

Aus der Klinik für Herz- Thorax- und Gefäßchirurgie
des Deutschen Herzzentrums Berlin

DISSERTATION

**Prophylactic implantable cardioverter defibrillator treatment
in patients with end-stage heart failure awaiting heart
transplantation.**

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Georg Marcus FRÖHLICH

aus Salzburg/Österreich

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Abschnitt I

Abstracts

Abstract – English

Objectives This study was designed to delineate the role of implantable cardioverter defibrillator (ICD) therapy for the primary and secondary prevention of sudden cardiac death in patients listed for heart transplantation.

Setting Retrospective observational multicentre study.

Patients 1089 consecutive patients listed for heart transplantation in two tertiary heart transplant centres were enrolled. Of 550 patients (51%) on the transplant list with an ICD, 216 had received their ICD for the primary prevention of sudden cardiac death and 334 for secondary prevention. 539 patients did not receive an ICD.

Intervention Treatment with or without an ICD was left to the discretion of the heart failure specialist.

Main outcome measure All-cause mortality.

Results ICDs appear to be associated with a reduction in all-cause mortality in patients implanted with the device for primary and secondary prevention compared to those without an ICD despite a median time on the waiting list of only 8 months (estimated 1-year: 88±3% vs 77±3% vs 67±3%; p=0.0001). A Cox regression hazard model (corrected for age, sex, underlying heart disease, atrial fibrillation, cardiac resynchronization therapy, New York Heart Association (NYHA) class, ejection fraction, co-medication and year of listing) suggested an independent beneficial effect of ICDs that was most pronounced in patients who had received an ICD for primary prevention (HR 0.4, 95% CI 0.19 to 0.85; p=0.016).

Conclusions ICD implantation appears to be associated with an immediate and sustained survival benefit for patients awaiting heart transplantation.

Abstract – Deutsch

Studienziele Diese Studie wurde dazu konzipiert den Vorteil eines implantierbaren Kardioverter Defibrillators (ICD) zur Primär- und Sekundärprävention des plötzlichen Herztodes bei Patienten welche zur Herztransplantation gelistet sind, zu eruieren.

Studien-Setting Retrospektive multicenter Studie

Patienten Es wurden 1089 konsekutive Patienten in die Studie eingeschlossen, welche zur Herztransplantation in zwei Herztransplantationszentren gelistet wurden. 550 Patienten (51%) auf der Warteliste erhielten einen ICD, 216 erhielten den ICD für die Primärprävention des plötzlichen Herztodes und 334 für Sekundärprävention. 539 Patienten erhielten keinen ICD. **Therapie** Behandlung mit oder ohne ICD.

Primärer Endpunkt Mortalität. **Resultate** Die ICD Implantation scheint mit einer Mortalitätsreduktion einherzugehen, sowohl bei Patienten mit Primärprävention also auch zur Sekundärprevention. Als Vergleichsgruppe wurden Patienten ohne ICD Implantation herangezogen. Dies ist umso bemerkenswerter, als die mediane Wartezeit bis zur Herztransplantation gerade 8 Monate betrug. Das geschätzte 1-Jahres Überleben war für die genannten Gruppen: $88\pm 3\%$ vs $77\pm 3\%$ vs $67\pm 3\%$; $p=0.0001$. Eine multivariate Cox Regressionsanalyse (korrigiert für Alter, Geschlecht, zu Grunde liegende Herzerkrankung, Vorhofflimmern, kardiale Resynchronisationstherapie, New York Heart Association (NYHA) class, Ejektionsfraktion, Co-Medikation and Jahr der Listung) suggeriert einen unabhängigen Überlebensvorteil für die ICD Implantation, welcher bei Patienten mit Primärprävention besonders ausgeprägt war (HR 0.4, 95% CI 0.19 to 0.85; $p=0.016$).

Conclusion Bei Patienten auf der Herztransplantationswarteliste war die Implantation eines ICDs mit einem sofortigen und anhaltenden Überlebensvorteil verbunden.

Abschnitt II

Eidesstattliche Versicherung

Eidesstattliche Versicherung

„Ich, Georg Marcus Fröhlich, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:“Prophylactic implantable cardioverter defibrillator treatment in patients with end-stage heart failure awaiting heart transplantation“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum 07.10.2014

Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Prophylactic implantable cardioverter defibrillator treatment in patients with end-stage heart failure awaiting heart transplantation.

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1. Idee
2. Koordination der Studienzentren in Zürich und im Herzzentrum Berlin
3. Datenbankerstellung mit unserem Statistiker der Universität Zürich (Prof. Seifert)
4. Erstellung des Manuskripts
5. Publikation

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

Unterschrift des Doktoranden/der Doktorandin

Abschnitt III

Auszug aus ISI Web of Knowledge

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Mark	Rank	Abbreviated Journal Title <i>(linked to journal information)</i>	ISSN	JCR Data ⁱ						Eigenfactor [®] Metrics ^j	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor [®] Score	Article Influence [®] Score
<input type="checkbox"/>	1	J AM COLL CARDIOL	0735-1097	79235	15.343	14.669	3.753	454	7.0	0.19946	5.368
<input type="checkbox"/>	2	CIRCULATION	0009-7322	158661	14.948	15.326	3.067	510	9.2	0.28712	5.900
<input type="checkbox"/>	3	EUR HEART J	0195-668X	36613	14.723	13.120	2.772	334	5.6	0.11100	4.685
<input type="checkbox"/>	4	CIRC RES	0009-7330	47185	11.089	10.759	2.450	262	8.5	0.09265	3.835
<input type="checkbox"/>	5	NAT REV CARDIOL	1759-5002	2196	10.154	10.058	2.057	53	2.9	0.01310	3.816
<input type="checkbox"/>	6	JACC-CARDIOVASC INTE	1936-8798	4558	7.440	7.424	1.265	132	3.2	0.02863	2.913
<input type="checkbox"/>	7	JACC-CARDIOVASC IMAG	1936-878X	3744	6.986	6.706	2.050	100	3.2	0.02302	2.622
<input type="checkbox"/>	8	CIRC-CARDIOVASC INTE	1941-7640	2311	6.982	6.950	0.659	82	2.9	0.01578	2.932
<input type="checkbox"/>	9	CIRC-CARDIOVASC IMAG	1941-9651	2341	6.752	6.947	0.952	125	2.9	0.01399	2.632
<input type="checkbox"/>	10	EUR J HEART FAIL	1388-9842	6854	6.577	5.511	1.396	159	4.4	0.02263	1.708
<input type="checkbox"/>	11	INT J CARDIOL	0167-5273	15179	6.175	5.101	0.926	1441	4.3	0.03528	1.291
<input checked="" type="checkbox"/>	12	HEART	1355-6037	15342	6.023	5.233	1.744	234	6.3	0.03859	1.743
<input type="checkbox"/>	13	BASIC RES CARDIOL	0300-8428	3697	5.955	5.607	1.459	85	4.7	0.00944	1.514
<input type="checkbox"/>	14	CIRC-HEART FAIL	1941-3289	2602	5.945	6.513	1.178	146	3.1	0.01714	2.765
<input type="checkbox"/>	15	CARDIOVASC RES	0008-6363	21631	5.808	6.196	1.375	248	7.4	0.04334	1.968
<input type="checkbox"/>	16	EUR HEART J SUPPL	1520-765X	985	5.640	2.246		0	>10.0	0.00162	0.771
<input type="checkbox"/>	17	J HEART LUNG TRANSPL	1053-2498	8078	5.611	4.209	1.504	141	5.7	0.02241	1.414
<input type="checkbox"/>	18	CIRC-ARRHYTHMIA ELEC	1941-3149	3017	5.417	6.291	0.929	169	3.0	0.01917	2.534
<input type="checkbox"/>	19	CIRC-CARDIOVASC GENE	1942-3268	1959	5.337	5.867	0.868	68	3.1	0.01300	2.415
<input type="checkbox"/>	20	J MOL CELL CARDIOL	0022-2828	12451	5.218	5.133	0.995	220	6.5	0.03143	1.725

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Abschnitt IV

Publikation

ORIGINAL ARTICLE

Prophylactic implantable cardioverter defibrillator treatment in patients with end-stage heart failure awaiting heart transplantation

Georg M Fröhlich,¹ Johannes Holzmeister,¹ Michael Hübler,² Samira Hübler,² Mathias Wolfrum,¹ Frank Enseleit,¹ Burkhardt Seifert,³ David Hürlimann,¹ Hans B Lehmkuhl,² Georg Noll,¹ Jan Steffel,¹ Volkmar Falk,⁴ Thomas F Lüscher,¹ Roland Hetzer,² Frank Ruschitzka¹

¹Cardiovascular Division, Cardiology, Heart Failure/Heart Transplant Unit, University Hospital Zurich, Zurich, Switzerland

²Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Berlin, Germany

³Division of Biostatistics, Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland

⁴Department of Cardiothoracic and Vascular Surgery, University Hospital Zurich, Zurich, Switzerland

Correspondence to

Prof. Dr. Frank Ruschitzka, University Hospital Zurich, Raemistrasse 100, Zürich CH-8091, Switzerland; frank.ruschitzka@usz.ch

GMF, JH and MH contributed equally to the study.

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ABSTRACT

Objectives This study was designed to delineate the role of implantable cardioverter defibrillator (ICD) therapy for the primary and secondary prevention of sudden cardiac death in patients listed for heart transplantation.

Setting Retrospective observational multicentre study.

Patients 1089 consecutive patients listed for heart transplantation in two tertiary heart transplant centres were enrolled. Of 550 patients (51%) on the transplant list with an ICD, 216 had received their ICD for the primary prevention of sudden cardiac death and 334 for secondary prevention. 539 patients did not receive an ICD.

Intervention Treatment with or without an ICD was left to the discretion of the heart failure specialist.

Main outcome measure All-cause mortality.

Results ICDs appear to be associated with a reduction in all-cause mortality in patients implanted with the device for primary and secondary prevention compared to those without an ICD despite a median time on the waiting list of only 8 months (estimated 1-year: 88±3% vs 77±3% vs 67±3%; $p=0.0001$). A Cox regression hazard model (corrected for age, sex, underlying heart disease, atrial fibrillation, cardiac resynchronisation therapy, New York Heart Association (NYHA) class, ejection fraction, co-medication and year of listing) suggested an independent beneficial effect of ICDs that was most pronounced in patients who had received an ICD for primary prevention (HR 0.4, 95% CI 0.19 to 0.85; $p=0.016$).

Conclusions ICD implantation appears to be associated with an immediate and sustained survival benefit for patients awaiting heart transplantation.

INTRODUCTION

In December 2010, a total of 3225 patients in the USA were listed for heart transplantation, while 232 had died on the waiting list the year before.¹ To improve the survival rates of patients with end-stage heart failure, treatment with implantable cardioverter defibrillators (ICDs) has been proposed to prevent sudden cardiac death.^{2–3} Large scale randomised clinical trials have confirmed a significant survival benefit of ICD implantation in patients with mild to moderate chronic heart failure, but only a few patients in New York Heart Association (NYHA) class IV heart failure were

included in these landmark trials.^{4–6} Whether candidates for heart transplantation should receive an ICD to reduce the risk of sudden cardiac death while awaiting cardiac transplantation is matter of ongoing debate.^{7–8} Indeed, only a few relatively small studies have addressed the role of ICD implantation in patients on the waiting list for heart transplantation, with conflicting results.^{9–13} While these studies suggested the implantation of an ICD was beneficial for secondary prevention in patients who had survived a life-threatening ventricular arrhythmia, its efficacy has not yet been sufficiently investigated for primary prevention. The present study was therefore designed to evaluate the role of ICD therapy for the prevention of sudden cardiac death in heart failure patients listed for heart transplantation.

METHODS

Patient recruitment and inclusion criteria

Patients in two tertiary heart transplant centres (the Department of Cardiology, University Hospital Zurich and the German Heart Centre Berlin) from 1996 (the year the MADIT I study was published) to September 2010 were retrospectively included in the study.¹⁴ Decision criteria for transplant listing followed ISHLT standards and were similar in both centres,^{15–17} and included a history of NYHA class IV heart failure and a VO_2 max <14 mL/kg/min.

All patients aged 16 years or older listed for a heart transplant were eligible for inclusion. Patients were excluded if no data on prior ventricular arrhythmia (defined as sustained ventricular tachycardia or ventricular fibrillation) were available at the time of listing, or if serial follow-up data on ICD function and shock delivery were lacking. Patients who received a cardiac assist device before listing were also excluded. At the time of listing, current medication, NYHA functional class, ejection fraction, electrocardiography, data on cardiovascular risk factors and underlying heart disease were documented.

Patients were followed until heart transplantation for a maximum of 3 years. The date and cause of death, date of heart transplantation or date of assist device implantation was recorded. If cardiac death occurred, cases were sub-classified as 'sudden cardiac death' (defined as death within 1 h after the

onset of acute symptoms or unwitnessed, unexpected death in a patient known to have been stable within the previous 24 h¹²), 'non-sudden cardiac death' or death due to 'low cardiac output' (defined as death due to progressive congestive heart failure or with preceding symptoms lasting >1 h¹²). Patients in whom classification was not possible were termed 'not classified'.

ICD implantation and programming

Patients in the secondary prevention group received the ICD because of sustained ventricular arrhythmia, ventricular fibrillation or survival of sudden cardiac death. Patients in the primary prevention group were treated by heart failure specialists who decided if ICD implantation was indicated on an individual basis. This clinical practice reflects the inherent uncertainty regarding the eligibility of patients on the heart transplant waiting list to receive an ICD in the absence of trial outcome data.

ICD devices made by Medtronic, Guidant/Boston Scientific, Biotronik and St. Jude Medical were used. More than 90% of patients had one or two ventricular tachycardia zones programmed for antitachycardia pacing. The ventricular fibrillation zone was programmed at a cut-off heart rate of >200/min. Right ventricular pacing >50% of time occurred in less than 10% of patients (except in patients undergoing cardiac resynchronisation therapy (CRT)).

Study groups and study endpoints

The indication for ICD implantation was re-evaluated in each patient by two experienced investigators (GMF and MW) with consequent allocation to either the 'primary prevention' or the 'secondary prevention' group. A total of 478 patients (87%) had received their ICD before listing (with 1088 patient-years until listing). This guaranteed permanent rhythm surveillance and served as a basis to accurately assign the patients either to the primary or secondary prevention group.

The main criterion to classify implantation as secondary prevention was documentation of a previous severe ventricular arrhythmia (ie, sustained ventricular arrhythmia or ventricular fibrillation). Patients who had originally received the ICD for primary prevention, but who had shock delivery prior to transplant listing, were also allocated to the secondary prevention group. Patients who received the ICD after being listed for transplantation, were all allocated to the one of the ICD groups. In case of documented arrhythmic events before ICD implantation, these patients were assigned to the secondary prevention group. Investigators adjudicating outcome data were blinded for study group allocation to primary versus secondary prevention. Patients without an ICD were allocated to the control group.

The primary outcome measure of our study was death from any cause. Secondary endpoints were death from any cause, need for the implantation of a ventricular assist device, or appropriate shock delivery while on the transplant list. Safety issues concerning the ICD therapy (appropriate versus inappropriate shock delivery, need for reoperation while on the transplant list) were also recorded. Further, the subgroup of patients with cardiac resynchronisation therapy plus defibrillator (CRT-D) was analysed for overall survival versus those with ICDs alone and those without any devices.

Statistics

Statistical analysis was performed with SPSS V18.0 (SPSS, Chicago, Illinois) and STATA/IC V11.2 (StataCorp, College Station, Texas) software. Categorical data are presented as number of patients with percentages and continuous data as median with IQR. Patients were followed for a maximum of

3 years. Study groups were compared using the Mann-Whitney test, Kruskal-Wallis test and Pearson χ^2 test as appropriate. The Kruskal-Wallis test was also used to define differences in NYHA classification. A two-sided p value <0.05 was considered significant.

The date of listing for heart transplantation was the date for study inclusion (baseline) for ALL patients, also for those patients, who received the ICD after listing for transplantation. Kaplan-Meier survival charts analysing the time span from listing for heart transplantation until the endpoint was reached were computed for all endpoints. So that all ICD patients implanted after being listed would be included, analysis time was left truncated ('delayed entry') at implantation of ICD in these patients. The influence of ICD, age, sex, medication, heart rhythm, ejection fraction, year of listing, NYHA class, CRT and underlying heart disease on the primary endpoint was calculated with the help of a multiple Cox regression including an analysis of potential interactions with the ICD within the study groups. Only complete cases were analysed. The proportional hazard assumption was tested on the basis of Schoenfeld residuals. Due to the retrospective nature of the study, we also present a propensity score analysis for the primary endpoint in the control group versus the primary prevention group. The propensity score was computed using logistic regression, where the same variables were included as in the multiple Cox regression. The propensity score then was divided into quintiles and a stratified log-rank test was performed. Only complete cases were analysed.

RESULTS

Patient population and characteristics

Between 1996 and September 2010, a total of 1489 patients were listed for heart transplantation at the two centres. Of these, 221 patients were excluded due to implantation of an assist device before listing, and 30 due to incomplete source documentation. In addition, 149 patients were less than 16 years of age and were excluded. As a result, 1089 patients (944 patients from the German Heart Center Berlin and 145 patients from University Hospital Zurich) were included in the analysis (figure 1). Heart failure therapy, follow-up procedures and the selection of patients for heart transplantation were comparable in the two centres. Baseline characteristics are summarised in table 1. Median ejection fraction at the time of listing was 20% (IQR 15–25%) and most patients were in NYHA functional class III (n=713, 66%). The main cause of heart failure was dilated cardiomyopathy (n=602, 55%), followed by ischaemic cardiomyopathy (n=352, 32%).

Of the 1089 patients included in the study, 583 (54%) underwent transplantation within 3 years of being listed for heart transplantation after having been on the transplant list for a median (IQR) time of 281 (80–664) days. A total of 290 patients (27%) listed for transplantation died during the observational period of 3 years after listing for cardiac transplantation, which is in line with recent US and European data.¹⁸ A total of 228 patients (21%) received an assist device (table 2).

Of the 550 patients with an ICD, 478 (87%) had received an ICD before listing for transplantation and 72 (13%) after being listed (median (IQR) 108 (14–320) days after listing).

Effect of ICD on all-cause mortality

A total of 550 patients (51%) on the transplant list received an ICD, which was implanted in 216 (20%) and 334 patients (31%) for primary and secondary prevention, respectively. As regards all-cause mortality, ICD treatment may have a beneficial

Figure 1 Flow chart showing which patients were excluded from the study.

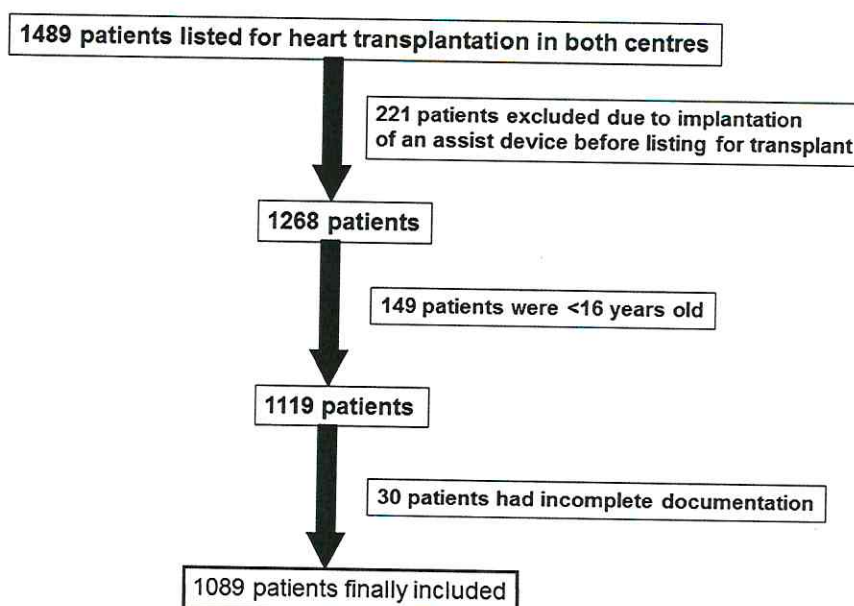


Table 1 Baseline characteristics at the time of listing for heart transplantation

	No ICD (n=539)	Primary prevention ICD (n=216)	Secondary prevention ICD (n=334)	p Value
Age, years (IQR)	52 (43–59)	53 (43–59)	55 (47–59)	0.02
Male, n (%)	432 (80)	189 (88)	288 (86)	0.01
Body mass index, kg/m ² (IQR)	25 (22–28)	25 (23–29)	25 (23–28)	0.05
Rhythm, n (%)				0.01
Sinus rhythm	330 (66)	120 (57)	191 (60)	
Atrial fibrillation	100 (20)	42 (20)	60 (19)	
Pacemaker	64 (13)	47 (23)	67 (21)	
Left bundle branch block, n (%)	215 (44)	97 (46)	159 (49)	0.39
Ejection fraction (%)	20 (15–25)	20 (15–25)	20 (15–25)	0.24
CRT-D, n (%)		52 (24)	52 (16)	<0.0001
NYHA functional class, n (%)				0.27
II	15 (3)	11 (5)	20 (6)	
III	343 (68)	148 (70)	222 (67)	
IV	145 (29)	52 (25)	90 (27)	
Cardiovascular risk factors, n (%)				
Arterial hypertension	164 (36)	86 (47)	135 (49)	0.001
Dyslipidemia	169 (37)	90 (50)	138 (50)	0.0005
Diabetes	95 (21)	50 (28)	66 (24)	0.18
Smoking	96 (21)	51 (28)	69 (25)	0.13
Cause of cardiomyopathy, n (%)				0.0004
Dilated cardiomyopathy	282 (52)	119 (56)	201 (60)	
Ischaemic cardiomyopathy	167 (31)	80 (37)	105 (31)	
Valvular heart disease	25 (5)	10 (5)	11 (3)	
Congenital cardiomyopathy	22 (4)	2 (1)	4 (1)	
Other	41 (8)	3 (1)	12 (4)	
Medication, n (%)				
β-Blocker	271 (57)	169 (80)	240 (74)	<0.0001
ACE inhibitor/ATII blocker	417 (87)	191 (90)	276 (85)	0.28
Spironolactone	213 (44)	149 (70)	191 (59)	<0.0001
Digoxine	360 (75)	140 (66)	229 (71)	0.05
Amiodarone	102 (22)	52 (25)	125 (39)	<0.0001
Diuretics	435 (90)	196 (93)	292 (90)	0.66

Number of patients (%) and median (IQR) are shown for categorical and continuous data, respectively.

CRT-D, cardiac resynchronisation therapy plus defibrillator; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.

Table 2 Three-year follow-up and adverse events

	No ICD (n=539)	Primary prevention (n=216)	Secondary prevention (n=334)	p Value
Heart transplantation, n (%)	286 (53)	119 (55)	178 (53)	
Waiting time on list, days (IQR)	194 (56–489)	420 (144–883)	331 (103–708)	<0.0001
Death on list, n (%)	162 (30)	39 (18)	89 (27)	0.0001
Cardiac death	113 (70)	22 (56)	42 (47)	
Cerebral event leading to death	10 (6)	3 (8)	9 (10)	
Fatal bleeding	0	0	1 (1)	
Multiorgan failure	12 (8)	5 (13)	10 (11)	
Malignancy	2 (1)	0	0	
Septic shock	17 (11)	8 (21)	23 (26)	
Unknown	7 (4)	1 (3)	2 (2)	
Other	1 (1)	0	2 (2)	
Ventricular assist device, n (%)	86 (16)	48 (22)	94 (28)	
Patients with appropriate shock delivery on list, n (%)		22 (10)	58 (18)	
Appropriate shock delivery (1-year event free survival, %)		89±3	80±3	0.003
Appropriate shocks for VT, n (%)		40 (34)	134 (53)	
Appropriate shocks for VF, n (%)		23 (20)	79 (31)	
Cardiac death (1-year cardiac survival, %)	76±2	94±2	88±2	<0.0001
Sudden cardiac death	76±3	99±1	96±2	<0.0001
Low cardiac output	94±1	95±2	91±2	0.11
Unclassified	94±1	99±1	98±1	0.04

Number of patients (%) and median (IQR) are shown for categorical and continuous data, respectively. ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

effect in the primary as well as in the secondary prevention group when compared to patients without an ICD (control group) ($p=0.0001$; figure 2A). The survival benefit was more pronounced in the primary prevention (1-year estimator: $88\pm3\%$ vs $67\pm3\%$; $p<0.0001$) than the control group, as compared to patients who received an ICD for secondary prevention versus the control group ($77\pm3\%$ vs $67\pm3\%$; $p=0.01$). This survival benefit remained after correction for several covariates in a Cox regression model which included 969 complete cases (table 3; proportional hazard assumption: $p=0.38$). No interactions of ICD treatment with other covariates on the outcome measure could be detected. A stratified propensity score analysis (including 586 complete cases from the primary

prevention and control groups) suggested a similar survival benefit for the primary prevention group as for the control group ($p=0.017$).

The p value of the Hosmer–Lemeshaw test was 0.54, and the c value was 0.80. Importantly, the number needed to treat over a 6-month period at risk was eight, indicating that eight patients would need to be implanted with an ICD for a primary prophylactic indication over 6 months to save one life.

Similarly, in patients who received an ICD after listing ($n=72$), a significant survival benefit was observed for the primary as well as for the secondary prevention group when compared to those without an ICD (1-year event free survival: $86\pm6\%$ vs $78\pm9\%$ vs $67\pm3\%$; $p=0.009$) (figure 3A).

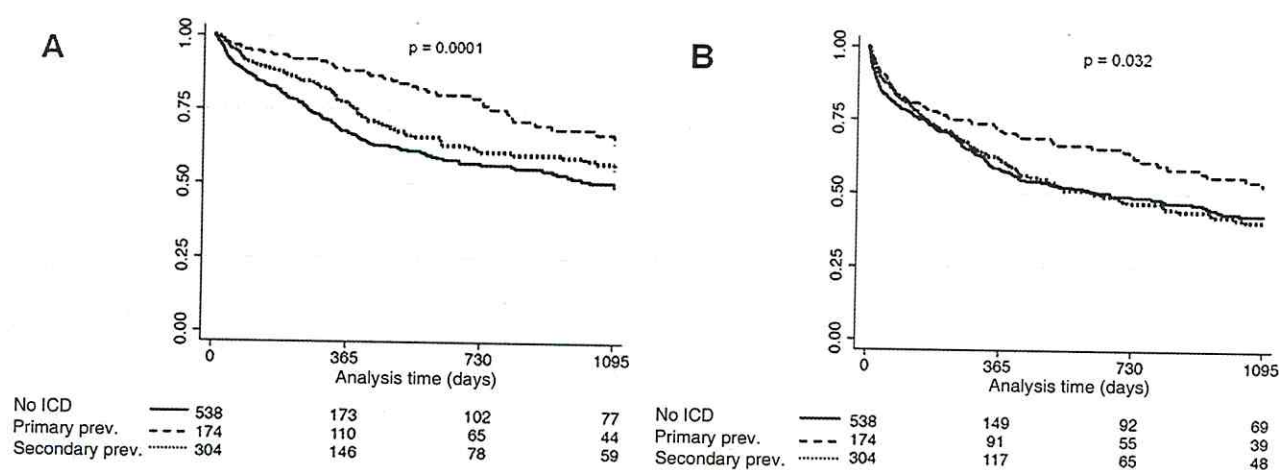


Figure 2 Effect of ICD treatment on all-cause mortality and/or need for an assist device. Kaplan–Meier curves for freedom from all-cause mortality (A) and death from any cause or need for implantation of an assist device (B) in patients without ICDs, primary prevention ICD recipients, and secondary prevention ICD recipients. ICD, implantable cardioverter defibrillator; prev., prevention.

Table 3 Cox regression analysis for the primary endpoint of all-cause mortality

	HR	95% CI	p Value
Primary prevention versus no ICD	0.40	0.19 to 0.85	0.016
Secondary prevention versus no ICD	0.48	0.26 to 0.89	0.019
CRT-D versus ICD	0.76	0.45 to 1.29	0.31
Age (>60 years vs <60 years)	1.21	0.87 to 1.68	0.27
Male	0.63	0.43 to 0.92	0.02
Ischaemic cardiomyopathy	0.76	0.52 to 1.1	0.15
Atrial fibrillation versus sinus rhythm	1.51	0.99 to 2.29	0.05
β -Blocker	0.80	0.59 to 1.09	0.17
Spironolactone	0.96	0.72 to 1.27	0.78
Amiodarone	1.15	0.75 to 1.76	0.52
NYHA class III versus NYHA II	1.79	0.78 to 4.1	0.17
NYHA class IV versus NYHA II	2.28	0.98 to 5.34	0.06
EF (>20% vs <20%)	0.83	0.62 to 1.09	0.18
Year of listing for transplantation (per year)	1.02	0.98 to 1.06	0.37

HRs and 95% CIs are presented.

CRT-D, cardiac resynchronisation therapy plus defibrillator; EF, ejection fraction; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.

Effect of ICD treatment on mortality and need for an assist device

Overall, 203 patients (38%) in the control, 64 (30%) in the primary prevention and 132 (40%) in the secondary prevention group died or needed an assist device (figure 2B). On Kaplan-Meier analysis, event free survival was documented in more patients in the primary prevention (1-year estimator: $71\pm 4\%$) as compared with the secondary prevention ($61\pm 3\%$) and control cohorts ($58\pm 3\%$; $p=0.03$). This benefit became evident from the first day of study inclusion (figure 2). In contrast, no significant difference was observed between the secondary prevention and the control group.

In the group of patients who received the ICD after listing, event free survival was significantly prolonged in both groups who received the ICD for primary and secondary prevention as compared to patients without an ICD (1-year estimator: $80\pm 7\%$ vs $75\pm 9\%$ vs $58\pm 3\%$; $p=0.002$; figure 3B).

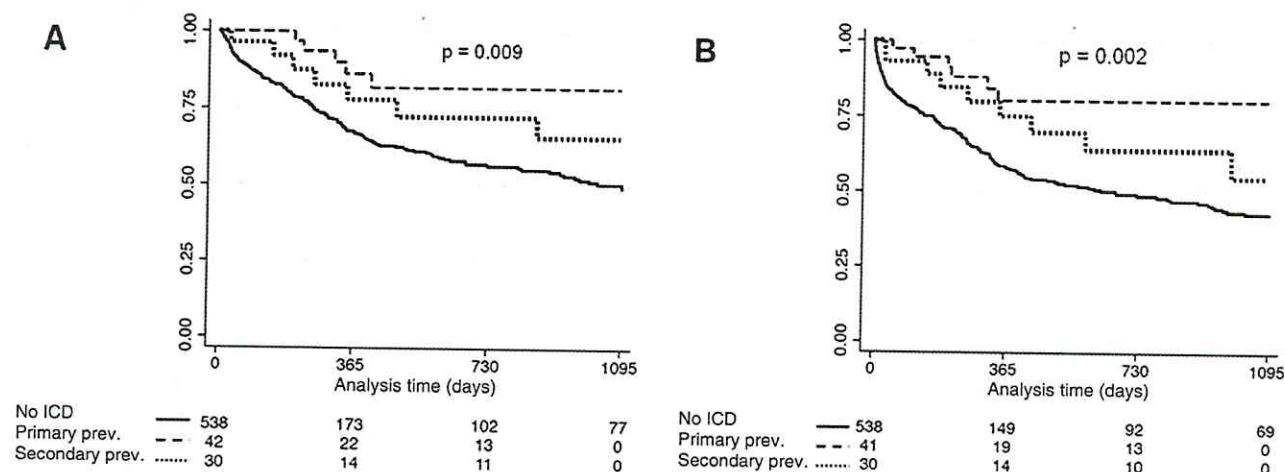


Figure 3 Effect of ICD in patients implanted while on the transplant waiting list. The effect of ICD treatment on freedom from all-cause mortality (A) and death from any cause or need for implantation of an assist device (B) in patients implanted on the transplant waiting list. ICD, implantable cardioverter defibrillator; prev., prevention.

Table 4 Safety issues in patients after implantable cardioverter defibrillator (ICD) implantation while listed for heart transplantation

	Primary prevention (n=216)	Secondary prevention (n=334)
Patients with inappropriate shocks, n (%)	10 (5)	17 (5)
(Inappropriate) shocks for atrial fibrillation, n (%)	7 (6)	11 (4)
Inappropriate shocks for device/electrode malfunction, n (%)	47 (40)	21 (8)
Patients with need for ICD surgery while on the transplant list, n (%)	6 (3)	18 (5)

Causes of cardiac death

Overall, 113 (70%), 22 (56%) and 42 (47%) patients died of a cardiac cause in the control, primary prevention and secondary prevention groups, respectively (table 2). Patients in the control group were more likely to die from sudden cardiac death (1-year event free survival: $86\pm 2\%$) as compared to patients with an ICD ($99\pm 1\%$; $p<0.0001$). In contrast, no differences in death from low cardiac output were observed between the control ($94\pm 1\%$), primary prevention ($95\pm 2\%$) and secondary prevention groups ($91\pm 2\%$; 1-year event free survival estimator: $p=0.11$).

Safety of ICD therapy

Tables 2 and 4 summarise the total number of patients with shock deliveries as well as the number of shock deliveries. Appropriate (ventricular tachycardia or ventricular fibrillation) and inappropriate shock deliveries (atrial fibrillation, electrode or device defects) while patients were listed for heart transplantation were identified. The striking difference in the number of inappropriate shocks between the primary and secondary prevention groups is due to one patient with an electrical storm who received 36 shocks. All re-operations for lead dislocation, lead fracture or malfunction of the ICD device occurring during the listing period are presented in table 4.

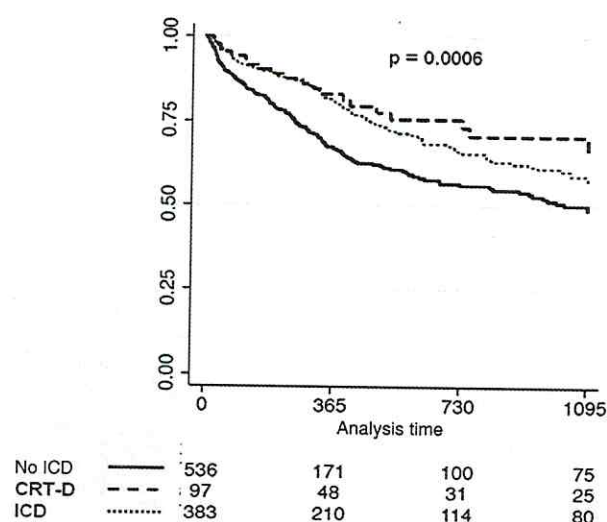


Figure 4 Effect of CRT-D on survival. Kaplan-Meier curves for death from any cause are shown for ICD only recipients, CRT-D recipients or patients without ICDs. CRT-D, cardiac resynchronisation therapy plus defibrillator; ICD, implantable cardioverter defibrillator.

Impact of CRT on survival

Of the 550 patients with an ICD, 104 (19%) had a biventricular CRT-D system (52 patients (24%) in the primary prevention group and 52 patients (16%) in the secondary prevention group). Patients without an ICD were more likely to die on the list as compared to the CRT-D and ICD groups (1-year estimator: $67\pm 3\%$ vs $83\pm 4\%$ vs $81\pm 2\%$; $p=0.0006$; figure 4). Although the HR was lowered by 24% in the CRT-D group, this was not statistically significant when compared to patients with an ICD alone (table 3). However, the investigated number of cases with CRT-D might have been too low to detect a significant survival benefit.

DISCUSSION

This observational study suggests that ICD implantation results in a reduction in sudden cardiac death, leading to an immediate and sustained survival benefit for candidates listed for heart transplantation despite a median time on the waiting list of only 8 months. Patients who received the ICD for primary prevention before listing as well as patients receiving an ICD (primary and secondary prevention) after being listed for transplantation appear to derive the greatest benefit.

Although ICD trials have demonstrated a benefit of ICD implantation for primary prevention in high-risk patients with ischaemic and non-ischaemic cardiomyopathy, the subgroup of highly symptomatic patients in NYHA class IV with a particularly poor prognosis was mostly excluded from these earlier trials.^{4 14 19 20} Indeed, the SCD-HeFT study included only patients with stable NYHA class II or III heart failure, and excluded those with NYHA class IV heart failure and/or candidates for heart transplantation.²¹ In contrast, MADIT-II inclusion criteria required only a low ejection fraction and did not include clinical symptoms of heart failure. In view of the paucity of end-stage heart failure patients in ICD trials, recommendations on prophylactic ICD implantation in patients with end-stage heart failure are somewhat conflicting.² The ACC/AHA guidelines currently assign a class IIa (level of evidence C) recommendation for ICD implantation in non-hospitalised patients awaiting heart transplantation. In contrast,

ICD implantation is not recommended for patients without a reasonable expectation of survival with an acceptable functional status for at least 1 year (class III, level of evidence C).² As a result, only 57% of patients who were eligible for ICD implantation, already had an ICD at the first consultation in a tertiary cardiac care centre.²²

As randomised clinical trials addressing this issue are unavailable and it might be difficult to conduct them due to ethical concerns, only a few retrospective studies, mostly including low numbers of patients, are currently used to guide clinical practice. The largest study so far, which enrolled 854 patients listed for transplantation, demonstrated a survival benefit for the 102 patients (12%) with an ICD awaiting heart transplantation; however, no information was provided on whether the decision to implant an ICD was based on a primary or secondary prevention indication.¹² Importantly, the latter study was published in 2001, several years before large scale randomised trials demonstrated the benefit of ICD implantation for the primary prevention of sudden cardiac death, which may explain the low overall number of implanted ICDs.^{4 21}

A survival benefit comparable to that in our report was observed in a recent study of 310 patients listed for heart transplantation, of whom 59 (19%) received an ICD for secondary prevention^{10 11}; however, no patients with primary preventive ICD implantation were included in this study. In another cohort of 194 patients on the transplant list and in which only 35 patients underwent ICD implantation, 40 (25.2%) patients died in the control group and three (8.6%) in the ICD groups.^{10 11}

In contrast, our study evaluated a total of 1089 patients, of whom 550 (51%) received an ICD during the period 1996–2010, thus reflecting the implementation of recent landmark trial results in addition to state-of-the art heart failure treatment algorithms in a large cohort of patients. Importantly, while most of the previous studies examined the effect of ICD treatment for secondary prevention, we here for the first time observed a pronounced survival benefit of primary and secondary preventive ICD therapy in patients listed for heart transplantation. While ICD implantation appears to be associated with a reduction in all-cause mortality in patients who received the device for primary or secondary prevention, when the combined outcome measure consisting of death or need for assist device implantation was analysed, no advantage could be observed in patients who received an ICD for secondary prevention. This result is due to the increased propensity of low cardiac output failure in these patients and a consequent increased need for cardiac assist device implantation.

Moreover, patients who had received ICD implantation after being listed for transplantation derived a significant benefit as regards both all-cause mortality and the combined outcome measure of all-cause mortality or need for assist device implantation as compared to those without an ICD. Taken together, our data hence imply that patients accepted for listing and those already listed for cardiac transplantation will derive a substantial benefit from ICD implantation independent of a previously documented life-threatening arrhythmic event.

Indications for ICD implantation need to be critically evaluated for their efficacy, especially if the time at risk of sudden cardiac death is relatively short as in patients awaiting heart transplantation. Indeed, with a number needed to treat of eight patients to save one life over 6 months, the present study provides strong evidence that this treatment is highly effective. This apparent benefit, however, has to be carefully weighed against the safety concerns potentially associated with ICD therapy, particularly as the retrospective cohort study of cases

submitted to the US National Cardiovascular Data Registry ICD Registry demonstrated that adverse events were significantly higher in patients who received a currently non-evidence-based device.⁷

Importantly, the ICD related complication rate in the present study was comparable to that of large randomised ICD trials and observational studies.^{4 23} Therefore, any decision to implant an ICD in this patient cohort at particularly increased risk needs to be individualised and the clinical equipoise of ICD therapy considered.⁷

Of note, while patients with ICD only and those with CRT-D showed a significant survival benefit compared to the control group, no statistically significant difference between the ICD group and the CRT-D group could be detected, indicating that CRT did not provide an additional survival benefit in this patient population. Similarly, a smaller prospective study including 80 patients with NYHA class IV heart failure failed to detect any survival benefit between the patients with ICDs only versus those with CRT-D,²⁴ suggesting a 'point of no return' in ventricular remodelling after which the otherwise highly effective treatment with CRT may no longer improve ventricular structure and function. These findings have to be interpreted with caution, as the number of patients who received CRT-D might have been too low to detect a survival benefit for resynchronisation therapy. Further, prospective trials are now needed to confirm or refute the findings of this observational study.

Limitations

The three study groups differ slightly with respect to several baseline characteristics, including underlying heart disease and co-medication, reflecting the inclusion of patients in a real world setting. Indeed, compared to large scale prospective randomised clinical trials that included patients with NYHA class III or IV heart failure, such as the COMPANION trial, the proportion of patients receiving β -blockers (67% vs 62%), ACE/ATII inhibitors (89% vs 82%) or spironolactone (54% vs 51%) in our study was very similar.⁶ In line with our findings, it has been demonstrated previously that the ICD benefit is independent of concomitant β -blocker or amiodarone therapy.¹⁰

To overcome the problem of different proportions of patients receiving β -blocker and spironolactone co-medication and the relatively long observational period, we also performed a survival analysis including only patients listed for transplantation after 2002 (ie, when MADIT II was published; n=439). In this patient population, β -blocker and spironolactone treatment was balanced between the study groups, but the survival benefit for the ICD treatment groups was comparable to the entire study population (data not shown).

Moreover, a large proportion of our patients enrolled in the control group (n=386, 71%) were listed for transplantation before 2002, whereas the 62% in the ICD group (n=341) were listed for transplantation after that date, most likely reflecting changing clinical practice over time associated with the publication of landmark studies such as MADIT-II. Assessment of unequal patient numbers during different time periods, however, is an unavoidable limitation of retrospective real world studies such as the present one. Importantly, the survival benefit of ICD implantation was independent of the time of listing for heart transplantation on multivariate analysis.

Overall, 13% of patients in the treatment group received their ICD after being listed for cardiac transplantation, which might be a source of bias. However, analysis was adjusted for the delayed entry of these patients into the study.

While a retrospective study design is subject to inherent limitations, it is important to note that patients awaiting cardiac transplantation were excluded from all previous ICD trials. Since a prospective randomised trial to assess the effect of ICD in end-stage heart failure is difficult to perform in a patient population that has been selected for heart transplantation, large scale observational studies provide the highest quality data available to address the clinically relevant question of whether these patients at particularly high risk will benefit from ICD implantation.

CONCLUSION

The present study suggests that both primary and secondary ICD implantation are associated with improved survival in patients with end-stage heart failure. Based on these results, patients listed for heart transplantation for whom in-hospital rhythm monitoring cannot be guaranteed until transplantation, might be considered for ICD implantation, irrespective of probable waiting time on the transplant list. While rates of ICD related complications, particularly inappropriate shocks and ICD related reoperation, were similar to those of previous randomised clinical trials, any decision to implant an ICD in a patient awaiting cardiac transplantation needs to be individualised and take into account the clinical equipoise of ICD therapy. Further, prospective randomised trials are now needed, before the findings of this study may be implemented in future guidelines.

Contributors All authors contributed significantly to the manuscript and meet the criteria for authorship.

Competing interests Johannes Holzmeister is a guest speaker for St. Jude Medical, Boston Scientific and Biotronik and has received an honorarium from Biotronik. David Hürlimann is a guest speaker for St. Jude Medical and Medtronic and has received a consulting honorarium from St. Jude Medical and educational grants from Medtronic and Boston Scientific. Thomas F Lüscher has received research grants from Biotronik, Medtronic and St. Jude. Jan Steffel has received research grants and consulting honoraria from St. Jude Medical. Frank Ruschitzka is a guest speaker for St. Jude Medical and Biotronik.

Ethics approval Informed consent complying with the ICH Good Clinical Practice guidelines was obtained if required by the institutional review board or ethics committee, and the protocol was approved by the institutional review board or ethics committee in each country.

Provenance and peer review Not commissioned; externally peer reviewed.

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Abschnitt V

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Wissenschaftlicher Leistungsausweis

Deputy Editor für Open Heart – British Medical Journals, London, United Kingdom

Reviewer für: European Heart Journal (impact factor: 14.723)

Heart (impact factor: 6.023)

Transplant International (impact factor: 3.12)

Journal of Interventional Cardiology (impact factor: 1.318)

Abschnitt VI

Publikationsliste

Original articles

1. White SK, **Fröhlich GM**, Sado DM, Maestrini V, Fontana M, Treibel TA, Tehrani S, Flett AS, Meier P, Ariti C, Davies JR, Moon JC, Yellon DM, Hausenloy DJ. Remote Ischemic Conditioning Reduces Myocardial Infarct Size and Edema in Patients With ST-Segment Elevation Myocardial Infarction. **JACC cardiovasc interventions** 2014 Sep 9. pii: S1936-8798(14)01073-5
Impact factor: 7.440
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Impact factor: 13.25
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Impact factor: 6.023

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Impact factor: 1.302

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Impact factor: 1.07

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Impact factor: 0.72

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19. **Georg M Fröhlich**, Heerajnarain Bulluck, Shah Mohdnazri, Reto Gamma, John Davies, Gerald Clesham, Jerry Sayer, Rajesh Aggarwal, Kare Tang, Paul Kelly, Rohan Jagathesan, Alamgir Kabir, Nick Robinson, Alex Sirker, Anthony Mathur, Daniel Blackman, Steven White, Pascal Meier, John P Greenwood, Derek J Hausenloy. **Rationale and Design for the Mineralocorticoid receptor antagonist pre-treatment to MINIMISE reperfusion Injury after ST-elevation myocardial Infarction: The MINIMISE STEMI trial.**

20. **Georg M Fröhlich**, Paul D Baxter, Christopher J Malkin, Julian A Scott , Neil E Moat, David Hildick-Smith, David Cunningham, Philip A MacCarthy, Uday Trivedi, Mark A de Belder, Peter F Ludman, Daniel J Blackman on behalf of the National Institute for Cardiovascular Outcomes Research (NICOR)
Access route and survival in Transcatheter Aortic Valve Implantation (TAVI) Data from the UK TAVI Registry

21. Heerajnarain Bulluck, Steven K White MD, **Georg Frohlich**, Steven G Casson, Celia O'Meara, Ayla Newton, Jennifer Nicholas, Simon Wan, Alex Sirker, James C Moon, Derek M Yellon, Ashley Groves, Leon Menezes, Derek J Hausenloy
Hybrid PET/MR metabolic imaging in the reperfused heart.

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Impact factor: 2.044

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Letters to the Editor

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33. **Froehlich G**, Crake T, Meier P. Exercise training for refractory angina: improving the coronary collateral circulation. **Cardiology**. 2012;123(2):78-9
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34. **Fröhlich GM**, Enseleit F, Wolfrum M, von Babo M, Frank M, Berli R, Hermann M, Holzmeister J, Noll G, Lüscher TF, Ruschitzka F, Rufibach K, Wilhelm M, Falk V. Response to letters regarding article, “statins and the risk of cancer after heart transplantation”. **Circulation**. 2013 Feb 5;127(5):e442.

Most recent oral presentations

PCR London Valves meeting 2014 (28th-30th September)

- Late mechanical left main obstruction following TAVI: what next?
“Best clinical case presentation” Award
- **Plan B for a valve-in-valve TAVI procedure - Antegrade approach to cross an aortic bio-prosthesis**

Abschnitt VII

Danksagung

Meinen Eltern