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

PhD Thesis Booklet

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Introduction

Sudden cardiac death (SCD) is one of the major cause 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 defibrillators 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. Unfortunately, there is a paucity of data about the efficacy of ICD therapy in elderly patients 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 prospective 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). 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 canulation 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 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 tachyarryhthmias 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 ≤ 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 ballon-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 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 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 (De Novo) and patients with a pre-existing right ventricular device undergoing upgrade to CRT (Upgrade). 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 our analysis.

Table 1: 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
Primary prevention	125 (33)	102 (37.4)	23 (22.5)	0.007 *
Coronary artery disease	315 (84)	222 (81.3)	93 (91.2)	0.026 *
LVEF (%)	32.8±11.4	33.2 ± 11.7	32.01 ± 10.4	ns
NYHA functional class – no. (%)				ns
I	134 (35.7)	99 (36.2)	35 (34.3)	
II	163 (43.5)	115 (42.1)	48 (47.1)	
III-IV	88 (23.5)	59 (21.6)	19 (18.6)	

means ± 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 1. 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 (77%), angiotensin converting enzyme inhibitors or AT1 receptor blockers (90%), and statins (67%).

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.

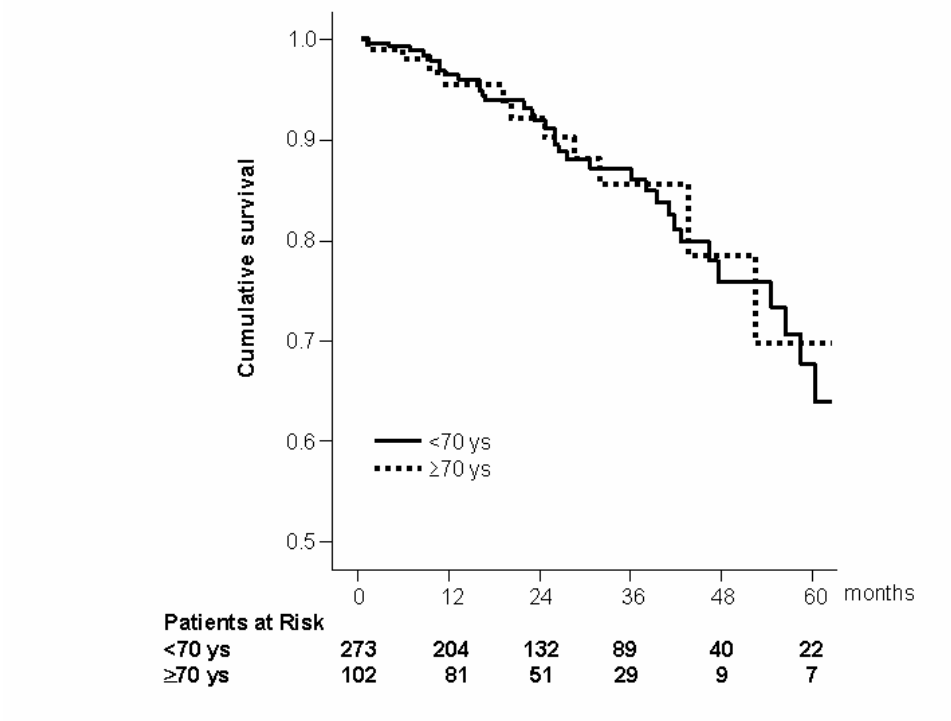

Figure 1 Cumulative survival curves after ICD implantation in patients younger and older than 70 years

Time from device implantation to first ICD therapy delivery on ventricular tahiarrhythmias. 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.

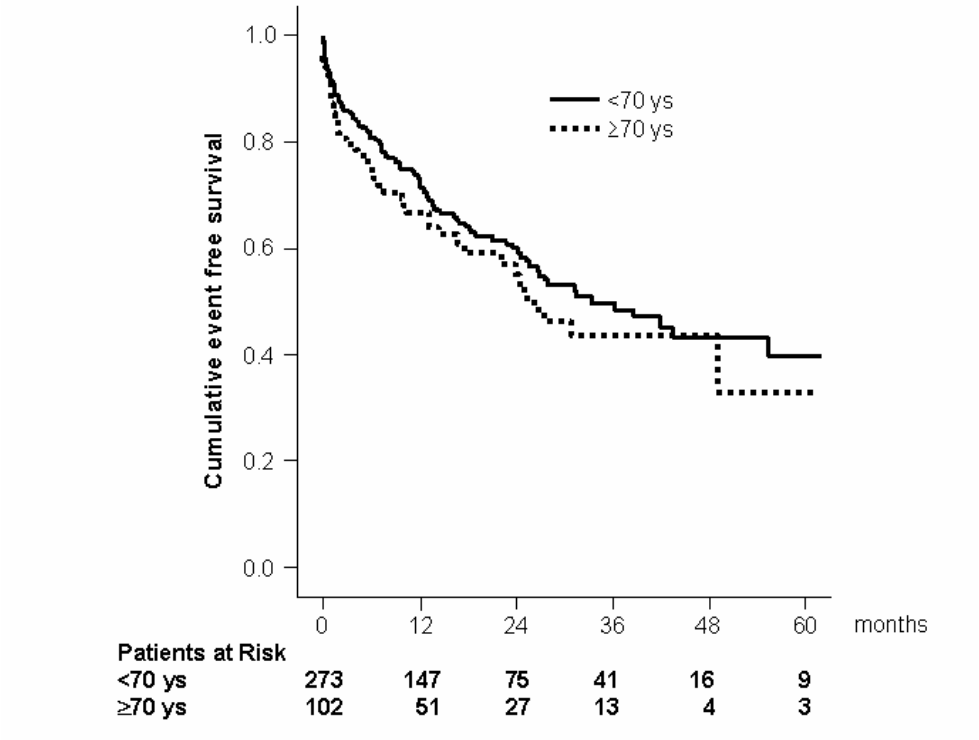

Figure 2. Cumulative survival free of ICD therapy of ventricular tachyarrhythmias in patients younger and older than 70 years

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).

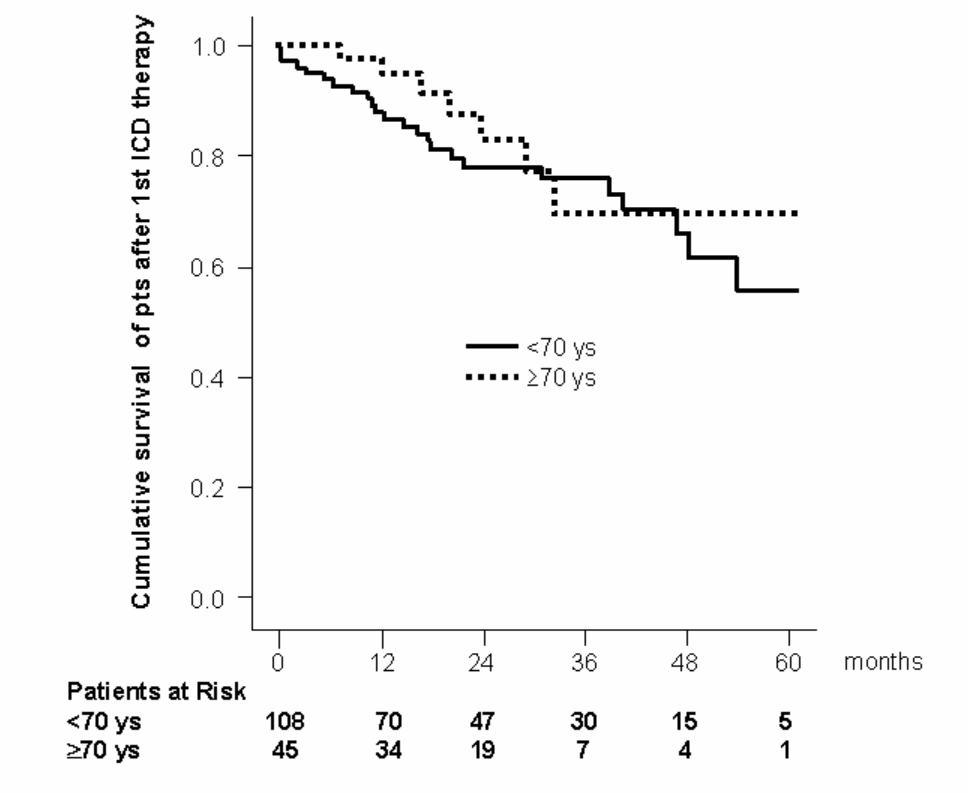

Figure 3. Cumulative survival after first device therapy (shock or ATP) delivery in patients younger and older than 70 years

ICD-related complications. Device-related complications during the perioperative phase and during the subsequent observation period were comparable between the patient groups (10.1 % in group 1, 9.8% in group 2). There was no implantation-related mortality.

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. Baseline characteristics of the two groups are shown in Table 2. Medical therapy was optimized in all patients

Table 2: 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
Ischemic cardiomyopathy	38 (48)	30 (49)	8 (44)	0.72
LVEF (%)	23 ± 8	22 ± 7	25 ± 9	0.35
NT-proBNP (pg/ml)	3158 ± 4477	3273 ± 4959	2781 ± 2433	0.75
VO2 max (ml/kg/min)	13.2 ± 4.2	13.4 ± 4.3	12.3 ± 3.4	0.39
NYHA functional class (n, %)				0.13
II	22 (28)	20 (33)	2 (11)	
III-IV	57 (72)	41(67)	16 (89)	
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 AT1 - 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. We used the nomenclature according to the definition proposed by van Ludighausen in reporting the coronary ven side branch distribution.

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%) (Figure 3). 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%).

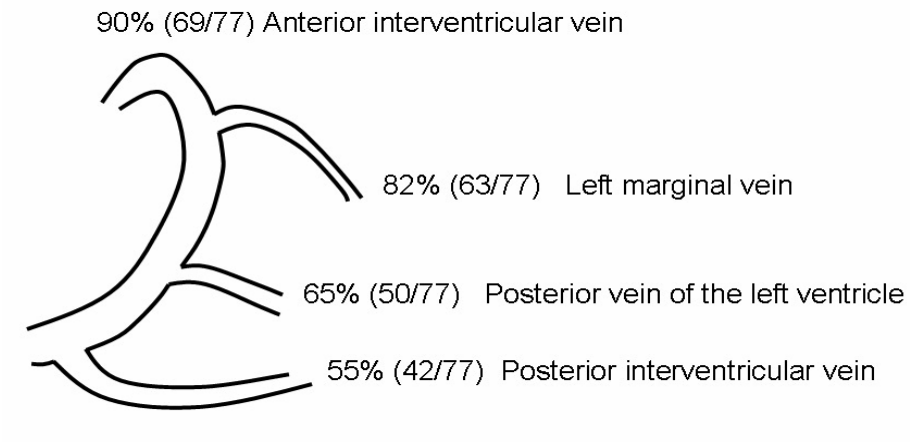

Figure 3. Presence of the four major coronary sinus side branches in the present patient cohort. Schematic LAO 40° view.

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 4).

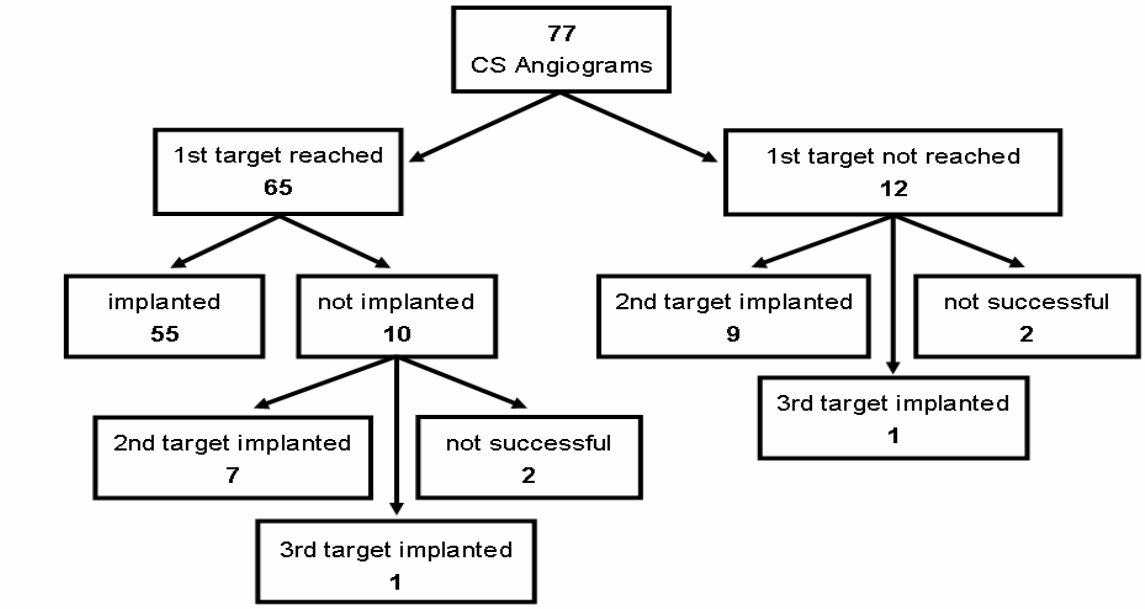

Figure 4: Flow chart of LV lead implantation in predefined target coronary sinus side branches

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.

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 3). The lowest rate of unsuitable measurements (14%) was found in the marginal position, the highest rate in the posterior interventricular vein (50%). 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. Of the 73 patients with a successful LV- lead implantation 38 patients were implanted with a unipolar lead, 35 with a bipolar one.

Table 3: Failure to use coronary sinus side branches

	Marginal	**Posterior**	**Anterior**	**PIV**	**All**
CS branch reached (reference 100%)	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

Procedural data (B and C). 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). Implantation (143 ± 41 vs. 179 ± 47 min, p=0.002) and the fluoroscopy times (20 ± 13 vs. 38 ± 21, p= 0.002) were significantly lower in patients where the lead implantation could be performed in the first target vein compared to the patients where the first chosen target vein was not suitable. Implantation was successful in 56 of 61 de novo implantations (92%) and 17 of 18 upgrade procedures (94%, p=1.0). 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. In 2 patients, the CRT upgrade procedure was complicated by an occlusion of the left subclavian vein. 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. Implantation (164 ± 63 vs. 154 ± 44 min, p=0.42), fluoroscopy times (32 ± 22 vs. 25 ± 18 min, p= 0.18) and X-ray dosis (52 ± 49 vs. 41 ± 31 Gy cm^2, p=0.22) showed no significant difference between the de novo and upgrade implantations. There were no significant difference in the perioperative and late complications as well.

Response to CRT (B and C). 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 (marginal 25/42 pts (60%), posterior 11/18 pts (61%), anterior 9/11 pts (82%), posterior interventricular 2/2 pts (100%)) albeit the number of patients with LV leads in the anterior or posterior interventricular veins were small.

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).

Description of a new lead defect mechanism (D)

We described possibly new lead defect mechanism at the level of the tricuspid valve: In a patient reporting an ICD shock delivery double potentials in the ventricular channel lead to detection of presumed ventricular fibrillation episode with consequent inadequate discharge. 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 5, postero- anterior and LAO 40° views, white arrows). The lead could not be extracted because of a stiff scar forming around it. A new ICD lead was implanted with a tip position in a safe distance from the old lead. The revision procedure was performed without any complications.

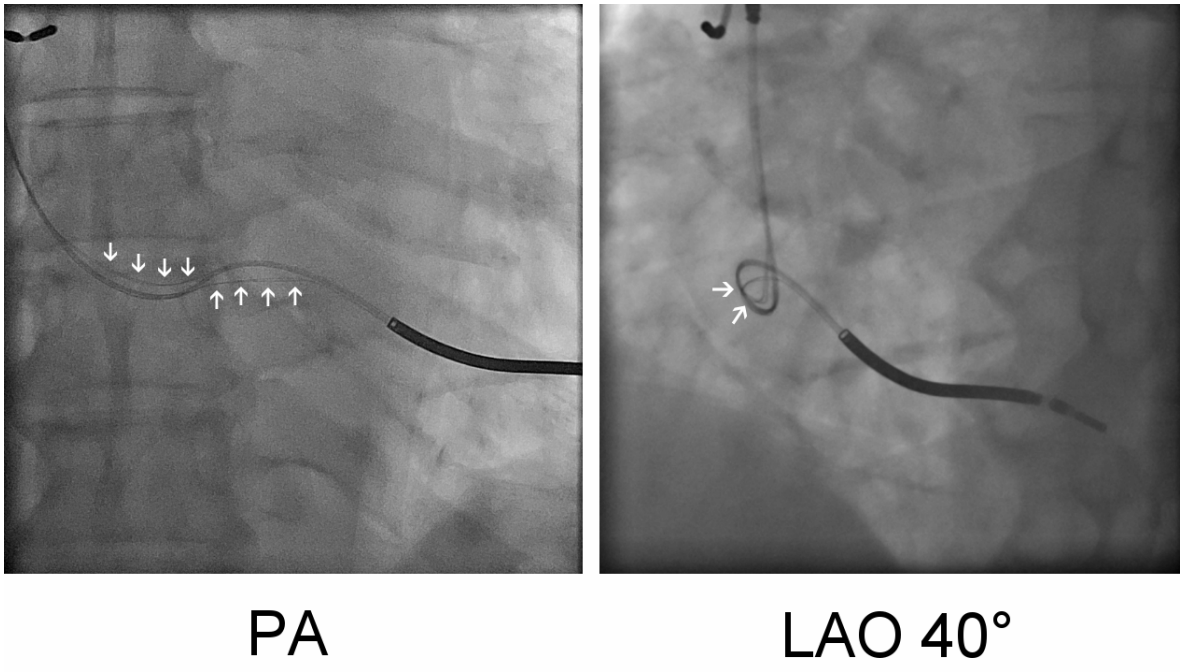

Figure 5 Lead splitting at the level of the tricuspid valve, with two thinner electrode components outside the main lead body (postero- anterior and LAO 40° views, white arrows)

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.

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Publications related to the PhD thesis

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