

Opportunities and problems of device therapy in the treatment of ventricular arrhythmias and heart failure

PhD Thesis

Gábor Zoltán Duray M.D.

Semmelweis University
Basic Medicine PhD School



Supervisor: István Préda M.D. DSc. Professor of Medicine

Consultant: Stefan. H. Hohnloser M.D. Dr. med. habil,
Professor of Medicine

Reviewers: József Borbola M.D. Ph.D. Professor of Medicine
Endre Zima M.D. Ph.D.

President of Examiners' Committee: Béla Merkely M.D. DSc.
Professor of Medicine

Members of Examiners' Committee: József Tenczer M.D. DSc.
Professor of Medicine
Violetta Kékesi, M.D. Ph.D.

Budapest
2009

Table of Contents

TABLE OF CONTENTS	2
LIST OF ABBREVIATIONS	3
INTRODUCTION	5
<i>Prevention of sudden cardiac death.....</i>	<i>5</i>
<i>Pharmacological therapy.....</i>	<i>5</i>
<i>Implantable cardioverter defibrillator therapy.....</i>	<i>7</i>
<i>Clinical use of prophylactic ICD therapy</i>	<i>13</i>
<i>Cardiac resynchronisation therapy</i>	<i>14</i>
BACKGROUND OF OUR STUDIES	16
AIMS/OBJECTIVES.....	18
METHODS	18
RESULTS.....	22
DISCUSSION.....	41
<i>Main findings.</i>	<i>41</i>
<i>ICD therapy in the elderly</i>	<i>42</i>
<i>Anatomy of the left cardiac veins</i>	<i>43</i>
<i>Implantation of a left ventricular lead through the coronary sinus.</i>	<i>45</i>
<i>Alternative left ventricular implantation methods.</i>	<i>47</i>
<i>Response to CRT.....</i>	<i>48</i>
<i>Feasibility and safety of CRT upgrade procedures.....</i>	<i>49</i>
<i>Clinical implications.....</i>	<i>51</i>
CONCLUSIONS	52
SUMMARY	53
BIBLIOGRAPHY	55
PUBLICATIONS RELATED TO THE PHD THESIS.....	71
PUBLICATIONS UNRELATED TO THE PHD THESIS.	71
ACKNOWLEDGEMENTS.....	80

List of abbreviations

ACC	American College of Cardiology
ACE	angiotensin converting enzyme
AHA	American Heart Assotiation
AT1	AT1 angiotensin receptor
AV	atrioventricular
CAD	Coronary artery disease
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CS	coronary sinus
CS-SB	coronary sinus side branch
DEFINITE	Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
EBCT	electron beam computed tomograpy
ESC	European Society of Cardiology
ICD	implantable cardioverter-defibrillators
LAO	left anterior oblique
LV	left ventricular
LVEF	left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MI	myocardial infarction
MRI	magnetic resonance imaging
MSCT	multislice computed tomography
NASPE	North American Society of Pacing and Electrophysiology
NICMP	Non-ischemic cardiomyopathy
NT-pro-BNP	N-terminal-pro- brain natriuretic peptide
NYHA	New-York Heart Association (class)
OTW	over-the-wire
PA	postero- anterior
PIV	posterior interventricular
PM	pacemaker

RCT	randomized controlled trials
RV	right ventricular
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death Heart Failure Trial.
VF	ventricular fibrillation
VT	ventricular tachycardia

Introduction

Prevention of sudden cardiac death

Sudden cardiac death (SCD) remains one of the leading killers in the industrialized world, responsible for an estimated 300,000–400,000 deaths every year in the USA. Episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) are the underlying cause in the majority of cases of SCD; at the time of emergency intervention, VF is found in approximately 40% of SCD victims, with asystole and electromechanical dissociation becoming more frequent the longer the intervention is delayed (Weaver et al 1988). In patients in whom the time interval between the clinical event and the first ECG is less than 4 min, the incidence of VF has been documented to be as high as 95%. Most victims of SCD suffer from structural heart disease that may not have been known prior to the event. In the best of all worlds, approximately 5–15% of all victims of cardiac arrest can be resuscitated and leave the hospital without major neurological deficits. Given these numbers, recent years have seen major research efforts around the world aimed at primary prevention of SCD by both pharmacological and non-pharmacological means.

Pharmacological therapy

Many trials have evaluated the potential of various membrane- active antiarrhythmic drugs to prevent SCD (CAST 1989, Waldo et al. 1996, Julian et al. 1997, Cairns et al. 1997, Camm et al. 2004). In general, none has demonstrated a benefit associated with prophylactic treatment with a class I or III antiarrhythmic compound in patients deemed to be at high risk for SCD.

At best, the antiarrhythmic drug proved to be not inferior to placebo without any clear benefit (Julian et al. 1997, Cairns et al. 1997, Camm et al. 2004) and many other trials confirmed that there is harm associated with prophylactic administration of specific antiarrhythmic drugs (CAST 1989, Waldo et al. 1996). Randomized controlled trials (RCT) evaluating the effects of various groups of non-antiarrhythmic drugs for prevention of cardiovascular death and SCD in particular have yielded more promising results. Beta-blockers, angiotensin- converting enzyme inhibitors (ACEI),

angiotensinreceptor blockers, and aldosterone antagonists have been demonstrated to reduce all-cause mortality as well as SCD in high-risk patients.

Beta-Blockers

The antifibrillatory efficacy of β -blockers has been established for a long time. RCT have established the beneficial effects of these compounds beyond any doubt in patients after myocardial infarction (MI) (Gottlieb et al. 1998) and those with congestive heart failure (MERIT- HF 1999, CIBIS-II 1999). For instance, the carvedilol postinfarct survival control in left ventricular dysfunction trial (The CAPRICORN investigators 2001) randomized patients 3–21 days after MI who had an left ventricular ejection fraction (LVEF) < 0.40 to receive carvedilol or matching placebo. There was a significant reduction in overall mortality in patients on antiadrenergic therapy compared with the controls. More importantly, sustained ventricular tachyarrhythmic events were reduced by more than 70% over the follow-up period (hazard ratio (HR) 0.24, 95% confidence interval (CI) 0.11–0.49) (McMurray et al. 2005). Accordingly, that RCT convincingly demonstrated that, even in the era of reperfusion therapy, during the acute phase of MI β -blocker therapy improves survival.

ACEI

The ACEI are one of the mainstay therapeutic modalities in patients with congestive heart failure that has been shown to improve survival. Even in high-risk cardiovascular patients without signs of heart failure or LV dysfunction, these medications yield significant survival benefits (The Heart Outcomes Prevention Evaluation Investigators 2000). In 1999 Domanski et al (1999) conducted a meta-analysis of all published ACEI trials (15 studies including 15,104 patients) and found a 20% relative risk reduction for the endpoint of SCD (HR 0.80, 95% CI 0.70–0.92). More recently, the heart outcomes prevention evaluation trial database was examined to see whether in this large population of 9,297 high-risk cardiovascular patients without clinical heart failure or overt LV dysfunction the composite endpoint of unexpected death, documented arrhythmic death and resuscitated cardiac arrest was reduced by the ACEI, ramipril (Teo et al. 2004). Compared with the placebo group, the endpoint was reduced by 21% (HR 0.79, 95% CI 0.64–0.98; $p=0.028$) in patients treated with the ACEI. According to

these findings, therefore, there can be no doubt that ACEI have preventive potential against SCD in high-risk CAD patients.

Aldosterone Antagonists

Recently, 2 well-designed RCT have evaluated the effects of spironolactone (Pitt et al. 1999) and eplerenone (Pitt et al. 2003) on mortality in patients with congestive heart failure and in MI survivors with LV dysfunction who were enrolled 3–14 days after the index event. In both of these trials, not only was all-cause mortality in patients on aldosterone antagonists significantly reduced but also SCD mortality. In the EPHESUS trial, for instance, the risk for SCD was reduced by 21% (HR 0.79; 95% CI 0.64–0.97; $p=0.03$) (Pitt et al. 2003). The mechanisms underlying these beneficial effects are not entirely clear. Besides the beneficial effects of aldosterone antagonists on electrolytes and plasma volume, these drugs have been shown to reduce coronary vascular inflammation and the risk of subsequent interstitial fibrosis, to improve endothelial dysfunction, and to decrease sympathetic drive.

Statins

To date, there is not a published RCT on the effects of statins on SCD in a high-risk population. However, there are at least 2 retrospective studies in implantable cardioverter- defibrillators (ICD) populations that point to a potential beneficial effect of these compounds on ventricular tachyarrhythmic events (De Sutter et al. 2000, Chiu et al. 2005). Both studies suggest that appropriate ICD therapy occurs less frequently in patients treated with statins as compared with those who have not taken these lipid-lowering drugs. Again, the pathophysiological mechanisms responsible for a decrease in ventricular tachyarrhythmic events remain speculative. However, there is experimental evidence that statins may reduce myocardial ischemia, improve angiogenesis, and decrease ventricular dilatation and fibrosis. Currently, a randomized placebo controlled trial in ICD recipients is being conducted to prospectively evaluate the effects of statins on ventricular tachyarrhythmias.

Implantable cardioverter defibrillator therapy

Twenty-five years ago, the first defibrillator was implanted worldwide in a patient at the Johns Hopkins University in Baltimore, USA, by Michel Mirowski and colleagues

(Mirowski et al. 1980). Since then, contemporary implantable cardioverter defibrillator (ICD) therapy has evolved into a cornerstone of prevention of sudden cardiac death for patients suffering from coronary artery disease or from non-ischemic cardiomyopathy. Following several large randomized clinical trials in patients with aborted sudden death, sustained ventricular tachycardia, and syncope with inducible sustained ventricular tachycardia or ventricular fibrillation (Connolly et al. 2000). ICD therapy is now generally recommended as the prime therapy for secondary prevention of sudden death. Most patients, however, who have an out-of-hospital cardiac arrest do not survive. Accordingly, the use of prophylactic ICD therapy is a conceptually attractive option for high-risk patients. Several trials on primary preventive ICD therapy have been conducted over the last 10 years and have helped to better define the role of ICD therapy in improving overall survival (Moss 1996, Bigger 1997, Buxton 1999, Moss 2002, Hohnloser 2004, Bristow 2004). We summarize here briefly the four latest major randomized controlled ICD trials (Table 1) (Hohnloser 2004, Bristow 2004, Bardy 2005, Kadish 2004) on prophylactic ICD therapy in patients with ischemic or non-ischemic cardiomyopathy.

Table 1 Key features of four recent prophylactic implantable cardioverter defibrillator trials. ^aDifferent follow-up duration for the three treatment arms.

	DINAMIT	SCD-HeFT	DEFINITE	COMPANION
Patients	742	2521	458	1520
Age(years)	62	60 (median)	58	67
Heart disease	CAD	CAD, NICMP	NICMP	CAD, NICMP
Time from most recent infarct	18 days	24.5 months	ND	ND
LVEF (mean)	0.28	0.25	0.21	0.21
NYHA III (%)	28	30	21	85

	DINAMIT	SCD-HeFT	DEFINITE	COMPANION
Follow-up (months)	30	45.5	29	11.9–16.2 ^a
Deaths in ICD pts	62/332	182/829	28/229	131/595
Deaths in control patients	58/342	244/847	40/229	77/308
Hazard ratio ICD therapy	1.08 (0.76-1.55)	0.77 (0.62-0.96)	0.65 (0.40-1.06)	0.64 (0.48-0.86)

Defibrillator in Acute Myocardial Infarction Trial

The international Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) asked the important question of whether patients would benefit from ICD therapy applied shortly after a large acute myocardial infarction resulting in significant impairment of left ventricle (LV) function and with additional evidence of impaired cardiac autonomic tone (Hohnloser 2004). A total of 674 infarct survivors were randomized to ICD therapy or control during the first 6–40 days after their heart attack. After a mean follow-up of 30 months, all-cause mortality was not substantially different between the two groups despite a highly significant reduction in arrhythmic mortality (hazard ratio 0.42, 95% confidence intervals 0.22-0.83; $P = 0.009$). This reduction, however, was completely offset by an increase in non-arrhythmic mortality in the group of ICD recipients (hazard ratio 1.75, 95% confidence intervals 1.11-2.76; $P = 0.02$). Accordingly, there was no difference between the ICD and the control group with respect to the primary endpoint of the trial, all cause mortality. Most of this mortality was due to cardiovascular non-arrhythmic deaths. Accordingly, this trial identified a group of coronary artery patients with risk factors for sudden death from cardiac causes in whom device therapy may not provide a survival benefit. The results were in contrast to other prior ICD studies in infarct survivors (Moss 1996, Bigger 1997, Buxton 1999). The characteristics of the DINAMIT patients, however, differed in important ways from those of prior studies. The most important differences were the short time interval after the index infarct and the presence of autonomic dysbalance. All prior primary prevention studies have enrolled patients after much longer time periods; for instance, the mean time interval

between the most recent myocardial infarction and study enrollment was 6.5 years in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II (Moss 2002). Interestingly, a recent sub-study of MADIT II demonstrated that in this patient population no survival benefit existed for patients in whom this time interval was less than 18 months (Wilber 2004). This result confirms therefore the findings of DINAMIT. Preliminary data from the DINAMIT study (Dorian 2004, Grönefeld 2004) indicate that recurrent ischemic events may have played an important role in causing the increase in non-arrhythmic mortality of these patients. In addition, one must consider the possibility that the presence of markers of autonomic dysfunction identified a patient cohort at high risk for death from progressive heart failure. As pointed out in a recent editorial (Gillis 2004), recurrent sustained ventricular tachyarrhythmias may be a harbinger of advancing heart failure. This would imply that although sustained ventricular tachyarrhythmias occurred and were successfully treated by the device, patients died of subsequent heart failure. It appears important to emphasize similarities between DINAMIT and the Coronary Artery Bypass Graft-Patch trial. The latter also reported that the ICD reduced arrhythmic mortality by 45% but did not reduce all-cause mortality because the majority of deaths (71%) were non-arrhythmic in nature (Bigger, 1997). Accordingly, these two studies support the concept that successful termination of ventricular tachycardia or ventricular fibrillation occurring as a consequence of progressive heart failure or recurrent myocardial ischemia may simply convert what would have been a sudden death to a death from other cardiovascular causes, without an effect on survival. Accordingly, the Centers for Medicare and Medicaid Services have recently decided that ICD therapy should be deferred at least for 1 month after an infarct.

Sudden Cardiac Death Heart Failure Trial

The second most recently reported trial is the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) (Bardy 2005). This important trial enrolled patients with left ventricular dysfunction of any cause and used the presence of heart failure despite medical therapy and a LV ejection fraction of 0.35 or below as a selection criterion. In SCD-HeFT, patients were randomized to one of three arms: placebo therapy, treatment with amiodarone, or to the ICD. Therapy in the first two arms consisted of double-blind

administration of amiodarone or placebo. Fifty-two percent of the enrolled patients (n = 1310 patients) suffered from ischemic cardiomyopathy, 48% from non-ischemic cardiomyopathy. Patients were followed for a median of 45 months. The trial convincingly demonstrated that amiodarone therapy did not reduce mortality among heart failure patients. The trial also showed that ICD therapy was associated with a significant 23% reduction in the risk for all-cause mortality compared with placebo. The absolute risk reduction was approximately 1.2% per year of follow-up. This risk reduction was smaller than that reported in earlier studies (Moss 1996, Buxton 1999, Moss 2002) which may be a reflection of better medical background therapy (Table 2). For the subgroup of patients with ischemic congestive heart failure (n = 1310), total mortality was reduced by the ICD by 21% (hazard ratio 0.79; 95% CI 0.60–1.04; P = 0.05). In patients with non-ischemic cardiomyopathy (n = 1211) there was a hazard ratio of 0.73 (95% CI 0.50–1.07; P = 0.06), indicating comparable efficacy of the ICD irrespective of the underlying heart disease.

Table 2 Background medical therapy in the four most recent prophylactic implantable cardioverter defibrillator trials.

	DINAMIT	SCD-HeFT	DEFINITE	COMPANION
Patients	742	2521	458	1520
β-blocker (%)	87	69	85	68
ACE Inhibitors (%)	95	96	86	70
Statins (%)	80	47	NR	NR
Aldosterone (%)	NR	NR	NR	53

DINAMIT: Defibrillator in Acute Myocardial Infarction Trial; ICD: implantable cardioverter defibrillator; SCD-HeFT: Sudden Cardiac Death Heart Failure Trial, DEFINITE: Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation, COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure. NR: not reported.

Two other features of this study deserve particular emphasis. SCD-HeFT again enrolled patients who presumably were at a period a long time after their myocardial infarction with the average duration of heart failure amounting to 24 months. Secondly, patients with New York Heart Association class II had a significant benefit from device therapy whereas patients in functional class III did not. Although the latter may have been a by-chance finding, it does emphasize the importance of timing of ICD therapy. In summary, this largest of all primary prevention ICD trials emphasizes that ICD therapy in patients with coronary artery disease and with non-ischemic cardiomyopathy and left ventricular dysfunction should be considered a long-term rather than a short-term intervention.

Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation study

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial enrolled 458 patients with non-ischemic dilated cardiomyopathy, a LV ejection fraction of 0.35 or below, and asymptomatic ventricular premature complexes or non-sustained ventricular tachycardia. Patients were randomly assigned to receive medical therapy alone or in addition to an ICD. On average, patients had a 2.8-year history of congestive heart failure emphasizing the more chronic nature of their cardiovascular condition. Patients were followed for a mean of 29 ± 14 months until the prespecified number of 68 deaths had occurred. All-cause mortality was reduced by the ICD by 35% (hazard ratio 0.65, 95% C.I. 0.40–1.06; $P = 0.08$) (Kadish 2004). The hazard ratio for sudden death was 0.20 (95% C.I. 0.06–0.71; $P = 0.006$). Of note, if only patients with New York Heart Association functional class III were considered, the hazard ratio for all-cause mortality was 0.37 in favor of the ICD (95% CI 0.15–0.90; $P = 0.02$). The role of ICD therapy in non-ischemic cardiomyopathy was recently also emphasized by a meta-analysis by Desai and colleagues (Desai et al 2004) who summarized findings of five randomized studies with a total of 1854 patients. The risk ratio for total mortality for the ICD group was 0.69 (95% C.I. 0.55–0.87; $P = 0.002$), indicating that device therapy may prolong life in selected patients with non-ischemic cardiomyopathy.

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

The fourth important ICD study which was reported in the last years is the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (Bristow 2004). This study tested the hypothesis that prophylactic cardiac resynchronization therapy by means of biventricular stimulation with or without an ICD would reduce the risk of death and hospitalization (primary study endpoint) in patients with advanced chronic heart failure and intraventricular conduction delays. These investigators enrolled 1520 patients, of whom 837 (55%) suffered from ischemic cardiomyopathy. Patients were randomly assigned to medical therapy alone, or to receive a biventricular pacing device alone or to receive such a device including an ICD. As compared with medical therapy alone, cardiac resynchronization therapy with the pacemaker reduced the risk of the primary endpoint by 19% as did the combined resynchronization ICD treatment (20% risk reduction). The secondary endpoint death from any cause was only significantly reduced by the combined resynchronization ICD therapy (36% relative risk reduction, $P = 0.003$). Importantly, however, when mortality was analyzed according to the presence of ischemic versus non-ischemic cardiomyopathy, the reduction in the risk of death from any cause was no longer statistically significant for patients with coronary artery disease (hazard ratio 0.73; 95% confidence interval 0.52–1.04; $P = 0.082$). In contrast, among patients with non-ischemic cardiomyopathy, combined resynchronization/ICD therapy resulted in a hazard ratio of 0.50 (95% CI 0.29–0.88; $P = 0.015$) indicating a highly significant survival benefit compared with optimal medical therapy alone.

As pointed out recently, these results indicate that patients with advanced heart failure and intraventricular conduction delays who are candidates for prophylactic ICD therapy may have additional benefit from a device capable of biventricular pacing (Kadish 2005).

Clinical use of prophylactic ICD therapy

Over the last few years, several large-scale well-conducted RCT have tremendously increased our knowledge on potential treatment strategies to prevent SCD in patients with CAD and heart failure. As the main lesson from the trials of various drug treatments, optimal pharmacological therapy should include β -blockers, ACEI, aldosterone antagonists, and statins. With the background of this optimized

pharmacological therapy, the ICD has been demonstrated to significantly reduce all-cause mortality, and arrhythmic mortality in particular. Taken together, these trials allow an evidence-based approach to primary prevention of sudden cardiac death in patients with ischemic or non-ischemic cardiomyopathy who are already on optimal background medication.

Patients with chronic dilated cardiomyopathy (regardless of cause), a long history of heart failure, and an ejection fraction of 0.35 or less appear to benefit from preventive device therapy and are thus candidates for prophylactic defibrillator implantation. For this purpose, a single chamber device is appropriate in the majority of patients since there have been no prospective studies showing convincing clinical benefit by adding an atrial lead (Kadish 2005, The DAVID Investigators. 2002). For similar patients who have additional intraventricular conduction delays, a biventricular ICD must be considered. In the absence of additional convincing data from prospective randomized trials, however, this decision must be based on individual considerations. Such trials are currently underway. Finally, the clinical implications of the DINAMIT results are clear (Hohnloser et al. 2004). Prophylactic ICD therapy should not be used in patients with recent myocardial infarction. Since in MADIT I and II (Moss 1996, Moss 2002), 75% and 88% of the patients, respectively, were enrolled more than 6 months after myocardial infarction, it appears that ICD benefit in coronary patients accrues after a considerable time has elapsed from the most recent infarct, presumably at least 6 months or perhaps longer. Finally, we need better ways to predict which patient populations will benefit most from prophylactic device therapy.

Cardiac resynchronisation therapy

Over the last decade, several well-conducted randomised trial has been conducted in the field of cardiac resynchronisation therapy (Abraham et al. 2002, Abraham et al. 2004, Auricchio et al. 2002, Auricchio et al. 2003, Bristow et al. 2004, Cazeau et al. 2001, Cleland et al. 2005, Higgins et al. 2003, Kindermann et al. 2006, Leclerq et al. 2002, Leclerq et al. 2007, Young et al. 2003). All of the patients in these trials had a left ventricular dysfunction with a mean LV EF between 21-30 %, a widened QRS complex with a mean QRS width between 155-209 ms, and heart failure symptoms (NYHA III or IV in 91%, NYHA II in 9%). All attempt was made to optimise the medical therapy of

the patients. Approximately half of the patients randomised to resynchronisation received CRT alone (47%) and the other half CRT with defibrillator (53%). In a recent review of McAlister et al (2007) a clear benefit was seen in the reduction of the all cause mortality of about 22% (RR 0.78, 95% CI 0.67-0.91). A more prevalent reduction was seen in the heart failure deaths of 36% (RR 0.64, 95% CI 0.49-0.84). The longer the follow-up time was, the lesser number of patients had to be treated to prevent one death, reaching 9 patients at 3 years (Cleland et al 2006). Another clear benefit of the resynchronisation was the 47% decrease in the heart failure hospitalisation (RR 0.63, 95% CI 0.43-0.93).

Around 59% of the patients receiving CRT showed at least 1 NYHA class improvement at 6 months compared to 37% of the patients on optimal medical therapy (RR 1.55, 95% CI 1.25-1.92). Patients showed an improvement in LVEF (3.0%; 95% CI 0.9%-5.1%), in 6-minute walk test distance (24m improvement; 95% CI 13-35m) and in quality of life (Minnesota Living With Heart Failure Questionnaire, 8.0 points improvement; 95% CI 5.6-10.4 points).

There is currently no better selection criterion for cardiac resynchronisation therapy than the LVEF, QRS width and heart failure status of NYHA III-IV, as no clear subgroup effects were demonstrated in the RCTs. Most importantly there was no difference between the patients with and without ischemia in the three RCTs with an a priori planned analysis of this interaction (Higgins et al. 2003, Bristow et al. 2004, Cleland et al. 2005).

The only trial with a direct comparison of CRT- pacemakers and CRT defibrillators was the COMPANION trial (Bristow et al. 2004). The patient group randomised to CRT defibrillators showed a significant reduction in the secondary endpoint of all cause mortality, whereas the CRT pacemaker group showed only a non significant trend. In the primary endpoint of death from or hospitalisation for any cause both patient groups showed a significant benefit compared to the patients with pharmacologic therapy. Although the direct comparison of the efficacy of the CRT-pacemaker and CRT-defibrillator groups is underpowered and was not prespecified, there was no statistical difference in the all cause mortality and in the time to death or heart failure hospitalisation between the two groups. The difference between the effects of CRT-pacemaker and CRT-defibrillator therapy was not directly studied in other trials, and

therefore merely speculative. The decision between CRT-P and CRT-D is widely variable throughout Europe depending on health political decisions on the reimbursement of these treatments.

Background of our studies

Sudden cardiac death (SCD) is one of the major causes of death and most often (up to 95%) due to sustained episodes of ventricular tachycardia and ventricular fibrillation.

Recently, several randomized controlled trials (RCT) have shown that implantable cardioverter-defibrillators (ICDs) reduce not only sudden cardiac death but also all-cause mortality in patients with structural heart disease and high risk for life threatening ventricular arrhythmias.

(A) The implantable cardioverter defibrillator has been demonstrated to be superior to other treatment modalities in primary or secondary prevention of sudden cardiac death (AVID et al. 1997, Connolly et al. 2000; Kuck et al. 2000, Moss et al. 1996, Buxton et al. 1999, Moss et al. 2002, Hohnloser et al. 2004, Bristow et al. 2004, Bardy et al. 2005). However, device therapy is associated with significant expenditures in health care costs. Particularly in societies where health care cost is rapidly becoming a major consideration in decision making, it is important to determine the effect of innovative and costly therapy in patient groups which may be different from those enrolled in major prospective studies. The previous ACC/AHA/NASPE (Gregoratos et al. 2002), the current ACC/AHA/HRS (Epstein et al. 2008) and ESC (Vardas et al. 2007) guidelines do not include age in the decision of indication of ICD therapy (only the patients with terminal illness and life expectancy lower than 6 month are suggested to be excluded from device therapy). In several RCTs there was no upper age limit in the patient selection (MADIT II, SCD-HeFT, AVID; CIDS), while in some other trials an upper age limit of 80 years was selected (CABG-PATCH, MADIT, DINAMIT). Currently, there is no evidence concerning the age-dependency of the effectiveness of ICD therapy in the every day clinical practice. In the clinical setting however, the selection of the patients for ICD implantation is often influenced by the patient age. Accordingly, the question whether ICD therapy is justified in elderly patients has been raised. Unfortunately, there is a paucity of data to answer this question based on results from prospective studies since the average age of patients at the time of study

enrollment was between 58 - 65 years in secondary (AVID et al. 1997, Connolly et al. 2000; Kuck et al. 2000) and 58 – 66 years in primary preventive ICD trials (Moss et al. 1996, Buxton et al. 1999, Moss et al. 2002, Hohnloser et al. 2004, Bristow et al. 2004, Bardy et al. 2005). Only very sparse data from observational studies regarding the effect of increasing age on ICD efficacy have been published (Tresch et al. 1991, Panotopoulos et al. 1997). These studies, however, have several limitations, particularly the use of epicardial ICD systems, background therapy not complying with contemporary standards, or the lack of use of mortality as the primary study outcome measure.

(B) Cardiac resynchronization therapy (CRT) improves outcome, quality of life and exercise capacity in patients with heart failure of NYHA functional class III-IV, a left ventricular ejection fraction (LVEF) ≤ 0.35 , and a QRS duration ≥ 120 ms. The indication for CRT therapy has been constantly widened following publication of randomized prospective clinical trials (Abraham et al. 2002; Linde et al. 2002, Bristow et al. 2004, Cleland et al. 2005).

The least invasive method to implant a left ventricular (LV) lead is the transvenous approach. Reported success rates of coronary sinus (CS) lead implantation are 87-92% in randomized clinical trials (Abraham et al. 2002; Linde et al. 2002, Bristow et al. 2004, Cleland et al. 2005). Implantation success may rise to $> 95\%$ following a second implantation attempt (Cleland et al. 2005).

With the continuous development of LV-lead implantation tools, lead implantation through the coronary sinus is getting faster and safer. Although there are some data from multislice computer tomography and magnetic resonance imaging concerning the number and the size of the CS tributaries (Mao et al. 2005; Tada et al. 2005; Abbara et al. 2005), there are no systematic prospective data available about the results of the left ventricular lead implantation and possible technical difficulties through the coronary sinus. The implantation of the left ventricular lead in a desired position depends on the anatomy of the coronary sinus, the stimulation threshold, and the proximity to the n. phrenicus

(C) Among other important unanswered questions regarding CRT, it has not been prospectively assessed whether patients with previously implanted right ventricular pacemakers or cardioverter defibrillator systems derive similar benefit from

resynchronization therapy compared to patients undergoing de novo CRT implantation. Important clinical issues related to upgrading pre-existing non-CRT devices to CRT concern the complexity and possible technical difficulties during implantation (e. g. venous obstruction, passage of ingrown old leads, coronary sinus cannulation from the right subclavian vein), and clinical response to CRT in this particular patient group.

Unfortunately, only rarely have these questions been evaluated in published studies (Leon et al. 2002, Horwich et al. 2004, Valls-Bertault et al. 2007). However, all of these studies are limited, for instance by including only patients after AV node ablation (Leon, Valls-Bertault), by small sample sizes or without a normal control group.

(D) Lead-related complications are among the most important potential complications requiring reoperation in ICD recipients. Lead durability and integrity depend upon several factors such as lead design, lead material, and mechanical stress. More than half of all lead complications are insulation defects (Kleeman et al 2007), most frequently due to subclavian crush syndrome, abrasion of the lead by the ICD generator, or at the level of lead fixation.

Aims/Objectives

The present report aims to evaluate these four clinically relevant issues: (A) First we evaluated the effects of ICD therapy in patients aged 70 or older compared to younger patients.

(B) Second we examined the feasibility and the intraoperative difficulties during implantation of the LV lead through the CS in consecutive patients scheduled for CRT with particular emphasis to individual CS anatomy.

(C) Third, we addressed the feasibility and outcome of upgrading preexisting pacemaker/ICD systems to CRT devices as compared to de-novo CRT implantation.

(D) Fourth, we looked for new complication mechanisms leading to surgical system revision.

Methods

A) Age dependence of ICD therapy

Patient population (A). We retrospectively analysed data from 434 consecutive patients who underwent ICD implantation between January 1999 and November 2003 at the J. W. Goethe University, Frankfurt, Germany, for primary or secondary prophylaxis of sudden cardiac death. For the purpose of this analysis, only data from patients with evidence of structural heart disease and follow-up data for at least 30 days after ICD implantation were considered. According to the analysis plans of two of the largest preventive ICD studies (AVID et al. 1997; Moss et al. 2002), patients were divided into two groups according to their age younger than 70 years (group 1) or 70 years or older (group 2) at time of ICD implantation.

Follow-up (A). Patients were followed in the ICD outpatient clinic in regular 6 month intervals or whenever clinical circumstances called for unscheduled visits. At each visit, the patient's clinical status was checked and the concomitant medications adjusted according to the individual needs. ICD's were carefully interrogated and all available data stored on disc. Electrograms from all ICD shock or antitachycardia pacing therapy were collected and classified by two independent reviewers who were blinded towards the age of the patient.

Statistical analysis (A). The following events were defined as outcome measures for this analysis: i.) time to death from any cause, ii.) time to first ICD therapy of ventricular tachyarrhythmias, and iii.) time from first ICD therapy of ventricular tachyarrhythmias to death from any cause. The cumulative risks of death over time was estimated separately for each patient group using the Kaplan-Meier method (Kaplan, Meier 1958) and compared via a Mantel-Haenszel test (Mantel 1966). Comparisons between the patient groups regarding baseline variables were made by the chi-square test or the Student t-test as appropriate. A value of $p \leq 0.05$ was considered significant.

B and C) Prospective studies on CRT therapy

Patient population (B and C) Implantation and follow-up data were collected from consecutive patients who underwent CRT implantation (new or upgrade) between March 2005 and January 2007 at the J. W. Goethe University, Frankfurt, Germany. Patients were considered for CRT if they had heart failure of NYHA functional class III or IV or a history of heart failure decompensation within the last 3 months and were in NYHA class II at the time of presentation. Furthermore, a LVEF $\leq 35\%$ and a QRS width > 120 ms were required. (Gregoratos et al. 2002, Hunt et al. 2005, Swedberg et al.

2005, Strickberger et al. 2005, Zipes et al. 2006). In patients with a previously implanted pacemaker or ICD and continuous ventricular pacing, paced QRS width had to be ≥ 200 ms (Linde et al. 2002). All implanted devices were ICDs according to present indications for primary or secondary prophylaxis of sudden cardiac death (Zipes et al. 2006).

Device implantation (B and C). CRT de-novo implantations and upgrades were performed according to current standard procedures. Coronary sinus guiding sheaths and left ventricular pacing leads of different manufacturers were used. After introducing a guiding sheath into the coronary sinus an occlusive venogram using a balloon-catheter was performed in posterior-anterior and LAO 30° views. An electrophysiologist experienced in CRT implantation who was not involved in the actual implantation procedure defined the 1st, 2nd, 3rd, and 4th target CS side branch according to the individual CS anatomy (von Ludinghausen M 2003) with preference to the posterolateral vein or a side branch in close proximity to the posterolateral area (Butter et al. 2001, Rosillo et al. 2004). The implanting physician placed the LV-lead in the predefined order in the side branches, starting with the 1st choice CS branch. The lead was implanted if the following implantation criteria were met: 1.) stimulation threshold below 2 V x 0.5 ms; 2.) no phrenic stimulation at 5 V x 0.5 ms; 3.) minimal 100 ms delay of the local activation of the right and left ventricular lead during stimulation of the opposite ventricular lead.

If applicable, right ventricular and atrial leads were implanted conventionally preferably using the cephalic vein. All lead measurements (old and new implanted leads) were repeated before final lead fixation and connection to the device. Since all devices were ICDs, shock testing (successful termination of induced ventricular fibrillation with an energy more than 10 J below maximum device energy twice in case of a new RV ICD lead implantation, only once in case of preexisting RV defibrillation lead) was performed in all patients.

Follow-up. Patients were followed in the ICD outpatient clinic at 1 and 6 months after ICD implantation and whenever clinical circumstances called for unscheduled visits. At each visit, functional heart failure status (NYHA class), serum NT-pro-BNP level, and at the 6 months visit the LVEF were determined. Concomitant medication was adjusted

according to the clinical status of the patient. An AV and VV time optimization was performed 4-8 weeks after implantation.

Definition of response to CRT (B). In the first analysis patients who survived to the 6 month follow-up and showed ≥ 1 NYHA functional class improvement were considered as responders to CRT (Bax et al. 2003).

Definition of response to CRT (C). The responder definition for our second analysis: Patients were considered responders to CRT if they survived to the 6 month follow-up and showed significant improvement in 2 out of 3 of the following criteria: Improved clinical status, i. e. improvement of at least 1 NYHA functional class; echocardiographic improvement measured by an absolute increase in LVEF of at least 5 %; or neurohormonal evidence of improvement of heart failure, expressed as a decrease in the NT-pro-BNP level of at least 30 % (Bax et al. 2003, Sinha et al. 2003).

Statistical analysis (B). Outcome parameters were 1.) success rate of LV lead implantation in the 1st choice CS side branch; 2.) number and position of the theoretically available CS side branches; 3.) success of introducing the LV lead in the selected side branches and success of implantation the LV lead in those positions; 4.) procedural characteristics (implantation time, fluoroscopy time, fluoroscopy dose); 5.) 6 month response to CRT.

Statistical analysis (C). In the second analysis of the prospective cohort patients were divided into two groups: patients with de novo CRT implantation (group 1) and patients with a pre-existing right ventricular device undergoing upgrade to CRT (group 2). Outcome parameters were 1.) procedural characteristics (implantation time, fluoroscopy time, fluoroscopy dose), 2.) implantation success rate (defined as successful implantation of all leads with capture at output levels < 2.5 V and lack of phrenic nerve stimulation at 5 V), 3.) implantation complications, 4.) six month response to CRT.

Baseline variables, implantation success rate, procedure and fluoroscopy time, X-ray dose, and response rates were compared using the chi-square test, Fischer's exact test or the Student t test where appropriate. A two-sided value of $p \leq 0.05$ was considered significant.

Results

Patient characteristics (A). From a total of 434 consecutive ICD recipients, 59 (14 %) were excluded from this analysis because they had inadequate follow up (n=24) or since they had no evidence for structural heart disease (n=35). Therefore, data from 375 patients constitute the basis of this report.

Table 3 Baseline characteristics.

Patients younger (Group 1) and older (Group 2) than 70 years

	All Pts	Group 1	Group 2	p value
Patients	375	273	102	
Age at ICD implantation (y)	63.6±10.0	59.7 ± 8.9	74.0 ± 3.1	
Range(y)	24-84	24-69	70-84	
Male Sex – no. (%)	309 (82)	229 (84)	80 (78)	ns
Follow-up (month)	26.5±18.1	26.8 ± 18.6	25.8 ± 16.5	ns
ICD indication – no. (%)				
Primary prevention	125 (33)	102 (37.4)	23 (22.5)	
Secondary prevention	250 (67)	171 (62.6)	79 (77.5)	0.007 *
Underlying disease – no. (%)				
Coronary artery disease	315 (84)	222 (81.3)	93 (91.2)	0.026 *
Dilated cardiomyopathy	67 (18)	57 (18.7)	10 (8.8)	0.015 *
LVEF (%)	32.8±11.4	33.2 ± 11.7	32.01 ± 10.4	ns
NYHA functional class – no. (%)				
I	134 (35.7)	99 (36.2)	35 (34.3)	ns
II	163 (43.5)	115 (42.1)	48 (47.1)	ns
III-IV	88 (23.5)	59 (21.6)	19 (18.6)	ns

	All Pts	Group 1	Group 2	p value
Pharmacologic therapy – no. (%)				
Amiodarone	85 (23)	57 (20.9)	28 (27.5)	ns
Beta-blockers	287 (77)	209 (76.6)	78 (76.5)	ns
ACE – inhibitors or AT ₁ - receptor blockers	336 (90)	242 (88.6)	94 (92.2)	ns
Statins	246 (66)	175 (64.1)	71 (69.6)	ns
Digitalis	131 (35)	96 (35.2)	35 (34.3)	ns
Diuretics	246 (66)	173 (63.4)	73 (71.6)	ns

means \pm SD.

* significant difference among the two groups in baseline characteristics ($p < 0.05$).

Among the 375 patients, 273 were younger than 70 years (group 1), and 102 were 70 years of age or older (group 2). Clinical baseline characteristics of the two groups are shown in Table 3. Younger patients underwent ICD implantation more often for primary prevention of sudden cardiac death (37% vs. 23%; $p=0.007$). Elderly patients suffered more often from coronary artery disease and less often from dilated cardiomyopathy compared with younger patients ($p < 0.03$). In both groups, background medical therapy was optimized with a high usage of beta-blockers, angiotensin converting enzyme inhibitors or AT₁ receptor blockers, and statins.

Time to death. Patients were followed for a mean of 26.5 ± 18.1 months with no significant difference in the average follow-up time between the two groups (26.8 ± 18.6 vs 25.8 ± 16.5 months, $p=ns$, median 23 vs 23 months). Time to all-cause death for the two groups are shown in Figure 1. During the observation period, 47 patients died, 34 in the younger patient group (12.5 %) and 13 in the elderly patient group (12.7 %). The average time to death was comparable among the two groups (28.4 ± 16.7 vs 30.4 ± 22.1 months, $p=ns$, median 26 vs 25 months). At 12 and 24 months, 2.6 % (7 patients) and

5.5 % (15 patients) in the younger and 2.9 % (3 patients) and 5.9 % (6 patients) in the older patient group died.

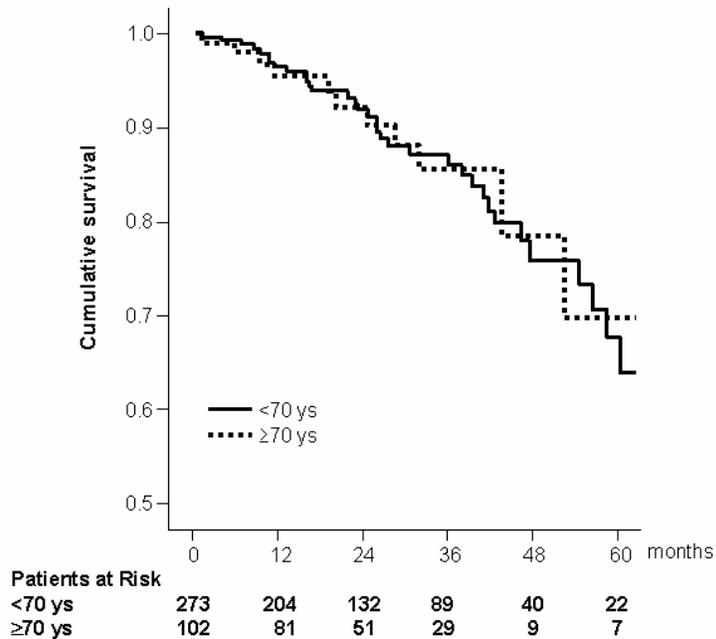


Figure 1 Cumulative survival curves after ICD implantation in patients younger and older than 70 years

Time from device implantation to first appropriate ICD therapy of ventricular tachyarrhythmias. During the follow-up period, at least one appropriate ICD therapy delivery on ventricular tachyarrhythmias was documented in 40 % (108 patients) of group 1 patients and 44 % (45 patients) of group 2 patients (p=ns). The average time to first adequate ICD therapy (shock or antitachycardia pacing) delivery was not significantly different among the two groups (11.0 ± 12.7 months vs 8.9 ± 10.9 months, p=ns) (Figure 2). At 12 and 24 months, 25 % (68 patients) and 33 % (91 patients) of group 1 and 31 % (32 patients) and 37 % (38 patients) of group 2 patients had experienced at least one appropriate ICD therapy episode.

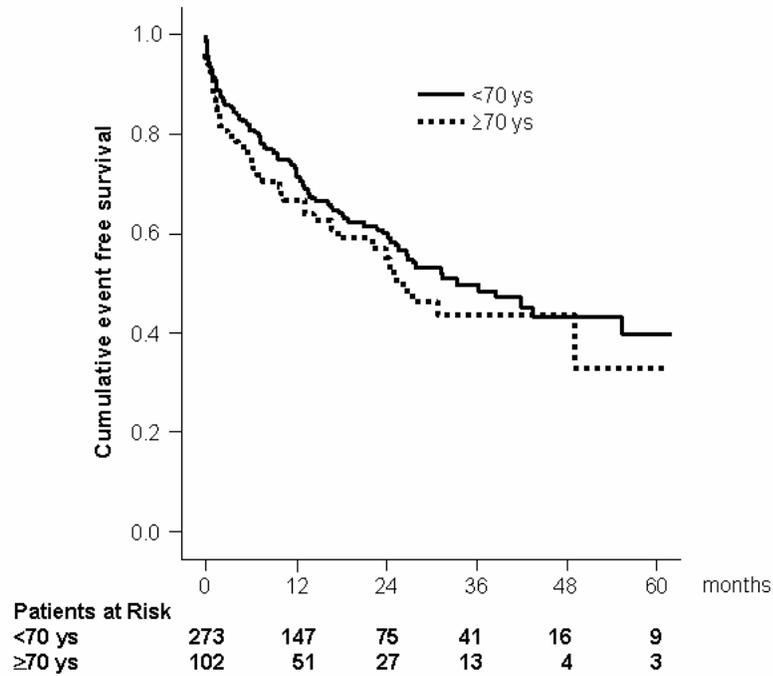


Figure 2 Cumulative survival free of ICD therapy of ventricular tachyarrhythmias in patients younger and older than 70 years

Time from first ICD therapy delivery on ventricular tachyarrhythmias to death from any cause. Twenty-four of 108 patients with appropriate ICD therapy of ventricular tachyarrhythmias in group 1 (22 %) subsequently died, compared to eight of 45 group 2 patients (18 %; $p=ns$). The average time from first adequate ICD therapy to death was not significantly different between the two groups (18.3 ± 16.4 months vs 25.7 ± 17.7 months, $p=ns$) (Figure 3).

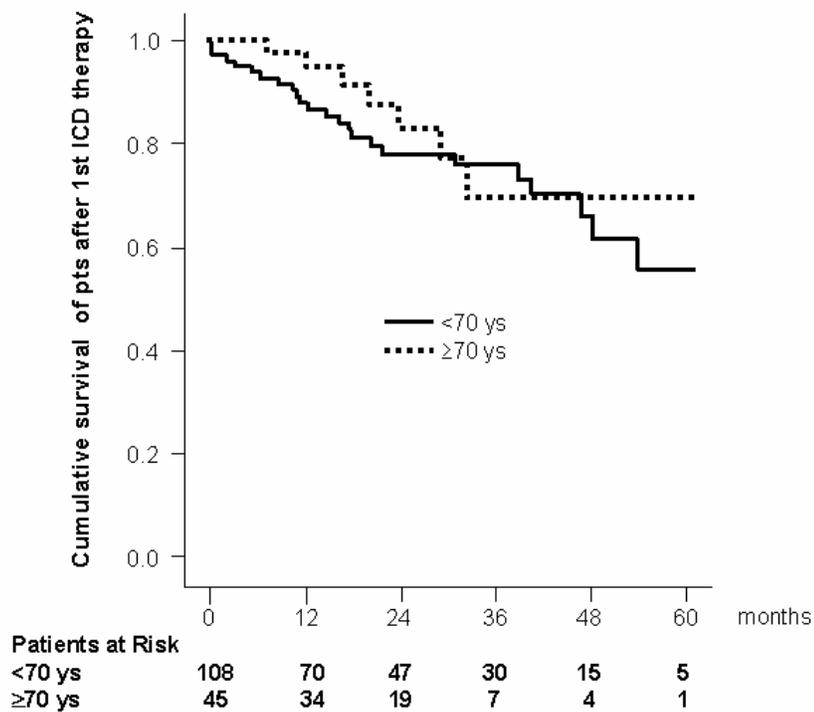


Figure 3 Cumulative survival after first ICD therapy (shock or ATP) delivery in patients younger and older than 70 years

ICD-related complications. Table 4 depicts device-related complications encountered during the perioperative phase and during the subsequent observation period. There was no difference in adverse events between both groups. There was no implantation-related mortality.

Table 4 ICD-related adverse events

	Group 1	Group 2
Patients	273	102
Perioperative complications		
Hematoma	6	6
Pneumothorax	1	1
Electrode dislodgement	1	

	Group 1	Group 2
Late complications		
Pacing failure	1	1
Electrode malfunctioning	16	2
Infection	1	
Generator dislodgement	2	
Total complications	28 (10.1%)	10 (9.8%)

Patient characteristics (B and C). Our observation is based on data obtained from 79 consecutive CRT recipients. Of this patient cohort, 18 patients (23 %) had a previously implanted right ventricular device (3 pacemaker; 15 ICD) and underwent an upgrade to CRT-ICD system. In 8 of 18 patients (44 %) right ventricular pacing was present for more than 50% of the time including 4 patients with permanent complete AV block. Five of 18 patients (28 %) had permanent atrial fibrillation. Baseline characteristics of the two groups are shown in Table 5. Medical therapy was optimized in all patients

Table 5 Baseline characteristics (B and C)

	All Pts	De Novo	Upgrade	p value
Patients	79	61	18	
Age at implantation (yrs)	64 ± 11 (35-83)	63 ± 11 (35-80)	66 ± 10 (40-83)	0.27
Male (n, %)	63 (80)	50 (82)	13 (72)	0.37
Underlying heart disease (n, %)				0.72
ICM	38 (48)	30 (49)	8 (44)	
NICM	41 (52)	31 (51)	10 (56)	
LVEF (%)	23 ± 8	22 ± 7	25 ± 9	0.35
NT-proBNP (pg/ml)	3158 ± 4477	3273 ± 4959	2781 ± 2433	0.75

	All Pts	De Novo	Upgrade	p value
VO ₂ max (ml/kg/min)	13.2 ± 4.2	13.4 ± 4.3	12.3 ± 3.4	0.39
NYHA functional class (n, %)				
II	22 (28)	20 (33)	2 (11)	
III-IV	57 (72)	41(67)	16 (89)	0.13
Pharmacologic therapy (n, %)				
Amiodarone	14 (18)	7 (12)	7 (39)	0.072
Beta-blockers	72 (92)	56 (93)	16 (89)	0.80
ACE – inhibitors or AT ₁ - receptor blockers	71 (91)	56 (94)	15 (83)	0.92
Statins	43 (55)	36 (60)	7 (39)	0.13
Digitalis	53 (68)	41 (68)	12 (68)	0.97
Diuretics	71 (91)	57 (95)	14 (78)	0.10
Aldosterone antagonists	47 (59)	38 (62)	9 (50)	0.35

Mean values ± standard deviation (range). *: significant difference among the two groups in baseline characteristics (p < 0.05).

Coronary sinus anatomy. A retrograde coronary sinus angiography was obtained in 77 of the 79 patients (Figure 3). This report is thus based on findings in these 77 patients.

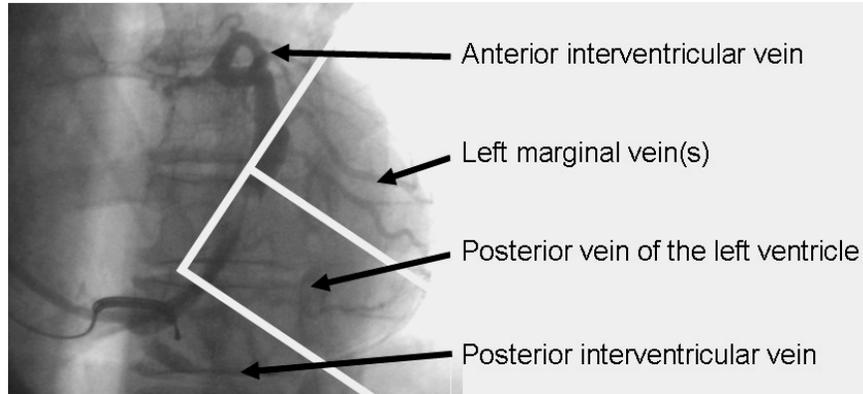


Figure 3 Coronary vein side branches
Coronary vein side branches according to the definition proposed by van Ludighausen in the LAO 30° projection.

The anterior interventricular vein was present in 69 of the 77 patients (90%), the left marginal (lateral) vein in 63 / 77 patients (82%), and the LV posterior vein in 50 / 77 patients (65%). The posterior interventricular vein was visualized in 42 / 77 patients (55%). In three patients (4%) there was only one coronary sinus side branch available, in 20 patients (26%) two, in 36 patients (47%) 3, in 18 patients (23%) 4. In the posterior-lateral region there was only one available coronary sinus side branch (CS-SB) in 41 / 77 patients (53%), two or more CS-SB in 36 / 77 patients (47%).

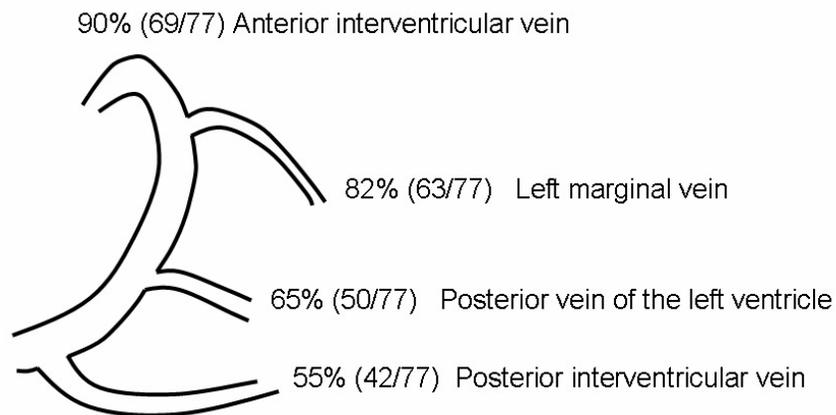
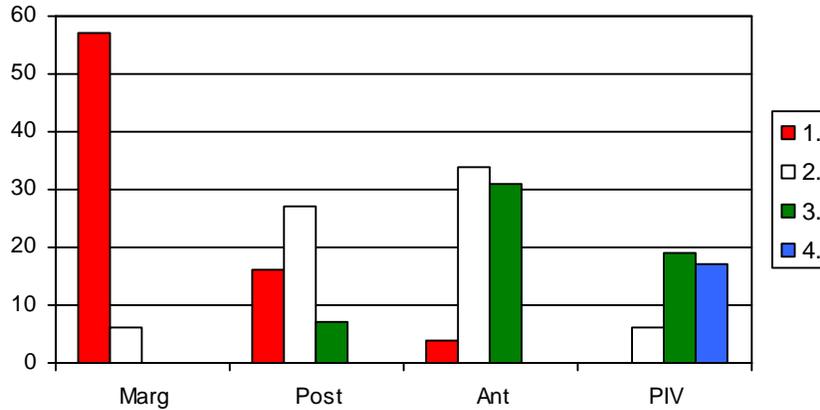


Figure 4 Presence of the four major coronary sinus side branches in the present patient cohort.

Figure 5 depicts the selection of the 1st 2nd, 3rd and 4th target according to the sidebranch regions. The marginal vein was in 90% as first target, in 10% as second target selected. 30 % of the posterior and 5% of the anterior veins were 1st choice.



	1 st	2 nd	3 rd	4 th	All veins
Marginal	57	6	0	0	63
Posterior	16	27	7	0	50
Anterior	4	34	31	0	69
Post. interventricular	0	6	19	17	42

Figure 5 Definition of the target CS branches
(Number of veins in different positions)

Implantation of the LV leads. A LV lead was successfully implanted in 73/77 patients (95%) following coronary sinus angiography. Implantation success in the first targeted vein was 71% (55/77 patients), in the second targeted vein in an additional 21% (16/77), and in the third targeted vein in further 3% (2/77) (Figure 6).

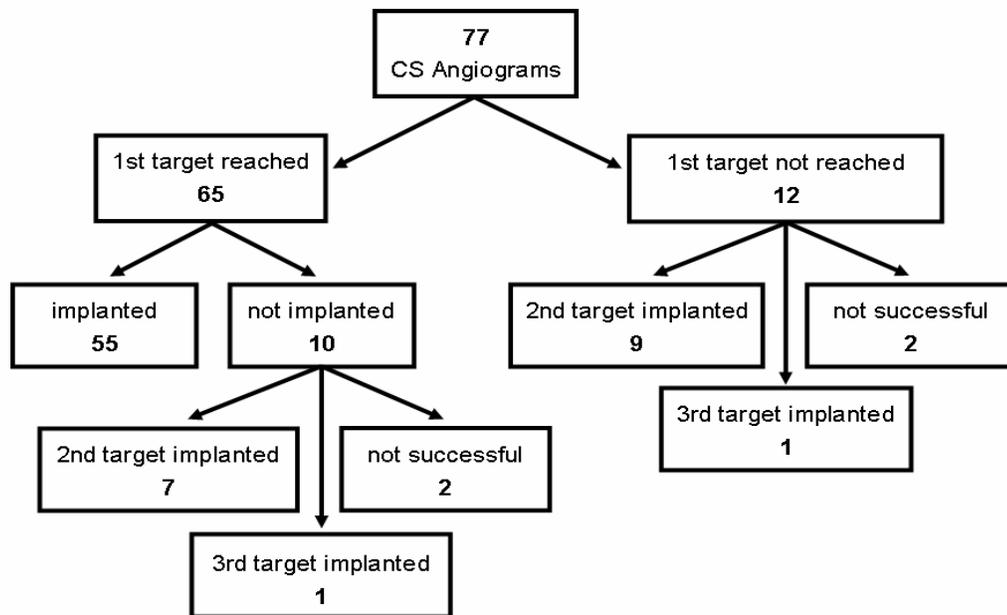
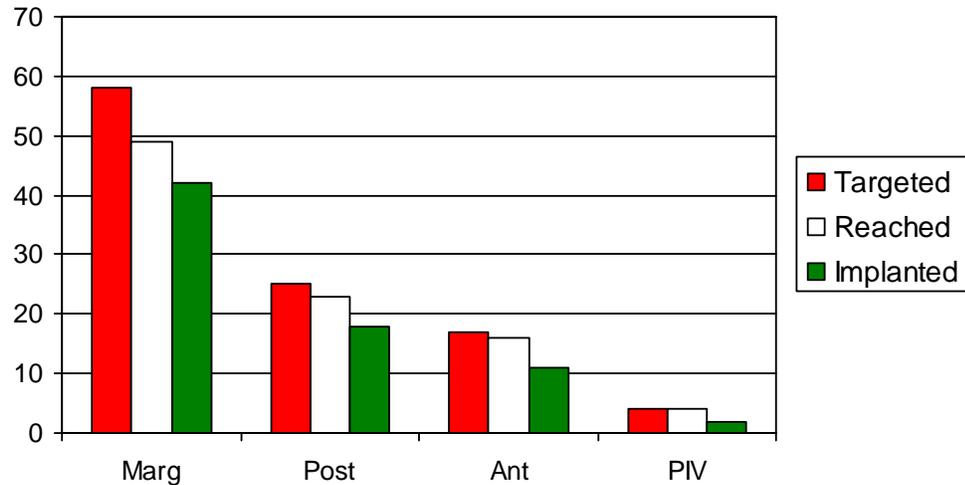


Figure 6 Flow chart of LV lead implantation in predefined target coronary sinus side branches

The success rate for reaching the targeted lead position was 84% for the marginal vein, 92% for the posterior vein, 94% for the anterior interventricular vein, and 100% for the posterior interventricular vein (Figure 7).



	Targeted	Reached	Implanted
Marginal	58	49 (84%)	42 (72%)
Posterior	25	23 (92%)	18 (72%)
Anterior	17	16 (94%)	11(65%)
Posterior interventricular	4	4 (100%)	2 (50%)
All	104	92 (88%)	73 (70%)

Craddock-Flood's Chi² p=0.75

Figure 7 Implantation success in different coronary sinus branches

A lead repositioning in the same side branch was needed because of lead instability (4 cases), of high stimulation threshold (5 cases) or of phrenic nerve stimulation (10 cases). Of all reached veins tested (92 veins in 77 patients), the vein had to be completely abandoned in 21%, mainly because of lead instability (8 cases, 9%) and high pacing threshold (7 cases, 8%) (Table 6). The lowest rate of unsuitable measurements (14%) was found in the marginal position, the highest rate in the posterior interventricular vein (50%). None of the leads were implanted in the apical region of the anterior interventricular vein; all leads in the anterior position were placed in anterolateral side branches of the anterior interventricular vein. There was no difference in the presence of stimulation threshold problems in patients with (3/26 patients, 12%) or without a previous myocardial infarction (8/53, 15% p=0.47). Successful LV lead

implantation was performed in 72% of targeted marginal, in 72% of posterior, in 65% of anterior interventricular and in 50% of the posterior interventricular vein.

Table 6 Failure to use coronary sinus side branches

	Marginal	Posterior	Anterior	PIV	All
CS branch reached	49	23	16	4	92
CS branch not suitable	7 (14%)	5 (22%)	5 (33%)	2 (50%)	19 (21%)
Lead instability	5#	2*	2		8
High stimulation threshold	3#	3*	3§		7
Phrenic nerve stimulation	1#	2*		1	3
RV-LV conduction time			1§	1	1
Repositioning within the CS branch needed	10 (20%)	7 (30%)	2 (13%)	0 (0%)	19 (21%)
Lead instability	2	1	1		4
High stimulation threshold	3	2			5
Phrenic nerve stimulation	5	4	1		10
Lead implanted in the CS branch	42	18	11	2	73

In some of the cases more than one reason were the cause of leaving a reached sidebranch: * 1 pt: Instability+ Phren; 1 pt: Thresh+ Phren; # 1 pt: Instability+Threshold +Phrenicus Stim; § 1 pt Threshold + RV-LV-Cond time
 PIV: Posterior interventricular
 Craddock-Flood's Chi² p =0.23

Of the 73 patients with a successful LV- lead implantation 38 patients were implanted with a unipolar lead, 35 with a bipolar one. We had to switch from using one to the other type of electrode in 10 patients: In 4 of 6 cases, the switch from using a bipolar lead to unipolar LV-lead enabled implantation in the first target vein; the remaining 2 patients were implanted with a unipolar lead in the 2nd target vein. In 3 cases, a unipolar lead was changed to a bipolar one which could be implanted in a 1st, a 2nd, and a 3rd target vein. In one case the procedure was started with a bipolar lead, then the

introduction of a unipolar lead was unsuccessfully attempted into two sidebranches, and finally, the bipolar lead was successfully implanted in the 1st target position

Procedural data (B). CRT implantation was successful in 73 of the 77 patients. Causes of unsuccessful implantations were: electrode instability in the only accessible vein (1 patient); high pacing threshold in two different veins (1 patient); high pacing threshold + electrode instability + phrenic nerve stimulation in 2 different veins (2 patients). Procedural data for the first versus the 2nd-3rd choice targeted veins are shown in Table 7. Implantation and the fluoroscopy times were significantly higher in the patients where the first chosen target vein was not suitable.

Table 7 Procedural data of CRT implantations according to successful LV-Lead implantation in the 1st or \geq 2nd choice target CS-SB

	1 st choice (55 pts)	2 nd -3 rd choice (18 pts)	P
Operation-Time (min)	143 \pm 41	179 \pm 47	0.002
X-Ray time (min)	20 \pm 13	38 \pm 21	0.002
X-Ray dose (Gy x cm ²)	36 \pm 27	58 \pm 52	0.103

Response to CRT (B). During the 6 months after device implantation 6 patients died. The cause of death was intractable ventricular arrhythmia in 1, progressive heart failure in 3, septicemia in 2 patients. According to our definition of response, 35/55 (64%) of the patients with a first choice LV lead position and 12/18 (67%) patients with LV leads implanted in the second or third chosen CS side branch responded to CRT (p=0.95). There was no difference between the response rates according to different LV lead positions (Table 8), albeit the number of patients with LV leads in the anterior or posterior interventricular veins were small.

Table 8 Response to CRT according to the left ventricular lead position

	Patients	Responder
Marginal	42	25 (60%)
Posterior	18	11(61%)
Anterior	11	9 (82%)
Posterior interventricular	2	2 (100%)

Procedural data (C). Implantation was successful in 56 of 61 de novo implantations (92%) and 17 of 18 upgrade procedures (94%, p=1.0). Preexistent devices were single chamber ICD in 13 pts, dual chamber ICD in 2 pts, and dual chamber pacemaker in 3 patients. The previous device was implanted submuscularly in 12 and subcutaneously in 6 patients. In addition to the left ventricular lead, a right atrial lead had to be implanted in 12, a right ventricular ICD lead in 3, and an additional vena cava superior shock-coil in one patient. Causes of unsuccessful implantations were: Coronary sinus not accessible (2 patients); electrode instability in the single accessible vein (1 patient); high pacing threshold in ≥ 2 different veins (1 patient); high pacing threshold + electrode instability + phrenic stimulation in 2 different veins (2 patients). In 2 patients, the CRT upgrade procedure was complicated by an occlusion of the left subclavian vein (Figure 8A). In both cases, successful venous recanalization could be accomplished. In one additional upgrade patient there was a large subclavian vein aneurysm which could be passed using a long sheath (Figure 8B). Procedural data comparing the de novo and upgrade implantations are shown in Tables 9 and 10. There were no significant differences between the 2 groups in any of the relevant parameters.

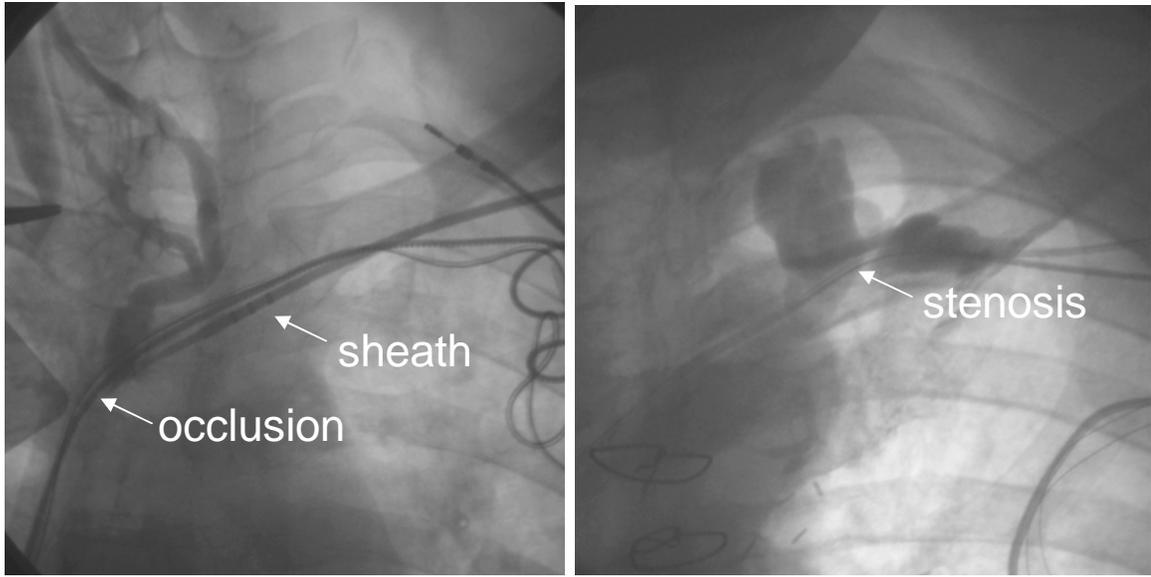


Figure 8

A (left panel): occlusion / stenosis of the v. subclavia - successful recanalisation

B (right panel) v. subclavia stenosis + aneurysma - difficult CS cannulation

Table 9 Procedural data

	De Novo (61 pts)	Upgrade (18 pts)	p value
Implantation success	56 (92%)	17 (94%)	1.00
Right sided implantation	2 (3%)	3 (17%)	0.75
Procedure time (min)	154 ± 44	164 ± 63	0.42
Range	90-310	75-300	
X-ray time (min)	25 ± 18	32 ± 22	0.18
Range	4.6-78.8	6.1-79.8	
X-ray dosis (Gy cm ²)	41 ± 31	52 ± 49	0.22
Range	4.1-127	14-222	

Position of LV electrode (n, %)	De Novo	Upgrade	p value
Not successful	5 (8)	1 (6)	0.46
Anterior/anterolateral	9 (15)	2 (11)	
Lateral	33 (54)	9 (50)	
Posterior	13 (21)	4 (22)	
Posteroseptal	1 (2)	2 (11)	

Mean values \pm standard deviation. *: Significant difference among the two groups in baseline characteristics ($p < 0.05$).

Table 10 Complications

Perioperative complications	De Novo (61 pts)	Upgrade (18 pts)	p value
Tamponade	0	0	n. s.
Perforation	0	0	n. s.
Vena cava superior dissection	0	1	n. s.
CS dissection	1	1	n. s.
Significant pocket hematoma	1	0	n. s.
CRP increase >5 mg/dl requiring i. v. antibiotic treatment >3 days	5	4	n. s.
Bleeding requiring transfusion	1	0	n. s.
Allergic reaction ¹	1	0	n. s.
Pneumothorax ²	1	0	n. s.
Periprocedural mortality	0	0	n. s.

Late complications	De Novo	Upgrade	p value
Infection requiring intervention	0	0	n. s.
Explantation	0	0	n. s.
Lead revision (exit block/ dislodgement) ³	2	0	n. s.
Patients with any adverse event	10 (16 %)	5 (28 %)	n. s.

¹: allergic reaction to povidon iodine solution, ²: without the need for thoracic drainage, ³: 1 LV lead due to twiddler syndrome, 1 RV lead due to threshold increase/exit block. CRP: C-reactive protein, CS: coronary sinus.

Response to CRT depending on upgrade or new implantation. During the 6 months after device implantation, 6 patients died (4 after de-novo implantations, 2 following upgrade procedures). The cause of death was intractable ventricular arrhythmias in 1 patient, progressive heart failure in 3, and septicaemia in 2 patients. According to the predefined criteria, 37/56 de-novo implanted patients (66%) and 10/17 upgraded patients (59%) were considered responders to CRT (p=0.80). As part of the combined definition, the NYHA functional class, the LVEF and the NT-proBNP level showed significant improvement in the responders compared to the non-responder patients, as follows. NYHA functional class changed from 2.8 ± 0.7 to 1.7 ± 0.7 ($p < 0.0001$) in responders while it remained unchanged in non-responders (2.8 ± 0.6 to 2.7 ± 0.5 p=n.s.). LVEF remained in the same range for non-responders and increased in responders. The NT-proBNP level decreased in responders and increased in non-responders (Table 11)

Table 11 Changes in NYHA class, LVEF, LVEDD and Nt-Pro-BNP in responder and non-responder patients before and 6 months after CRT implantation.

	Responder	Non-responder
NYHA class	$2.8 \pm 0.7 \rightarrow 1.7 \pm 0.7$ p<0.001	$2.8 \pm 0.6 \rightarrow 2.7 \pm 0.5$ p=n.s.

	Responder	Non-responder
LVEF (%)	23±8 → 33±10 p<0.001	24±8 → 28±10 p=0.06
LVEDD (mm)	68±11 → 65±12 p=0.007	69±9 → 67±11 p=0.09
Nt-Pro-BNP (pg/ml)	3598±5241 → 1721±2753 p=0.001	2120±1282 → 3641±2211 p=0.002

Two of the six patients (33%) with unsuccessful CRT implantation died within the first 6 months compared to 4 of 73 patients (6%) with successful device implantation (p=0.063).

Description of a new lead defect mechanism (D)

A frequent complication of the ICD therapy is the inadequate ICD shock delivery (Ezekowitz et al. 2007). We present here a patient reporting an ICD shock delivery. Analysis of the stored electrograms demonstrated inadequate ICD shock therapy elicited by artifacts leading to detection of a presumed ventricular fibrillation episode (Figure 9). Earlier non-sustained episodes without ICD shock delivery demonstrated similar double potentials in the ventricular channel leading to detection of presumed ventricular fibrillation episode. The patient never experienced a sustained ventricular tachyarrhythmia since his ICD was implanted. Fluoroscopy revealed that an approximately 6 cm long portion of the ICD lead (Riata 1580, St Jude Medical, Sylmar, Ca) was split at the level of the tricuspid valve, with two thinner electrode components outside the main lead body (Figure 10, postero- anterior and LAO 40° views, white arrows). Unfortunately the lead could not be extracted due to presence of long, stiff scar tissue formation around it. A new right ventricular ICD lead was implanted and subsequent device testing showed normal device function.

To the best of our knowledge, this is the first documentation of disintegration of electrodes that have been embedded into a multiluminar ICD lead (Gradaus et al. 2003).

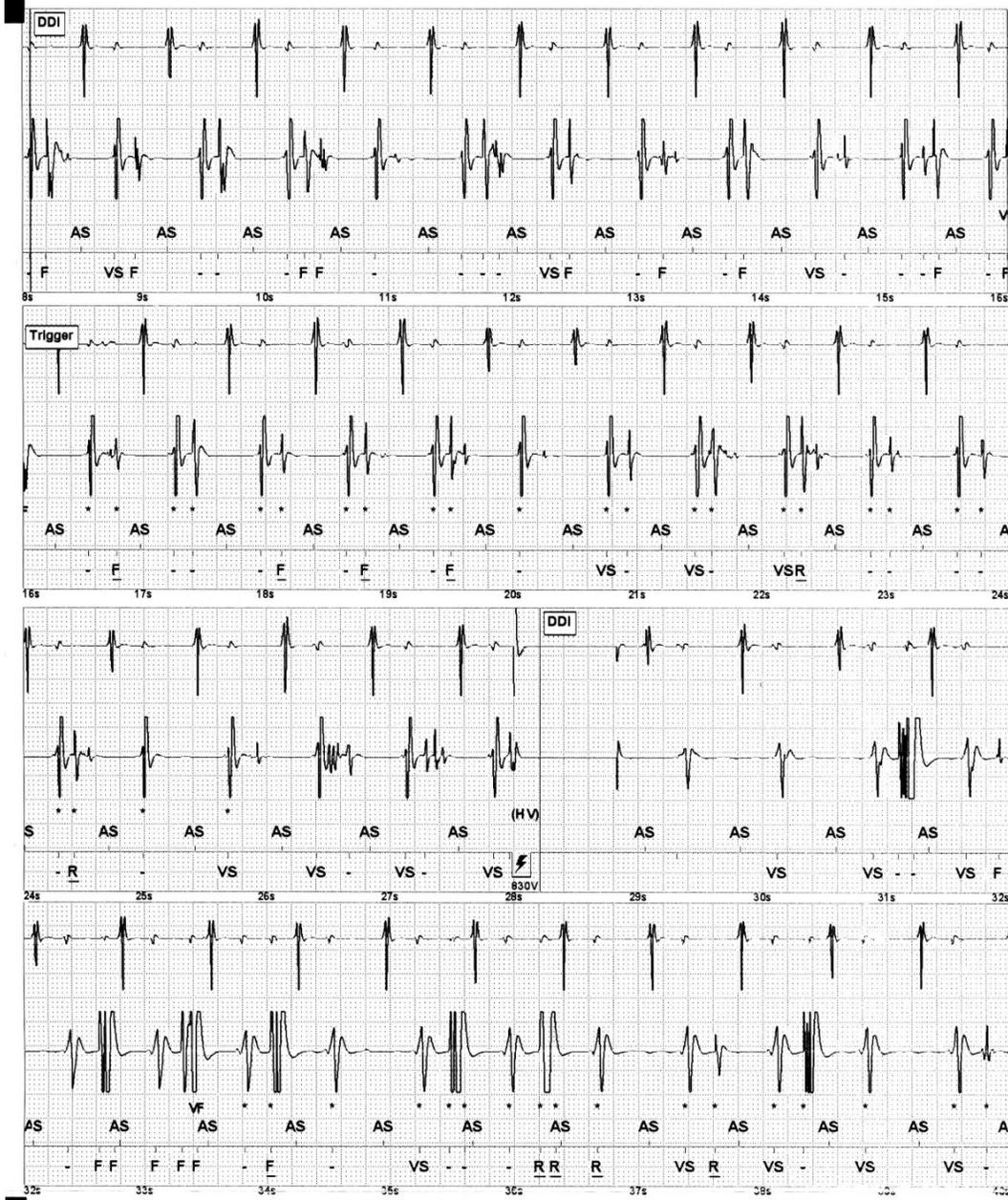


Figure 9 Double potentials in the ventricular channel leading to detection of presumed ventricular fibrillation episode.

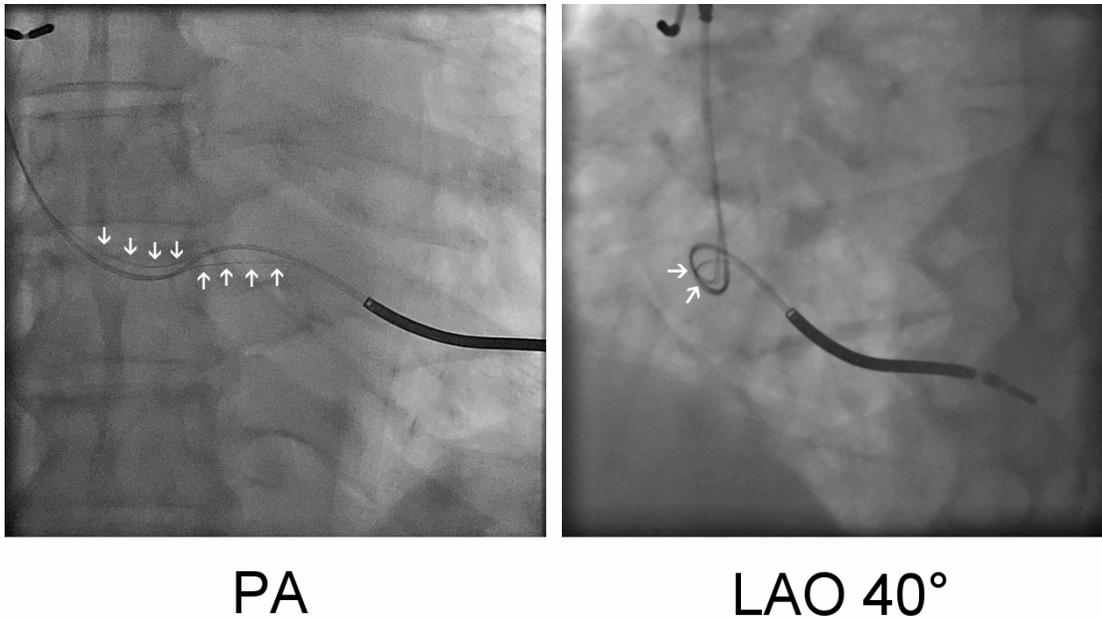


Figure 10 Lead splitting at the level of the tricuspid valve, with two thinner electrode components outside the main lead body (postero- anterior and LAO 40° views, white arrows)

Discussion

Main findings.

- (A) We were the first who showed, that, ICD recipients who were 70 years of age or older at the time of ICD implantation have a similar benefit compared to patients of younger age in a large single-center consecutive patient population.
- (B) Our prospectively designed observational study is the first that demonstrates that in 70% of heart failure patients undergoing CRT device implantation at least 3 potential sinus coronary side branches are available for LV lead implantation. The implantation success in the 1st choice CS-CB was 71% without significant differences for any particular side branch region.
- (C) We performed the first comparative analysis of upgrading existing right ventricular pacing systems to CRT versus de novo implantation. We demonstrated, that an upgrade procedure can be safely carried out with similar implantation success, procedural times, and complication rates as de novo CRT implantation.

(D) We presented a new lead failure mechanism, possibly caused by the mechanical stress of the tricuspid leaflet motions. This lead defect may occur only in the modern multiluminar ICD leads.

ICD therapy in the elderly

ICD therapy has been shown in several large-scale randomized trials to improve outcome in patients at high risk for sudden arrhythmogenic death (AVID et al. 1997, Connolly et al. 2000; Kuck et al. 2000, Moss et al. 1996, Buxton et al. 1999, Moss et al. 2002, Hohnloser et al. 2004, Bristow et al. 2004, Bardy et al. 2005). However, elderly persons have been significantly underrepresented in both the primary and secondary prevention trials. Although within some populations studied the protective effect of device therapy was seen across all age groups (AVID et al. 1997), the power of this observation is limited by the underrepresentation of patients older than 70 – 75 years of age (Ferrick 2005). Despite this limitation, rates of ICD implantations have increased 10-fold over the past 15 years (Hlatky et al 2002). In fact, further exponential growth of use of device therapy in the face of expanded indications and the demographics of an aging population is expected. This will result in a significant increase in costs associated with device therapy which has resulted, and will continue to do so, raised concerns as to whether societies can afford this treatment modality.

Similarly to the lack of data stemming from prospective trials, there is a paucity of data on ICD effectiveness stemming from observational studies. An early report on 54 elderly patients implanted before 1990 showed that even with the epicardial devices used at that time, ICD therapy in patients older than 65 years was safe and effective (10). However, no mortality data were reported. Panotopoulos et al compared outcome of 74 ICD patients older than 75 to that of 695 younger patients (Panotopoulos et al 1997). There was no significant difference in terms of appropriate ICD activation in elderly compared to younger patients, and only few sudden deaths occurred in the older group. However, advanced age turned out to be a significant predictor of adverse outcome again emphasizing the problem of extrapolating results from younger patients which may overestimate ICD benefit in the elderly. In contrast to this study, there was no increased all-cause mortality in our study which may reflect advances in background medical therapy. In fact, our patients were treated with state of the art pharmacological therapy particularly for concomitant heart failure.

Safety of ICD therapy in the elderly.

In agreement with previous studies, our results show that ICD therapy can be safely accomplished in elderly subjects. There was no excess in perioperative morbidity and no mortality related to ICD implantation.

Limitations of our study on elderly ICD recipients.

Our study is limited by its design as a retrospective data analysis which may imply some potential patient selection bias. Especially in the elderly group a pre-selection of the most healthy patients with the least co-morbidity could have happened. Over the time course of patient recruitment, indications for ICD implantation were subject to major changes according to the results of the prospective trials. Nevertheless, the observations were made in a large series of consecutive patients with accepted ICD indications treated with optimized background therapy.

Anatomy of the left cardiac veins.

The cardiac venous system shows substantial anatomic variation. In a study of human cadaver hearts examining the coronary sinus and its tributaries, the hearts with abnormal weight or left ventricular size were excluded. A summarized difficulty grade for coronary vein branch catheterisation was defined, based on the presence and shape of the Thebesian and Vieussens valves and on the size and the takeoff degree of the side branches. Optimal anatomic situation for side branch catheterisation was found in 18 of the 52 specimens (35%), suboptimal in 25 (48%) and worst conditions in 9 (17%) cases. Two to six (3.5 in average) side branches could be found between the PIV and the great cardiac vein, three or four CS-SB could be found in 75%, and at least one side branch that could be easily cannulated in 86% of cases (Karaca et al. 2005). The anatomy of the cardiac veins has been evaluated using multislice computed tomography (8-64 slices MSCT; Tada et al. 2005; Abbara et al. 2005, Jongbloed et al. 2005, Van de Veire et al. 2006, Christiaens et al. 2007) or electron beam computed tomography (EBCT) (Mao et al. 2005). These studies described patients mainly with a suspected coronary artery disease (453 pts) or patients undergoing left atrial catheter ablation procedure (74 pts), and only ten patients before a planned CRT implantation. In the patient group with paroxysmal atrial fibrillation nearly 10% of the 8 slice MSCT studies could not be evaluated because of insufficient image quality. The venous system shows a substantial anatomic variation. The posterior interventricular vein and the anterior interventricular

vein could be visualized in nearly 100 %. The left marginal vein was present in 61-93%, the posterior vein in 80-98 %. In 40 % of 231 patients scanned with EBCT only one dominant posterior or marginal vein could be visualized (Mao et al. 2005). Using MSCT, 2% (Christiaens et al. 2007), 13% (Tada et al. 2005), 20% (Abbara et al. 2005), and 40% (Jongbloed et al. 2005) of the patients showed only one posterior or marginal vein. On the other hand in 26 – 45% of the patients had 3 or more venous branches in this region (Tada et al. 2005; Abbara et al. 2005, Christiaens et al. 2007). The noninvasive studies have shown a side branch diameter between 2,6-3,4 mm with a range from 1 to 5 mm. The spatial resolution of the different methods has a huge effect on the visualisation of a vein in the different positions). In our study 53% (41 /77) of the patients had only one, and 47 % (36/77) had two or more venous branches. Van de Veire et al. showed, using 64 slice MSCT, that in the patients with a previous myocardial infarction a left marginal vein could be less often identified (27%) compared to patient with coronary artery disease without infarction (61%) or to control patients (71%). The most striking difference was seen in the patients with lateral (0%) or with an anterior (22%) scar (Van de Veire et al. 2006). We did not observed such a difference in patients with a previous anterior or any infarction localisation.

However, in none of these studies a correlation between coronary sinus anatomy and the success of left ventricular lead implantation was addressed.

There are only sparse data regarding the yield of coronary venous angiography for determining CS anatomy (Mischke et al. 2007, Delarche et al. 2007). In one study the retrograde coronary sinus angiography via femoral venous access and ballon occlusion of the CS was compared with the venous phase CS angiography. Both approaches were sufficient for planning the lead implantation. The contrast agent need, and the radiation exposure was higher in the retrograde angiography. Unfortunately no data about the number of the different venous branches is presented (Mischke et al. 2007). The other study compared the intraoperative retrograde angiography with the preoperative venous phase angiography. They showed that the image quality was comparable and the CS catheterization time, the total implantation time of the left ventricular lead was shorter, however slightly more contrast media was needed for the preoperative venous phase angiography. A posterior vein was present in all patients, and an average of 1.5 vein

was detected in lateral positions (Delarche et al. 2007). However, no detailed information on individual CS anatomy was presented

Accordingly, our study is the first one with a consecutive intraoperative evaluation of the sinus coronarius tributaries using a retrograde occlusive angiography of the sinus coronarius.

Implantation of a left ventricular lead through the coronary sinus.

In our series, CRT implantation was successfully accomplished in 92% of patients, a similar success as reported in randomized trials (Abraham et al. 2002; Linde et al. 2002, Bristow et al. 2004). The left ventricular electrodes could be implanted in the optimally selected (Butter et al. 2001, Rossillo et al. 2004) target veins in 71% of our patients (with an additional 19% and 3% in the second and third target veins). A posterior or lateral electrode position could be reached in 78 % which is comparable to the earlier studies (Linde et al. 2002, Macias et al. 2007). Most likely due to the continuous improvement of implantation tools, and due to our combined approach using electrophysiologic catheters and angiography during cannulation, the inability for the CS cannulation was only 2.6% of patients which is a lower failure rate than that of 5.5% reported previously (Macias et al. 2007, Giudici et al. 2002, Meisel et al. 2001). Macias et al. (2007) have found that the presence of permanent atrial fibrillation and a dilated left atrium were independent predictors of an implantation failure. The prevalence of a previous cardiac surgery was significantly higher in the patients with a failed implant (26%) compared to the patients with a successful implantation (6%). The rate of an unsuccessful implantation in their study was 12.5 % compared to our cohort with 8%. We did not find a difference in the implantation success according to permanent atrial fibrillation or previous heart surgery.

There is insufficient data in the literature concerning two important steps of LV lead placement, namely the frequency at which a target vein can actually be reached and the rate at which the successfully reached target vein has to be abandoned for lead-related difficulties. In the present study, the predefined target vein could be reached in 84-100% of attempts without significant differences between different CS side branch areas. However, in 21% of cases we had to reposition the electrode within the same vessel, and more importantly, the selected vein could not be used for electrode implantation in another 21% of patients, The main limits of implantation of a lead in the targeted vein

were: unsuccessful positioning the lead in 12 cases; lead instability in 8 cases; high stimulation threshold in 7 cases, phrenicus stimulation in 3 cases.

These considerations are pertinent to contemporary CRT therapy even in the light of new techniques and materials which have been proposed to facilitate LV lead positioning (Meade et al. 2005, Chierchia et al. 2005, Gallagher et al. 2007). Using special selective catheters and guidewires for a vein with a difficult takeoff is often helpful. Two more easily available techniques should be mentioned at this point. For implantation in an acute takeoff vein Meade et al. (2005) used an inflated balloon catheter just distally to the vein. An angioplasty wire could be advanced into the vein with an acute angle of takeoff this way. After that the balloon catheter could be removed, and an over-the-wire lead could be placed in the vein. The other technique was promoted by Chierchia et al. (2005). A second, stiffer larger guidewire can be introduced in the sharply angulated vein, that „opens the vein“, and providing more support for the introduction of the over the wire lead over the first wire. A new investigational technique uses electromagnetic field to pull the magnetic guidewire into the targeted side branch, and to track the OTW lead in the vein. This technique is promising for sharply angulated takeoffs or highly tortuous veins, but actually the technical background and the costs do not let using this technique in the everyday practice (Gallagher et al 2007). In our practice we used special preshaped catheters or in some cases steerable guiding catheters within the coronary sinus.

The second problem was the lead instability. One solution is the use of commercial available active fixation coronary sinus leads. If this is not available, the following methods could be considered. In a report a stiff stylet was inserted in the lead after reaching the desired position with OTW technique. The end of the stylet was cut off, and the lead was fixated. No pericardial effusion, lead dislocation, insulation defect or threshold rise was observed during the one year follow-up of the 35 patients (Sharifkazemi et al. 2007). De Cock et al (2004) described a retained guidewire technique to anchor the leads after dislocations. They used guidewires with polymer coating to prevent electrical interference. The wire was advanced into a distal branch and was coiled up with rotations to anchor it. The wire was left within the electrode as described before (De Cock et al. 2004). Further possibility is to implant a stent 5-15 mm proximal to the tip of the electrode with 6-14 atmosphere pressure. During a one year

follow-up no dislocation or clinically important threshold rise has been observed. (Szilagyi et al. 2007). During the implantations we used only the commercially available active fixations leads, as the previously mentioned were not widely accepted without clear long term data. Whether these approaches for active LV lead fixation will enhance implantation success, remains to be seen.

Phrenic nerve stimulation was the most frequent cause for repositioning the lead within the same vein, in the posterior vein in up to 17 % of the cases. The repositioning was in most of the cases sufficient for lead implantation. In only 3 (3% of the veins) cases did we have to leave the side branch because of this problem. In a previous report the most frequent intraoperative problem was the phrenic nerve stimulation (16/121 pts, Hansky et al. 2002), which could be solved with repositioning the lead partially in the same vein or selecting another vein for implantation.

Finally, we demonstrated that – as expected – successful LV lead implantation in the CS side branch of first choice was associated with significant lower procedure and fluoroscopy times compared to cases in which several veins had to be tested.

Alternative left ventricular implantation methods.

In cases of implantation failure of a LV lead via the coronary sinus, surgical epicardial lead implantation via minimally invasive alternatives can be attempted (Navia et al. 2005, Doll et al. 2005). Some observational studies report from the early period of CRT implantation (1997-2003) that a transvenous implantation of the LV lead could lead to more adverse events and higher LV stimulation threshold through a follow-up of two years compared to the surgical implantation (Mair et al. 2005). Another study with CRT implantations between 1998 and 2001 showed similar one year data in the lead performance, and a higher prevalence of a heart failure exacerbation (48% vs 3%) after a thoracotomic approach (Daoud et al. 2002). The implantation of the LV lead through the coronary sinus lead to shorter hospitalization, with higher rate of lead revisions during the following year (12% vs 4%) compared to the thoracotomic group. The lead positions were more posterior, and the response to the CRT therapy was higher in the patients with transvenous implantation (Koos et al. 2004). The surgical methods are tending into the minimal invasive surgery, using a limited thoracotomy approach, with the difficulties of a posterior lead positioning (Koos). Video assisted thoracoscopy does not eliminate the general anesthesia but gives the possibility to a posterior lead placement

and leads to shorter hospital stays (Lattouf et al. 2003). Robot-enhanced thoracoscopy implantations were also reported, with the possibility to use steroid eluting leads, which was not the case during video assisted thoracotomy (Kleine et al 2002). Another alternative approach was reported using endocardial LV stimulation (Leclercq et al. 1999, Jais et al. 1998, Garrigue et al. 2001) after an atrial transseptal puncture in a small number of patients with the consecutive need of continuous anticoagulation. Actually – because the need for general anesthesia, an increased risk and hospital stay – the surgical approach is mainly remains as a second choice after an unsuccessful transvenous implantation.

Response to CRT

Although the main focus of our study was not the response to CRT, some important observations emerged from it. There were no differences in clinical response rates whether the LV lead was implanted in the first or second choice CS side branch. Response rates were similar for marginal, posterior or anterior positions of the LV electrode (Table 8). Previous studies reported that LV stimulation from the anterior veins was less beneficial compared to the stimulation from the free wall (Butter et al. 2001) or from the lateral (marginal) and posterolateral CS branches (Rossillo et al. 2004). In our patients, in whom we could not reach a marginal or a posterior CS-SB, we tried to reach the anterolateral side branches of the anterior interventricular vein and placed the electrode in the basal or in the middle third on the basal – apical axis. We believe that this may account for the similarly successful outcome in these patients. These are overall results, but optimal LV lead positions may vary from one patient to another, an issue that was not addressed by the study protocol. The presence of a posterolateral extended scar tissue (determined with MRI) may counteracts with the effect of the CRT therapy (Bleeker et al. 2006), despite the similar dyssynchrony echo-criteria prior to implantation. Three studies have demonstrated (Suffoletto et al 2006, Murphy et al. 2006, Becker et al. 2007), that the patients with a match between the LV pacing lead and the site of the latest mechanical activation on echocardiography showed the most benefit (largest reduction in the left ventricular volumes and increase in LVEF) from CRT compared to the patients with a mismatch. Should one plan the left ventricular lead implantation to the site of the latest mechanical activation before implanting, he should have information on the venous anatomy of the specific patient as

well, for example using multi-slice CT or EBCT. Whether the use of these new techniques may help to increase clinical CRT response rate by choosing optimally located veins remains to be seen. It is conceivable that the findings of the present study may be helpful in implementing new techniques in clinical practice.

Feasibility and safety of CRT upgrade procedures.

There are only sparse data comparing success rates, implantation/fluoroscopy time, and complications in de novo CRT implantations to CRT upgrade procedures. In recent controlled clinical studies, CRT de novo implantation was generally successful in approximately 90-95% of patients (Cleland et al. 2005, Bristow et al. 2004, Doshi et al. 2005, McAlister et al. 2004). In contrast, a study in 56 patients with CRT upgrade procedures reported implantation success in only 82 % of attempts (Leclercq et al. 2007). Almost all other studies on CRT upgrade procedures were retrospective in nature and included only patients with successful implantation or did not report success or failure rates (Leon et al. 2002, Howich et al. 2004, Witte et al. 2006, Eldadah et al. 2006, Valls-Bertault et al. 2004, Marai et al. 2006). Of note, there is no prospective observational comparison regarding success in upgrade versus de novo implantations. Our study demonstrates that CRT upgrade can be achieved with similar success as de novo implantations. Problems such as a more difficult access to the coronary sinus from the right side, passage of preexistent chronically implanted leads which may have grown into the venous wall or may obstruct the subclavian or caval veins, or may be attached to the tricuspid valve prohibiting cannulation of the coronary sinus ostium, should be anticipated in upgrade procedures (Haghjoo et al. 2007). It may therefore be prudent to perform an angiography of the subclavian vein before planning an upgrade procedure to CRT, especially in patients having already multiple transvenous leads, to exclude a complete obstruction of the subclavian or brachiocephalic veins (Haghjoo et al. 2007). Our study also indicates that implantation and fluoroscopy times are similar in upgrade compared to new implantations. Finally, there were no significant differences in CRT related complications in both patient groups. Of note, serious complications such as cardiac tamponade (reported in 0.5 – 1 % in COMPANION (Bristow et al. 2004) and the Italian InSync Registry (Gasparini et al. 2006), infection and explantation (1.3 % in MIRACLE (Abraham et al. 2002), 1 % in CARE-HF (Cleland et al. 2005)), or peri-procedural mortality (0.8 % in COMPANION (Bristow et al. 2004)) were not observed

in our patients. A dissection between the wall of the vena cava superior and ingrown old ICD leads occurred in a patient undergoing CRT upgrade but remained without clinical sequelae, and did not prevent continuation of the procedure and successful CRT implantation.

Previous studies on upgrading PM / ICD systems to CRT.

There are only a few studies which have examined procedural aspects and clinical outcome in patients with preexisting right ventricular pacemaker or ICD undergoing upgrade to CRT (Leon et al. 2002, Witte et al. 2006, Marai et al. 2006, Baker et al. 2002). In one of these previous studies, a highly selected small group of 20 patients after AV nodal ablation and chronic heart failure was studied (Leon et al. 2002). Results from these observations can not be generalized to heart failure patients with intact AV node conduction and / or undergoing ICD implantation.

From the remaining 3 studies, one was retrospective in nature (Witte et al. 2006) and comprised 32 patients with upgrade procedures and 39 with de novo CRT implantations. Only one follow up visit at 3 month was evaluated, at which time similar improvements in LV function and symptoms were found for both patient groups (Witte et al. 2006). From the other two studies, one did not include a control group, and was therefore purely descriptive in nature (Garparini et al. 2006). Marai et al compared 25 patients with upgrade procedure to 73 patients with de novo CRT implantations (Marai et al. 2006). They reported similar changes in echocardiographic parameters, NYHA functional status, and 6 minute walking test. However, in this study no established response criteria to CRT had been prospectively applied; thus, individual response rates are lacking for both patient groups.

Accordingly, our prospective observational study not only confirms these previous observations but extends those findings. In essence, our patients undergoing upgrade procedures responded in 59% of cases compared to 66% in our de novo CRT patients, the difference being not significant. All patients received optimized pharmacological heart failure treatment according to contemporary guidelines.

During the 6 months follow up, 6 of the 79 patients died (7.6%). According to the mortality figures for the CRT patients reported in the Care-HF (Cleland et al. 2005) and Companion (Bristow et al. 2004) studies one would predict a one year all cause

mortality rate in our patient cohort of approximately 10-12%. Accordingly, the observed mortality rate in our study is within expected ranges.

Clinical implications

Our observations indicate similar benefits of device therapy in elderly and in younger ICD recipients. However, given the retrospective nature of our study it is not possible to state this with certainty. Only a randomized prospective trial on effectiveness and safety of ICD therapy in the elderly could properly answer this question particularly with the expanding ICD indications and associated costs in aging populations.

Results from our prospective study on CRT implantation suggest that CRT upgrade procedures may be more complex in some patients than CRT de novo implantations but are not associated with a higher incidence of complications. Importantly, clinical response to CRT in patients undergoing upgrade procedures is as good as in patients with de novo CRT implantations. Accordingly, patient selection for upgrading should be the same as for conventional new CRT implantation.

Our study delivers important information for the implanters, who plan to implant the left ventricular lead in a pre-specified vein. We have shown, that the positioning the leads in a targeted vein could be performed with 92 % success rate, and a definite lead implantation in a preselected location could be done with a 70% success rate. The main limiting factors are: 1.) unsuccessful positioning the lead in the desired position; 2.) lead instability; 3.) high stimulation threshold; and 4.) phrenicus stimulation. Results from the present study suggests that the further development of the implanting tools or introducing new methods for lead implantation or stabilization could further improve the effect of the CRT, making the optimal lead positioning increasingly available. The subjective response of the patients may be comparable independent from the successful lead implantation in the first target vein.

We presented a new lead failure mechanism, possibly caused by the mechanical stress of the tricuspid leaflet motions. This mechanism – leading to a disintegration of a lead - may mainly affect the leads with a multilumen design. Describing this lead defect mechanism delivers new information for the lead developers.

Conclusions

- Our retrospective observations indicate no significant difference in overall mortality in ICD recipients with an age < 70 years or ≥ 70 years.
- There was no difference in time from device implantation to first adequate ICD therapy and time from first appropriate ICD therapy to death among the two groups (p=ns). Device associated complications were comparable in both groups.
- In 70 % of pts with heart failure undergoing CRT device implantation, at least 3 suitable CS side branches are available.
- Implant success of the CS-SB of 1st choice is 71% without significant differences for any particular CS-SB region. Lead implantation in an alternative CS-SB results in significantly longer implantation and fluoroscopy times.
- The response rate is not dependent on the successful implantation of the LV lead in the first target vein.
- Implantation of a CRT system in patients with preexisting right ventricular systems can be more difficult - mainly because of a chronic occlusion or stenosis of the vena subclavia.
- The implantation success of a CRT system is similar in patients with and without preexisting right ventricular systems.
- The procedure time, X-ray- time, and X-ray doses are not significantly higher in CRT- upgrade procedures.
- The criteria for response at 6 month were equally met in patient with de novo CRT implantation and in patients with pre-existing RV systems.
- We presented a new possible lead failure mechanism, possibly caused by the mechanical stress of the tricuspid leaflet motions.

Summary

Implantable cardioverter-defibrillator (ICD) therapy has been shown to improve survival in patients with structural heart disease and at high risk for life threatening ventricular arrhythmias. Whether elderly patients benefit from device therapy in a similar way as younger patients is largely unknown. In a retrospectively analysis of 375 consecutive ICD recipients with structural heart disease with a mean follow-up of 26.5 ± 18.1 months, no significant difference in overall mortality was observed in patients with an age < 70 years or ≥ 70 years. Moreover there was no difference in time from device implantation to first adequate ICD therapy and time from first appropriate ICD therapy to death among the two groups ($p=ns$). Device associated complications were comparable in both groups.

Cardiac resynchronization therapy is indicated in patients with heart failure and bundle branch block. It is less clear whether this includes patients with pre-existing right ventricular pacemaker/defibrillator systems, particularly with respect to implantation success and clinical benefit. In consecutive patients scheduled for CRT, we prospectively compared implantation success, procedural parameters, and clinical response in “de novo” (61 pts) versus upgrade (18 pts) procedures of previously implanted right ventricular systems. Implant success (92 versus 94%, $p=1.00$), procedure duration (153 ± 43 versus 164 ± 65 min, $p=0.51$), fluoroscopy time (25 ± 18 versus 32 ± 22 min, $p=0.18$) or dose (40 ± 31 versus 52 ± 49 Gy/cm², $p=0.35$) and response rate (66 % versus 59 %, $p=0.5$) were comparable for both groups.

There is only sparse data concerning anatomical specifications of coronary side branch (CS-SB) anatomy and its relationship to LV lead implantation for cardiac resynchronization therapy (CRT) in patients undergoing CRT device implantation.

An implantation of a CRT defibrillator was attempted in 79 consecutive pts. A selective CS-SB venography (77 pts) showed at least 1 CS-SB suitable for LV lead implantation in over 70% of the patients. The LV lead was successfully implanted in the 1st choice CS-SB in 71% of pts, in the 2nd choice in 21%, in the 3rd choice in 3%. In 4 pts (5%) no LV lead could be implanted. Implant success was similar for the different CS-SB regions (anterior interventricular, left marginal, posterior interventricular vein and posterior vein of the left ventricle). Successful LV lead implantation in the CS-SB of 1st

choice was associated with lower fluoroscopy and procedure time compared to patients with implantation in the CS-SB of ≥ 2 nd choice (20 ± 13 vs. 38 ± 21 min, and 143 ± 41 vs. 179 ± 47 min respectively). In 13% of the pts the 1st choice CS-SB was not accessible, the electrode position in the 1st choice CS-SB had to be abandoned in 16% of the cases with a reached 1st choice electrode position.

Bibliography

1. Abbara S, Cury RC, Nieman K, Reddy V, Moselewski F, Schmidt S, Ferencik M, Hoffmann U, Brady TJ, Achenbach S: Noninvasive evaluation of cardiac veins with 16-MDCT angiography. *Am J Roentgenol* 2005; 185:1001–6.
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE Study Group: Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346:1845-53
3. Abraham WT, Young JB, León AR, Adler S, Bank AJ, Hall SA, Lieberman R, Liem LB, O'Connell JB, Schroeder JS, Wheelan KR; Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;110:2864-8.
4. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Böcker D, Block M, Kirkels JH, Kramer A, Huvelle E; Pacing Therapies in Congestive Heart Failure II Study Group; Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003;42:2109-16.
5. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schöndube F, Wolfhard Longterm clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay (PATH CHF Trial). *J Am Coll Cardiol* 2002; 39:2026-33.
6. Baker CM, Christopher TJ, Smith PF, Langberg JJ, Delurgio DB, Leon AR. Addition of a Left Ventricular Lead to Conventional Pacing Systems in Patients with Congestive Heart Failure: Feasibility, Safety, and Early Results in 60 Consecutive Patients. *Pacing Clin Electrophysiol* 2002; 25: 1166–1171
7. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Andersen J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-

- ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352: 225-237
8. Bax JJ, Marwick TH, Molhoek SG, Bleeker GB, van Erven L, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: Left Ventricular Dyssynchrony Predicts Benefit of Cardiac Resynchronization Therapy in Patients With End-Stage Heart Failure Before Pacemaker Implantation. *Am J Cardiol* 2003; 92:1238–40
 9. Becker M, Kramann R, Franke A, Breithardt OA, Heussen N, Knackstedt C, Stellbrink C, Schauerte P, Kelm M, Hoffman R. Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography. *Eur Heart J* 2007; 28:1211–1220.
 10. Bleeker GB, Kaandorp TA and Lamb HJ, Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy, *Circulation* 2006; 113: 926–928.
 11. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004; 350:2140-50
 12. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, Spinelli J; Pacing Therapy for Chronic Heart Failure II Study Group: Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001; 104:3026–9
 13. Buxton AE, Lee KL, Fischer JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Eng J Med* 1999;341:1882-1890.
 14. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. *Lancet* 1997; 349: 675 – 682.

15. Camm AJ, Pratt CM, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ, Karam R, Sonnenblick EH, Brum JM; Azimilide post Infarct survival Evaluation (ALIVE) Investigators. Mortality in patients after a recent myocardial infarction: A randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004; 109: 990 – 996.
16. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay (MUSTIC SR). *N Engl J Med* 2001; 344:873-80.
17. Chierchia GB, Geelen P, Rivero-Ayerza M, Brugada P: Double wire technique to catheterize sharply angulated coronary sinus branches in cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2005; 28:168-170.
18. Chiu JH, Abdelhadi RH, Chung MK, Gurm HS, Marrouche NF, Saliba WI, Natale A, Martin DO. Effect of statin therapy on risk of ventricular arrhythmia among patients with coronary artery disease and an implantable cardioverter-defibrillator. *Am J Cardiol* 2005; 95: 490 – 491.
19. Christiaens L, Ardilouze P, Ragot S, Mergy S, Allal J: Prospective evaluation of the anatomy of the coronary venous system using multidetector row computed tomography. *Int J Cardiol.* 2007 May 8; [Epub ahead of print]
20. CIBIS-II investigators and Committee. The Cardiac Insufficiency Bisoprolol study II (CIBIC II): A randomised trial. *Lancet* 1999; 353: 9–13.
21. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators: The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005; 352:1539-49.
22. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CARDiac RESynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006; 27:1928-32
23. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian Implantable Defibrillator Study

- (CIDS): A Randomized Trial of the Implantable Cardioverter Defibrillator Against Amiodarone. *Circulation*, Mar 2000; 101: 1297 - 1302.
24. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. *Eur Heart J* 2000; 21:2071–2078.
 25. Daoud EG, Kalbfleisch SJ, Hummel JD, Weiss R, Augustini RS, Duff SB, Polsinelli G, Castor J, Meta T. Implantation techniques and chronic lead parameters of biventricular pacing dual-chamber defibrillators. *J Cardiovasc Electrophysiol*. 2002; 13:964-70.
 26. De Cock CC, Jessurun ER, Allaart CA, Visser CA: Repetitive intraoperative dislocation during transvenous left ventricular lead implantation: Usefulness of the retained guidewire technique. *Pacing Clin Electrophysiol* 2004; 27:1589-93.
 27. De Sutter J, Tavernier R, De Buyzere M, Jordaens L, De Backer G. Lipid lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. *J Am Coll Cardiol* 2000; 36: 773– 775.
 28. Delarche N, Bader H, Lasserre R, Derval N, Debeugny S, Denard M, Estrade G: Importance of anterograde visualization of the coronary venous network by selective left coronary angiography prior to resynchronization. *Pacing Clin Electrophysiol*. 2007; 30:70-6.
 29. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy. A meta-analysis of randomized controlled trials. *JAMA* 2004; 292:2874–2879.
 30. Doll N, Opfermann UT, Rastan AJ, Walther T, Bernau H, Gummert JF, Mohr FW: Facilitated minimally invasive left ventricular epicardial lead placement. *Ann Thorac Surg*. 2005; 79:1023-5
 31. Domanski MJ, Exner DV, Borkow CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction: A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1999; 33: 598 – 604.

32. Dorian P, Connolly S, Hohnloser SH. Why don't ICDs decrease all-cause mortality after MI? Insights from the DINAMIT study [abstract]. *Circulation* 2004; 110(Suppl III):502.
33. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA; PAVE Study Group. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005; 16(11): 1160-5
34. Eldadah ZA, Rosen B, Hay I, Edvardsen T, Jayam V, Dickfeld T, Meininger GR, Judge DP, Hare J, Lima JB, Calkins H, Berger RD. The benefit of upgrading chronically right ventricle-paced heart failure patients to resynchronization therapy demonstrated by strain rate imaging. *Heart Rhythm* 2006; 3(4): 435-42.
35. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation*. 2008; 117: e350-408.
36. Ezekowitz JA, Rowe BH, Dryden DM, Hooton N, Vandermeer B, Spooner C, McAlister, FA. Systematic review: implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Ann Intern Med*. 2007; 147:251-62.

37. Ferrick KJ. Antiarrhythmic therapy in elderly persons: a device-based approach. *Am J Geriatr Cardiol* 2005;14:10-15
38. Gallagher P, Martin L, Angel L, Tomassoni G: Initial clinical experience with cardiac resynchronization therapy utilizing a magnetic navigation system. *J Cardiovasc Electrophysiol.* 2007;18:174-80.
39. Garrigue S, Jaïs P, Espil G, Labeque JN, Hocini M, Shah DC, Haïssaguerre M, Clementy J: Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure, *Am. J. Cardiol.* 2001, 88: 858–862
40. Gasparini M, Lunati M, Santini M, Tritto M, Curnis A, Bocchiardo M, Vincenti A, Pistis G, Valsecchi S, Denaro A; INSYNC/INSYNC ICD ITALIAN Registry Investigators. Long-term survival in patients treated with cardiac resynchronization therapy: a 3-year follow-up study from the InSync/InSync ICD Italian Registry. *Pacing Clin Electrophysiol* 2006; 29 Suppl 2: S2-10.
41. Gillis AM. Prophylactic implantable cardioverter-defibrillators after myocardial infarction: not for everyone. *N Engl J Med* 2004; 351:2540–2542.
42. Giudici M, Winston S, Kappler J, Shinn T, Singer I, Scheiner A, Berrier H, Herner M, Sample R: Mapping the coronary sinus and great cardiac vein. *Pacing Clin Electrophysiol.* 2002; 25:414-9.
43. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998; 339: 489 – 497.
44. Gradaus R, Breithardt G, Böcker D. ICD leads: design and chronic dysfunctions. *Pacing Clin Electrophysiol.* 2003; 26:649-57.
45. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RI, Antman EM, Alpert JS, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC Jr, American College of Cardiology/American Heart Association Task Force on Practice Guidelines American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology Committee: ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. A report of the

- American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Cardiovasc Electrophysiol*. 2002; 11:1183-99.
46. Grönefeld G, Thorpe KE, Connolly SJ, Hohnloser SH. Competing risks for arrhythmic versus non-arrhythmic death in prophylactic ICD therapy early after myocardial infarction [abstract]. *Circulation* 2004; 110(Suppl. III):502.
 47. Haghjoo M, Nikoo MH, Fazelifar AF, Alizadeh A, Emkanjoo Z, Sadr-Ameli MA. Predictors of venous obstruction following pacemaker or implantable cardioverter-defibrillator implantation: a contrast venographic study on 100 patients admitted for generator change, lead revision, or device upgrade. *Europace* 2007; 9: 328-32.
 48. Hansky B, Vogt J, Gueldner H, Lamp B, Tenderich G, Krater L, Heintze J, Minami K, Horstkotte D, Koerfer R: Left heart pacing—experience with several types of coronary vein leads. *J Interv Card Electrophysiol* 2002; 6:71–75.
 49. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003; 42:1454-9.
 50. Hlatky MA, Saynina O, McDonald KM, Garber AM, McClellan MB. Utilization and outcomes of the implantable cardioverter defibrillator, 1978 to 1995. *Am Heart J* 2002;144:397-403
 51. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Randomized trial of prophylactic implantable cardioverter defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-2488
 52. Horwich T, Foster E, De Marco T, Tseng Z, Saxon L. Effects of resynchronization therapy on cardiac function in pacemaker patients "upgraded" to biventricular devices. *J Cardiovasc Electrophysiol* 2004; 15(11): 1284-9.
 53. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B: American College of Cardiology; American Heart

- Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society: ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005; 112:e154-235.
54. Jaïs P, Douard H, Shah DC, Barold S, Barat JL, Clémenty J. Endocardial biventricular pacing, *Pacing Clin. Electrophysiol*. 1998; 21: 2128–2131
 55. Jongbloed M, Lamb H, Bax J, Schuijf J, de Roos A, van der Wall E, Schalij M: Noninvasive visualization of the cardiac venous system using multislice computed tomography. *J Am Coll Cardiol* 2005; 45:749–753.
 56. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, Simon P. Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997; 349: 667 – 674.
 57. Kadish A. Prophylactic defibrillator implantation: toward an evidence-based approach. *N Engl J Med* 2005; 352:285–287.
 58. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
 59. Karaca M, Bilge O, Dinckal MH, Ucerler H: The anatomic barriers in the coronary sinus: implications for clinical procedures. *J Interv Card Electrophysiol*. 2005;14:89-94.
 60. Kindermann M, Hennen B, Jung J, Geisel J, Böhm M, Fröhlig G. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol* 2006; 47:1927-37.
 61. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in

- implantable cardioverter-defibrillators over a period of >10 years. *Circulation*. 2007;115:2474-80.
62. Kleine P, Grönefeld G, Dogan S, Hohnloser SH, Moritz A, Wimmer-Greinecker G. Robotically enhanced placement of left ventricular epicardial electrodes during implantation of a biventricular implantable cardioverter defibrillator system, *Pacing Clin Electrophysiol*. 2002; 25: 989-91.
 63. Koos R, Sinha AM, Markus K, Breithardt OA, Mischke K, Zarse M, Schmid M, Autschbach R, Hanrath P, Stellbrink C. Comparison of left ventricular lead placement via the coronary venous approach versus lateral thoracotomy in patients receiving cardiac resynchronization therapy, *Am. J. Cardiol*. 2004; 94: 59–63.
 64. Kuck KH, Cappato R, Siebels J, Ruppel R, for the CASH Investigators. A randomized comparison of antiarrhythmic drug therapy with implantable defibrillators resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000 ;102:748-754
 65. Lattouf O, Thourani V, Leon A. Minimizing ionizing radiation: a new alternative method for minimally invasive surgical biventricular resynchronization, *J. Am. Coll. Cardiol*. 2003; 43: 1138 (abs).
 66. Leclercq C, Cazeau S, Lellouche D, Fossati F, Anselme F, Davy JM, Sadoul N, Klug D, Mollo L, Daubert JC. Upgrading from Single Chamber Right Ventricular to Biventricular Pacing in Permanently Paced Patients with Worsening Heart Failure: The RD-CHF Study. *Pacing Clin Electrophysiol* 2007; 30 Suppl 1: S23-30.
 67. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert JC. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation (MUSTIC AF). *Eur Heart J* 2002; 23:1780-7.
 68. Leclercq F, Hager FX, Macia JC, Mariottini CJ, Pasquié JL, Grolleau R. Left ventricular lead insertion using a modified transseptal catheterization technique: a totally endocardial approach for permanent biventricular pacing in end-stage heart failure. *Pacing Clin. Electrophysiol*. 1999; 22:1570–1575.
 69. Leon AR, Greenberg JM, Kanuru N, Baker CM, Mera FV, Smith AL, Langberg JJ, DeLurgio DB. Cardiac resynchronization in patients with congestive heart

- failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002; 39(8):1258-63.
70. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC: Long-term benefits of biventricular pacing in congestive heart failure: results from the Multisite Stimulation in Cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002; 40:111—118
 71. Macías A, García-Bolao I, Díaz-Infante E, Tolosana JM, Vidal B, Gavira JJ, Berruezo A, Brugada J, Mont L: Cardiac resynchronization therapy: predictive factors of unsuccessful left ventricular lead implant. *Eur Heart J*. 2007; 28:450-6.
 72. Mair H, Jansens JL, Lattouf OM, Reichart B, Dabritz S. Epicardial lead implantation techniques for biventricular pacing via left lateral mini-thoracotomy, video-assisted thoracoscopy, and robotic approach. *Heart Surg Forum*. 2003; 6:412-7.
 73. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70
 74. Mao S, Shinbane JS, Girsky MJ, Child J, Carson S, Oudiz RJ, Budoff MJ: Coronary venous imaging with electron beam computed tomographic angiography: three-dimensional mapping and relationship with coronary arteries. *Am Heart J* 2005; 150:315–22.
 75. Marai I, Gurevitz O, Carasso S, Nof E, Bar-Lev D, Luria D, Arbel Y, Freimark D, Feinberg MS, Eldar M, Glikson M. Improvement of congestive heart failure by upgrading of conventional to resynchronization pacemakers. *Pacing Clin Electrophysiol* 2006; 29(8): 880-4.
 76. McAlister FA, Ezekowitz JA; Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH. Cardiac Resynchronization Therapy for Patients With Left Ventricular Systolic Dysfunction. A Systematic Review *JAMA* 2007; 297:2502-2514
 77. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, Hartling L, Klassen T, Abraham W. Systematic Review: Cardiac Resynchronization in Patients with Symptomatic Heart Failure. *Ann Intern Med* 2004; 141: 381-390.

78. McMurray J, Køber L, Robertson M, Dargie H, Colucci W, Lopez-Sendon J, Remme W, Sharpe DN, Ford I. Antiarrhythmic effect of carvedilol after acute myocardial infarction: Results of the carvedilol post-infarct survival control in left ventricular dysfunction (CAPRICORN) trial. *J Am Coll Cardiol* 2005; 45: 525 – 530.
79. Meade TH, Lopez JA: Balloon occlusion technique to cannulate angulated and tortuous coronary sinus branches in cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2005; 28:1243-4.
80. Meisel E, Pfeiffer D, Engelmann L, Tebbenjohanns J, Schubert B, Hahn S, Fleck E, Butter C: Investigation of coronary venous anatomy by retrograde venography in patients with malignant ventricular tachycardia. *Circulation* 2001; 104:442–447.
81. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure. *Lancet* 1999; 353: 2001– 2007.
82. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980; 303:322–324.
83. Mischke K, Knackstedt C, Muhlenbruch G, Schimpf T, Neef P, Zarse M, Plisiene J, Stanzel S, Eickholt C, Fache K, Frechen D, Spuntrup E, Hanrath P, Kelm M, Schauerte P: Imaging of the coronary venous system: retrograde coronary sinus angiography versus venous phase coronary angiograms. *Int J Cardiol.* 2007;119:339-43.
84. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmias. *N Engl J Med* 1996;335:1933-40
85. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83

86. Murphy RT, Sigurdsson G, Mulamalla S, Agler JD, Popovic ZB, Starling RC, Wilkoff BL, Thomas JD, Grimm RA. Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy. *Am J Cardiol* 2006; 97:1615–1621.
87. Navia JL, Atik FA: Minimally invasive surgical alternatives for left ventricle epicardial lead implantation in heart failure patients. *Ann Thorac Surg.* 2005; 80:751-4.
88. Panotopoulos PT, Axtell K, Anderson AJ, Sra J, Blanck Z, Deshpande S, Biehl M, Keelan ET, Jazayeri MR, Akhtar M, Dhala A: Efficacy of the Implantable Cardioverter-Defibrillator in the Elderly. *J Am Coll Cardiol* 1997;29:556-60
89. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348: 1309– 1321.
90. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709 – 717.
91. Quan KJ, Lee JH, Costantini O, Konstantakos AK, Murrell HK, Carlson MD, Mackall JA, Biblo LA, Geha AS. Favorable results of implantable cardioverter-defibrillator implantation in patients older than 70 years. *Ann Thorac Surg.* 1997;64:1713-7
92. Rossillo A, Verma A, Saad EB, Corrado A, Gasparini G, Marrouche NF, Golshayan AR, McCurdy R, Bhargava M, Khaykin Y, Burkhardt JD, Martin DO, Wilkoff BL, Saliba WI, Schweikert RA, Raviele A, Natale A: Impact of coronary sinus lead position on biventricular pacing. *J Cardiovasc Electrophysiol* 2004;15:1120–5.
93. Sharifkazemi MB, Aslani A: Stabilization of the coronary sinus lead position with permanent stylet to prevent and treat dislocation. *Europace.* 2007; 10:875-7.
94. Sinha AM, Filzmaier K, Breithardt OA, Kunz D, Graf J, Markus KU, Hanrath P, Stellbrink C. Usefulness of brain natriuretic peptide release as a surrogate marker

- of the efficacy of long-term cardiac resynchronization therapy in patients with heart failure. *Am J Cardiol.* 2003 Mar 15;91(6):755-8.
95. Strickberger SA; Conti J; Daoud EG; Havranek E; Mehra MR; Piña IL; Young J: Patient Selection for Cardiac Resynchronization Therapy - From the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Heart Rhythm Society *Circulation.* 2005; 111:2146-2150
 96. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J III. Novel speckletracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006; 113:960–968.
 97. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ: Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: full text (Update 2005). *EHJ* doi:10.1093/eurheartj/ehi205
 98. Szilagyí S, Merkely B, Roka A, Zima E, Fulop G, Kutyifa V, Szucs G, Becker D, Apor A, Geller L: Stabilization of the coronary sinus electrode position with coronary stent implantation to prevent and treat dislocation. *J Cardiovasc Electrophysiol.* 2007;18:303-7
 99. Tada H, Kurosaki K, Naito S, Koyama K, Itoi K, Ito S, Ueda M, Shinbo G, Hoshizaki H, Nogami A, Oshima S, Taniguchi K: Three-dimensional visualization of the coronary venous system using multidetector row computed tomography. *Circ. J.* 2005; 69:165–70.
 100. Teo KK, Mitchell LB, Pogue J, Bosch J, Dagenais G, Yusuf S. Effect of ramipril in reducing sudden deaths and nonfatal cardiac arrests in high-risk individuals without heart failure and left ventricular dysfunction. *Circulation* 2004; 110: 1413– 1417.
 101. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in

- patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med.* 1997 Nov 27;337(22):1576-83.
102. The CAPRICORN investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: The CAPRICORN randomised trial. *Lancet* 2001; 357: 1385– 1390.
 103. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report of the effects of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; 321: 406– 412.
 104. The DAVID Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. *JAMA* 2002; 288:3115–3123.
 105. The Heart Outcomes Prevention Evaluation Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145–153.
 106. Tresch DD, Troup PJ, Thakur RK, Veseth-Rogers J, Tucker V, Wetherbee JN, Hoffmann RG, Chapmann PD. Comparison of efficacy of automatic implantable cardioverter defibrillator in patients older and younger than 65 years of age. *Am J Med* 1991; 90: 717-724.
 107. Valls-Bertault V., Fatemi M., Gilard M., Pennec P.Y., Etienne Y., Blanc J.J., Assessment of upgrading to biventricular pacing in patients with right ventricular pacing and congestive heart failure after atrioventricular junctional ablation for chronic atrial fibrillation. *Europace* 2004; 6: 438-443.
 108. Van de Veire NR, Schuijf JD, De Sutter J, Devos D, Bleeker GB, de Roos A, van der Wall EE, Schalij MJ, Bax JJ: Non-invasive visualization of the cardiac venous system in coronary artery disease patients using 64-slice computed tomography. *J Am Coll Cardiol.* 2006; 48:1832-8.
 109. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M; European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy: the task force for cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology.

- Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J*. 2007; 28: 2256-95.
110. von Ludinghausen M: The venous drainage of the human myocardium. *Adv Anat Embryol Cell Biol*. 2003;168:1-104.
 111. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; 348: 7–12.
 112. Weaver WD, Hill D, Fahrenbruch CE, Copass MK, Martin JS, Cobb LA. Use of automatic external defibrillator in the management of out-of-hospital cardiac arrest. *N Engl J Med* 1988; 319: 661– 666.
 113. Wilber DJ, Zareba W, Hall WJ, Brown MW, Lin AC, Andrews ML, Burke M, Moss AJ. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004; 109:1082–1084
 114. Witte KK, Pipes RR, Nanthakumar K, Parker JD. Biventricular pacemaker upgrade in previously paced heart failure patients--improvements in ventricular dyssynchrony. *J Card Fail* 2006;12(3):199-204.
 115. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003; 289:2685-94.
 116. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the

prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace*. 2006; 8:746-837.

Publications related to the PhD thesis

Duray GZ, Hohnloser SH, Israel CW. Coronary Sinus Side Branches for Cardiac Resynchronization Therapy: Prospective Evaluation of Availability, Implant Success, and Procedural Determinants .

J Cardiovasc Electrophysiol. 2008; 19:489-94.

Duray GZ, Israel CW, Pajitnev D, Hohnloser SH. Upgrading to biventricular pacing/defibrillation systems in right ventricular paced congestive heart failure patients: prospective assessment of procedural parameters and response rate.

Europace 2008 10:48-52.

Duray G, Richter S, Manegold J, Israel CW, Gronefeld G, Hohnloser SH. Efficacy and safety of ICD therapy in a population of elderly patients treated with optimal background medication.

J Interv Card Electrophysiol. 2005; 14:169-73.

Duray GZ, Israel CW, Schmitt J, Hohnloser SH. ICD Lead Disintegration at the Level of the Tricuspid Valve.

Heart Rhythm. 2008; 5:1224-5.

Duray G, Israel CW, Hohnloser SH. Recent primary prevention implantable cardioverter defibrillator trials.

Curr Opin Cardiol. 2006; 21: 15-9.

Richter S, **Duray G**, Gronefeld G, W Israel C, H Hohnloser S. Prevention of sudden cardiac death: lessons from recent controlled trials.

Circ J. 2005; 69: 625-9.

Publications unrelated to the PhD thesis.

Articles in peer reviewed international journals:

Original

Ehrlich JR, Wegener FT, Anneken L, **Duray G**, Israel CW, Hohnloser SH. Biventricular Pacing Does Not Affect Microvolt T-Wave Alternans In Heart Failure Patients. Heart Rhythm. 2008; 5:348-52.

Vereckei A, **Duray G**, Szénási G, Altemose GT, Miller JM. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. Heart Rhythm. 2008; 5:89-98.

Manegold JC, Israel CW, Ehrlich JR, **Duray G**, Pajitnev D, Wegener FT, Hohnloser SH External cardioversion of atrial fibrillation in patients with implanted pacemaker or cardioverter-defibrillator systems: a randomized comparison of monophasic and biphasic shock energy application. *European Heart Journal* 2007; 28:1731-1738;

Vereckei A, **Duray G**, Szenasi G, Altemose GT, Miller JM. Application of a new algorithm in the differential diagnosis of wide QRS complex tachycardia. *Eur Heart J.* 2007; 28:589-600.

Medvegy M, Savard P, Pinter A, Tremblay G, Nasmith JB, Palisaitis D, **Duray G**, Preda I, Nadeau RA. Simple, quantitative body surface potential map parameters in the diagnosis of remote Q wave and non-Q wave myocardial infarction. *Can J Cardiol.* 2004; 20: 1109-15.

Bohm A, Pinter A, **Duray G**, Lehoczky D, Dudas G, Tomcsanyi I, Preda I Complications due to abandoned noninfected pacemaker leads. *Pacing Clin Electrophysiol.* 2001; 24:1721-4.

Reviews

Hohnloser SH, **Duray GZ**, Baber U, Halperin JL. Prevention of stroke in patients with atrial fibrillation: current strategies and future directions *European Heart Journal Supplements* 2008 10: H4-H10

Wegener FT, Gronefeld GC, **Duray G**, Ehrlich JR, Hohnloser SH. Pharmacological therapy for ventricular arrhythmias: evidence for current treatment strategies and perspectives for the future Was kommt, was bleibt, was geht? [Pharmacological therapy for ventricular arrhythmias: evidence for current treatment strategies and perspectives for the future.] *Internist (Berl).* 2006; 47: 297-307. German.

Richter S, **Duray G**, Hohnloser SH How to analyze T-wave alternans. *Heart Rhythm.* 2005; 2:1268-71.

Medvegy M, **Duray G**, Pinter A, Preda I. Body surface potential mapping: historical background, present possibilities, diagnostic challenges. *Ann Noninvasive Electrocardiol.* 2002; 7:139-51.

Case reports

Duray GZ, Israel CW, Wegener FT, Hohnloser SH Tachycardia after pacemaker implantation in a patient with complete atrioventricular block. *Europace.* 2007;9: 900-3.

Richter S, **Duray G**, Israel CW, Groenefeld G, Hohnloser SH. Beat-to-beat cycle length variation during narrow QRS complex tachycardia: what is the mechanism? *Pacing Clin Electrophysiol.* 2005; 28:1317-9

Bohm A, Hajdu L, Pinter A, **Duray G**, Preda I. Runaway pacemaker syndrome and intermittent nonoutput as manifestations of end of life of a VVI pacemaker. *Pacing Clin Electrophysiol.* 2000; 23: 2143-4.

Articles in peer reviewed hungarian journals

Pintér A, Székely Á, Zámolyi K, **Duray G**, Borsányi T, Préda I: Radiofrequency Catheter Ablation of Tachycardia Involving Atypical Accessory Pathway, (in Hungarian) *Magy. Belorv. Arch.* 2000; 53: 201-208

Bőhm Á, Pintér A, Lehoczky D, **Duray G**, Dudás G, Préda I: Complications Assotiated with Non-functioning Pacemaker Electrodes (in Hungarian) *Orvostudományok LXXV.* 2000/1-2, p71-75

Pintér A, Zámolyi K, Székely Á, **Duray G**, Borsányi T, Préda I: Localisation of overt atrioventricular accessory pathways by the delta wave using standard 12-lead ECG (in Hungarian) *Cardiologia Hungarica* 2000;3: 149-154

Pintér A, Székely Á, **Duray G**, Zámolyi K, Borsányi T, Préda I: Case report of a patient with two accessory atrioventricular pathways (in Hungarian) *Cardiologia Hungarica* 2000;4: 267-268

Book chapters

Székely Á, **Duray G**. Supraventricular arrhythmias (in Hungarian: Szupraventrikuláris ritmuszavarok.) In: *A belgyógyászat alapjai I-II.* Ed: Tulassay Zsolt. Medicina Kiadó Zrt Budapest, 2006

Czuriga I, **Duray G**, Halmay L, Jánosi A, Lengyel M, Karlócai K, Préda I, Rudas L, Simon K. ST-elevációval járó akut myocardialis infarktus. *Kardiológiai Útmutató* 2003;II:35-52.

Medvegy M, **Duray G**, Préda I, Paksy A, Pintér A, Nadeau R, Savard P, Tremblay G, Palisaitis D: Relationship Between the Potential Loss and the Injury of the Non-Infarct Related Coronary Artery in Myocardial Infarction, in: *Electrocardiology '98 /Proceedings of the XXV International Congress on Electrocardiology/* ed.: I. Préda, World Scientific, Singapore-New Jersey-London-Hong Kong 1999 pp 123-126

Székely Á, Pintér A, Kayser S, **Duray G**, Préda I, Zámolyi K, Csanádi Z: Is It Easy To Localize Overt Kent Accessory Pathways by the Delta Wave? in: *Electrocardiology '98 /Proceedings of the XXV International Congress on Electrocardiology/* ed.: I. Préda, World Scientific, Singapore-New Jersey-London-Hong Kong 1999 pp 139-141

Medvegy M, Préda I, Nadeau RA, Savard P, Pintér A, Tremblay G, Nasmith T, Palisaitis D, **Duray G**: Relationship between the Response to Exercise test and the Extension of Potential Loss in Non Q Wave Myocardial Infarction in: *Electrocardiology '99 /Proceedings of the XXVI International Congress on Electrocardiology/* ed.:M.P. Roshchevsky, Institute of Physiology Syktyvkar 2000 pp 172-176

Préda I, Pintér A, Székely Á, **Duray G**, Zámolyi K: Unusual Manifestations Of Preexcitation in Patients with the Wolff-Parkinson-White Syndrome in: *Electrocardiology '99 /Proceedings of the XXVI International Congress on Electrocardiology/* ed.:M.P. Roshchevsky, Institute of Physiology Syktyvkar 2000 pp 177-179

Duray G, Medvegy M, Préda I: Repolarisation time intervals in ischemic Heart Disease in Acute Nitroglycerin Effect in: *Electrocardiology 2000 /Proceedings of the XXVII International Congress on Electrocardiology/* ed.:L. De Ambroggi, Casa Editrice Scientifica Internationals, Roma, 2000 pp 159-161

Vari, S.; **Duray, G.**; Preda, I.; Nagy, G.; Ungi, I. Integrated international and regional services for interventional cardiology Information Technology Applications in Biomedicine, 2000. Proceedings. 2000 IEEE EMBS International Conference on Volume , Issue , 2000 Page(s):152 - 152

Préda I, Medvegy M, **Duray G**: Clinical Value of Body Surface Potential Maps, New diagnostic Challenges in: *Electrocardiology 2001 /Proceedings of the XXVIII International Congress on Electrocardiology/* ed.:C. A Pastore, Atheneu, Sao Paulo, 2001 pp 21-27

Published Abstracts:

G. Duray, M. Medvegy, I. Préda, A. Paksy, A. Pintér, R. Nadeau, P. Savard, G. Tremblay, D. Palisaitis: Relationship between Body-Surface Mapping and Coronary Artery Status in Myocardial Infarction, *Cardiologica Hungarica Suppl 98/1*, p 26

Á. Székely, A. Pintér, **G. Duray**, I. Préda: AV Node Modification (Slow Pathway Ablation) in AV Nodal Reentry Tachycardia With Preexisting Chronic Bifascicular Block: A Case Report, *Cardiologica Hungarica Suppl 98/1*, p 68

G. Duray, M. Medvegy, I. Préda: The Effect of Nitroglycerin on the Repolarisation Time Intervals in Ischemic Heart Disease, *Cardiologica Hungarica Suppl 99/2*, p 15

M. Medvegy, I. Préda, R.A. Nadeau, P. Savard, A. Pintér, G. Tremblay, J.B. Nasmith, D. Palisaitis, **G. Duray**: Quantitative Body Surface Potential Mapping Parameters in Q and Non-Q Wave Myocardial Infarction, *Cardiologica Hungarica Suppl 99/2*, p 53

Á. Székely, A. Pintér, **G. Duray**, K. Zámolyi, I. Préda: Ablation of Left Free Wall Accessory Pathway From the Coronary Sinus, the Importance of Subepicardial Accessory Connections, *Cardiologica Hungarica Suppl 99/2*, p 47

K. Zámolyi, Á. Székely, A. Pintér, **G. Duray**, I. Préda: Causes of Failure in Radiofrequency Catheter Ablation, *Cardiologica Hungarica Suppl 99/2*, p 48

A. Pintér, K. Zámolyi, Á. Székely, **G. Duray**, I. Préda: Is It Easy To Localize Overt Kent Accessory Pathways by the Delta Wave? PACE, June 1999, Vol. 22. No.6. Part II, p A34

A. Pintér, **G. Duray**, Á. Böhm, Á. Székely: Antiarrhythmic Effect of Atrial Pacing (in hungarian), *Cardiologica Hungarica* 99/4, p 195

Á. Székely, K. Zámolyi, A. Pintér, **G. Duray**, T. Borsányi, I. Préda: Radiofrequency Ablation in Our Center in The Last Year (in hungarian), *Cardiologica Hungarica* 99/4, p 198

G. Duray, A. Pintér, T. Borsányi, Á. Székely, K. Zámolyi, I. Préda: Radiofrequency Catheter Ablation of Supraventricular Tachycardias by Patients over 65 Years (in hungarian), *Cardiologica Hungarica* 99/4, p 205

M Medvegy, **G. Duray**, A. Pintér, I. Préda: Evaluation of the Electrical Viability by Nitroglycerin-Test in Ischemic Heart Disease (Preliminary study), *Cardiovascular Drugs and Therapy* Vol 14, No 2, March 2000, p 195

M. Medvegy, I. Préda, R.A. Nadeau, P. Savard, A. Pintér, G. Tremblay, B. Nasmith, D. Palisaitis **G. Duray**: Comparison of Invasive and Non-Invasive Cardiologic Parameters In Non Q Wave Myocardial Infarction and Unstable Angina, *Cardiologica Hungarica Suppl.* 2000/3, p 3.

G. Duray, W. Kaltenbrunner, F. Freihoff, K. Steinbach, Á. Székely, M. Medvegy, I. Préda: Number of Distinct Ventricular Tachycardia Morphologies by Patients Underwent Catheter Ablation. *Cardiologica Hungarica Suppl.* 2000/3, p 26.

Á. Böhm, **G. Duray**, D. Lehoczky, G. Dudás, I. Préda: Factors Influencing Pacemaker Dependency, *Cardiologica Hungarica Suppl.* 2000/3, p 71.

T. Borsányi, **G. Duray**, A. Pintér, A. Szabó, Á. Székely, I. Préda: Radiofrequency Catheter Ablation of Ventricular Ectopy *Cardiologica Hungarica Suppl.* 2000/3, p 85.

I. Préda, M. Medvegy, P. Savard, A. Pintér, G. Tremblay, J.B. Nasmith, D. Palisaitis. R.A. Nadeau, **G. Duray**: Minor Potential Losses Detected by Body Surface Isopotential Maps in Unstable Coronary Artery Disease, *Medicina Interna de México*, Vol.16, Supp., 2000

G. Duray, W. Kaltenbrunner, F. Freihoff, K. Steinbach, I. Préda: The Influence of Segmental Wall Motility Disorder on the Number of Distinct Ventricular Tachycardia Morphologies by Patients Undergoing Catheter Ablation, *Europace*, July 2000. Vol I, Suppl D

Á. Böhm, A. Pintér, Á. Székely, G. Dudás, **G. Duray**, I. Préda: Is Atrial Pacing Preventive for Atrial Fibrillation? *Annals of Noninvasive Electrocardiology*, October 2000, Vol 5. No 4. Part 2 S8, No 31.

G. Duray, Á. Székely, T. Borsányi, A. Szabó, A. Pintér, I. Préda: Treatment of Bundle Branch Reentry tachycardia with radiofrequency catheter ablation, *Cardiologica Hungarica Suppl* 2001/2, p 18.

T. Bauernfeind, M. Medvegy, **G. Duray**, A. Pintér, T. Borsányi, I. Préda: Changes in the Left Atrial Potentials Following Nitroglycerin Administration in Ischemic Heart Disease *Cardiologica Hungarica Suppl* 2001/2, p 29.

M. Medvegy, T. Bauernfeind, **G. Duray**, A. Pintér, I. Préda: Investigation of the Electrical Viability of the Heart by Body Surface Potential Mapping (Preliminary Study) *Cardiologica Hungarica Suppl* 2001/2, p 47.

Á. Böhm, **G. Duray**, A. Pintér, D. Lehoczky, G. Dudás, I. Préda: Pacemaker Clinic Emergencies *Cardiologica Hungarica Suppl* 2001/2, p 70.

Á. Böhm, A. Pintér, **G. Duray**, I. Préda: Complications in Patients With Retained, Non-Infected Electrodes *Europace Supplements*. Vol.2. June 2001 B131

Á. Böhm, A. Pintér, **G. Duray**, G. Dudás, I. Préda: Incidence of Pacemaker Dependency *Europace Supplements*. Vol.2. June 2001 B142

Á. Böhm, **G. Duray**, A. Pintér, D. Lehoczky, G. Dudás, I. Préda: Incidence of emergency situations in the pacemaker clinic. *European Heart Journal* Vol.22, September 2001 Abstract Supplement P1077

Á. Böhm, A. Pintér, **G. Duray**, G. Dudás, I. Préda : Factors influencing pacemaker dependency. *European Heart Journal* Vol.22, September 2001 Abstract Supplement P2352

E. Marosi, **G. Duray**, T. Borsányi, A. Szabó, Á. Székely: Acute Ablation of AVNRT – a Case Report (in hungarian) *Cardiologica Hungarica* 2001/3, p 240

A. Szabó, Á. Székely, **G. Duray**, T. Borsányi, I. Préda: One-session RF Ablation of a Dual AV Nodal Pathway and a Kent-bundle in a PSVT with Cycle Length Alternans (in hungarian) *Cardiologica Hungarica* 2001/3, p 240

G. Duray, Á. Székely, B. Merkely: Sustained Fast Ventricular Tachycardia in a Patient with ICD – coincidence of Multiple Provocative Factors (in hungarian) *Cardiologica Hungarica* 2001/3, p 230

G. Duray, Á. Székely, T. Borsányi, A. Szabó, E. Marosi, I. Préda: Cases of patients treated with radiofrequency catheter ablation of AV nodal reentry tachycardia, who needed revascularisation *Cardiologica Hungarica Suppl* 2002/1, p 17.

Á. Székely, **G. Duray**, A. Szabó, T. Borsányi, E. Marosi, I. Préda: Characteristics of our elderly (>65 years) radiofrequency ablation patients (1996-2001) *Cardiologica Hungarica Suppl* 2002/1, p 17.

E. Szűcs, M. Medvegy, **G. Duray**, T. Bauernfeind, G. Somogyi, F. Molnár, L. Major, Gy. Bokori, RA Nadeu, I Préda: Prediction of the coronary artery status with body surface potential mapping in unstable coronary syndrome *Cardiologica Hungarica Suppl* 2002/1, p 38.

G. Duray, W. Kaltenbrunner, F. Freihoff, K. Steinbach, Á. Székely, I. Préda: The First Appearance and Return of Distinct Ventricular Tachycardia Morphologies by Patients Undergoing Catheter Ablation. *JACC* 2002;39 No 9 Suppl.B, 75B

M. Medvegy, **G. Duray**, J. Nasmith, RA Nadeau, A Pintér, T Bauernfeind, E Szűcs, I Préda: Minor Electrical Potential Losses can Provide Hemodynamic Information In Unstable Coronary Artery Disease *JACC* 2002;39 No 9 Suppl.B, 113B

T. Bauernfeind, M. Medvegy, **G. Duray**, A. Pintér, T. Borsányi, I. Préda: Relationship Between the Left Atrial Electric Activity and the Positivity of the Exercise Test *JACC* 2002;39 No 9 Suppl.B, 116B

M. Medvegy, **G. Duray**, T. Bauernfeind, E. Szűcs, A. Pintér, I. Préda: Electrical Viability - A New Term by Body Surface Potential Mapping (Preliminary study) *JACC* 2002;39 No 9 Suppl.B, 399B

M. Medvegy, **G. Duray**, J. Nasmith, RA Nadeau, A Pintér, T Bauernfeind, E Szűcs, I Préda: Left Ventricular Function in Unstable Coronary Artery Disease Depending on Minor Electrical Potential Losses *JACC* 2002;39 No 9 Suppl.B, 463B

G. Duray, Á. Székely, T. Borsányi, A. Szabó, E. Marosi, I. Préda: Patients underwent revascularisation and slow pathway ablation did not report typical angina by supraventricular tachycardia *International Journal of Bioelectromagnetism* 2002, Vol. 4, No. 2 pp. 293 – 294

Szűcs E, Medvegy M, **Duray G**, Bauernfeind T, Molnár F, Nadeau RA, I. Préda: Possible Prediction of Coronary Angiographic Results with the Use of the Series of Body Surface Potential Mapping *International Journal of Bioelectromagnetism* 2002, Vol. 4, No. 2 pp. 331 - 332

T. Bauernfeind, M. Medvegy, **G. Duray**, E. Szűcs, A. Pintér, T. Borsányi, Krisztina Szakolczay, I. Préda: Resting body surface maps combined with nitroglycerine test may predict elevated left atrial pressure due to exercise induced ischemia. *International Journal of Bioelectromagnetism* 2002, Vol. 4, No. 2 pp. 333 - 334

M. Medvegy, E. Szűcs, T. Bauernfeind, **G. Duray**, G. Simonyi, F. Molnár, L. Major, A. Paksy, K. Szakolczai, I. Préda: The Use of body surface potential mapping with nitroglycerin administration in patients with unstable coronary artery disease. *Cardiologica Hungarica Suppl* 2003/2, p 7.

G. Duray, W. Kaltenbrunner, F. Freihoff, K. Steinbach, Á. Székely, I. Préda: Significance of inducible ventricular tachycardias with morphologies differing from the clinical ventricular tachycardia. *Cardiologica Hungarica Suppl* 2003/2, p 33.

M. Medvegy, E. Szűcs, G. Simonyi, T. Bauernfeind, **G. Duray**, É. Patarcsics, B. Merkely, R. Kiss, J. Bedros, R. Nadeau, I. Préda: Electrocardiological assessment of the effectiveness of percutaneous coronary artery intervention. *Cardiologica Hungarica Suppl* 2004/C, p 17.

Israel CW, Pajitnev D, **Duray G**, Mangegold J, Richter S, Groenefeld GC, Hohnloser SH : Ventricular pacing causes atrial electrical remodeling: Evidence from serial electrophysiological testing *Circulation*, 2005; 112 Suppl S: U499

Vereckei A, **Duray G**, Altemose GT, Miller JM, Zipes DP: A new algorithm devised for the differential diagnosis of wide complex QRS tachycardia-final results. *Eur. Heart J.* 2005; 26 Suppl 1:679-679

Duray G, Böhm A, Pinter A, Preda I. Incidence of emergency situations in the pacemaker clinic. *Eur Heart J.* 2001; 22 Suppl S :184

Duray G, Pinter A, Dudas G, Preda I: Factors influencing pacemaker dependency. *Eur Heart J.* 2001; 22 Suppl S:445

Abstracts in abstract book / on abstract CD

M. Medvegy, I. Préda, A. Pintér, **G. Duray**, J. Bencze: Hemodynamic Importance of the Various Right Ventricular Conduction Defects, Abstract Book of the XXVII International Congress on Electrocardiology, Milan p 130

G. Duray, M. Medvegy, I. Préda: Repolarisation Time Intervals in Ischemic Heart Disease in Acute Nitroglycerin Effect, Abstract Book of the XXVII International Congress on Electrocardiology, Milan p 145

M. Medvegy, **G. Duray**, T. Bauernfeind, E. Szucs, A. Pinter, I. Preda: A New Term By Body Surface Potential Mapping - Electrical Viability
26th International Congress of Internal Medicine 2002 Abstract CD,: 2-PO-46

G. Duray, W. Kaltenbrunner, F. Freihoff, K. Steinbach, A. Szekely, I. Preda
New Distinct Ventricular Tachycardia Morphologies By Patients Undergoing Catheter Ablation
26th International Congress of Internal Medicine 2002 Abstract CD,: 2-PO-53

M. Medvegy, **G. Duray**, J. Nasmith, R.A. Nadeau, A. Pinter, T. Bauernfeind, E. Szucs, I. Preda
Hemodynamic Information Of The Electrical Potential Losses In Unstable Coronary Artery Disease
26th International Congress of Internal Medicine 2002 Abstract CD,: 2-PO-60

M. Medvegy, I. Preda, P. Savard, A. Pinter, G. Tremblay, J.B. Nasmith, D. Palisaitis, **G. Duray**, R.A. Nadeau

New Quantitative Electrical Parameters In The Diagnosis Of The Myocardial Infarction
26th International Congress of Internal Medicine 2002 Abstract CD,: 2-PO-63

T. Bauernfeind, M. Medvegy, **G. Duray**, A. Pinter, T. Borsanyi, I. Preda

Left Atrial Electric Activity As A Predictor Of The Exercise Test Positivity
26th International Congress of Internal Medicine 2002 Abstract CD,: 2-PO-64

M. Medvegy, **G. Duray**, J. Nasmith, R.A. Nadeau, T. Bauernfeind, E. Szucs, I. Preda
Electrical Potential Losses Can Predict Left Ventricular Function In Unstable Coronary
Artery Disease

26th International Congress of Internal Medicine 2002 Abstract CD,: 2-PO-65

Medvegy,M., F. Szűcs, G. Simonyi, T. Bauernfeind, **G. Duray**, K. Szakolczai., G. R. Kiss, J.R. Bedros, A. Nadeau and I. Preda(2004): The effect of percutaneous coronary artery intervention on body surface potential maps. The 31st International Congress on Electrocardiology, Kyoto, Japan, June 27- July 1, 2004. Book of Abstracts, p.200

Bauernfeind, T., I. Preda, E. Szűcs, **G. Duray**, G. Simonyi, K. Szakolczai, R.G. Kiss, R.J. Bedros and M. Medvegy: Assessment of The diastolic function by body surface potential maps in ischemic heart disease. The 31st International Congress on Electrocardiology, Kyoto, Japan, June 27- July 1, 2004. Book of Abstracts, p.201

Medvegy, M., Simonyi, G., Patarcsics, É., **Duray, G.**, Szűcs, E., Bauernfeind, T., Király, J., Müller, G., Bedros, J.R., Préda, I.: Az EKG-ból nyerhető új diagnosztikai információk. Belügyi Orvosi Napok 2004. nov. 18-20, Abstract book

Acknowledgements.

The patient cohort depicted in this study was treated at the Department of Cardiology, J.W.Goethe University, Frankfurt am Main. The study was completed in Budapest.

I would like to thank my supervisor Prof. István Préda for supporting my clinical and encouraging my scientific career. I am indebted to him for his supervision and suggestions.

I am grateful to Prof. Stefan Hohnloser (J.W.Goethe University, Frankfurt, Germany) for supporting me during the whole clinical project, for his guidance, expert criticism and for his friendship.

I would like to thank the support of all of my senior colleagues (Prof. Ádám Böhm, Dr. Ádám Székely, Dr. Péter Horányi, Dr. Mihály Medvegy, Dr. András Vereckei), who taught me how to find a balance between the every day clinical work and research.

I would like to thank all of my other colleagues in Hungary and in Germany not listed above, for supporting my daily work, making our research projects possible.

I am grateful to my parents and to my two sisters for encouraging and supporting me during my studies and for helping in the organization during the whole preparatory process.

And last but not least, I thank my children, Boglárka, Csilla and Boróka and my wife, Nóra for supporting my studies.