

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

PhD Thesis Booklet

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Budapest

2018

INTRODUCTION

In patients with symptomatic chronic heart failure (HF) the first line therapy consists of the pharmacological treatment with neurohormonal antagonists. 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. On top of 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. This present work focuses on the safety of digitalis glycosides and novel functions and indications of cardiac resynchronisation therapy.

(A-B) 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 (AF). 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]. With regards to the second indication, rate control in atrial fibrillation, there is not a randomised placebo-controlled study yielding supportive data. Nevertheless, both indications are endorsed by recent guideline recommendations [Ponikowski et al. 2016; Kirchhof et. al. 2016;]. 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 HF treatment. In fact, some observations have indicated that digoxin may have a negative effect on mortality [Hallberg et al. 2007; Freeman et al. 2013; Whitbeck et al. 2013; Turakhia et al. 2014; Shah et al. 2014; Gamst et al. 2014; Chao et al. 2014; Freeman et al. 2015; Pastori et al. 2015]. Moreover, 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 episodes in patients treated with digitalis, but no difference in mortality [Lee et al. 2015].

(C) Unfavourable prognostic impact of recurrent hospitalisations in HF is 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 hospitalisations 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™ 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, rapid ventricular rate during AF, low patient activity levels, high night heart rate, low heart rate variability, low percentage of biventricular pacing, and ventricular arrhythmias with ICD shocks [Whellan et al. 2010]. 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 hospitalisation with high probability, only 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].

(D) The beneficial impact of newly implanted cardiac resynchronisation therapy on morbidity and mortality are well described in selected patients with heart failure [Al-Majed et al. 2011; Cleland et al. 2013; Lewis et Gold 2015]. Patients already fitted with a conventional pacemaker or implantable cardioverter defibrillator (ICD) system are often considered for a CRT upgrade. In the latest European pacemaker and CRT guidelines, upgrade procedures from conventional pacemakers or ICDs to CRT are suggested as a class I indication (level B) for HF patients with a New York Heart Association (NYHA) functional class of III to ambulatory IV, left ventricular ejection fraction (LVEF) $\leq 35\%$,

and a high percentage of ventricular pacing [Brignole et al. 2013]. However, there is only weak scientific evidence about the outcomes of patients undergoing upgrade procedures.

OBJECTIVES

(A) 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.

(B) 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 in the University Hospital Frankfurt.

(C) 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.

(D) 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.

METHODS

(A) **Study selection.** A comprehensive PubMed and Cochrane search was conducted from 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). 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 requirements, prospectively defined by our review protocol were met: (i) inclusion of AF or HF patient populations; (ii) report of adjusted results of effects of digoxin on all-cause-mortality; (iii) effect sizes provided as hazard ratios (HR).

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. 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 was used to calculate HR for the overall effect and for the two subgroups (AF, CHF) in this meta-analysis. A forest plot was constructed showing the individual trials with the pooled estimates.

(B) Patient population and outcomes. Our retrospective observational study is based on the analysis of data collected in consecutive patients who received an ICD or a cardiac resynchronisation defibrillator (CRT-D) at the J.W. Goethe University Frankfurt between 1996 and 2010 and who were followed at the same institution. Follow-up data were prospectively collected from the index hospitalisation at the time of initial ICD implantation and at each follow-up visits that took place every 6 months or at the time of unscheduled visits in the out- or inpatient clinic. The primary outcome measure was time to all-cause mortality. Cause-specific mortality was defined according to the Hinkle and Thaler classification.

Statistical analysis. Statistical analysis was performed using SPSS program version 22 (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.

(C) 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, 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 hospitalisation.

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

New device diagnostic algorithm development. Our refined diagnostic algorithm was derived from an OptiVol alert (Fluid Index \geq 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:** \geq 6 h on at least 1 day
- **High ventricular rate during AF:** average ventricular rate during AF \geq 90 bpm on at least 24 h
- **Lower patient activity level for at least 5 days:**
 - -2 h/day, if the prior average was \geq 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 extra cardiac 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)

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. Multivariate discriminant analysis was used to assess the association between device based parameters and 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 a cross-validation was performed. The cross-validation of ROC-curves and the confidence interval calculations were performed with the “Proc Logistic” procedure.

(D) Patient population and outcomes. 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 $\leq 35\%$, 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). Patients were followed-up in the outpatient clinic of participating hospitals in 6 months' intervals or when clinically indicated. 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 resynchronisation therapy.

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 χ^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 assessed by the χ^2 test and by a multivariate logistic regression model. To assess the effects of procedure type (i.e., de novo versus upgrade) on survival, the Cox proportional hazards regression model was used. The statistical models were adjusted for potential baseline confounders (listed in footnote of Table 2.). 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 as 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).

RESULTS

(A) 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. This yielded a total of 19 studies which were selected for the present analysis. Nine reports dealt with AF patients, seven with patients suffering from CHF, and three with both clinical conditions. Patients were followed between 0,83 and 4,7 years (average observation period $2,6 \pm 1,1$ years) in the individual studies. Of all identified studies, only one was a randomized controlled clinical trial [Garg et al. 1997] whereas the remainder of studies were retrospective or prospective observational studies.

Based on the analysis of adjusted mortality results of all 19 studies comprising 326.426 patients, digoxin use was associated with an increased relative risk of all-cause mortality (HR 1,21, 95% CI, 1,07 to 1,38, $p < 0,01$) (Figure 1.). Compared with subjects not receiving glycosides, digoxin was associated with a 29% increased mortality risk (HR 1,29; 95% CI, 1,21 to 1,39) in the subgroup of publications comprising 235.047 AF patients. Among 91.379 heart failure patients, digoxin-associated mortality risk increased by 14% (HR 1,14, 95% CI, 1,06 to 1,22).

Six of the 19 studies reported data on the mean daily digoxin dose (0,126-0.250 mg) and/or the mean digoxin plasma levels (0,8-1,02 ng/ml). A sensitivity analysis of these studies revealed a similar HR (1,26, 95% CI, 0,91 to 1,74) as the analysis of all 19 studies, although this was no more statistically significant.

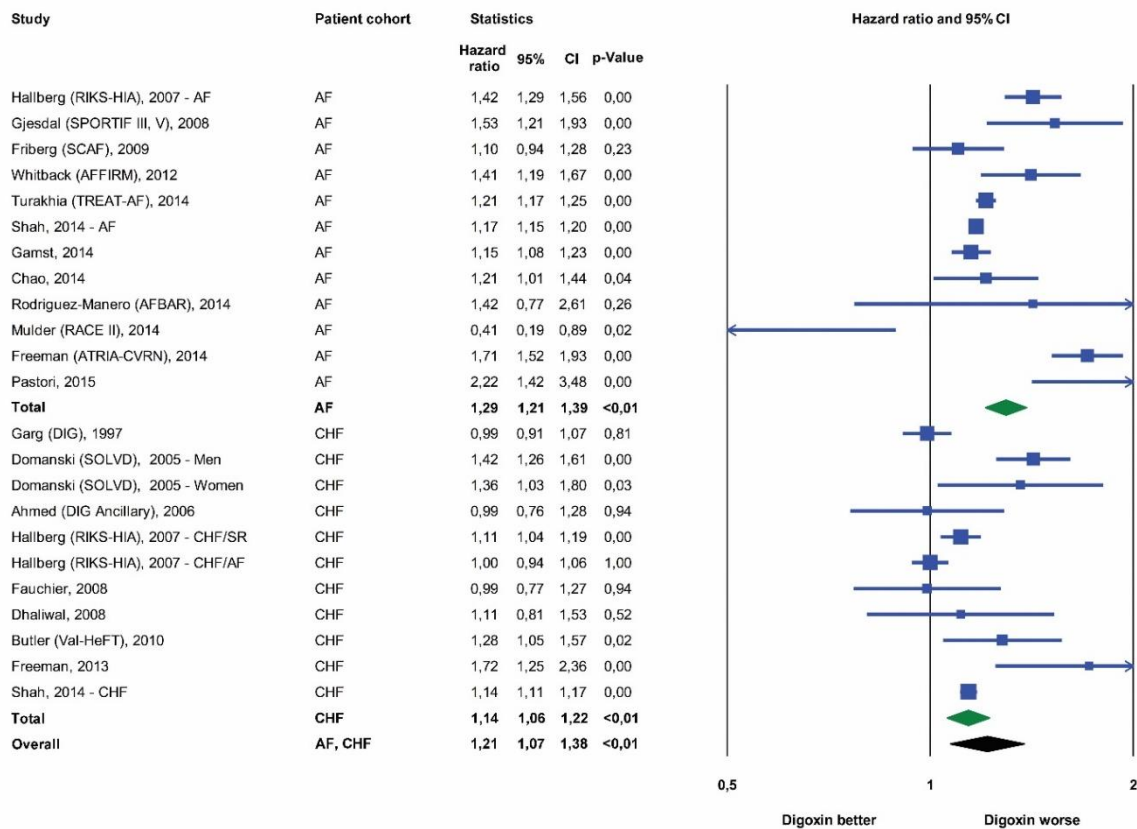


Figure 1. Forest plot of studies describing the effects of digoxin on mortality, both for studies in atrial fibrillation (AF) and congestive heart failure (CHF). Data had been adjusted for potential confounders in the various studies.

(B) 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 formed 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). Digitalis medication was prescribed either for the treatment of CHF 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 ($p < 0,001$).

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 2.). To correct for potential confounders, Kaplan-Meier analysis was repeated with data adjusted for all variables found significantly different between both patient groups in a multivariate analysis. These independent predictors of mortality were age, male gender, NYHA classification, and prolonged QRS duration. 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 2.).

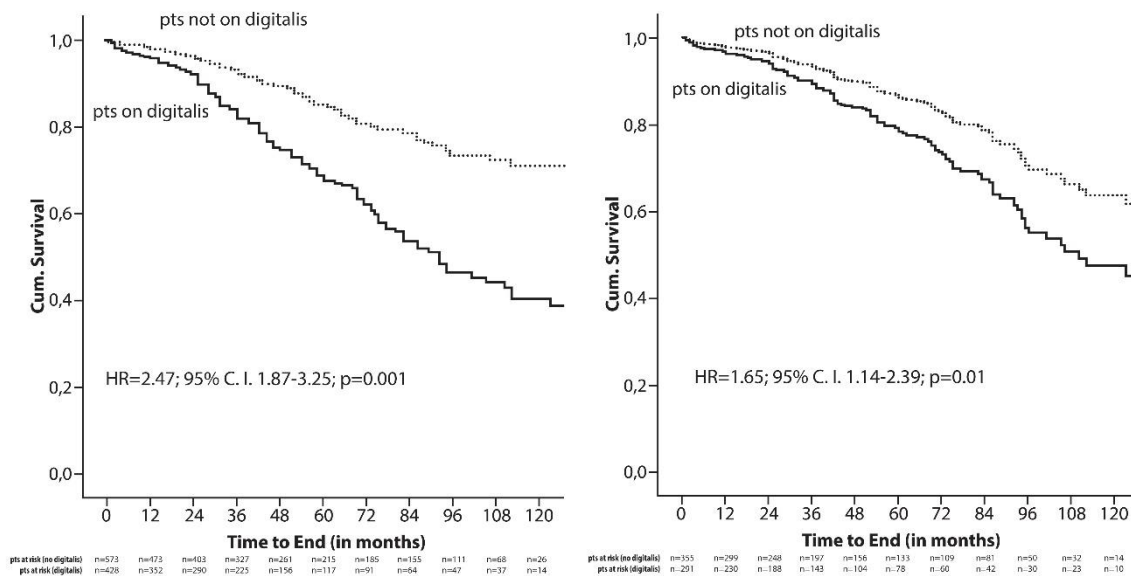


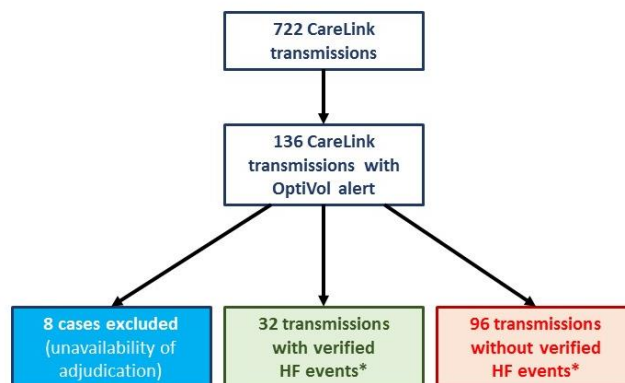
Figure 2. Crude (A) and adjusted (B) Kaplan-Meier analysis of all-cause mortality by digitalis use.

Cause-specific mortality. 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.) 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 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.

Digoxin/digitoxin. Two different digitalis preparations were used in our patient population. The majority of the patients received digitoxin (n = 306), and 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).

(C) OptiVol alerts and heart failure events. The average follow-up of the 42 enrolled patients was 38.0 ± 23.6 months. 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. 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 3.) with need for hospitalisation in eight cases.



* Identifiable signs and symptoms of decompensated HF required an increase in diuretics in an outpatient setting or hospitalization.

Figure 3. Flowchart of CareLink transmissions during the study period.

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 1.).

Table 1. Prognostic characteristics of the original and the refined diagnostic criteria.

	PARTNERS HF classic	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

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 (all p <0,001). Applying our refined algorithm which includes OptiVol alert events (Fluid Index \geq 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 1.). 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 1). 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 1).

(D) 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.

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 ($p=0,021$). 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 ($\Delta\text{EF } 6,7\pm 9,4$ versus $2,9\pm 9,0$, $p<0,001$; $\Delta\text{LVEDD } -3,5\pm 6,7$ versus $0,0\pm 12,2$, $p=0,003$; Figure 4.).

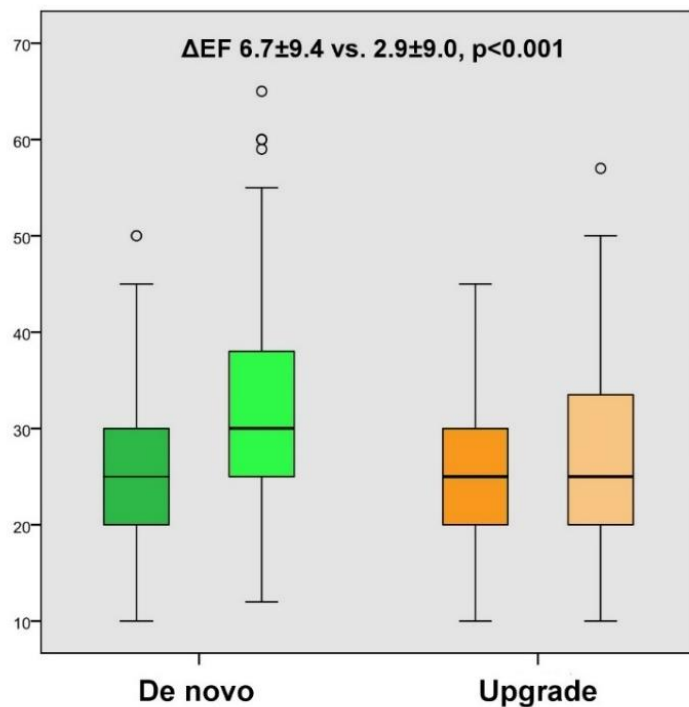


Figure 4. LVEF at baseline and at 6 months follow-up .

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)(Figure 5., Table 2.). 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 2.). 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. 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 2.).

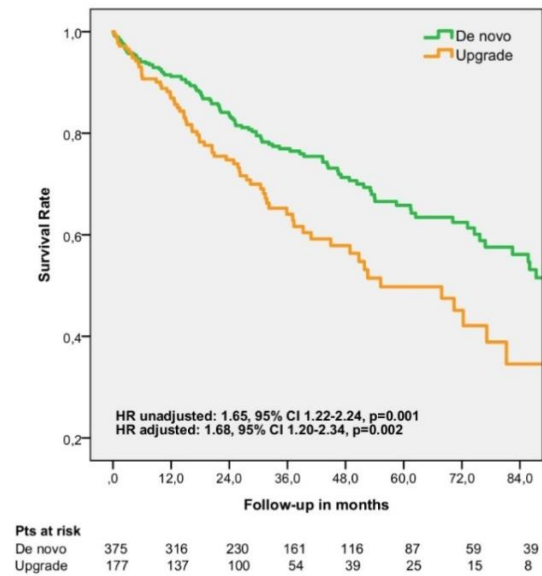


Figure 5. Kaplan-Meier curves for all-cause mortality by implantation type.

Table 2. 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, β -blockers, ACEIs/ARBs, diuretics, mineralocorticoid receptor antagonists, statins, amiodarone, and digitalis.

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).

CONCLUSIONS

(A) Our meta-analysis on the effects of digoxin on all-cause mortality is the largest one published until 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. Coupled with the notion emphasized by Rathore et al. [Rathore et al. 2003], this calls for randomised trials of dose-adjusted digoxin therapy. Until such proper randomised controlled trials are being completed, digoxin should be used with great caution, including monitoring plasma levels.

(B) 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 therefore should be used with great caution in clinical practice. Randomised placebo-controlled trials of digitalis use in patients with heart failure are urgently warranted.

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

(D) 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 [NCT02270840]. Until these results become available, our observations need to be considered when counselling individual patients on the need for a CRT upgrade.

ACKNOWLEDGEMENT

First of all, I would like to thank my supervisor, Dr. Gábor Zoltán Duray for introducing me into invasive electrophysiology and inspiring me for scientific work. I am very grateful for his grandiose support to achieve my professional and scientific goals.

I am grateful to Prof. Stefan H. Hohnloser (University Hospital Frankfurt, Goethe University, Germany) who has formulated my scientific thinking as a master, given me the opportunity to engage several clinical researches, supported throughout their accomplishments, from design to drafting the manuscripts. I am indebted to him for all his professional, scientific and personal guidance, expert criticism and friendship.

I would like to thank Dr. Noémi Nyolczas for teaching me how to treat heart failure, work precise and showing me what the true doctor-patient relationship is. I am grateful to Dr. Ádám Székely, Dr. Éva Nieszner, Dr. Tünde Borsányi, and Dr. Róbert Gábor Kiss for their professional and personal support on my medical career.

I would also like to thank Dr. Julia W. Erath, Dr. Zsolt Bári, Dr. Alexander Benz, Dr. Péter Bógyi, Dr. Balázs Muk, Antje Steidl and all my other colleagues in Hungary and Germany not listed above, for supporting my daily work and making my research possible.

The statistical expertise of Prof. Dr. Eva Herrmann, Dr. András Paksy and Prof. Dr. Elek Dinya is greatly appreciated.

I am very grateful to my parents who have made my studies possible; always encouraged me and helped me during the whole preparation process. Last but not least, I thank my wife, Krisztina, on whom I can always count, and without whose support I could not have succeeded any of my projects.

Deo Gratias!

ORIGINAL PUBLICATIONS RELATED TO PhD THESIS

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EUROPEAN HEART JOURNAL 36(28):1831-1838. (2015)

IF: 15,064

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