROC-analysis / Area under the curve (95% CI)*	0,787 (0,704-0,869)	0,922 (0,869-0,974)
Area under the curve with validation (95% CI)†	0,679 (0,568-0,790)	0,858 (0,767-0,948)

*p between the two algorithms < 0,01; †p between the two algorithms < 0,01

5.3.4. Assessment of the new device diagnostic algorithm

In the multivariate discriminant analysis of the refined diagnostic criteria lower activity levels, increased nocturnal heart rate, and suboptimal biventricular pacing proved to be independent predictors for cardiac decompensation (Table 10.).

Table 10. Results of the multivariate discriminant analysis

Device measured parameters	**Wilks' Lambda**	**Partial Lambda**	**p-value**
New AF episode	0,421	0,986	0,19
Elevated HR during AF	0,422	0,996	0,47
Patient activity	0,663	0,638	< 0,001
Elevated nocturnal HR	0,485	0,871	< 0,001
Decreased HR variability	0,428	0,989	0,23
BiV pacing < 90%	0,532	0,795	< 0,001
ICD therapy (ATP/shock)	0,424	0,9784	0,1

Applying our refined algorithm which includes OptiVol alert events (Fluid Index ≥ 60 Ω-day) and the presence of at least one of the aforementioned modified diagnostic criteria the number of false positive alerts decreased from 60 to 13 (specificity 86,5%, CI 95% 78,0-92,6%; positive predictive value 69,8%, CI 95% 53,9-82,8%) without compromising the sensitivity (sensitivity 93,8%, CI 95% 79,2-99,2%; negative predictive value 97,6%, CI 95% 91,8-99,7%) (Table 9.). The diagnostic yield of the modified OptiVol algorithm assessed with ROC-analysis was also improved compared to classic PARTNERS HF diagnostic

algorithm (AUC 0,787, CI 95% 0,704-0,869 vs. AUC 0,922, CI 95% 0,869-0,974, p<0,01) (Table 9).

On cross-validation of the ROC-curves the difference between the two algorithms remained significant (AUC 0,679, CI 95% 0,568-0,790 vs. AUC 0,858, CI 95% 0,767-0,948, p<0,01) (Table 9).

5.4. Upgrade CRT

5.4.1. Patients characteristics

A total of 552 CRT-D recipients (Frankfurt 332, Bielefeld 103, and Budapest 117) were included in this analysis of whom 375 (68%) underwent a de novo implantation. A total of 177 patients (32%) had a previously implanted pacemaker or ICD system and underwent an upgrade procedure. Patients in the upgrade group were more often implanted for secondary prevention, suffered more often from atrial fibrillation, chronic kidney disease with a lower estimated glomerular filtration rate, diabetes mellitus, dyslipidaemia, and had more often a non-LBBB wide QRS complex, and a lower LVEF. Furthermore, amiodarone and digitalis were more often prescribed for patients undergoing upgrade procedures (Table 11).

5.4.2. Response to CRT

Follow-up data on the NYHA status at 6 months were available in 96% of patients. After an upgrade procedure, 96 of 169 (57%) patients responded to CRT by improving their NYHA functional status by at least 1 class compared with 247 of 360 (69%) patients in the de novo group (p=0,008). The lower response rate among upgrade patients remained statistically significant in a multivariate logistic regression analysis (p=0,021; Figure 12). Pairwise echocardiographic measurements (baseline and 6 months of follow-up) were available in 358 patients for LVEF (65%) and in 316 patients for LVEDD (57%). The echocardiographic changes were in line with the results of observed response rates based on the assessment of NYHA functional class. The improvement of LVEF and the decrease of LVEDD at 6 months were higher in the de novo group compared to the upgrade patients (ΔEF 6,7±9,4 versus 2,9±9,0, p<0,001; ΔLVEDD −3,5±6,7 versus 0,0±12,2, p=0,003; Figure 13).

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Table 11. Baseline characteristics (D)

	All (552)	**De novo (375)**	**Upgrade (177)**	**p-value**
Male	427 (77,4%)	288 (76,8%)	139 (78,5%)	0,650
Age (Mean±SD)	67,1±11,1	66,5±11,3	68,3±10,4	0,141
Primary prevention	438 (79,3%)	335 (88,9%)	103 (58,2%)	**<0,001**
Ischemic cardiomyopathy	298 (54,0%)	195 (51,7%)	103 (58,2%)	0,173
Atrial fibrillation	198 (35,9%)	124 (32,9%)	74 (41,8%)	**0,046**
Chronic kidney disease	282 (51,1%)	165 (43,8%)	117 (66,1%)	**<0,001**
Hypertension	381 (69,0%)	258 (68,8%)	123 (69,5%)	0,870
Diabetes Mellitus	195 (35,3%)	117 (31,2%)	78 (44,1%)	**0,003**
Dyslipidaemia	246 (44,6%)	155 (41,3%)	91 (51,4%)	**0,026**
Stroke/TIA	69 (12,5%)	47 (12,5%)	22 (12,5%)	0,973
Peripheral artery disease	52 (9,4%)	36 (9,6%)	16 (9,0%)	0,833
Chronic obstructive pulmonary disease	67 (12,1%)	50 (13,3%)	17 (9,6%)	0,211
Left bundle branch block[a]	404 (74,8%)	287 (78,6%)	117 (66,9%)	**0,003**
NYHA baseline (Mean±SD)	2,76±0,65	2,75±0,66	2,81±0,61	0,229
EF baseline (Mean±SD)[b]	25,4±7,3	25,3±7,0	24,0±7,9	**0,026**
LVEDD baseline (Mean±SD)[c]	65,9±10,4	66,1±9,8	65,5±11,4	0,431
QRS width baseline (Mean±SD)[d]	160.3±28.7	155,3±26,8	170,8±29,8	**<0,001**
eGFR (Mean±SD)[e]	62.1±52.6	65,4±59,2	55,1±34,1	**<0,001**
Haemoglobin (Mean±SD)[f]	13.2±2.0	13,2±2,0	13,4±1,8	0,334
Antiplatelet therapy	309 (56.0%)	213 (56,8%)	96 (54,2%)	0,571
Anticoagulation	272 (49.3%)	178 (47,5%)	94 (53,1%)	0,216
ß-Blocker	533 (96.6%)	361 (96,3%)	172 (97,2%)	0,585
ACE-Inhibitors/Angiotensin receptor blockers	524 (94.9%)	358 (95,5%)	166 (93,8%)	0,401
Diuretics	497 (90.0%)	335 (89,3%)	162 (91,5%)	0,422
Mineralocorticoid receptor antagonists	397 (71.9%)	269 (71,7%)	128 (72,3%)	0,887
Statin	368 (66.7%)	250 (66,7%)	118 (66,7%)	1,000
Amiodarone	116 (21.0%)	56 (14,9%)	60 (33,9%)	**<0,001**
Digitalis	213 (38.6%)	128 (34,1%)	85 (48,0%)	**0,002**

[a]Available information for 540 patients; [b]Available information for 550 patients; [c]Available information for 431 patients; [d]Available information for 546 patients; [e]Available information for 539 patients; [f]Available information for 456 patients

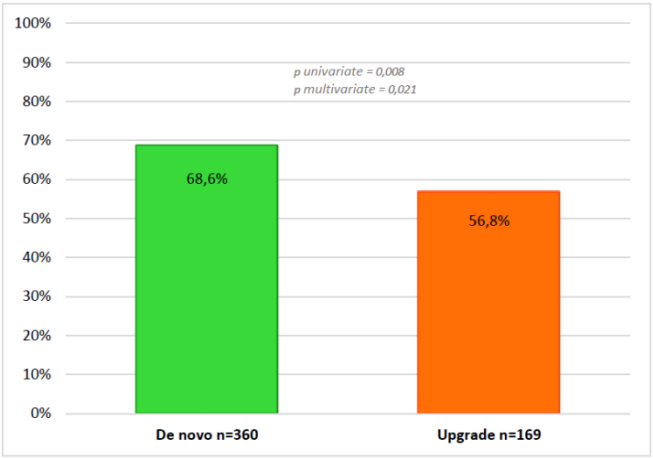

Figure 12. Clinical response rate at 6 months follow-up.

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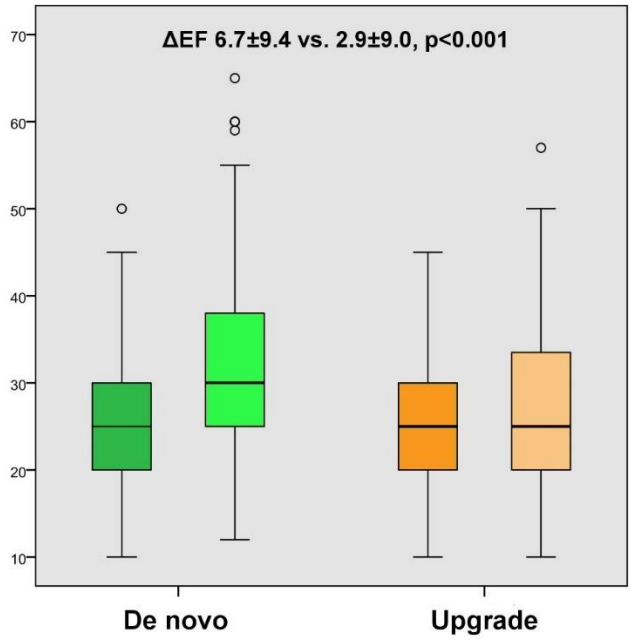

Figure 13. LVEF at baseline and at 6 months follow-up

5.4.3. Mortality during follow-up

During a mean follow-up period of 37±28 months, survival was significantly worse among patients undergoing upgrade procedures compared to de novo CRT-D implantations (HR 1,65; 95% CI, 1,22-2,24; p=0,001; Table 12; Figure 14). After adjustment for potential confounders, all-cause mortality continued to be higher for patients in the upgrade group (adjusted HR 1,68; 95% CI, 1,20-2,34; p=0,002; Table 12; Figure 14). Using a 1:1 nearest neighbour matching protocol, a cohort of 121 pairs of patients undergoing de novo or upgrade CRT operation was assembled. Compared with prematched patients, those in the matched cohort showed completely balanced clinical parameters across a spectrum of the 26 baseline characteristics (Table 13 and Figure 15). Also in this propensity-matched cohort, patients undergoing upgrade procedures had a higher mortality risk than patients undergoing de novo implantations (propensity-adjusted HR 1,79; 95% CI, 1,08-2,95; p=0,023; Table 12; Figure 16).

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Table 12. Risk of death by implantation type: de novo versus upgrade CRT

	Univariate cohort (n=552)		Multivariate cohort (n=501)*		Propensity-matched cohort (n=242)†	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**	**HR (CI 95%)**	**p-value**
All-cause mortality	1,65 (1,22-2,24)	0,001	1,68 (1,20-2,34)	0,002	1,79 (1,08-2,95)	0,023

*,† Models were adjusted for sex, age, primary prevention, aetiology, atrial fibrillation, hypertension, dyslipidaemia, diabetes, stroke/TIA, peripheral artery disease, chronic obstructive pulmonary disease, baseline NYHA class, baseline EF, LBBB, QRS with at baseline, eGFR, NYHA response, and therapy with antiplatelet drugs, anticoagulants, ß-blockers, ACEIs/ARBs, diuretics, mineralocorticoid receptor antagonists, statins, amiodarone, and digitalis.

Figure 14. Kaplan-Meier curves for all-cause mortality by implantation type (all patients)

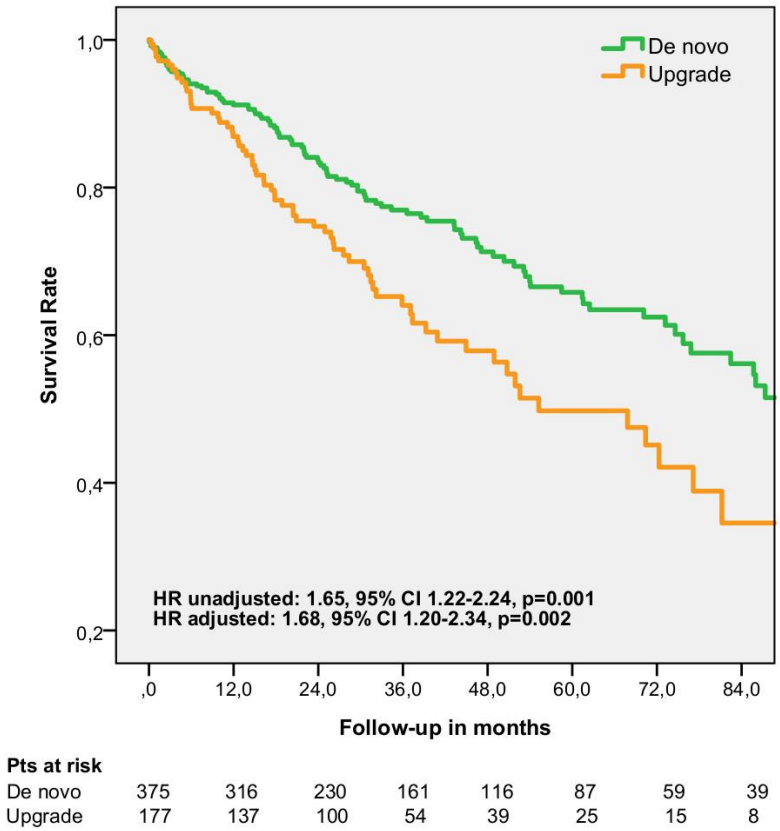

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Table 13. Baseline characteristics of propensity-matched patients (D)

	All (242)	**De novo (121)**	**Upgrade (121)**	**p-value**
Male	182 (75,2%)	90 (74,4%)	92 (76,0%)	0,766
Age (Mean±SD)	67,5±10,8	67,4±11,4	67,6±10,2	0,898
Primary prevention	185 (76,4%)	93 (76,9%)	92 (76,0%)	0,880
Ischemic cardiomyopathy	136 (56,2%)	68 (56,2%)	68 (56,2%)	1,000
Atrial fibrillation	93 (38,4%)	46 (38,0%)	47 (38,8%)	0,895
Chronic kidney disease	140 (57,9%)	66 (54,5%)	74 (61,2%)	0,298
Hypertension	172 (71,1%)	88 (72,7%)	84 (69,4%)	0,571
Diabetes Mellitus	93 (38,4%)	45 (37,2%)	48 (39,7%)	0,692
Dyslipidaemia	120 (49,6%)	60 (49,6%)	60 (49,6%)	1,000
Stroke/TIA	25 (10,3%)	12 (9,9%)	13 (10,7%)	0,833
Peripheral artery disease	19 (7,9%)	10 (8,3%)	9 (7,4%)	0,811
Chronic obstructive pulmonary disease	21 (8,7%)	11 (9,1%)	10 (8,3%)	0,819
Left bundle branch block	178 (73,6%)	94 (77,7%)	84 (69,4%)	0,145
NYHA baseline (Mean±SD)	2,77±0,65	2,77±0,68	2,77±0,66	0,908
EF baseline (Mean±SD)	25,1±7,3	25,1±7,1	25,0±7,5	0,783
QRS width baseline (Mean±SD)	165,7±26,0	166,2±25,2	165,3±26,9	0,773
eGFR (Mean±SD)	58,8±31,0	59,0±22,6	58,6±37,7	0,229
Antiplatelet therapy	132 (54,5%)	65 (53,7%)	67 (55,4%)	0,796
Anticoagulation	123 (50,8%)	63 (52,1%)	60 (49,6%)	0,700
ß-Blocker	238 (98,3%)	119 (98,3%)	119 (98,3%)	1,000
ACE-Inhibitors/Angiotensin receptor blockers	231 (95,5%)	115 (95,0%)	116 (94,5%)	0,758
Diuretics	221 (91,3%)	112 (92,6%)	109 (90,1%)	0,493
Mineralocorticoid receptor antagonists	177 (73,1%)	92 (76,0%)	85 (70,2%)	0,310
Statin	159 (65,7%)	79 (65,3%)	80 (66,1%)	0,892
Amiodarone	52 (21,5%)	25 (20,7%)	27 (22,3%)	0,754
Digitalis	102 (42,1%)	51 (42,1%)	51 (42,1%)	1,000

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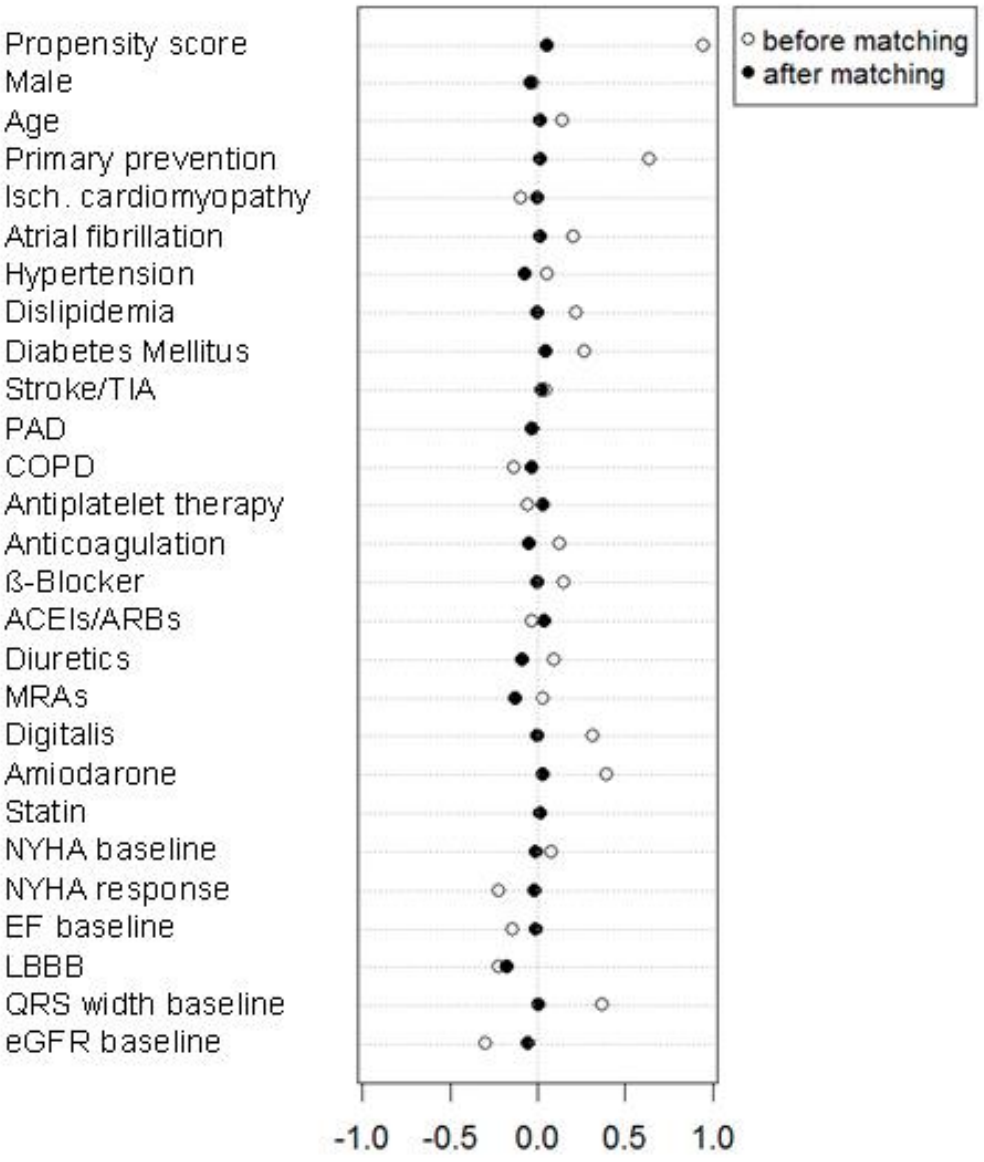
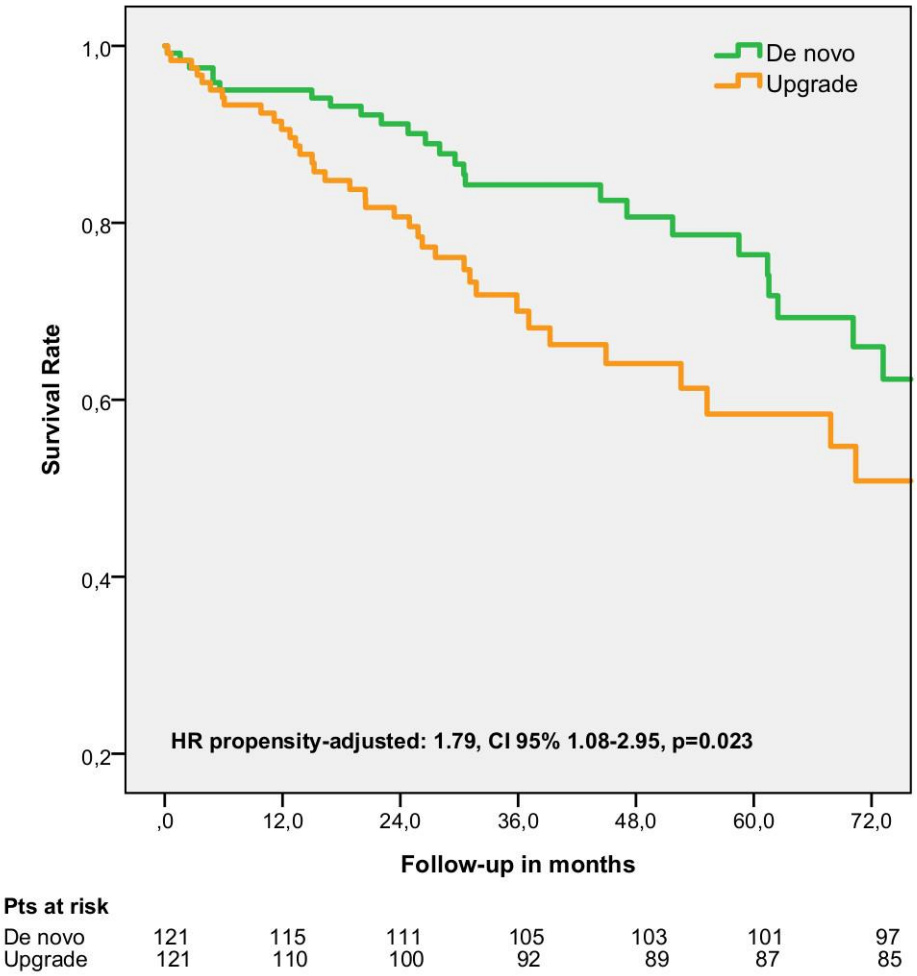


Figure 15. Dotplot of standardized mean differences for 26 baseline characteristics between patients undergoing de novo or upgrade CRT implantation, before and after propensity score matching

Figure 16. Kaplan-Meier curves for all-cause mortality by implantation type (propensity-matched patients)



5.4.4. Subgroup analysis

Among patients with NYHA functional class II, there was no statistically significant difference in survival after de novo versus upgrade implantations (HR 1,27; 95% CI, 0,61-2,65; p=0,527). However, in the subgroup of patients with NYHA class III–IV, the risk of all-cause mortality was higher in the upgrade group (HR 1,67; 95% CI, 1,19-2,35; p=0,003; Figure 17). The response rate for de novo versus upgrade procedures was 67% versus 60% and 71% versus 62% in the subgroups of patients with LBBB or LBBB and QRS >150 ms (p=NS; Table 14). The risk of death after upgrade CRT was increased in both the subgroups (Table 14).

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Figure 17. All-cause mortality in subgroups according to NYHA functional class (Kaplan-Meier curves by implantation type).

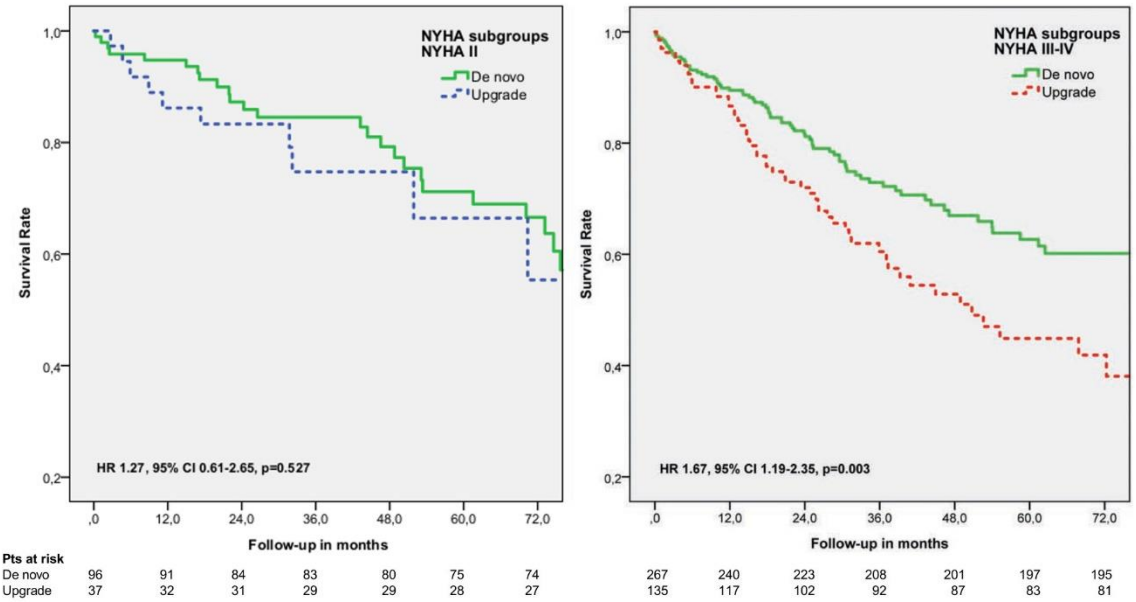

Table 14. Response rate and risk of mortality in the subgroups of patients with LBBB or LBBB and QRS > 150ms

Subgroups	Response Rate			Mortality	
	De novo	Upgrade	p-value	HR (CI 95%)	p-value
Pts with LBBB	67% (185/275)	60% (68/113)	0,182	1.63 (1,12-2,37)	0,010
Pts with LBBB and QRS > 150 ms	71% (117/166)	62% (45/73)	0,178	1.96 (1,25-3,08)	0,004

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6. DISCUSSION

6.1. Digitalis associated mortality

6.1.1. Main findings

Our meta-analysis on the effects of digoxin on all-cause mortality is to the best of our knowledge the largest one published till April 2015. It is based on 19 published studies comprising data from more than 300.000 patients suffering from AF or CHF. Our results indicate that digoxin therapy is associated with an increased mortality risk in these patients, particularly in those treated for AF.

Furthermore, in our study with ICD patients digitalis was independently associated with an increased risk of death. To the best of our knowledge, this is the first time that such an association is described in a single-centre cohort study of consecutive ICD recipients treated according to contemporary guideline recommendations [Yancy et al. 2013; McMurray et al. 2012; Camm et al. 2010]. A second noteworthy finding is that the type of digitalis preparation - digoxin vs. digitoxin - carries a similar risk of mortality.

6.1.2. Effects of digitalis on mortality

Digitalis glycosides are used to treat congestive heart failure in patients with reduced left ventricular function [Yancy et al. 2013; McMurray et al. 2012] and in AF to control the ventricular rate [Camm et al. 2010]. There is only one randomised controlled trial of digoxin in patients with a left-ventricular ejection fraction of < 0.45 and sinus rhythm, the so-called DIG-trial [Garg et al. 1997]. Digoxin was administered in 3397 patients and matching placebo in 3403 in addition to diuretics and ACE-inhibitors. After an average follow-up of 37 months, digoxin did not reduce mortality in comparison to placebo (34,8 vs. 35,1%) but reduced the rate for hospitalization due to heart failure. Of note, the trial was conducted at a time when β-blockade and the use of mineralocorticoid receptor antagonists were not yet part of modern heart failure therapy. For the indication of rate control in AF, there is a complete lack of controlled randomised studies. Based on the DIG trial, digoxin is currently recommended in the ESC and the US guidelines on heart failure as a class IIb, level B, or class IIa, level B, for consideration in patients with reduced LVEF in sinus rhythm to reduce the risk of hospitalization [McMurray et al. 2012; Yancy et al. 2013]. The ESC guidelines on AF recommend digoxin for rate control in patients with heart failure and LV dysfunction

(IIa, level C) [Camm et al. 2012]. In essence, these recommendations reflect the highly unsatisfactory data basis on which to judge the supposed benefits of digoxin [Opie 2013].

Since the publication of the DIG trial, several uncontrolled retrospective [Butler et al. 2010; Freeman et al. 2013; Gjesdal et al. 2008; Withbeck et al. 2013; Turakhia et al. 2014; Shah et al. 2014; Gamst et al. 2014; Chao et al. 2014; Freeman et al. 2015; Domanski et al. 2005] and prospective [Hallberg et al. 2007; Pastori et al. 2015, Rodríguez-Mañero 2014] observational studies have raised serious concerns as to the safety of digoxin therapy for AF or for CHF. For instance, the largest of all studies, the retrospective TREAT-AF study, reported data from 122.465 patients with newly diagnosed non-valvular AF [Turakhia et al. 2014]. Digoxin use was independently associated with mortality after multivariate adjustment and after careful propensity matching. Similarly, in a recent post-hoc analysis of the randomised ROCKET-AF trial in 14 171 patients with AF, the use of digitalis was associated with a 17% increase in the risk of mortality [Washam et al. 2015]. Others have reported similar findings from studies conducted in patients with CHF [Freeman et al. 2013]. Shah et al. found in 27.972 heart failure and in 46.262 AF patients a hazard ratio of 1,14 and 1,17 for mortality, respectively, in digitalis-treated patients [Shah et al. 2014].

Our meta-analysis provides further evidence for a harmful effect of digoxin on mortality. Utilizing data from all studies published over the last two decades and reporting data on all-cause mortality, it demonstrates an increase in the relative risk of dying of 21% in subjects treated with cardiac glycosides compared with patients not receiving digoxin. Importantly, all studies reported data which were carefully adjusted for potential confounders. The increase in risk seemed to be more pronounced in patients who were treated with digoxin for rate control in AF (HR 1,29, 95% CI 1,21 to 1,39) than in patients treated for CHF (HR 1,14, 95% CI 1,06 to 1,22). This differential effect was similarly evident when the three large studies reporting on AF and on heart failure populations based on identical methodology were examined separately. Digoxin therapy in AF carried a HR of 1.28 (95% CI, 1,12 to 1,46) compared with a HR of 1,05 (95% CI, 0,91 to 1,20) in heart failure. As to potential explanations for these seemingly disparate effect sizes, positive effects of glycosides on haemodynamics (increased cardiac output, decreased pulmonary wedge pressure) or neurohumoral mechanisms (vagomimetic action, improved baroreceptor sensitivity, decreased activation of the renin–angiotensin system, etc.) [Georghiade et al. 2006] may yield some overall positive effects in heart failure patients, while such effects are unlikely to

play a role in the treatment of AF. In the latter clinical condition, unwanted electrophysiological effects resulting in the occurrence of brady- or tachyarrhythmias may be operational without any beneficial haemodynamic digoxin effects.

Our findings in the population of ICD recipients are in line with the aformentioned reports and extend the observations on digitalis. By multivariate analysis, digitalis was an independent predictor of death next to other established risk factors. Crude Kaplan-Meier survival analysis demonstrated a 2,5-fold increased mortality risk in subjects treated with digitalis. In order to minimize potential confounding, this analysis was repeated after careful adjustment for known risk factors of mortality in ICD recipients. This adjusted analysis continued to demonstrate a 1,7-fold increased risk. This notion support for the detrimental effects of digitalis stems from our comprehensive meta-analysis.

6.1.3. Potential mechanisms of digoxin-associated mortality increase

It is well appreciated that digoxin has a narrow therapeutic window. Maintaining strict serum levels is therefore essential. In fact, Rathore et al. [Rathore et al. 2003] could demonstrate in a post-hoc analysis of the DIG trial that higher serum digoxin levels (defined as ≥1,2 ng/mL) were significantly associated with increased mortality whereas at lower plasma concentrations there seemed to be clinical benefit. Other potentially detrimental digoxin effects, particularly in AF, include digoxin mediated increase in vagal tone, reduced AV-node conduction, and shortening of atrial refractory periods; all of these effects may render the atrium more susceptible to AF. Digoxin has been found to be associated with doubling of relapses of AF following cardioversion [Holmqvist et al. 2006]. Finally, digoxin may provoke paroxysmal atrial tachycardias, ventricular tachyarrhythmias including fascicular or bi-directional ventricular tachycardia or torsade de pointes tachycardia, and serious bradyarrhythmias including high-degree AV block, particularly when electrolyte disorders are present [Eckardt et Breithardt 2014]. These proarrhythmic effects of glycosides may be caused or further accentuated by significant drug-drug interactions, for instance with antiarrhythmic drugs such as amiodarone or quinidine [Fromm et al. 1999]. This is exemplified in a recent randomised trial of dronedarone in patients with AF [Hohnloser et al. 2014]. This trial was stopped prematurely because of excess mortality in the dronedarone compared with the control arm. In a post-hoc analysis, it could be demonstrated that 11 out of 13 arrhythmic deaths in the dronedarone arm occurred in patients who simultaneously received digoxin. The most likely explanation for this is the drug-drug interaction between

dronedarone and digoxin at the level of the P-glycoprotein transport system which resulted in significantly elevated serum digoxin levels in patients who died.

6.1.4. Cause-specific mortality

The most common causes of death in heart failure patients treated with digitalis are cardiac arrhythmic or cardiac non-arrhythmic deaths due to pump failure [Garg et al. 1997, Whitback et al. 2013]. This was confirmed in our study, where patients on digitalis therapy died predominantly from cardiac arrhythmic and cardiac non-arrhythmic deaths ($p = 0,044$; $p = 0,036$). These findings are endorsed by a recent published subgroup analysis of the MADIT-CRT collective demonstrating an increased risk of high-rate VT/VF (≥200 bpm) in patients on digitalis [Lee et al. 2015]. Digitalis is a well-known cause of cardiac arrhythmias such as AV conduction disturbances, atrial tachycardias with or without block, and ventricular tachyarrhythmias including Torsade de Pointes and bidirectional VT [Eckardt et al. 2014]. Also, patients on digitalis suffered more often from ICD shock therapy, especially appropriate shocks. It remains speculative to which extend such specific arrhythmias have contributed to the observed mortality figures, but delivered ICD shock therapy is known to be an independent predictor of mortality [Poole et al. 2008; Powell et al. 2013]. Furthermore, digitalis works physiologically as a positive inotropic agent with its intensity depending on the plasma concentration [Kim et al. 1975; Felker et al. 2001]. Other inotropes such as milrinone have also been afflicted with increased mortality rates in patients with severe congestive heart failure [Packer et al. 1991]. In support of our findings, a retrospective analysis of the ROCKET-AF trial showed that - after adjustment - digoxin was associated with increased all-cause mortality (HR = 1.17; 95% CI 1.04–1.32; $p = 0.01$), vascular death (HR = 1,19; 95% CI 1,03-1,39; $p = 0,02$), and sudden death (HR = 1,36; 95% CI 1,08-1,70; $p=0,01$) [Washam et al. 2015].

6.1.5. Digitalis plasma concentrations

A post hoc analysis of the DIG trial showed that there was an association between digitalis plasma levels and mortality [Rathore et al. 2003]. In the subgroup of patients with digoxin concentrations ranging from 0,5 to 0,8 ng/mL, there was a mortality benefit, whereas in subjects with higher digoxin concentrations, mortality was increased. The majority of our patients was treated after the publication of this analysis, hence physicians aimed to adhere to low digitalis plasma concentrations. Due to the retrospective nature of our study, we had digitalis plasma concentrations available only in 50% of patients. These data, however,

showed that for the majority mean plasma concentration tended to be in the low range. Similar observations were made regarding prescribed mean daily dosages of digitalis.

6.1.6. Limitations

Our meta-analysis is subject to all potential limitations of this kind of analysis. We did not have access to individual patient data from all studies reviewed and had to rely on published information. All identified studies used contemporary sophisticated statistical adjustments to counteract potential confounding but residual confounding cannot be completely excluded [Wyse 2014]. However, the large number of data sets obtained in more than 300.000 patients and the internal consistency of findings emphasize the validity of this meta-analysis. Finally, only a few studies provided data on digoxin dose or plasma levels but no relationship of mortality and such data was reported except in the publication of Rathore et al. [Rathore et al. 2003]. However, the majority of the articles on digoxin therapy are based on data from contemporary studies during which the importance of daily digoxin dose and low target plasma levels was already appreciated.

Our study with ICD recipients is retrospective in nature, hence all potential limitations of such a design apply to this analysis. This needs to be considered for interpreting the main findings of the study and also for the mortality verification [i.e. arrhythmic or (non-)cardiac death]. We aimed to minimize potential confounding by carefully adjusting data to important patient characteristics found on univariate and multivariate analysis. Despite this, residual confounding cannot be entirely excluded. Digitalis use was assessed at ICD implantation but not during follow-up or at time of death. Digitalis serum concentrations were not controlled in fixed intervals. Data on the type of digitalis used were not available for 50% of the population. Strengths of our study consist of the large patient cohort, the long follow-up duration, and the consistency with our data from the comprehensive meta-analysis.

6.2. Intrathoracic impedance monitoring with CRT-devices

6.2.1. Main results

In our prospective, long-term follow-up study of optimally treated heart failure patients with remote monitoring capable CRT-D devices, the diagnostic yield of OptiVol alerts could be improved using a newly developed diagnostic algorithm based on the original PARTNERS HF criteria.

In the new diagnostic algorithm, the modification of the original PARTNERS HF criteria included the refinement of cut-off values and the exclusion of cases with permanent positivity of assessed parameters. Lower activity levels, increased nocturnal heart rate, and suboptimal biventricular pacing proved to be predictors for HF events.

6.2.1. Prognostic parameters

Patient activity measured by CIEDs were evaluated alone [Conraads et al. 2014; Vega et al. 2014; Kramer al. 2015] or together with other diagnostics [Whellan et al. 2010; Sharma et al. 2015] in previous studies. Conraads et al. demonstrated that higher level of physical activity early after defibrillator implantation was associated with better outcomes in terms of mortality and HF hospitalisation [Conraads et al. 2014]. In a single-centre study of 164 CRT recipients both 6-minute walk test and device-based measures of higher physical activity predicted reverse remodelling and HF hospitalisations [Vegh et al. 2014]. In a recent, large-volume observational study derived from the ALTITUDE registry, device-detected activity strongly correlated with survival [Kramer al. 2015]. Several comorbidities and clinical factors (such as chronic obstructive lung disease, elective surgery, musculoskeletal disorders, etc.) were not taken into account in these analyses, however, these conditions could strongly influence the physical activity. We tried to eliminate these confounding factors with the modifications of the original criterion to exclude the cases, where prior average was < 1 h/day permanently or activity decline was related to an extra cardiac reason.

Elevated heart rate is thought to be the marker of pathological autonomic response and correlates with worse prognosis in HF [McAlister et al. 2009]. Post-hoc-analyses of BEAUTIFUL and SHIFT studies have confirmed the prognostic importance of HR [Fox et al. 2009; Böhm et al. 2010]. In the observational study of Adamson et al., night-time HR was higher in CRT recipients who were hospitalised or died, compared with those with only minor exacerbations or without any HF events [Adamson et al. 2004].

According to the current guidelines CRT pacing rate should be as close to 100% as possible. The clinical benefit is strongly associated with a higher percentage of biventricular pacing as demonstrated in several reports [Brignole et al. 2013]. Decrease in CRT pacing (<80% over 48h) was also one of the most frequent findings in the telemetry data, leading to additional follow-up visits in the IN-TIME study [Hindricks et al. 2014]. This randomised, controlled, multi-centre study could demonstrate that remote monitoring (thoracic

impedance measurements were not included) could improve mortality over the standard care.

6.2.3. Non-prognostic parameters

The overall low specificity of the original PARTNERS HF algorithm may reflect the low clinical relevance of some parameters that were used. Consistently positive parameters such as long-term low patient activity level, long-standing low heart rate variability, or persistently low percentage of biventricular pacing prior to an event do not play a role in prediction. These parameters represent the clinical status of the patient, but do not have enough predictive power to identify clinical events occurring in the next few weeks. Therefore, the change but not the absolute value of these parameters may have significantly greater clinical relevance during the index period.

Although several clinical data suggest that heart rate variability can have an inverse correlation with progression of HF [Adamson et al. 2004] and could improve with CRT [Fantoni et al. 2005], we strongly believe that this parameter (HRV in patients treated with CRT) is responsible for several false positive cases when applying the classic PARTNERS HF criteria. In patients on beta blockers with a maximum tolerated dose, high percentage of atrial pacing is frequently present which makes the HRV calculation useless or misleading. Even in cases of permanent AF, the value of HRV should be expected permanently under 60 ms, but it does not necessarily mean an unstable clinical condition. Figure 18. illustrates a case with an increase in HRV, while the patient status worsened because of an increase in heart rate and loss of CRT stimulation.

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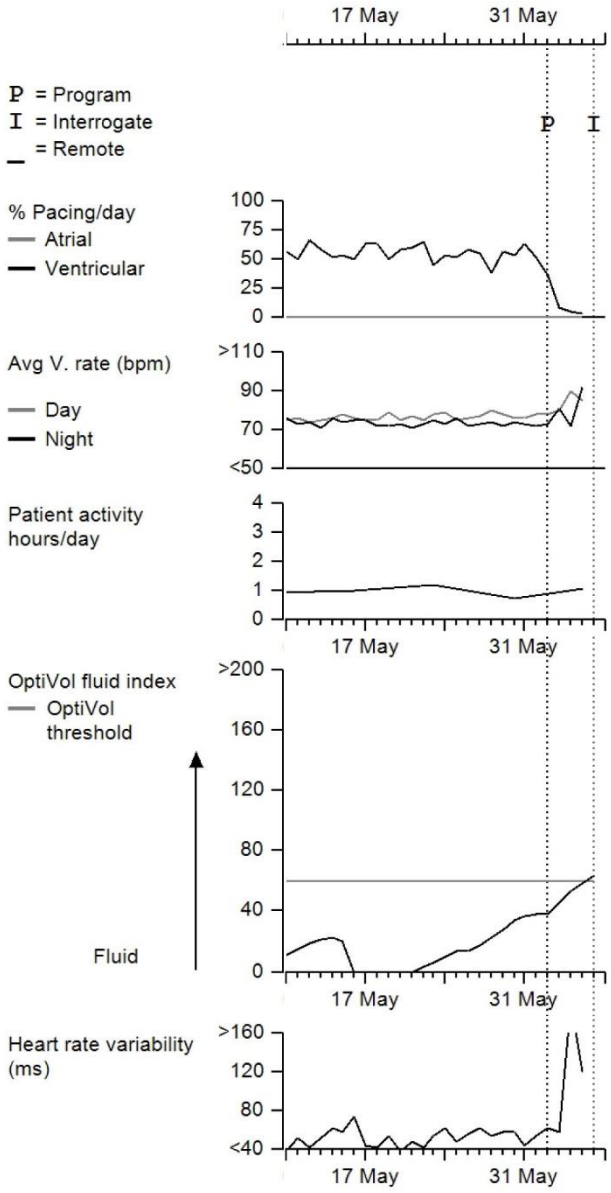

Figure 18. Changes of device detected parameters in a patient with decompensated heart failure (heart rate variability increases, while the patient status was worsened because of an increase in average ventricular rate and loss of biventricular stimulation).

Acute exacerbations of congestive HF are believed to trigger ventricular arrhythmias through multiple potential mechanisms. The phenomenon described as mechano-electrical feedback causes an acute increase in filling pressure, which can lead to electrical instability [Sarubbi et al. 1998; Narayan et al. 2007]. A temporal association between malignant

ventricular arrhythmias and volume overload detected by OptiVol was already demonstrated in two observational studies [Ip et al. 2011; Abi-Saleh et al. 2014]. The most likely reason for statistical non-significance of this parameter was the rare occurrence of malignant arrhythmias in our patient cohort.

6.2.4. Predictive value of combined diagnostic algorithm in previous studies

Since the publication of PARTNERS HF trial several attempts have been made to develop a more reliable risk assessment model based on combined device based data. In the EVOLVO study some of the original PARTNERS HF criteria were used for remote monitoring of ICD patients, and a reduction in the rate of emergency admissions and urgent in-office visits was demonstrated in the remote arm [Abi-Landolina et al. 2012]. Gula et al. acknowledging the limitations of the original PARTNERS HF criteria worked out a novel diagnostic algorithm and validated it with convincing results in a post-hoc analysis of the RAFT trial [Gula et al. 2014]. In the phase 1 of the MORE-CARE randomised study delay from the device-detected events to clinical decision was shorter and fewer in-hospital visits were required in the remote monitored group, however, the annual rate of all-cause hospitalizations could not be reduced [Boriani et al. 2017]. Nonetheless, in two recent published, randomised trials of OptiVol combined with remote monitoring no significant influence on HF-related hospitalizations, ICD shocks, or mortality was found [Lüthje et al. 2015; Böhm et al. 2016]. Also, the second phase of the MORE-CARE study could not demonstrate that decision making guided by such remote-monitoring protocol exerts a positive impact on hard endpoints [Boriani et al. 2017].

6.2.5. Limitations

Our single-centre observational study is subject to all potential limitations of this kind of analysis. First of all, the limited number of included patients should be highlighted. However, the average follow-up period (38 months) was longer with a high number of OptiVol alerts than in most of the previous reports. Furthermore, our findings can only help to exclude false positive cases from the current OptiVol alerts, as the study design was not aimed to identify heart failure episodes undetectable by the OptiVol algorithm. Our study protocol consisted of at least one patient contact after an OptiVol alert. Since OptiVol alerts may occur 7-14 days before clinical symptoms of HF develop, repeated patient contact after the initial OptiVol alert could have possibly revealed some additional HF events. One important difference to the original PARTNERS HF study design should be also highlighted:

Fluid Index ≥ 100 Ω-day has not been assigned in our analysis. Although the main idea of such monitoring tool is to early identify risk patients as they reached an alert level, a scoring system using higher fluid index values might alarm too late. It should be also noted that recently a new OptiVol algorithm (OptiVol 2.0) was developed by the manufacturer for the calculation of the Fluid Index and the Reference Impedance [Sarkar et al. 2011]. In our patient population one part of the investigated devices was still working with OptiVol 1.0 (Concerto CRT-D, Concerto II CRT-D, Consulta CRT-D) the other part with the new algorithm (Viva Quad XT CRT-D, Protecta XT CRT-D, Brava Quad CRT-D).

6.3. Upgrade CRT

6.3.1. Main findings

The principal finding of our multicentre study comprising >550 CRT-D recipients is that survival after upgrade procedures was worse than after de novo implantations. All-cause mortality continued to be significantly higher for patients in the upgrade group after adjusting for potential confounders with multivariate Cox regression analysis and after applying propensity score matching. Similarly, clinical response was less favourable after an upgrade procedure compared with de novo implantations. To the best of our knowledge, this is one of the largest observational studies demonstrating worse outcomes in patients undergoing a CRT upgrade compared to de novo CRT-D implantations.

6.3.2. Outcomes after upgrade CRT

There is only sparse clinical evidence about clinical response to CRT after upgrade procedures. The few observational studies providing head-to-head comparisons with de novo CRT implantations showed, in general, comparable results on various clinical parameters (i.e. NYHA class, quality of life, 6-minute walk test, LVEF, end-systolic diameter, BNP levels, or hospitalizations) [Marai et al. 2006; Foley et al. 2009; Paparella et al. 2010; Fröhlich et al. 2010; Gage et al. 2014; Tayal et al. 2016]. However, most of these studies were limited by their small patient sizes. In a recent European survey, similar improvements in NYHA functional class and similar reduction in QRS duration were found; however, more patients reported unchanged global assessment status in the upgrade group [Bogale et al. 2011].

Unfortunately, randomised, controlled data on the mortality of patients undergoing upgrade procedures are completely lacking. The available evidence mostly stems from the already mentioned survey report [Bogale et al. 2011] and from smaller retrospective analyses, which have yielded partially contradictory results. In the largest single-centre observational study [Gage et al. 2014], patients upgraded to CRT from previous RV-pacing tended to have better outcomes in terms of all-cause mortality (adjusted HR, 0,73; 95% CI, 0,53-1,01; p=0,055) compared with CRT patients without previous RV pacing. However, upgraded patients had smaller end-systolic and end-diastolic volumes at baseline; these different grades of remodelling may have influenced the response to CRT. Foley et al. [Foley et al. 2009] described a similar long-term risk of mortality and morbidity between 336 patients undergoing de novo and 58 CRT recipients undergoing upgrade procedures from RV pacing. Of note, however, our study comprises more than 3× as many upgrade patients. No significant differences were found in a composite end point of 1-year device-related complication rate including death after 134 upgrade CRT operations compared with a randomly matched, equally sized sample of de novo CRT implantations in a retrospective single-centre analysis [Ter Horst et al. 2016]. However, when analysed separately, 1-year mortality was more than doubled after upgrade procedures (19/113 versus 8/123).

The overall weak scientific evidence about the beneficial effects of a CRT upgrade has been recently emphasized by the 2016 European heart failure guidelines [Ponikowski et al. 2016]. These guidelines restrict the indication for upgrade CRT as a IIb class (level B) and do not indicate upgrade for patients with stable heart failure or with a QRS duration of <130 ms.

6.3.3. Factors responsible for reduced benefit of upgrade CRT

In our series, patients in the upgrade group had more advanced heart disease and more comorbidities, which could explain the observed worse outcome. To account for these differences, we carefully adjusted the data for these baseline differences by various methods, including propensity score matching. In these adjusted analyses, findings consistent with the crude unadjusted analysis were observed.

Several considerations may help to explain our findings. The first one relates to the fact that resynchronization therapy may have been initiated too late in subjects who were upgraded from conventional pacemaker/ICD systems. It is conceivable that these patients were further advanced in their disease process and hence cardiac resynchronization had less

chance to modify the risk for bad outcomes. This hypothesis is supported by the subgroup analysis according to NYHA functional class in which NYHA II patients showed similar mortality after both, de novo, and upgrade CRT. However, survival in NYHA III–IV patients was worse after upgrade procedures compared with de novo implantations. Chang et al. [Chang et al. 2014] showed recently that among patients who developed heart failure while being long-term paced from the RV only those responded to the CRT upgrade whose LVEF was ≥43.5% at the time of deployment of RV pacing.

In addition, there is convincing evidence that only patients with typical LBBB respond well to CRT, but not those with RBBB or nonspecific intraventricular conduction disturbances [Zereba et al. 2011; Sipahi et al. 2012; Cunnington et al. 2015]. Accordingly, the worse clinical response pattern in patients with unspecific QRS abnormalities including those with a paced wide QRS complex may constitute another factor disfavoring CRT therapy. Our subgroup analysis according to QRS morphology and duration supports this notion.

Finally, CRT upgrade procedures may be associated with greater surgical risk than de novo procedures. Generally, reoperations could be more complex and carry a higher risk of acute complications, such as venous access issues, the risk of damage or extraction of old leads, higher infection rates, and longer procedure times. Notably, the incidence of postoperative complications was highest in patients undergoing the addition of a transvenous lead for replacement or upgrade in the REPLACE registry (Implantable Cardiac Pulse Generator Replacement) [Poole et al. 2010]. In the report from the Danish Pacemaker and ICD Register comprising 5918 consecutive patients, a system upgrade was also associated with a significantly higher complication risk (adjusted risk ratio, 1,3; 95% CI, 1,0-1,7; p=0,02) [Kirkfeldt et al. 2014].

6.3.4. Limitations

Because our study comprises a non-randomised patient population, residual bias cannot be excluded. However, we aimed to minimize potential confounding by carefully adjusting our data to important patient characteristics possibly responsible for worse outcomes with two different statistical methods (i.e., adjusted multivariate Cox regression and propensity score matching). It should be also noted that the matched propensity score analysis excludes 32% of the upgrade subjects, and thus addresses the question of comparability in a somewhat

different population. Furthermore, echocardiographic follow-up parameters were not available for all patients.

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7. CONCLUSIONS

7.1. Our meta-analysis of the contemporary literature indicates that digoxin therapy is associated with an increased mortality risk in patients suffering from AF and CHF. Our sensitivity analysis, however, suggests negative effects of digoxin particularly in the AF population but somewhat less unfavourable effects in the CHF population. Coupled with the notion emphasized by Rathore et al. [Rathore et al. 2003], this calls for randomised trials of dose-adjusted digoxin therapy at least in CHF patients. Until such proper randomised controlled trials are being completed, digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control in AF.

7.2. In our retrospective, single-centre, long-term study of consecutive ICD recipients, we first described that digitalis use was independently associated with an increased mortality risk in this particular patient population. In addition, there was no difference in the mortality risk between patients treated with digitoxin or with digoxin. Digitalis should therefore be used with great caution in clinical practice. Randomised placebo-controlled trials of digitalis use in patients with heart failure are urgently warranted.

7.3. Refined device diagnostic algorithms based on the parameters of low activity level, high nocturnal heart rate, and suboptimal biventricular pacing could improve the clinical reliability of OptiVol alerts in our patient cohort. Our results are hypothesis generating, and hence this strategy of risk assessment should be prospectively tested in larger patient cohorts.

7.4. Both clinical response and long-term outcome were less favourable in patients undergoing CRT-D upgrade compared to de novo implantation in our multicentre, observational study, even after careful adjustment for possible confounders. These findings warrant confirmation in prospective randomised trials, such as the ongoing BUDAPEST-CRT Upgrade Study [Merkely et al. 2016]. Until these results become available, our observations need to be considered when counselling individual patients on the need for a CRT upgrade.

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8. SUMMARY

There are conflicting data regarding the effect of digoxin use on mortality in patients with atrial fibrillation or heart failure (HF). We performed a meta-analysis of the contemporary literature dealing with the effects of digoxin use on survival. Based on the analysis of adjusted mortality results of 19 studies comprising 326 426 patients, digoxin use was associated with an increased risk of all-cause mortality (HR 1,21, 95% CI, 1,07-1,38). Also in our retrospective single-centre long-term study of 1020 patients receiving ICD implantation at the University Hospital Frankfurt, we first described that digitalis use was independently associated with an increased mortality risk in ICD recipients even after careful adjustment for possible confounders (adjusted HR 1,65, 95% CI 1,14-2,39). Our results call for randomised trials of dose-adjusted digoxin therapy. Until such proper randomised controlled trials are being completed, digitalis glycosides should be used with great caution including a regular monitoring of plasma levels.

The reliability of intrathoracic impedance monitoring for early prediction of HF events by some of the currently used cardiovascular implantable electronic devices despite using additional device based parameters is controversially discussed. In our prospective single-centre study of 42 patients, 722 remote transmissions were analysed during an average follow-up of 38 months. Upon multivariate discriminant analysis, low patient activity, high nocturnal heart rate, and low biventricular pacing (<90%) proved to be independent predictors of true HF events (all p<0,01). Incorporating these three refined criteria in a new algorithm, the diagnostic yield of intrathoracic impedance monitoring was significantly improved (AUC from 0,787 to 0,922, p<0,01).

Although the number of upgrade procedures from single- or dual-chamber devices to cardiac resynchronization therapy (CRT) is increasing, there are only sparse data on the outcomes after upgrade procedures. We have performed a prospective, multicentre, international study of 552 CRT-D recipients to evaluate the clinical response and survival after de novo CRT implantations. Both clinical response (57% vs 69%, p=0,021) and long-term outcome (adjusted HR 1,68, 95% CI 1,20-2,34) were less favourable in patients undergoing CRT-D upgrade compared to de novo implantations. Until further data from randomised trials become available, our observations need to be considered when counselling individual patients on the need for a CRT upgrade.

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9. ÖSSZEFOGLALÁS

Több, a közelmúltban megjelent közlemény alapján felmerült, hogy a pitvarfibrillációban vagy szívelgtelenségben alkalmazott szívglikozidok negatívan befolyásolnák a túlélést. A digitálisz mortalitásra kifejtett hatását metaanalízis valamint a Frankfurti Egyetemi Klinikán ICD beültetésre kerülő betegek utánkövetési adatainak retrospektív elemzése során vizsgáltuk. 19 vizsgálat 326 426 betegének klinikai változókra korrigált halálozási adatainak metaanalízise során az addigi legnagyobb adatbázisban igazoltuk, hogy digoxin kezelés mellett emelkedik az összhalálozás (HR 1,21, 95% CI, 1.07-1,38). Hasonlóan, ICD regiszterünkben hosszú távon követett 1020 beteg adatainak elemzése során elsőként igazoltuk, hogy a digitáliszok ebben a betegcsoportban is a halálozás független rizikófaktorai (korrigált HR 1,65, 95% CI 1,14-2,39). Eredményeink alapján mielőbbi, dózis kontrollált, randomizált klinikai vizsgálatok szükségesek. Ameddig azonban ezek eredményei elérhetők lesznek, digitálisz alkalmazása csak kellő körültekintés, egyéni kockázat-haszon mérlegelés és rendszeres szérumszint-ellenőrzés mellett jöhet szóba.

A szívelégtelenség progressziójának előrejelzését teszik lehetővé egyes implantálható kardiológiai eszközök a mellkasi impedancia változás monitorozásával. A módszer diagnosztikus megbízhatósága az egyidejűleg monitorozott egyéb paraméterekre épülő kombinált algoritmus ellenére is kétséges. Egy-centrumos, prospektív vizsgálatunkban 42 CRT-D-vel elő beteg 722 telemetriás adatküldését dolgoztuk fel az átlagosan 38 hónapos utánkövetési idő alatt. Multivariábilis diszkriminancia analízis során a csökkent betegaktivitás, az emelkedett éjszakai szívfrekvencia és a csökkent biventrikuláris ingerlési arány (<90%) bizonyult a szívlégtelenség független előrejelzőinek (minden $p<0,01$). E három paraméterre épülő új diagnosztikus algoritmussal szignifikánsan javítottunk a mellkasi impedancia mérés diagnosztikus megbízhatóságát (AUC 0,787 vs. 0,922, $p<0,01$).

Bár az egy- ill. kétüregű készülékekről kardiális reszinkronizációs kezelésre (CRT) történő upgrade beavatkozások száma emelkedik, ebben a betegcsoportban kevés adattal rendelkezünk. 552 CRT-D beültetésre kerülő beteg adatait felölelő, multicentrikus, nemzetközi tanulmányunkban mind a CRT-re adott klinikai válasz (57% vs 69%, $p=0,021$), mind az összmortalitás (korrigált HR 1,68, 95% CI 1,20-2,34) kedvezőtlenebb volt a biventrikuláris upgrade beavatkozásokat követően összehasonlítva a de novo beültetésekkel. Ameddig randomizált klinikai vizsgálati eredmények elérhetőek lesznek, a CRT upgrade beavatkozások alapos egyéni kockázat-haszon mérlegelése szükséges.

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11. PUBLICATIONS

11.1. Original publications related to PhD thesis

Vamos M, Erath JW, Hohnloser SH.
Digoxin-associated mortality: a systematic review and meta-analysis of the literature.
EUROPEAN HEART JOURNAL 36(28):1831-1838. (2015)
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Erath JW[1], **Vamos M[1],** Hohnloser SH.
Effects of Digitalis on Mortality in a Large Cohort of ICD-Recipients: Results of a long-term Follow-Up-Study in 1020 Patients.
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Vamos M, Nyolczas N, Bari Zs, Bogyi P, Muk B, Szabo B, Ancsin B, Kiss RG, Duray GZ.
Refined heart failure detection algorithm for improved clinical reliability of OptiVol alerts in CRT-D recipients.
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Effects of upgrade versus de novo cardiac resynchronization therapy on clinical response and long-term survival: Results from a multicentre study.
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IF: 5,410

11.2. Original publications not related to PhD thesis

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The wearable cardioverter-defibrillator in a real-world clinical setting: experience in 102 consecutive patients
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