

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PH.D.)

**New observations with long-term follow-up after
implantable cardioverter defibrillator and cardiac
resynchronization therapy**

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The Examination takes place at the Department of Pediatrics, Medical and Health Science Center, University of Debrecen

December 7, 2012. 11:00

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The Ph.D. Defense takes place at the Lecture Hall of the 1st Department of Medicine, Institute for Internal Medicine, Medical and Health Science Center, University of Debrecen

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1. Introduction

The implantation of the first pacemaker (Senning, 1958) became a milestone in the development of cardiac device therapy, which was followed by a rapid improvement of conventional antibradycardia pacemakers. Not only the size was smaller and smaller during the decades, but pacemaker function also became more and more complicated: the number of programmable parameters may reach as many as 200 in recent devices providing the possibility of individualized pacemaker programming. One of the most important developments in the recent years was the launch of pacemaker generators and electrodes compatible with magnetic resonance imaging, which are now also available in Hungary. Parallel to the improvement of antibradycardia pacemakers took place the development of implantable cardioverter defibrillators (ICD): the original concept was created in the '60s, followed by early animal experiments in the '70s and eventually the first human implantation was performed in 1980. With the implantation of ICDs not only bradycardias, but malignant ventricular tachycardias could also be treated. First ICDs were implanted as a secondary prevention to patients who already survived an episode of sudden cardiac arrest or sustained, hemodynamically unstable malignant ventricular tachycardia. Later, prospective, randomized trials in the '90s identified several subgroups of patients who are at high risk for sudden cardiac death and a prophylactic ICD implantation may reduce arrhythmic and total mortality. Based on these results ICD implantation increases worldwide and in Hungary as well.

The implantation of the first biventricular pacemaker in 1990 proved to be the next milestone in the evolution of cardiac device therapy aiming patients without brady-, or tachyarrhythmia but with heart failure and electromechanical dyssynchrony. Owing to cardiac resynchronization therapy (CRT) in these patients ventricular remodelling may be reversed with an improvement in the functional status and consequently with a significant reduction in mortality as a result of the resynchronized ventricular contraction.

I would like to emphasise the results of implementing ICD and CRT therapies in Hungary: a continuous increase may be observed between 2003 and 2010. In this period the number of ICD implantations doubled with an octuple increase in CRT implantations.

The widespread and increasing use of ICD and CRT therapy with several unanswered questions makes current thesis actual and important.

2. Background

2.1 Implantable cardioverter defibrillator therapy

2.1.1. Design of ICDs and mode of function

ICDs consist of 6 main structure: battery (lithium-silver-vanadium), amplyfier, electronics, direct current transformer, two capacitors and telemetrics. Intrinsic electric activity of the heart is sensed by bipolar leads, which is amplified first then processed; based on it the device discriminates normal rhythm to ventricular arrhythmias. Delivering a shock therapy is performed through the capacitors controlled by a separate cicuit.

The size of ICDs is mainly dependent on the size of battery and capacitors: while first devices in the '80s were implanted abdominally due to their enormous size, nowadays prepectoral implantations became general owing to the significant decrease in the size of ICDs. Defibrillators not only terminate ventricular arrhyhtmias but are also capable saving the intracardiac electrograms of an episode, which can be interrogated by the doctor during check-ups or via telemetry. Different parameters of a ventricular arrhythmia (VA) episode can be withdrawn, such as: cycle length of VA, morpholgy of uni and bipolar electrograms, type, number and success of delivered therapies.

In some centers postimpant defibrillation threshold testing (DFT) is routinly performed. Ventricular fibrillation is initiated with a high frequency burst pacing or

with a shock on T wave, the device should appropriately recognize the arrhythmia and then terminate it effectively with a high energy shock. However, in the recent years several small studies and mathematical models questioned the need for routine DFT, which changed the clinical practice in some centers performing defibrillation test only in selected cases.

It should be emphasised that the lifetime of shock leads is significantly shorter compared to conventional pacemaker leads: as many as 40% of implanted shock leads require revision at 8 year follow-up according to a recent publication. A lead fracture or an insulation failure may result in ineffective shock therapy or, more frequently seen in clinical practice, in inappropriate shock therapy due to the electric noise generated by the intermittent contact of fractured ends.

2.1.2. Evidences in ICD therapy

First ICD implantations were performed only to patients who survived an episode of sudden cardiac death (sometimes several times) and arrhythmias cannot be suppressed by antiarrhythmic medications. Although evidence based therapy required the demonstration of effectiveness leading to the design and implementation of prospective randomized trials in the '90s in patients with a secondary preventive indication to ICDs; among them the most important were: AVID, CIDS, CASH. Patients surviving an episode of ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) were randomised to ICD or best available antiarrhythmic drug (amiodarone in most of the patients) therapy. These studies and a metaanalysis of them proved that ICD therapy is effective in reducing arrhythmic and total mortality in these patients. Interestingly, a subgroup analysis of AVID study showed only benefit of ICD therapy only in patients with a left ventricular ejection fraction below 35%; mortality rates did not differ in subjects with an ejection fraction equal or over 35%. Based on the results of smaller studies secondary preventive ICD indication was later extended to patients with a hemodynamically stable sustained

ventricular tachycardia and structural heart disease, because these patients are more likely to develop a hemodynamically unstable tachycardia as well later during the course of the disease.

Considering the fact that only a minority of patients survive an episode of sudden cardiac death subsequent investigations tried to identify those patients who are at very high risk for sudden cardiac death and may benefit from a prophylactic ICD implantation. MADIT, MADIT-II, MUST, SCD-HeFT studies were the most important proving ICD efficacy in mortality reduction as a primary prevention in patients with ischaemic and non-ischaemic cardiomyopathy compared to optimal medical therapy.

2.1.3 Clinical background of studies

Patients treated with an ICD as secondary prevention following sustained monomorphic ventricular tachycardia (mVT) are known to experience a higher ventricular arrhythmia burden during follow-up as compared with those implanted for primary prophylaxis or for ventricular fibrillation as the index arrhythmia. In large-scale multicenter studies dedicated to the problem of ICD programming, either none or only a minority of the patients received an ICD for sustained mVT. Moreover, current guidelines do not specifically address the issue of device programming in these patients.

It is a common practice to determine ventricular tachycardia detection zones on the basis of the cycle length (CL) of spontaneous VTs. The tachycardia detection interval is typically programmed with a safety margin of 30-60 msec above the slowest spontaneous arrhythmia. However, this general practice has not been validated by any study. Indeed, no investigation of the relation between the first spontaneous "index" VT and the subsequent VTs observed during the follow-up has been reported.

Our present study related to the long-term variability of VTs as regards both CL and morphology, with potential implications for device programming and the management of patients with an ICD implanted for sustained mVT.

2.2. Cardiac resynchronization therapy

2.2.1. Basic concept of CRT

ICDs effectively reduce mortality in selected patients, but they have no effect on the course of the underlying heart disease. On the contrary, CRT induces reverse structural remodelling in patients with heart failure and electromechanical dyssynchrony thereby improving functional capacity and reduces mortality. CRT diminishes inter- and intraventricular delays by simultaneously stimulating both ventricles leading to a better performance of the left ventricle. From the technical point three leads are attached to the pacemaker generator, which are positioned in the right atrium, the right ventricle, and in a posterolateral/lateral side branch of the coronary sinus, the latter one providing the left ventricular stimulation. Biventricular stimulation decreases the time for systole and consequently prolongs diastole resulting in a better ventricular filling and diastolic function.

In the acute phase of CRT contractility improves, and in the long-term end-systolic and end-diastolic volumes decrease, the left ventricular ejection fraction and the severity of mitral regurgitation improves. Importantly, CRT does not increase myocardial oxygen consumption.

According to current guidelines CRT is indicated for patients with heart failure symptoms (NYHA III-IV), reduced left ventricular ejection fraction (<35%) and a wide QRS complex (120 msec.<) on the resting ECG. In patients with NYHA II functional stage CRT is indicated only if the QRS width exceeds 150msec.

It should also be mentioned that biventricular pacemaker implantation is more challenging from the technical point of view compared to antibradycardia devices with prolonged procedure and fluoroscopic times.

2.2.2. Prospective, randomised studies in CRT

Prospective randomised studies investigating CRT mainly enrolled patients with a wide QRS on the resting ECG, reduced left ventricular ejection fraction and symptomatic heart failure despite optimal medical therapy. In early studies (MIRACLE, MIRACLE-ICD, MUSTIC) an improvement in soft, functional end-points was observed, while later, CARE-HF and COMPANION proved that CRT also reduces mortality compared to optimal medical heart failure therapy. In COMPANION, patients were randomised to optimal medical therapy, optimal medical therapy + biventricular pacemaker (CRT-P), and optimal medical therapy + biventricular defibrillator (CRT-D). CRT-P and CRT-D were significantly more efficient in the prevention of the primary endpoint (hospitalisation due to heart failure + all-cause mortality) and therefore the study was prematurely terminated. Only CRT-D decreased total mortality significantly compared to optimal medical therapy. In CARE-HF, patients were randomised to optimal medical therapy and optimal medical therapy + CRT-P. The primary end-point (combined end-point of all-cause mortality and hospitalisation due to a major cardiovascular event) was significantly lower in the CRT-P subgroup. In the extension phase the favourable effect of CRT-P on survival was also observed in the long-term also with a decrease in the incidence of sudden cardiac death in the device arm.

2.2.3. Clinical background of studies

CRT improves quality of life and decreases mortality in selected patients with heart failure; however, a relatively high proportion of such patients do not respond

to CRT: 20-40% in the majority of reports in which mostly functional end-points were used. A number of factors (including the etiology of the cardiomyopathy, the baseline QRS width, the positions of the right and left ventricular leads and multiple echocardiographic parameters) have already been investigated as regards their potential to predict a positive response to CRT. However, the results were either negative or conflicting, and an adequate predictor that could be used in routine clinical practice is therefore still lacking.

Obesity has rapidly become a major public health problem worldwide. The latest WHO statistics disclose that 32.2% of the general population in the United States are obese, with a body mass index (BMI) exceeding 30 kg/m². An elevated BMI is associated with well-known cardiovascular risk factors, such as hypertension, diabetes mellitus and dyslipidemia. Indeed, excess weight itself is an independent risk factor for coronary artery disease, stroke, new-onset heart failure and death. Obesity-related myocardial abnormalities include a diastolic dysfunction, LV hypertrophy, an increased LV end-diastolic diameter and in rare cases cardiomyopathy. Surprisingly, recent data indicate that an elevated BMI favorably alters the course of chronic heart failure, lowering the risk of hospitalization and death in the overweight and obese populations as compared with those with a normal BMI. In acute heart failure, a higher BMI was also associated with a lower in-hospital mortality. In a small study including patients with single or dual chamber implantable cardioverter defibrillators, a higher BMI was likewise associated with a better survival.

Incidence and prevalence of heart failure are increasing and despite the wider use of evidence-based drug treatment and preventive device therapy the prognosis remains poor. In general the 5-year mortality rate is about 50%; however, the course of the disease shows significant inter-individual variability with an annual mortality rate between 5-75%. Considering the high inter-individual variability in mortality of HF an accurate individualized prediction of survival would be essential to guide drug and device therapies or the timing of heart transplantation. In the past

years several risk scores were developed to predict mortality in HF with significant limitations in their use for routine clinical practice due to the need for invasive measurements of cardiac output or to suboptimal mortality prediction in some validation studies.

The recently published Seattle Heart Failure Model (SHFM) has also been developed for the individualized prediction of survival in the general heart failure population. The model was derived in the database of PRAISE 1 study and subsequently validated in the patient populations of 3 clinical trials (ELITE2, Val-HeFT, RENAISSANCE) and 2 observational registries (UW, IN-CHF), the latter ones including patients from a more general heart failure population thereby allowing a widespread application of the results. Importantly, these validation cohorts consisted of heterogenic patient populations regarding left ventricular EF, heart failure symptoms, age, and country of origin. The benefit of certain medications and devices could not be calculated properly either due to overly widespread or rare use, in which cases the hazard ratios were estimated from large prospective trials. With the use of easily accessible clinical (age, gender, NYHA class, EF, weight, systolic blood pressure, etiology of cardiomyopathy, QRS width), pharmacological, device, and laboratory parameters the model provides an accurate individual prediction of 1-, 2-, and 5-year mortality and the mean life expectancy. Potential additive benefit of different heart failure drugs and devices can also be predicted by using the model. To provide a user-friendly platform for daily clinical practice, an interactive web-based calculator of the mean life expectancy of an individual patient was developed. The SHFM has already been validated in several different HF populations such as patients with advanced HF, a community-based HF population, the elderly, and a subset of HF patients with an implantable cardioverter defibrillator. However, no prior studies investigated the performance of SHFM in patients with cardiac resynchronization therapy.

2.3 Aims

1. To assess long-term arrhythmia profile in patients with an ICD implanted after monomorphic VT.
2. To investigate the influence of arrhythmia variability on the effectivity of antitachycardia pacing in these patients.
3. To assess the potential influence of the BMI on the response to CRT: is an elevated BMI associated with a higher prevalence of a responder status?
4. To validate the SHFM for the prediction of survival in patients with CRT, and to compare model performance in certain subgroups of the study cohort: patients with biventricular pacemakers versus biventricular defibrillators, and patients with classical versus non-classical indication for CRT.
5. To investigate the potential prognostic value of certain parameters that are not included in the model but known to predict a worse outcome in patients with CRT (blood urea nitrogen, serum creatinine, glomerular filtration rate (GFR), diabetes as a comorbidity, end-systolic and end-diastolic diameters measured by two-dimensional echocardiography and left ventricular lead position)

3. Patients and methods

3.1 Arrhythmia profile in patients with an ICD after VT

Patients with single- or dual-chamber ICDs implanted for sustained mVT as the presenting arrhythmia were enrolled, while those with prophylactic indications or secondary prevention following VF or polymorphic VT were excluded from this analysis. Follow-up visits were routinely scheduled at 3-6-

month intervals and data were collected in a prospective ICD database, including electrograms of the mVTs retrieved from the device memory at each follow-up.

All mVT episodes were retrieved from the device memory during the follow-ups. Only episodes including documented far-field intracardiac electrograms were assessed. The diagnosis of mVT was based on the onset and stability criteria, the morphological features, the response to device therapy and atrio-ventricular dissociation when the atrial electrogram was also available. The CL of an arrhythmia episode was calculated as the average of the four RR intervals preceding the diagnosis of VT by the device. A difference of at least 50 msec in CL was considered significant. The electrogram morphology was evaluated based only on unipolar electrograms (RV coil - can) by two electrophysiologists familiar with intracardiac electrograms. Only spontaneously occurring mVT morphologies were included in the analysis, those presenting following an ineffective ATP were excluded. Only mVT episodes with clear differences in morphology were regarded as different.

We also assessed the efficacy of ATP in different subgroups of patients: An mVT episode was considered to be successfully terminated by ATP if one or more pacing sequences eliminated the arrhythmia and no shocks were delivered. ATP termination of an mVT was unsuccessful when pacing failed to eliminate the tachycardia and subsequent shocks were delivered, or, in rare cases when no shocks were programmed, the arrhythmia was ongoing.

In accordance with our practice, TDIs were programmed with a safety margin of 40 msec above the CL of the index arrhythmia. In cases of slow VTs (CL > 300 msec), not only the VF zone, but also 2 VT zones were programmed (a slow VT zone with 6 or 9 ATP therapies followed by shocks and a fast VT zone with 1 or 2 ATPs and subsequent shocks. In cases involving a fast (CL < 300 msec) VT, only 1 VT zone (a fast VT zone) was programmed.

3.2 BMI and responder status after CRT

Data on 229 consecutive patients who underwent CRT (biventricular pacemaker or defibrillator) implantation at our Department of Cardiology between September 2004 and August 2008 were reviewed. 56 patients were excluded from the study because of missing data or a postimplantation follow-up period shorter than 6 months. 173 patients with complete baseline (including adequate weight and height) and follow-up data were analyzed retrospectively. The indication criteria for CRT were: an impaired LV EF (<35%), clinical signs of heart failure (NYHA II-IV), a sinus rhythm and a left bundle branch block (QRS complex duration >120 msec). The underweight (BMI: $\leq 18.4 \text{ kg/m}^2$) patients (n=4) in our CRT population were subjects with end-stage heart failure and cardiac cachexia and were therefore excluded from further analysis. All patients received standard heart failure medical treatment with beta-blockers, angiotensin-converter enzyme inhibitors and diuretics, including spironolactone.

Weight was measured daily throughout hospitalization. To avoid the confounding effect of fluid retention in the calculation of the BMI, the discharge weight was used following intravenous diuretic therapy as necessary to compensate the patient. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Patients were categorized on the basis of the BMI according to the WHO classification as normal (BMI: $18.5\text{-}24.9 \text{ kg/m}^2$), overweight (BMI: $25\text{-}29.9 \text{ kg/m}^2$) or obese (BMI: $\geq 30 \text{ kg/m}^2$).

Echocardiography was performed prior to device implantation and at every follow-up visit. LV diameters were measured and EFs were calculated by the Quinones method. The responder status was evaluated via echocardiographic measurements at the 6-month follow-up: a patient was regarded as a responder if the LV EF had improved by at least 5% in absolute terms at the 6-month follow-up.

The responder status was also defined by an improvement in the clinical status: a patient was considered responder if the NYHA class improved by at least one class at the 6-month follow-up comparing to baseline.

3.3 Predictive value of SHFM after CRT

Prospectively collected clinical, pharmacological and laboratory data of 427 consecutive patients referred for CRT between 2004 and 2010 were evaluated. According to guidelines effective during the implantation period, classical indications for CRT were reduced left ventricular ejection fraction (LVEF) <35%, left bundle branch block with QRS duration >120msec on the surface ECG, and limited functional capacity: NYHA III-IV. However, in a significant proportion of patients not all of these criteria were fulfilled as they were either in a better (NYHA I-II) functional status or had a LVEF above 35%. CRT in these patients was performed based on non-classical indications. 12 patients were lost during follow-up; they were considered to be alive at the date of the last follow-up visit. Before device implantation all patients signed a written informed consent of using their medical records anonymously.

We compared model performance in subgroups of CRT patients: in subjects with biventricular pacemakers vs. defibrillators and in patients with classical vs. non-classical indication. The potential additive role of blood urea nitrogen, serum creatinine, glomerular filtration rate (GFR), diabetes as a comorbidity, end-systolic and end-diastolic diameters measured by two-dimensional echocardiography and left ventricular lead position was also investigated in our study group.

The endpoint of this study was total mortality. Urgent heart transplantation and left ventricular assist device implantation was not performed in any patient. Survival was assessed based on medical records and telephone survey.

Eight of the SHFM explanatory variables were incomplete (median of % missing 1.6, range 0.7 to 16.0) and were imputed via multiple imputation. Six additional explanatory variables were also imputed (median % missing 1.4, range 1.0 to 12.6) in a separate process. For each incomplete variable, 50 extra imputed variants were created using Stata's multiple imputation utility. Source variables included all complete SHFM factors and observed status at end of follow-up. Each

missing entry was replaced with the averages of imputed values for that variable and record. Rounding to nearest integer was applied if the variable was categorical (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Uric acid readings were unavailable and were set to a constant 437 mmol/L based on SHFM literature data. Episode-level scores were derived as per the applicable SHFM formula, and expected survival probabilities for each evaluation point were calculated. Validation was based on logistic regression models fitted with observed vital status (as applicable for each evaluation point) as the outcome, and corresponding SHFM-score-based, natural-log-transformed probability of death as the explanatory variable. Calibration profile was assessed using Hosmer-Lemeshow tests. Discrimination was assessed by calculating areas under receiver-operating characteristic (ROC) curves (AUC) derived from the models. Stratified analyses included testing for significance of between-strata AUC differences. The role of additional explanatory variables was assessed by adding them to the base SHFM logit model, describing the resulting calibration and discrimination profiles, and testing for significance of AUC improvements.

3.4 Statistics

Continuous variables are reported as means \pm standard deviation, while categorical variables are presented as percentages. Stochastic correlations between discrete variables were investigated by means of χ^2 test. Kolmogorov-Smirnov test was used for testing whether a distribution is Gaussian or not. Groups of continuous variables were compared by using the unpaired T-test and the ANOVA test, as appropriate. P values <0.05 were considered statistically significant.

4. Results

4.1 Arrhythmia profile in patients with an ICD after VT

4.1.1 Patient demographics

Among 184 consecutive patients with single- or dual- chamber ICDs implanted at our Institute between September 2004 and May 2009, 52 who received the ICD for a sustained mVT and had a subsequent follow-up of at least 3 months were enrolled in our study. Other patients with an index arrhythmia of ventricular fibrillation/polymorphic VT (n=60) and those implanted as a primary prevention (n=72) were excluded.

The mean \pm SD age of the 52 patients (41 male) was 63.7 \pm 10.1 years (range: 28-85 years), and the mean \pm SD left ventricular ejection fraction was 38 \pm 9.2% (range: 23-57%). All of these patients had structural, mostly ischemic heart disease.

4.1.2 Ventricular arrhythmias during follow-up

A total of 1637 mVT episodes occurred during a mean follow-up period of 30.3 \pm 12.3 (range: 3-58) months in 41 of the 52 patients (78.8%), however only those with an IEGM (n=833) were evaluated. Overwritten episodes (n=804) occurred in 8 patients: 306, 87 and 411 in patients with 1, 2 and 3 \leq morphologies, respectively. The average CL of the index arrhythmias was 320 \pm 52.2 msec (range: 240-470 msec), while the mean CL in subsequent spontaneous VTs was found to be 320 \pm 62.3 msec (range: 230-510 msec). 26 (50.0%) patients experienced VT with a different CL as compared with that of the index arrhythmia; mVTs with a longer CL than that of the index arrhythmia were found in 13, mVTs with a shorter CL in 4, and mVTs with both longer and shorter CLs in 9 patients.

Morphology analysis was also performed in the 34 patients with multiple VT episodes. In this cohort, the mean number of mVT episodes was 24.5 \pm 20.7 (median: 27, IQR: 39) and the number of morphologies was 3.2 \pm 2.0/patient. At least 2 different mVT morphologies were observed in 28 patients, with a maximum of 8 occurring in one patient.

The prevalence of VT storm (at least 3 VT episodes in 24 hours) was 83.3% (5/6), 41.7% (5/12) and 93.8% (15/16) in patients with 1, 2 and 3≤ morphologies, respectively.

4.1.3. Effects of morphological variability on the efficacy of ATP and on the shock burden

ATP was delivered in 780/833 episodes; others were treated primarily by shock therapy due to their short CLs. The overall ATP success rate for the whole study population was 78.2% (610/780). The average CL was longer in the arrhythmia episodes successfully terminated by ATP (346.1 ± 48.2 msec) than in those with failed ATP attempts (333.9 ± 54.0 msec) ($p < 0.006$). In the patients who presented with multiple mVT morphologies during the follow-up, the success rate of ATP was significantly lower (95.6%, 85.0% and 70.3% in the patients with 1, 2 and 3 or more mVT morphologies respectively; $p < 0.0001$), despite the similar baseline patient characteristics in the three subgroups.

As expected, together with the lower rate of success of ATP in the patients with multiple VT morphologies, the shock burden (the percentage of episodes treated by shock) increased significantly (4.2%, 19.3% and 24.7% in the patients with 1, 2 and 3 or more mVT morphologies respectively; $p < 0.0001$). The proportion of patients to whom 5 or more shocks were delivered during the follow-up was also significantly higher in the patients with multiple VT morphologies: 0%, 41.6% and 51.2% in the patients with 1, 2 and 3 or more mVT morphologies, respectively.

We also investigated the effects of ATP on the changes in VT morphology: in 5.6% (44/780) of the mVT episodes, the VT accelerated and changed its morphology following ATP. The prevalence of VT acceleration was found to be 1.1%, 3.2% and 8.1% in the patients with 1, 2 and 3 or more VT morphologies, respectively ($p = 0.0035$).

4.2 BMI and responder status after CRT

4.2.1 Patient demographics

A total of 169 patients (females: 49 {29.0%}; mean age 60.9 ± 10.86 years). There was a trend to higher prevalence of diabetes in the obese population relative to subjects with a normal BMI, but the difference did not reach the level of statistical significance. The average LV EF in the overall study population was $27 \pm 6.72\%$. Almost half of the patients received biventricular implantable cardioverter defibrillator (CRT-D) in all three BMI subgroups. Only 26.6% of the patients were within the normal BMI range, while 41.4% were overweight and 32% had a BMI ≥ 30 . The mean BMI was 28.7 ± 5.2 for males, and 27.0 ± 4.2 for female patients ($p=0.049$).

4.2.2. Influence of BMI on responder status

Echocardiographic measurements indicated that the overall proportion of responders to CRT was 61.5% (104/169). Only 44.7% (20/45) of the patients with a normal BMI were responders, whereas the patients with an elevated BMI were more likely to exhibit a positive response to CRT ($p=0.015$): 71.4% (50/70) of the overweight and 63.0% (34/54) of the obese. The odds ratio of the overweight patients displaying a positive response to CRT was 1.6 (CI: 1.12-2.30) relative to the patients with a normal BMI.

There was a tendency to a higher response among females in each category. Surprisingly, only 31% of the male patients in the normal weight group were responders.

Based on an improvement in the functional status (at least one NYHA class) 59.2% of the patients showed positive response to CRT. Similarly to the echocardiographic results, the highest prevalence of responder status was found in the overweight population (68.6%, 48/70), whereas only 53.3% (24/45) of patients

with normal BMI and 51.9% (28/54) of the obese were regarded as a responder, although the difference was not statistically significant ($p=0.111$)

4.3 Predictive value of SHFM after CRT

4.3.1. Patient demographics

In the study cohort 56.2% (240/427) of the patients received a biventricular pacemaker while 43.8% (187/427) a biventricular defibrillator. Patients were treated with optimal medical therapy before device implantation: almost 90% received beta-blocker and ACE-I/ARB and more than 60% aldosterone antagonists. The median follow-up time was 24.7 (IQR: 7.4-40.9) months. In the study group 36.0% (154/427) of patients did not fulfill the classical indication criteria for CRT: 79.2% (122/154) of them were in NYHA I-II, while 20.8% (32/154) had a LVEF above 35 (median LVEF: 38%, IQR: 36-40), and 7 of them had a left ventricular ejection fraction over 35% and were in NYHA I or II stage simultaneously.

4.3.2 Calibration and discrimination of the SHFM

A total of 72 deaths occurred during the follow-up period resulting in a cumulative mortality of (72/427) 16.9%. Observed outcomes were 34/303, 54/234, and 72/97 at years 1, 2, and 5, respectively. All Hosmer-Lemeshow tests showed good calibration profiles with sufficient consistency between predicted and observed numbers of outcome events. SHFM scores adequately discriminated survivors from non-survivors and, considering the whole data set, the model predicted deaths with reasonable accuracy: AUC values of 0.7377 (95%CI 0.6575 to 0.8179) at year 1, 0.7936 (95%CI 0.7317 to 0.8556) at year 2, and 0.7572 (95%CI 0.6455 to 0.8689) at year 5 were estimated.

When comparing patients with biventricular pacemakers to those with biventricular defibrillators, the model's performance was similar: in pacemaker

versus defibrillator recipients, AUC estimates were 0.7605 (95%CI 0.6531 to 0.8679) vs 0.7181 (95%CI 0.5934 to 0.8428), $p = 0.614$; 0.8201 (95%CI 0.7386 to 0.9016) vs 0.7735 (95%CI 0.6727 to 0.8697), $p = 0.468$; and 0.7776 (95%CI 0.6374 to 0.9178) vs 0.7310 (95%CI 0.5320 to 0.9299), $p = 0.708$ at years 1, 2, and 5, respectively. However, when patients with classical versus non-classical indication for CRT were compared, the model showed better discrimination in the non-classical group, reaching strong statistical significance at year 2. In subjects with classical and non-classical indication for CRT the ROC AUC values were 0.6598 (95%CI 0.5532 to 0.7665) vs 0.8349 (95%CI 0.7005 to 0.9693), $p=0.045$; 0.7188 (95%CI 0.6313 to 0.8064) vs. 0.9130 (95%CI 0.8396 to 0.9864), $p<0.001$; and 0.7238 (95%CI 0.5689 to 0.8786) vs. 0.7188 (95%CI 0.5167 to 0.9207), $p=0.969$ at years 1, 2 and 5, respectively.

4.3.3. Potential improvement in model discrimination

Assessment of additional parameters not represented in the SHFM including blood urea nitrogen, serum creatinine, GFR, diabetic status, left ventricular lead position and left ventricular diameters was also performed to evaluate whether they improve the performance of the model. Regarding left ventricular lead position only an anterior localization had a significant negative impact on survival (OR:16,7 at year 1 compared to a posterior LV lead position, $p=0.032$). Although end-systolic, end-diastolic diameters and left ventricular lead position had significant effects on mortality at years 1 and 2, these parameters by themselves did not improve the discrimination of the model. When end-diastolic diameter (Dd) and left ventricular lead position were both included, a significant improvement in the discrimination profile was observed at year 1 (SHFM only vs SHFM plus end-diastolic diameter and left ventricular lead position ROC AUC values were 0.7377 vs. 0.8069, $p=0.024$) but no improvement in the model performance was observed with longer follow-ups.

5. Discussion

5.1 Arrhythmia profile in patients with an ICD after VT

Patients receiving an ICD as secondary prevention after a sustained mVT are known to have a higher arrhythmia burden than other subgroups of ICD patients during the follow-up. Surprisingly, reported studies relating to the optimal management of these patients are lacking and this patient population is underrepresented in most trials.

A few studies have addressed the predictive value of VT induced by programmed electrical stimulation. Gillis et al. investigated the long-term reproducibility of VT induction in patients with secondary prevention ICDs. A considerable variability of VT induction was observed in 62% of the patients. The incidence of slow VTs was investigated in a multicenter prospective randomized study involving 374 secondary prevention patients without prior history of slow VT. A dual-chamber ICD was implanted in all of them to enhance the diagnostic accuracy and the detection interval of slow VTs was set between 101 and 148 bpm. During an 11-month follow-up period, the incidence of new-onset slow VTs was 30%. Glikson et al. followed up patients after ICD implantation for a hemodynamically stable mVT as the clinical arrhythmia. They specifically addressed the issue of the occurrence of unstable VT in these patients, and found that 12% of them developed mVT with a CL in the unstable range during a mean follow-up period of 23.6 months. Details regarding ICD programming and the type of device therapy were not reported, and the main conclusion was that mVT in patients with structural heart disease should be a class I indication, regardless of the stable or unstable nature of the arrhythmia, which was adopted in the most recent guideline.

Similarly to our study, Monahan et al. assessed VT morphology from far-field electrograms recovered from the Holter memory of the ICD and found that the first spontaneous episode was morphologically different in 68% of the cases from the VT induced predischARGE.

The purpose and design of our study was to evaluate the long-term arrhythmia profile of this subgroup of ICD recipients, with focus on the predictive value of the presenting clinical (index) arrhythmia for subsequent VTs and also on clinically important measures of device functioning, such as the shock burden and the efficacy of ATP. Our results confirmed previous findings that the VT burden is very high in this population. We also demonstrated that: 1. VTs display considerable variability in both CL and morphology. 2. In patients with multiple VT morphologies, the efficacy of ATP is lower and the shock burden is higher 3. Multiple VT episodes with variable CL and morphology occur even on amiodarone therapy.

VT presented during the follow-up in nearly 80% of our patients, and 65.9% of them had arrhythmia episodes with different (more commonly longer) CLs as compared with the index VT. The vast majority (82.4%) of the patients with multiple mVT episodes had 2 or more different VT morphologies. These results demonstrate that high variability can be observed both in CL and in morphology in the VT episodes during a long-term follow-up. The morphological variability of the VTs was of clinical relevance, as the multiple VT morphologies were associated with a lower ATP efficacy and a higher shock burden. More than 5 shocks occurred in 41.6% of the patients with 2, and in 56.2% of those with 3 or more mVT morphologies. These findings are in line with earlier experience when multiple mVTs were often induced by programmed stimulation during serial drug testing. It was also recognized in the pre-ICD era that the presenting VT morphology was no more likely to recur during follow-up than one of the induced morphologies. Furthermore, patients with only one monomorphic VT inducible at baseline EPS were more likely to have an arrhythmic drug regimen identified that suppressed inducible VT.

Amiodarone, the only available medication with a potential to control ventricular arrhythmias, was administered to some of our patients, mostly initiated after the index arrhythmia. As expected, the VT CL was longer in these

patients and a VT CL different from that of the index VT was observed more frequently than in those without amiodarone. However, VTs with different morphologies were also common (3.1 morphologies/patient), as were unsuccessful ATP and VT episodes treated by shocks (133/378) in these patients. VT ablation targeting the ongoing VT was successful in 3 of the 4 patients who exhibited a reduction in the total arrhythmia burden, but all 4 patients experienced VT recurrences. Although VT ablation has been used for patient comfort in ICD patients experiencing a high shock burden, the most appropriate timing of this procedure is debated. In a recent multicenter randomized trial, patients were randomized to undergo catheter ablation before ICD implantation or to ICD implantation alone. The time to the first sustained ventricular arrhythmia, the number of appropriate shocks and quality of life measures were significantly different, favoring the upfront ablation strategy, especially in patients with a left ventricular ejection fraction over 30%.

There are several potential clinical implications of our results that need to be investigated in further studies: 1. The programming of a wide range of VT detection intervals should be considered. 2. To enhance the diagnostic accuracy of slow VTs and to avoid inappropriate shocks, the implantation of dual-chamber devices might have advantages over single-chamber ICDs. 3. As mVTs are potentially ATP terminable, the programming of extra ATPs may reduce the shock burden. 4. Transcatheter substrate modification for patient comfort should be considered in cases of frequent VT episodes requiring ICD shocks despite optimized pharmacotherapy, or even at the time of device implantation in selected patients. 5. In general, this "difficult" subset of ICD patients probably requires more attention and a closer follow-up than the general ICD population.

5.2 BMI and responder status after CRT

The “non-response” phenomenon in CRT patients has been intensively studied almost since the clinical introduction of this therapy. The clinical variables tested for a possible correlation with a long-term effect were mostly related to the technical aspects of the CRT, such as lead positioning and device programming, the functional status of the heart, including the 12-lead ECG appearance and several echocardiographic parameters measured preimplantation, and other well-known prognostic factors in CHF, e.g. the renal function or the serum level of NT-proBNP. The main finding of our current work is that the baseline BMI exhibited a clear correlation with the improvement in the echocardiographic parameters 6 months after implantation. The very low (31%) response rate in our male patients with normal weight was especially striking. As far as we are aware, the only previous study of the BMI in patients after CRT was a post-hoc analysis of CARE-HF in a search for potential predictors of long-term effects among baseline categorical variables and continuous variables measured at baseline and 3 months. In CARE-HF, the BMI was not a predictor of long-term survival.

Obesity is a well-known independent risk factor for the development of cardiovascular diseases, but it favorably alters the prognosis in established chronic heart failure, a phenomenon known as the “obesity paradox”. This “reverse epidemiology” has likewise been demonstrated in other chronic, wasting diseases with a significantly reduced life expectancy, where obesity improved the short-term prognosis. The exact mechanism behind the obesity paradox is not fully understood. Proposed mechanisms include the increased hemodynamic stability of obesity, the protective adipokine profile, the endotoxin-lipoprotein hypothesis, the toxin sequestration of fat tissue and the antioxidative effect of muscle. The proportion of obese patients in our study population was 32%, while only 27% of the patients had a BMI within the normal range. These statistics are similar to those observed in the general population of the USA and several countries of the European Union, indicating that obesity is a major problem affecting a significant proportion of the population, including those with chronic heart failure. The phenomenon of the

obesity paradox calls attention to the fact that the relevant guidelines and initiatives might need to distinguish between healthy individuals and patients with certain chronic diseases. These latter individuals might require a different nutritional and weight management strategy in order to optimize their life expectancy.

5.3 Predictive value of SHFM after CRT

The course of HF shows significant inter-individual variability and considering currently available, mostly expensive therapeutic options (implantable cardioverter defibrillator, CRT, left ventricular assist device, heart transplantation), a reliable and individualized prediction of the course of the disease would be of utmost importance.

The SHFM was published in 2006 and since then several studies confirmed the validity of the model in different HF populations: in prospectively collected data of several HF study populations, in a community-based HF population or in the elderly. However, in a recent study Kalogeropoulos et al. demonstrated that the model underestimates mortality risk in patients with advanced HF. In these patients referred for evaluation of cardiac transplantation, the SHFM systematically underestimated the mortality risk despite an adequate discrimination. Model validity was also tested in a subgroup of 197 patients with an implantable cardioverter defibrillator and found to accurately predict total mortality. However, no prior studies investigated the performance of SHFM in patients with CRT.

In the present study we demonstrated that the SHFM accurately predicted survival in patients with CRT, and the discrimination profiles were generally similar to those reported by earlier validation studies with ROC AUC values exceeding 0.7. Comparing patients with biventricular pacemakers to those with defibrillators, model performance was similar; however, the SHFM was significantly better at predicting survival in patients with non-classical indication for CRT than in patients with classical indication. Patients with non-classical indication were either in NYHA I-II functional

stage or had a LVEF above 35%, thereby representing a population in an earlier stage of the disease. We do not have a clear explanation for the better mortality prediction in this patient cohort. However, similar observation was reported in one of the trials used for the primary validation of the SHFM. Patients of the Italian Heart Failure Registry had the lowest mean NYHA class (2.2) and the highest mean LVEF (35%) with a ROC AUC estimate of 0.749 at year 1 which is above the average of the combined data set of all six trials. The world-wide practice of implantation of CRT devices in patients at a less severe stage of the disease as well as similar changes in recent guideline recommendations underscores the importance of this observation with implications to a large patient cohort.

To improve model performance we also tested several parameters (renal function, diabetic status, left ventricular diameters and left ventricular lead position), known to influence outcome in patients with CRT, but not included in SHFM. None of these parameters had an additive value alone in model performance. The potential additive role of renal function was already tested in general HF populations. In a recent paper Giamouzis et al. confirmed the association between renal function and outcome in patients with advanced HF, however, only blood urea nitrogen (BUN) proved to be an independent risk factor and the incremental value of renal function over the SHFM was only marginal in mortality prediction. Similarly, neither renal function nor diabetic status did substantially add to the model in a community-based HF population. In our study, model performance improved at year 1 with the composite of left ventricular end-diastolic diameter and left ventricular lead position, but given the large number of statistical comparisons, this finding may be a Type I error.

6. Summary

The summary of our research investigating implantable cardioverter defibrillator and cardiac resynchronization therapy was given in this thesis. Our new observations:

1. We could confirm that ventricular tachycardia episodes are frequent during follow-up in patients receiving an ICD following sustained monomorphic ventricular tachycardia. As a new finding we could demonstrate a significant variability in cycle length and morphology of ventricular tachycardia episodes during follow-up and that the cycle length of the index arrhythmia is not predictive for subsequent spontaneous arrhythmia episodes.

2. In patients with multiple ventricular tachycardia morphologies during follow-up a lower ATP efficacy and a higher shock burden was observed.

3. A favourable effect of an elevated BMI on mortality is suggested in patients with a biventricular pacemaker or ICD based on an improvement in the left ventricular ejection fraction at 6 months.

4. The SHFM offers an accurate prediction of mortality in CRT patients with results similar to those found by earlier validation studies in non-CRT patients. Accuracy of survival prediction is similar in patients with biventricular pacemakers and biventricular defibrillators; however, better in patients with non-classical indication for CRT as compared to those with classical indication.

5. Other parameters and clinical variables including renal function, diabetic status, left ventricular diameters, left ventricular lead position do not provide a substantial improvement in model performance.

7. In extenso publications of the author



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Candidate: Marcell Clemens

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Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Clemens, M.**, Szegedi, Z., Kardos, L., Nagy-Baló, E., Sándorfi, G., Édes, I., Csanádi, Z.: The Seattle Heart Failure Model Predicts Survival in Patients With Cardiac Resynchronization Therapy: A Validation Study.
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4. **Clemens M., Csanádi Z.:** Az ICD-terápia indikációjának kérdései.
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