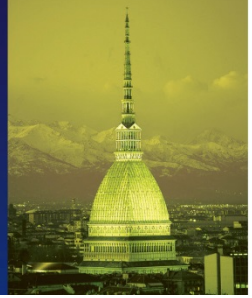
TURIN,
October
25th-27th
2018
Starhotels
Majestic

GIORNATE
CARDIOLOGICHE
TORINESI



UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

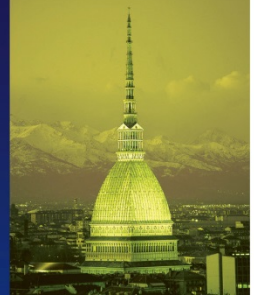
Heart Failure: An Update

Gaetano M. De Ferrari

Dept. of Molecular Medicine, University of Pavia, Italy;
Coronary Care Unit and Cardiovascular Clinical Research
Center , Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

OSPITALE DI S. MATTEO
PAVIA

CCRC

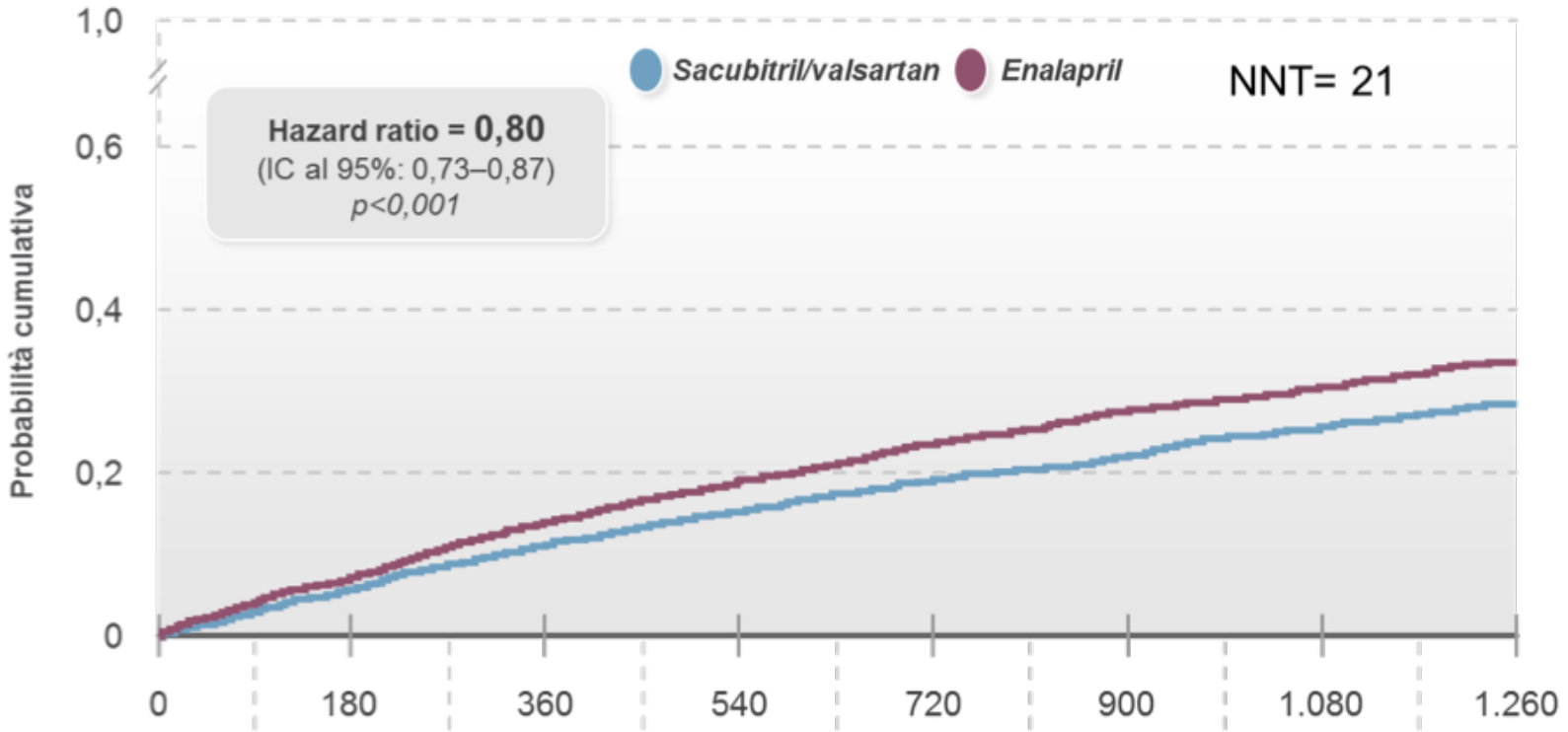


No conflict of interest

- Pharmacological treatment for HF: ARNI and SGLT2i
- Non-pharmacological treatment: Mitraclip
- Prediction of SCD risk in patients with nonischemic DCM
- Neuromodulation in patients with recurrent ICD shocks

- <u>Pharmacological treatment for HF: ARNI and SGLT2i</u>
- Non-pharmacological treatment: Mitraclip
- Prediction of SCD risk in patients with nonischemic DCM
- Neuromodulation in patients with recurrent ICD shocks

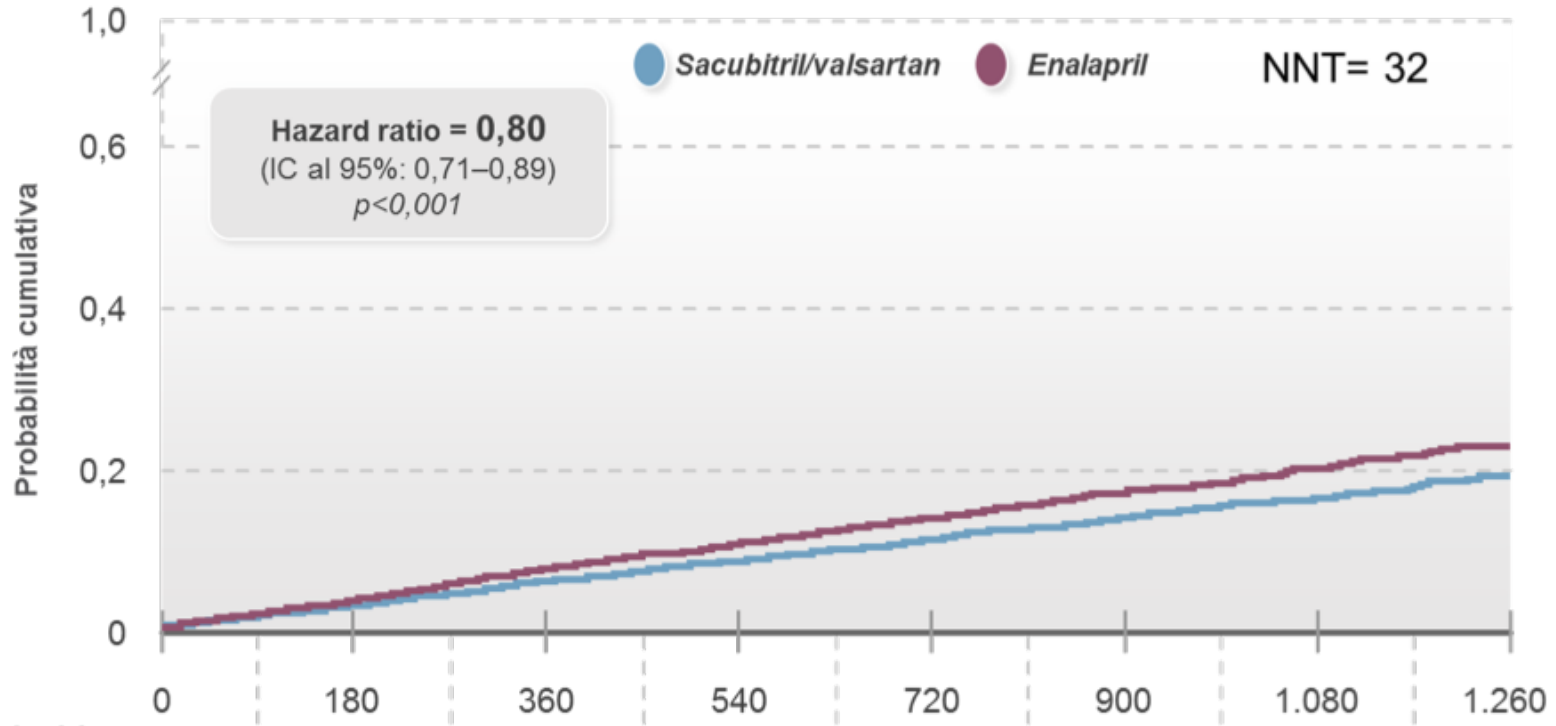
Paradigm – HF: CV Death or HF Hospitalization



N° a rischio								
Sacubitril/valsartan	4.187	3.922	3.663	3.018	2.257	1.544	896	249
Enalapril	4.212	3.883	3.579	2.922	2.123	1.488	853	236

McMurray et al. N Engl Med 2014;371:993–1004.

Paradigm – HF: Cardiovascular Death



N° a rischio								
Sacubitril/valsartan	4.187	4.056	3.891	3.282	2.478	1.716	1.005	280
Enalapril	4.212	4.051	3.860	3.231	2.410	1.726	994	279

McMurray et al. N Engl Med 2014;371:993–1004.

Implementation of Sacubitril/Valsartan

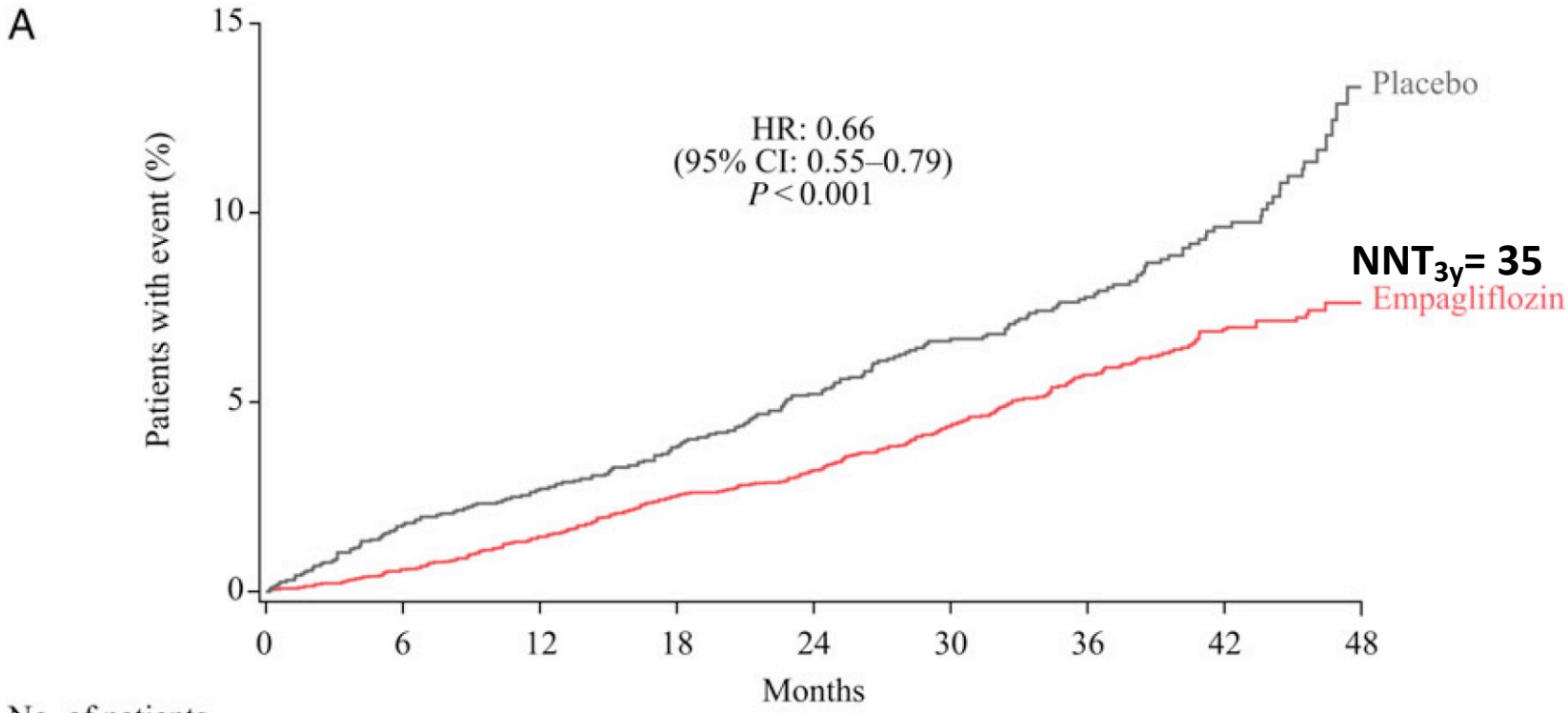
Table 2 Comparison of baseline characteristics with PARADIGM-HF sacubitril/valsartan arm

Variable	Real world (n = 120)	Sacubitril/valsartan arm (n = 4187)	P-value
Demographics			
Age, years	66.0 ± 10.5	63.8 ± 11.5	0.038
Male	98 (81%)	3308 (79%)	0.480
Heart failure aetiology			0.159
Ischaemic	80 (66.6%)	2506 (59.9%)	
Non-ischaemic	40 (33.3%)	1681 (40.1%)	
Physical features			
Systolic blood pressure, mmHg	120 ± 20	122 ± 15	0.154
BMI, kg/m^2	28.9 ± 9.0	28.1 ± 5.5	0.125
Heart rate, b.p.m.	69 ± 15	72 ± 12	0.007
Co-morbidities			
Atrial fibrillation	51 (42%)	1517 (36%)	0.159
Hypertension	56 (46%)	2969 (71%)	<0.001
Diabetes	29 (24%)	1451 (35%)	0.017
Laboratory analysis			
Serum creatinine, mg/dL	1.28 ± 0.4	1.13 ± 0.3	<0.001
NYHA class			0.013
Class I	0 (0%)	180 (4.3%)	
Class II	76 (63.5%)	2998 (71.6%)	
Class III	43 (35.5%)	969 (23.1%)	
Class IV	1 (1%)	33 (0.8%)	
Echocardiography			
LVEF, %	26 ± 6	29 ± 6	<0.001
Heart failure therapies			
ACE-I	98 (82%)	3266 (78%)	0.480
ARB	22 (18%)	929 (22%)	0.316
Beta-blocker	115 (95%)	3899 (93%)	0.520
Aldosterone antagonist	99 (82%)	2271 (54%)	<0.001
Loop diuretic	72 (60%)	3363 (80%)	<0.001
CRT	52 (43%)	292 (7%)	<0.001
ICD	67 (55%)	623 (15%)	<0.001

Reached dose : 219 ± 12 vs. 375 ± 75 mg, p<0.001

Martens et al ESC Heart Failure 2018; 5: 275–283

EMPA – REG: CV Death or HF Hospitalization



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Fitchett D, et al. Eur Heart J 2016 doi:10.1093/eurheartj/ehv728

Ongoing Studies with SGLT2i

Table 3 Ongoing randomized clinical trials with SGLT2 inhibitors directed to heart failure patients

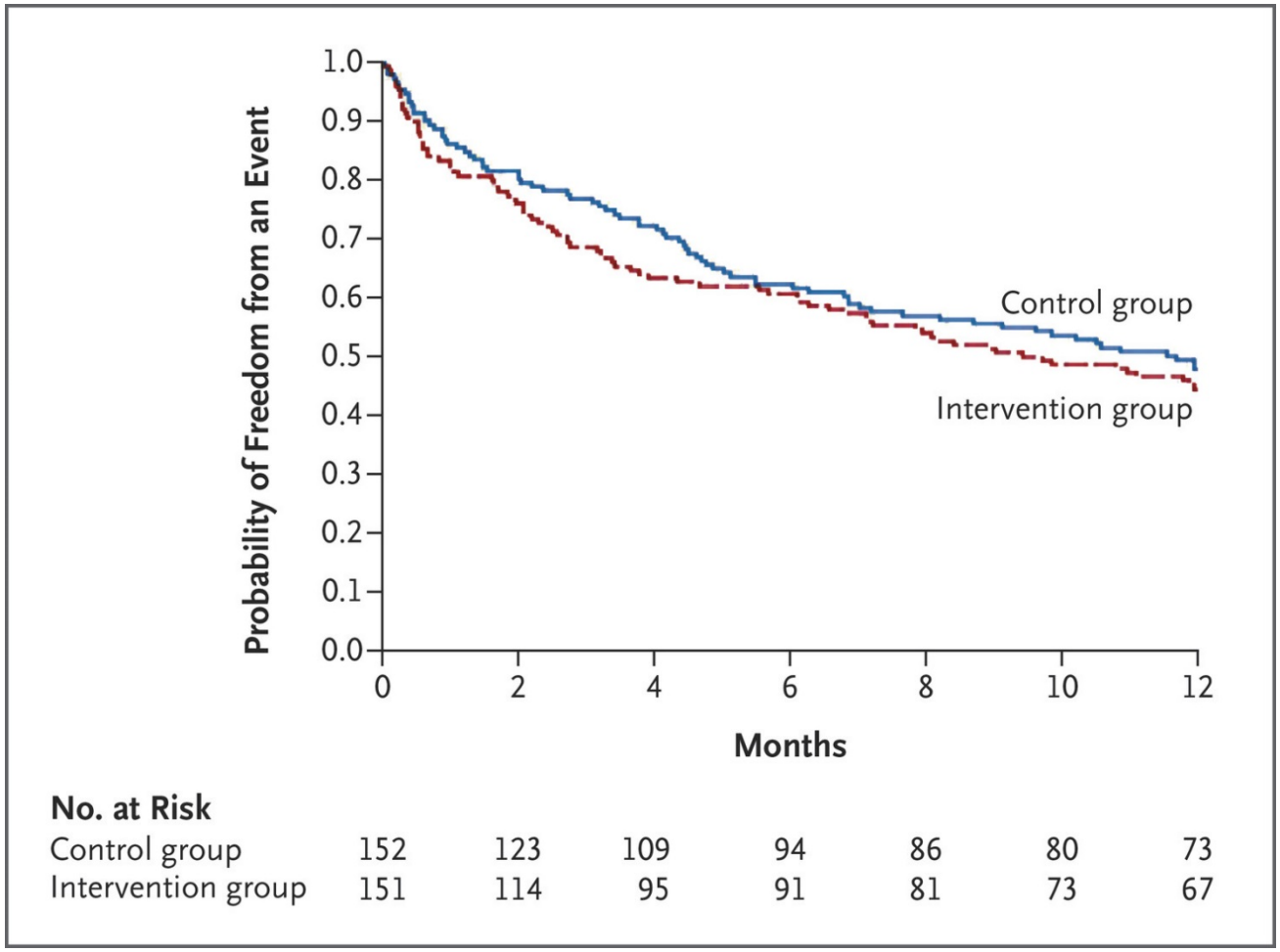
Study name	Agent	Unique identifier	Comparator	Type of heart failure patients included	T2DM as inclusion criteria	Primary outcome	Heart failure outcomes
–	Canagliflozin	NCT02920918	Sitagliptin	HFrEF	Yes	Change in aerobic exercise capacity and ventilator efficiency	Cardiac function, cardiac biomarkers
–	Dapagliflozin	NCT02751398	Placebo	HFpEF	Yes	Change in subclinical diastolic dysfunction assessed by diastolic stress echocardiography	Primary outcome, cardiac function
–	Luseogliflozin	UMIN000018395	Voglibose (alpha-glucosidase inhibitor)	HFpEF	Yes	Change in BNP levels	Primary outcome
Canacardia-HF	Canagliflozin	NCT03298009	Placebo	HFrEF	Yes	Change in myocardial dietary fatty acid uptake, assessed using [18F]-FTHA with PET/CT scanning	Cardiac biomarkers
CANDLE	Canagliflozin	UMIN000017669	Glimepiride	HFrEF and HFpEF	Yes	Change in NT-proBNP levels	Primary Outcome, cardiac function, cardiac biomarkers
DAPA-HF	Dapagliflozin	NCT03036124	Placebo	HFrEF	No	CV death or hospitalization for HF or an urgent HF visit	Primary Outcome, KCCQ questionnaire
DEFINE-HF	Dapagliflozin	NCT02653482	Placebo	HFrEF	Yes	Change in NT-proBNP levels	Primary Outcome, KCCQ questionnaire
ELSI	Empagliflozin	NCT03128528	Placebo	HFrEF and HFmrEF	No	Skin sodium content	NT-proBNP levels
EMBRACE-HF	Empagliflozin	NCT03030222	Placebo	HFrEF and HFpEF		Change in pulmonary artery diastolic pressure	NT-proBNP levels, KCCQ questionnaire
EMPATROPHY	Empagliflozin	NCT02728453	Glimepiride	HFrEF and HFpEF		Change in left ventricular mass	Cardiac function
EMPEROR-Preserved	Empagliflozin	NCT03057951	Placebo	HFpEF	No	Time to first adjudicated CV death or adjudicated hospitalization for heart failure	Primary outcome, KCCQ questionnaire
EMPEROR-Reduced	Empagliflozin	NCT03057977	Placebo	HFrEF	No	Time to first adjudicated CV death or adjudicated hospitalization for heart failure	Primary outcome, KCCQ questionnaire
ERADICATE-HF	Ertugliflozin	NCT03416270	Placebo	HFrEF	Yes	Proximal sodium reabsorption (FENa)	Cardiac function, cardiac biomarkers
EXCEED	Ipragliflozin	UMIN000027095	Other non-SGLT2 drugs	HFrEF	Yes	Change in echocardiography-based cardiac function test parameters	Primary outcome, cardiac function, cardiac biomarkers
PRESERVED-HF	Dapagliflozin	NCT03030235	Placebo	HFpEF	Yes (or pre-DM)	Change of NT-proBNP levels	Primary outcome, KCCQ questionnaire
RECEDE-CHF	Empagliflozin	NCT03226457	Placebo	HFrEF	Yes	Change in urine output	–
REFORM	Dapagliflozin	NCT02397421	Placebo	HFrEF	Yes	Change in LV end systolic volume or LV end diastolic volume	Primary outcome, cardiac function, cardiac biomarkers

3-point MACE (major adverse cardiac events): death from cardiovascular causes, non-fatal stroke, non-fatal myocardial infarction

LV, left ventricle; *HFpEF*, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction; *HFmrEF*, heart failure with mid-range ejection fraction; *KCCQ*, Kansas City Cardiomyopathy Questionnaire

- Pharmacological treatment for HF: ARNI and SGLT2i
- Non-pharmacological treatment: Mitraclip
- Prediction of SCD risk in patients with nonischemic DCM
- Neuromodulation in patients with recurrent ICD shocks

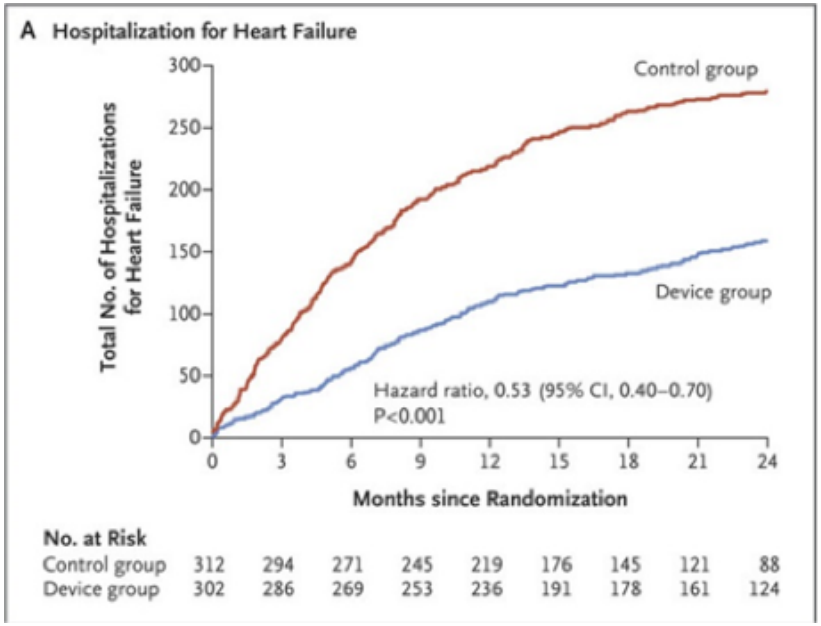
MITRA-FR All Cause Death + HF Hospitalization

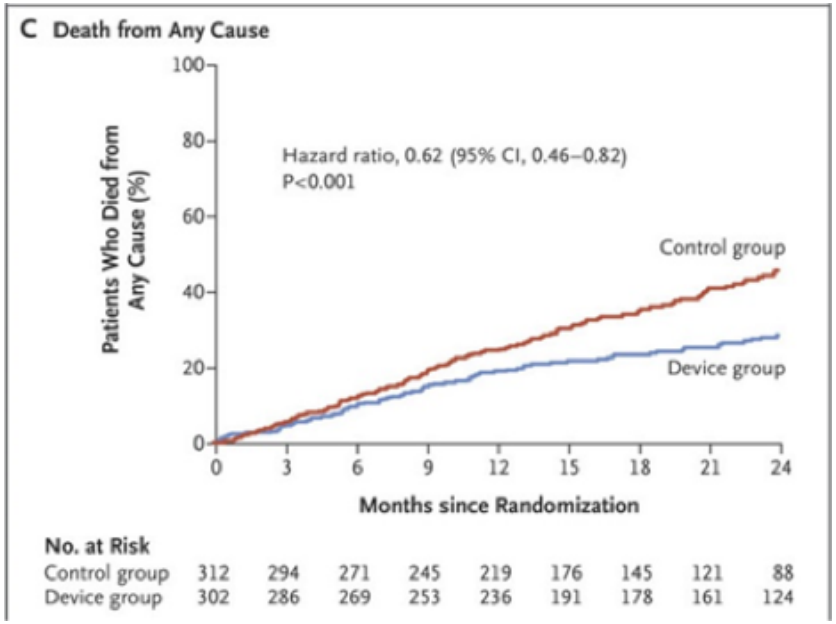


No. at Risk							
Control group	152	123	109	94	86	80	73
Intervention group	151	114	95	91	81	73	67

Obadia J, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1805374

COAPT - All Cause Death + HF Hospitalization





Stone GW, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1806640

MITRA-FR Endpoints

Table 3. Primary Outcome and Secondary Efficacy Outcomes at 12 Months (Intention-to-Treat Population).

Outcome	Intervention Group (N=152)	Control Group (N=152)	Hazard Ratio or Odds Ratio (95% CI)*	P Value†
Composite primary outcome: death from any cause or unplanned hospitalization for heart failure at 12 months — no. (%)	83 (54.6)	78 (51.3)	1.16 (0.73–1.84)	0.53
Secondary outcomes‡				
Death from any cause	37 (24.3)	34 (22.4)	1.11 (0.69–1.77)	
Cardiovascular death	33 (21.7)	31 (20.4)	1.09 (0.67–1.78)	
Unplanned hospitalization for heart failure	74 (48.7)	72 (47.4)	1.13 (0.81–1.56)	
Major adverse cardiovascular events§	86 (56.6)	78 (51.3)	1.22 (0.89–1.66)	

Obadia J, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1805374

COAPT - Endpoints

End Point	Device Group (N=302)	Control Group (N=312)	Hazard Ratio (95% CI)	P Value†
Primary				
Effectiveness: all hospitalizations for heart failure within 24 mo — no. of events/total no. of patient-yr (annualized rate)	160/446.5 (35.8)	283/416.8 (67.9)	0.53 (0.40 to 0.70)‡	<0.001§
Safety: freedom from device-related complications at 12 mo — Kaplan–Meier estimate of event-free rate (lower 95% confidence limit)	96.6 (94.8)	—	—	<0.001 for comparison with goal of 88.0%¶
Secondary, listed in hierarchical order				
Mitral regurgitation grade of 2+ or lower at 12 mo — no./total no. (%)‖	199/210 (94.8)	82/175 (46.9)	—	<0.001**
Death from any cause at 12 mo — no. of events (Kaplan–Meier estimate of event rate)	57 (19.1)	70 (23.2)	0.81 (0.57 to 1.15)††	<0.001 for noninferiority‡‡
Death or hospitalization for heart failure within 24 mo	—	—	—	<0.001§§
Change in KCCQ score from baseline to 12 mo — points¶¶	12.5±1.8	−3.6±1.9	16.1 (11.0 to 21.2)‖‖	<0.001***
Change in distance on 6-min walk test from baseline to 12 mo — m†††	−2.2±9.1	−60.2±9.0	57.9 (32.7 to 83.1)‖‖	<0.001***
All hospitalizations for any cause within 24 mo — no. of events/ total no. of patient-yr (annualized rate)	474/446.5 (106.2)	610/416.8 (146.4)	0.76 (0.60 to 0.96)	0.02§
NYHA functional class of I or II at 12 mo — no./total no. (%)	171/237 (72.2)	115/232 (49.6)	—	<0.001**
Change in left ventricular end-diastolic volume from baseline	−3.7±5.1	17.1±5.1	−20.8 (−34.9 to −6.6)‖‖	0.004***
Death from any cause within 24 mo — no. of events (Kaplan–Meier estimate of event rate)	80 (29.1)	121 (46.1)	0.62 (0.46 to 0.82)	<0.001‡‡‡
Freedom from death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication at 30 days — % (lower 95% confidence limit)	96.9 (94.7)	—	—	<0.001 for comparison with goal of 80.0%**

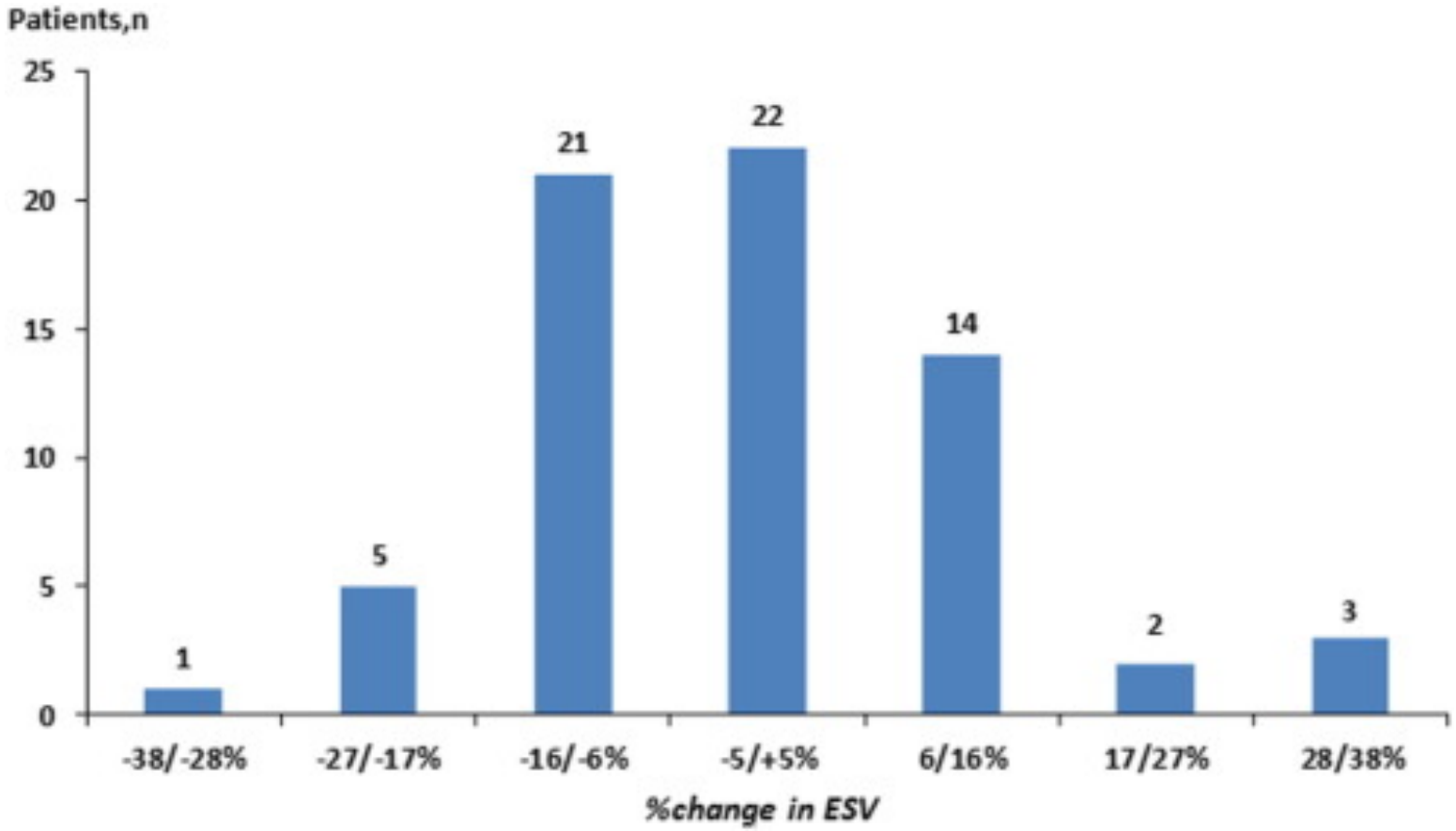
Stone GW, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1806640

Causes for contrasting Results?

- More severe MR in COAPT (EROA>30 vs >20 in MITRA-FR)
- Less dilated ventricles in COAPT (LVEDVI 101 vs 135)
- More procedural success and less complications in COAPT
- More aggressive uptitration of drugs in COAPT
- Very selected patients

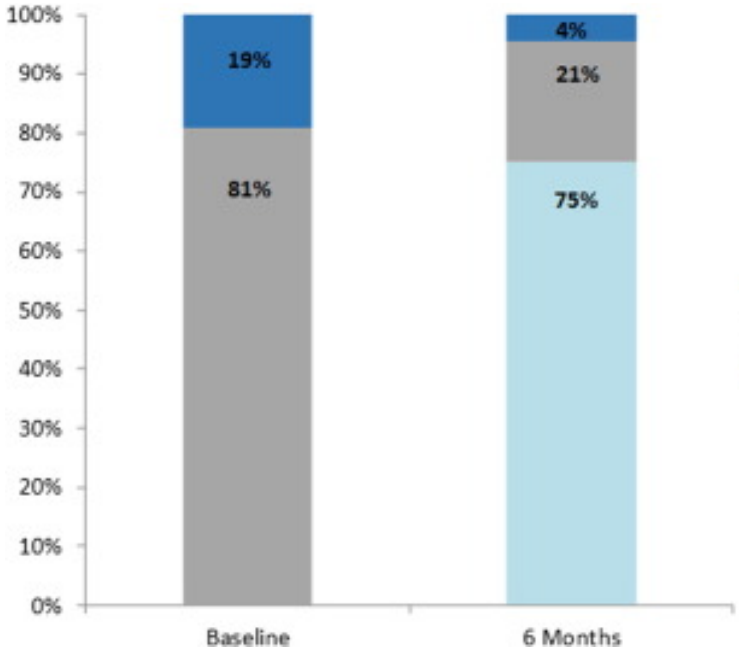
Future trials (such as RESHAPE-HF2) will help

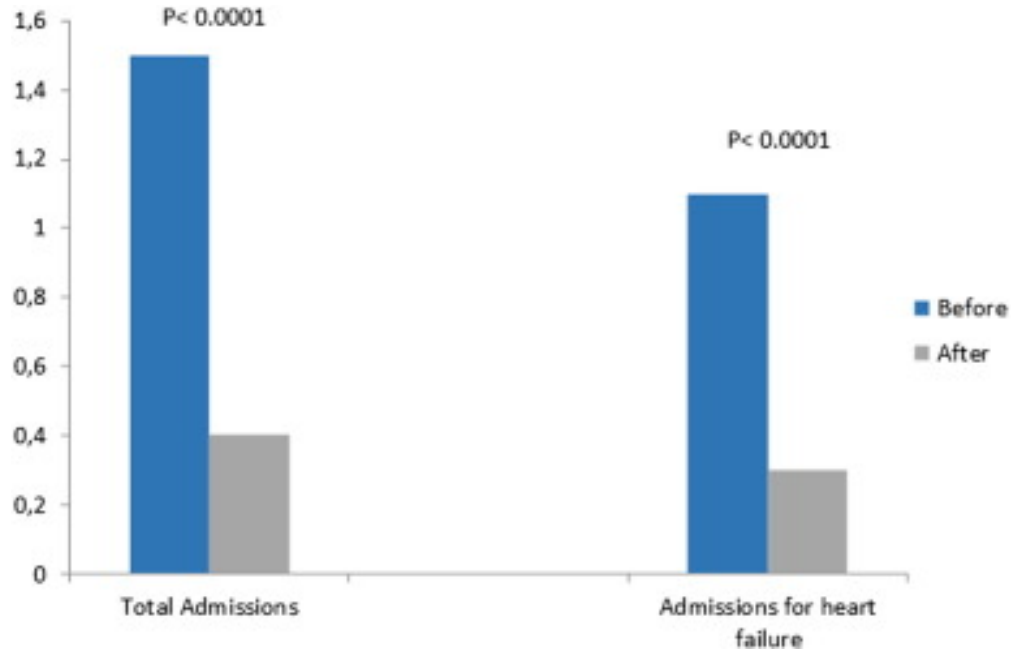
Short-term results of MitraClip in advanced refractory HF



Berardini A, et al. Int J Cardiol. 2017;228:191-197

Short-term results of MitraClip in advanced refractory HF

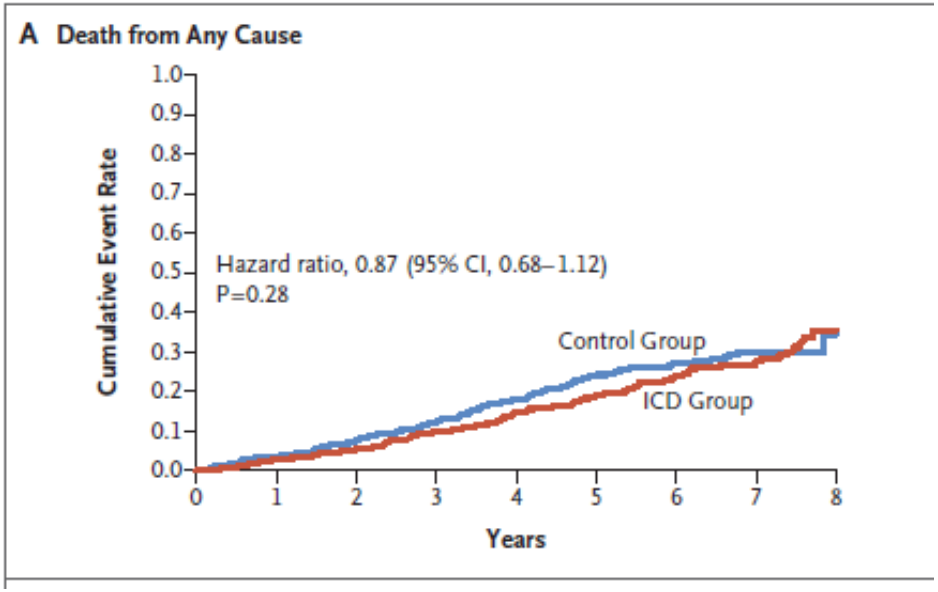


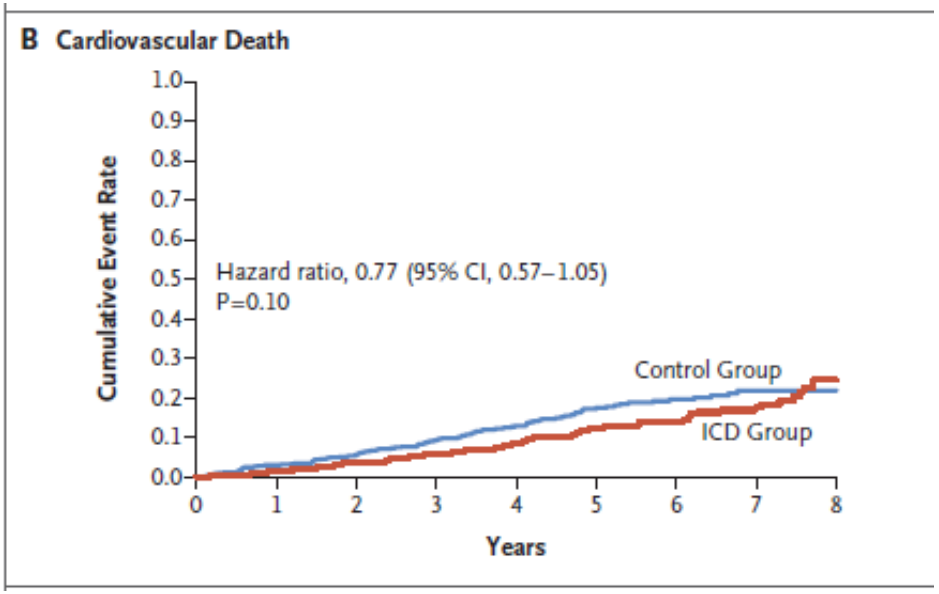


Berardini A, et al. Int J Cardiol. 2017;228:191-197

- Pharmacological treatment for HF: ARNI and SGLT2i
- Non-pharmacological treatment: Mitraclip
- Prediction of SCD risk in patients with nonischemic DCM
- Neuromodulation in patients with recurrent ICD shocks

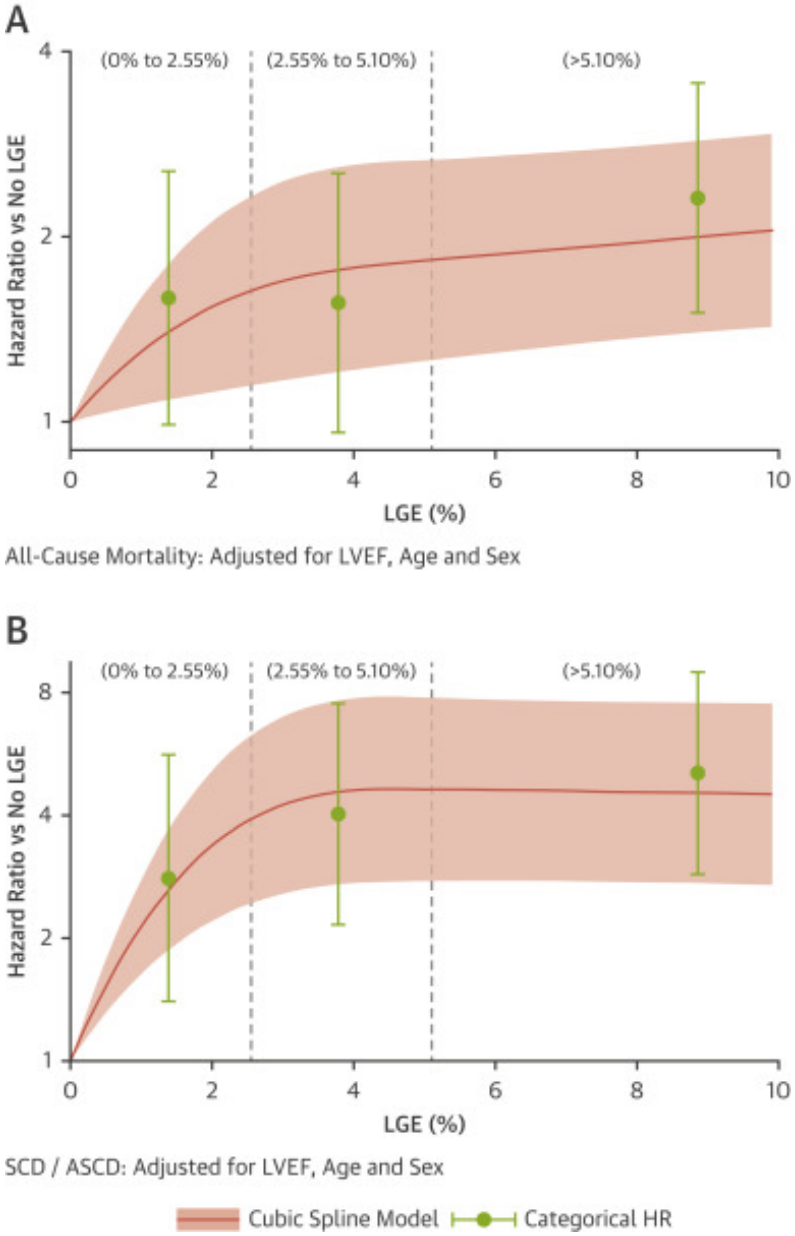
Danish Study - All-cause and Cardiovascular Death





Køber L, et al. N Engl J Med. 2016;375(13):1221-30

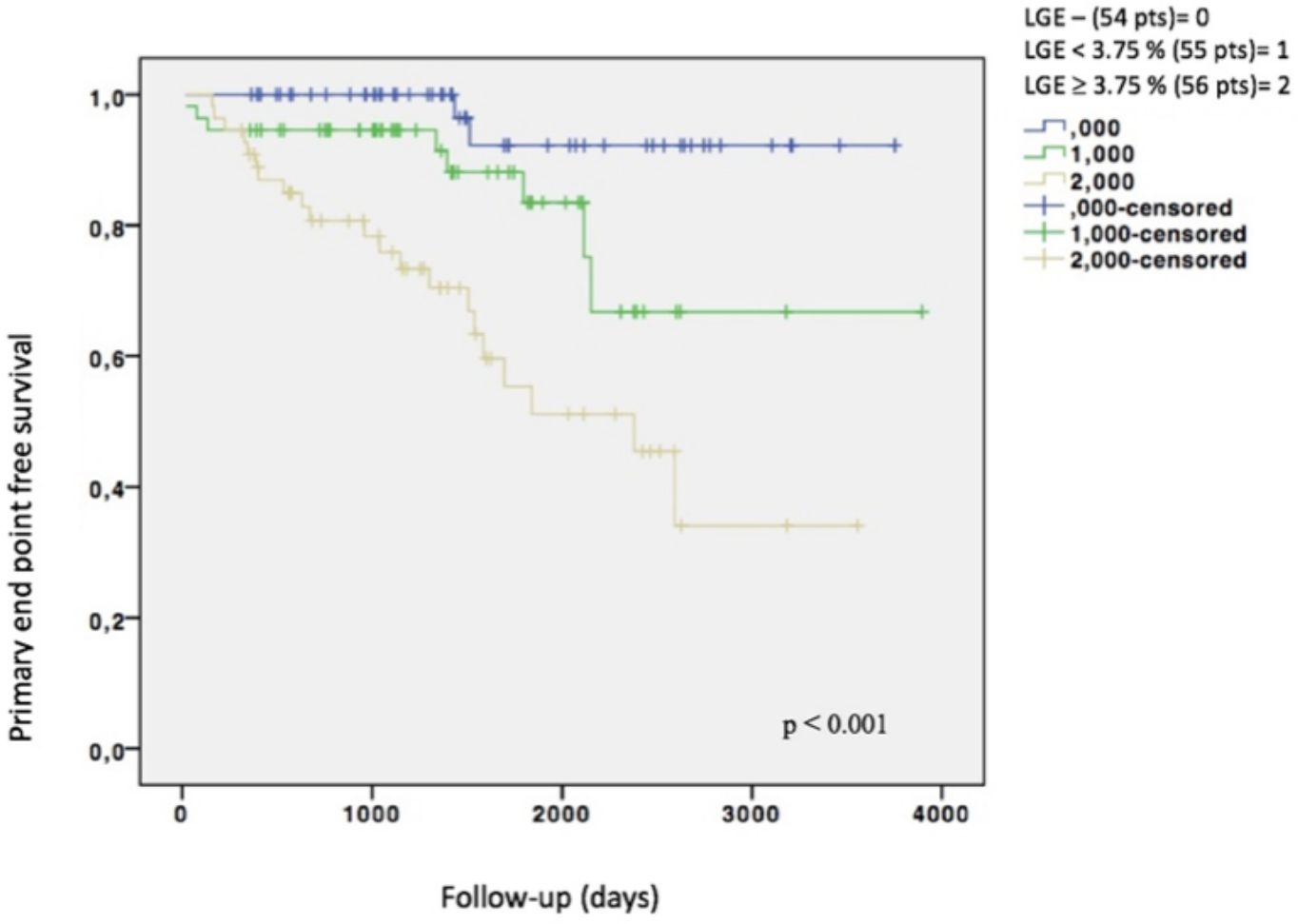
LGE at Cardiac MRI and HRs for Death and SC Death



N=874

Halliday BP, et al. JACC Cardiovasc Imaging. 2018 Sep 6. doi: 10.1016/j.jcmg.2018.07.015

LGE at Cardiac MRI and Event-free survival

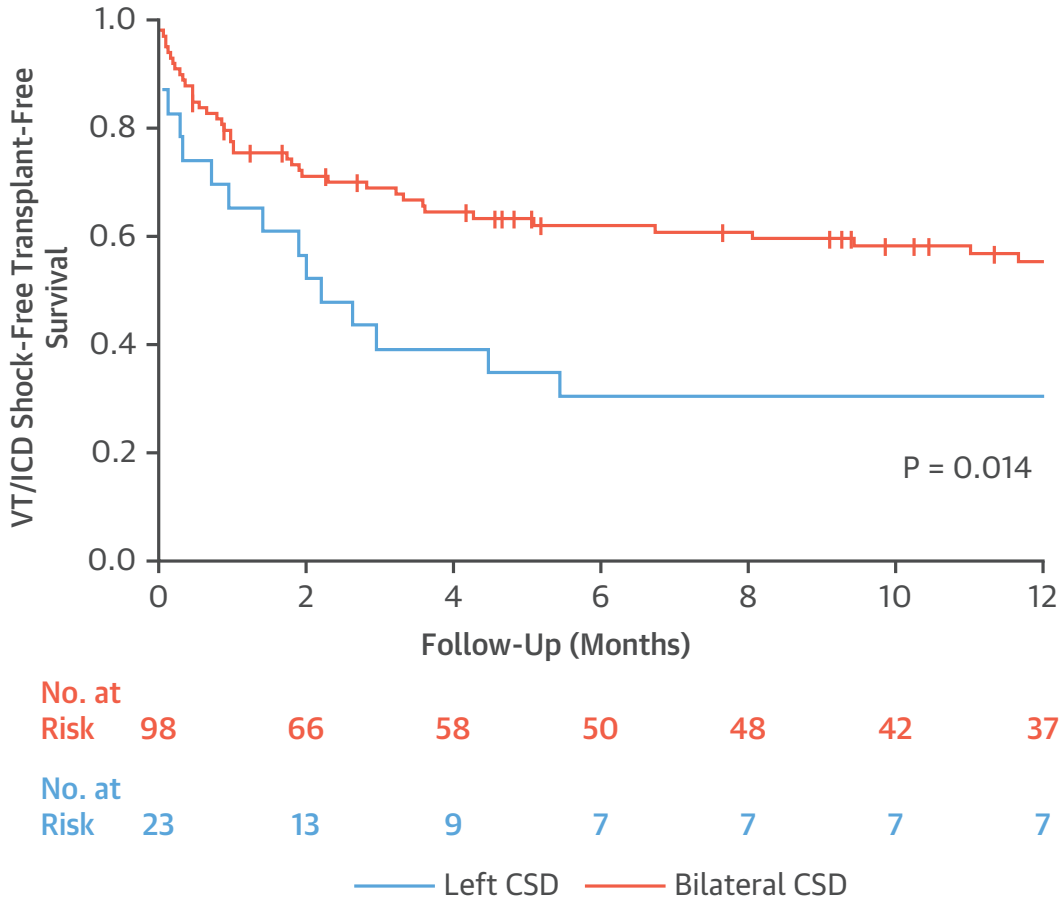


Raineri et al submitted

- Pharmacological treatment for HF: ARNI and SGLT2i
- Non-pharmacological treatment: Mitraclip
- Prediction of SCD risk in patients with nonischemic DCM
- Neuromodulation in patients with recurrent ICD shocks

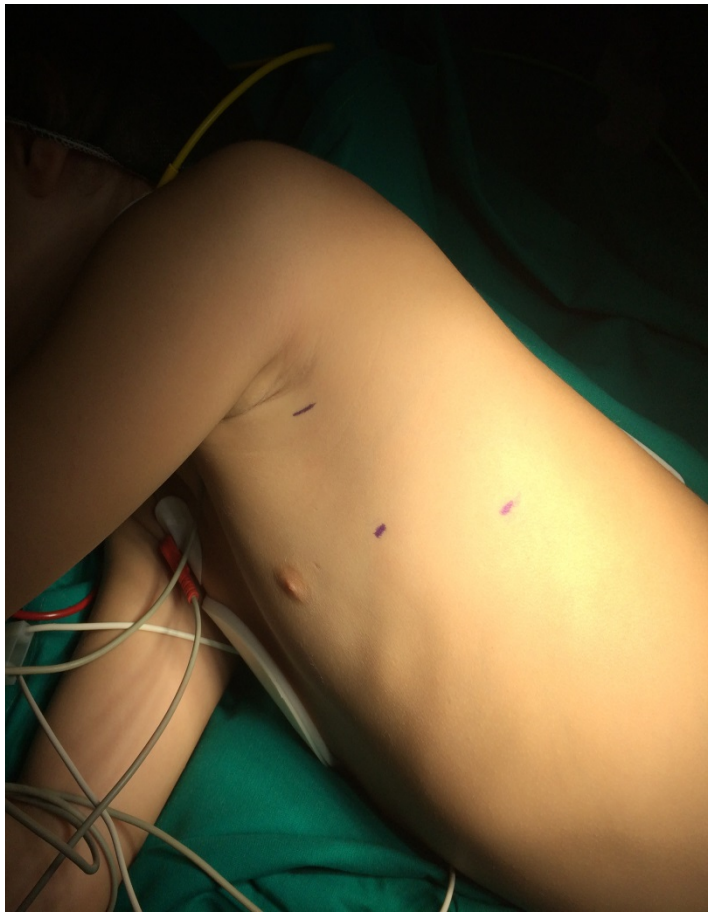
Survival Free from ICD Shock or Transplant

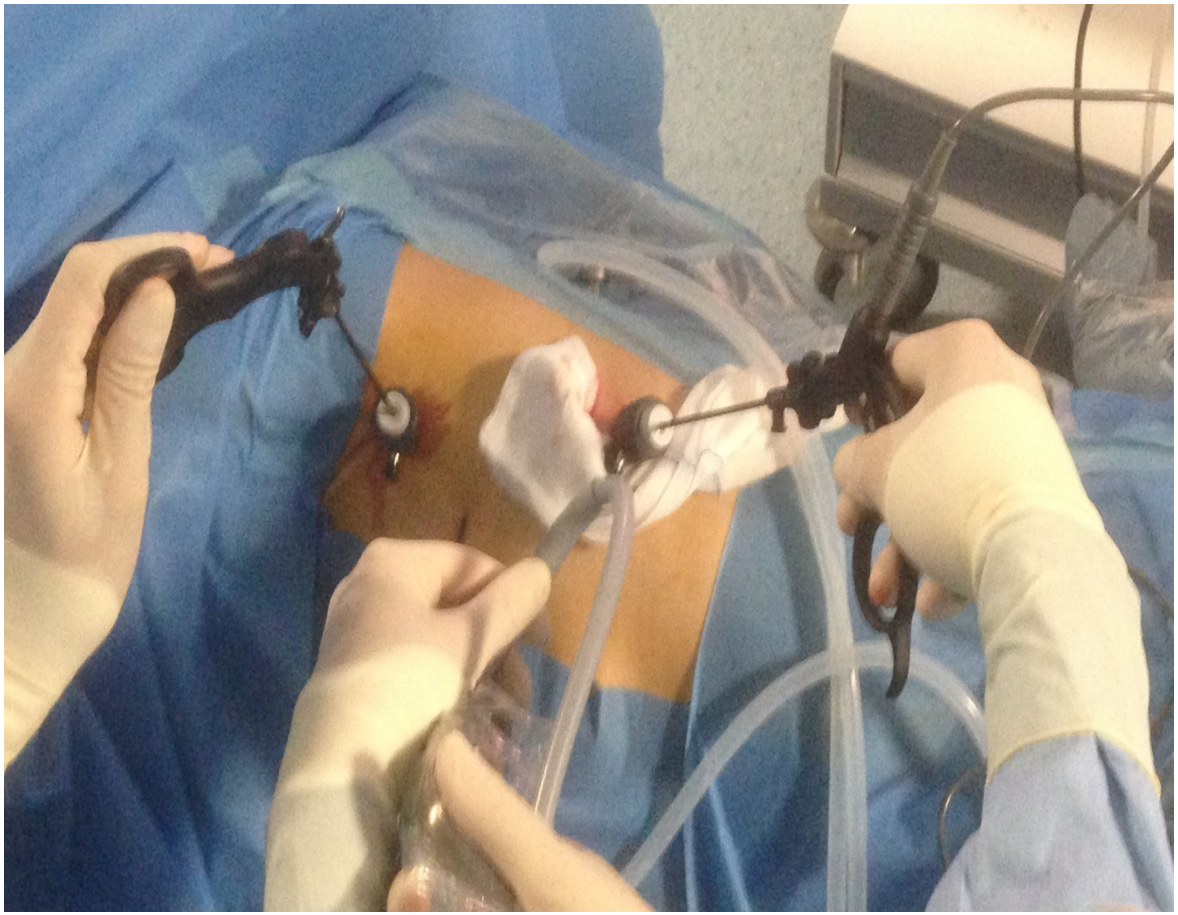
Effects of Left or Bilateral Cardiac Sympathetic Denervation



Vaseghi et al JACC 2017;69:3070-3080

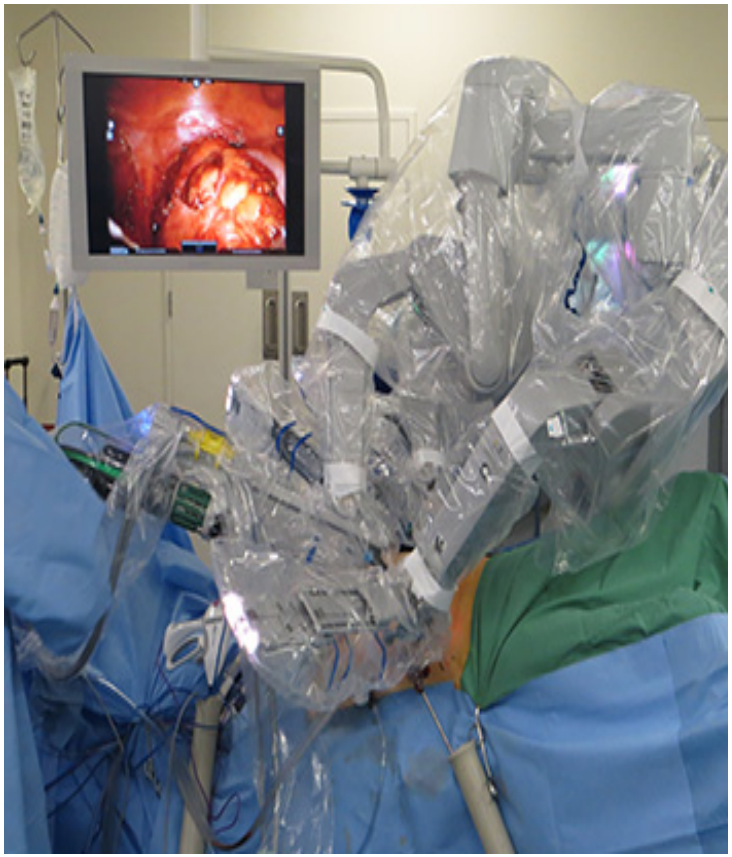
VATS-CSD: Surgical Technique





VATS-CSD Robotic Approach

da Vinci Si HD SURGICAL SYSTEM



VATS-BCSD: Population in Pavia

	N = 8
Male	6, 75%
Mean age (range)	55 ± 20 (range 17-75)
Robotic VATS	2, 25%
ICD (transvenous)	8, 100%
CRT-D	4, 50%
Previous VT ablation	2, 25%
Monomorphic VT only	2, 25 %
Previous Electrical Storm	8, 100%
Ongoing amiodarone	5, 62.5%
Amiodarone contraindication	2, 25%
NICM	4, 50%
ICM	2, 25%
ARVC	1, 12%
1 LMNA/C	1, 12%
LVEF (%)	32 ± 14
NYHA Class I/II/III	4/2/2
Indication to OHT/VAD	3, 37%

VATS-BCSD: Results

Median FU 10 months (IQ range2-19)

- 5 patients (62%) had no recurrences (4 NICM, 1 ARVC)
- 1 patient (ICM) had 3 shocks recurrences during severe amiodarone induced thyrotoxicosis (besides that only 3 ATP in 17 months after BCSD)
- 2 patients had ES recurrences, one (LMNA/C, LVEF 20%, severe MR, CI 1.4) during HF instabilization, the second one (ICM, LVEF 20%, CI 1.1) during sepsis .

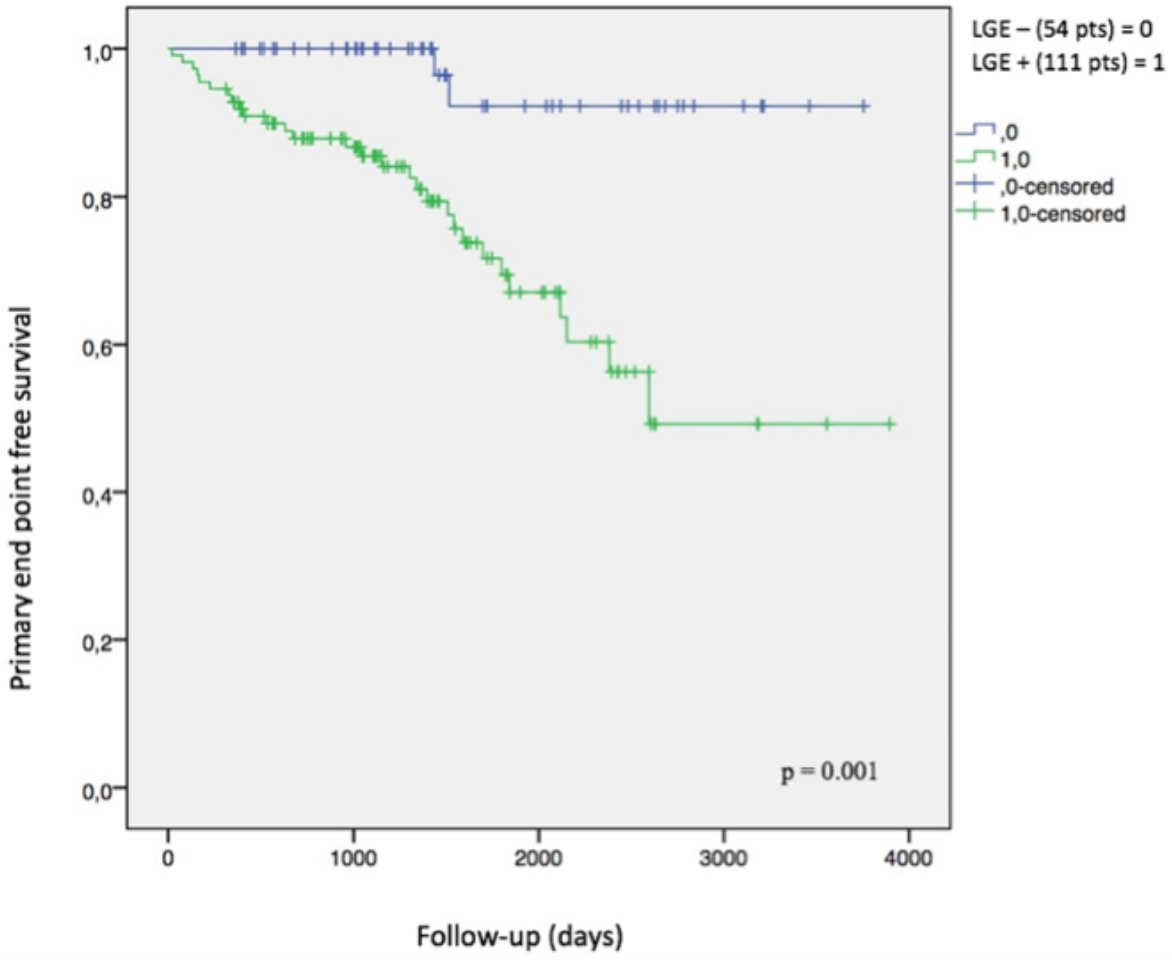
- **Overall, 6/8 (80%) patiens can be considered responders**

WHAT'S ON THE MENU

- Pharmacological treatment for HF: …GLT2i
- Non-pharmacological trea…
- Prediction of SCD … in nonischemic DCM
- Neurom… …ts with recurrent ICD shocks

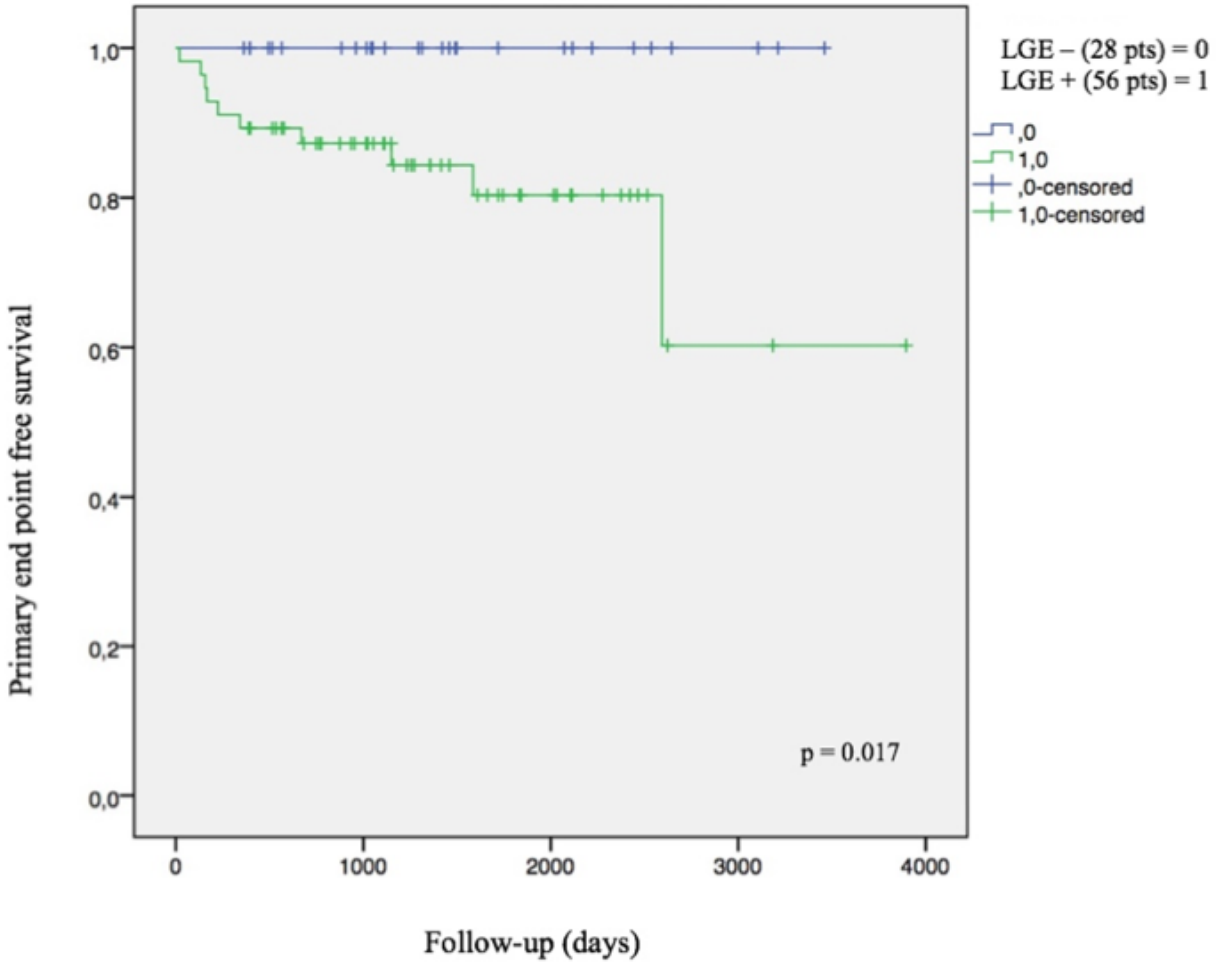
THANK-YOU

Survival curve showing freedom from the primary endpoint among patients with (green line) or without (blue line) late gadolinium enhancement at cardiac MR imaging



Raineri C. Unpublished

Survival curve showing freedom from the primary endpoint among patients with LV ejection fraction > 30% and < 50% and with (green line) or without (blue line) late gadolinium enhancement at cardiac MR imaging



Raineri C. Unpublished

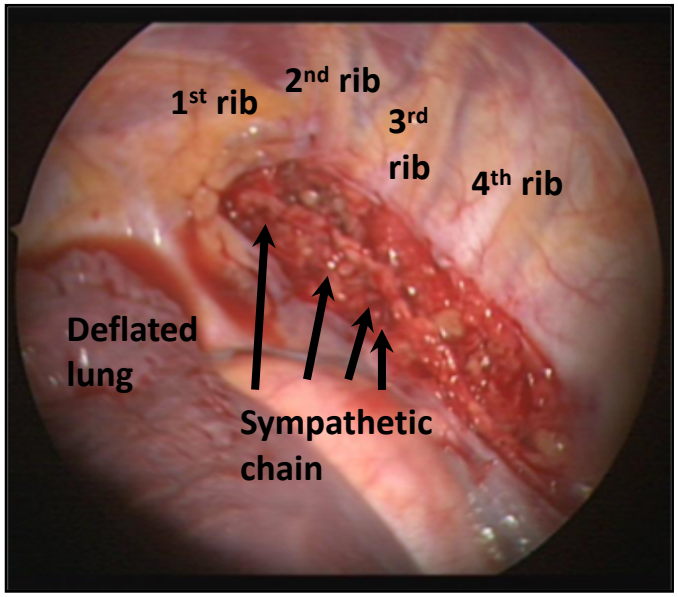
VATS-CSD: esperienza pavese

Da ottobre 2014 effettuiamo la procedura la per via toracoscopica mini-invasiva (VATS) e da novembre 2017 abbiamo implementato la tecnica robotica.

Parallelamente abbiamo esteso le indicazioni (comprendendo anche la BCSD):

- Malattie aritmogene ereditarie (LQTS, CPVT, FV idiopatica), prevenzione secondaria ma anche primaria

- Aritmie ventricolari refrattarie nelle cardiopatie strutturali (Sindrome di Barlow, ARVC, CMDI, CMDNI)



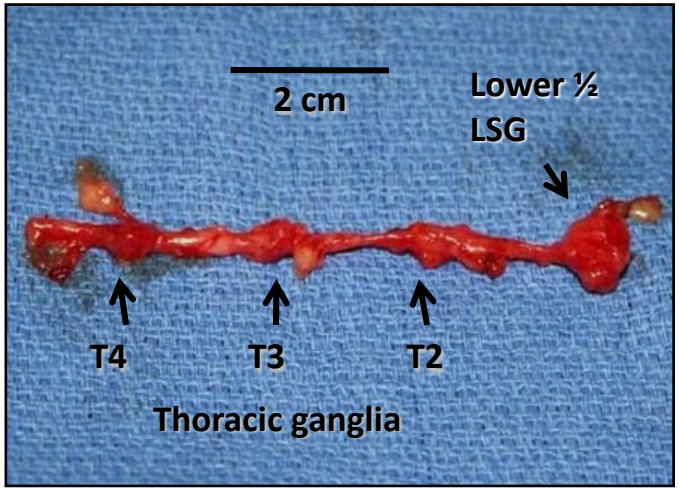


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Intervention Group (N=152)	Control Group (N=152)
Age — yr	70.1±10.1	70.6±9.9
Age >75 yr — no. (%)	51 (33.6)	59 (38.8)
Male sex — no. (%)	120 (78.9)	107 (70.4)
Medical and surgical history – no./total no. (%)		
Ischemic cardiomyopathy	95/152 (62.5)	85/151 (56.3)
Nonischemic cardiomyopathy	57/152 (37.5)	66/151(43.7)
Previous myocardial infarction	75/152 (49.3)	52/152 (34.2)
Previous coronary revascularization	71/152 (46.7)	64/151 (42.4)
Atrial fibrillation	49/142 (34.5)	48/147 (32.7)
Diabetes	50/152 (32.9)	39/152 (25.7)
Renal insufficiency	22/152 (14.5)	19/152 (12.5)
NYHA class — no. (%)		
II	56 (36.8)	44 (28.9)
III	82 (53.9)	96 (63.2)
IV	14 (9.2)	12 (7.9)
Systolic blood pressure — mm Hg	109±16	108±18
Heart rate — beats/min	73±13	72±13
Median EuroSCORE II (IQR)†	6.6 (3.5–11.9)	5.9 (3.4–10.4)
Left ventricular ejection fraction — %	33.3±6.5	32.9±6.7
Left ventricular end-diastolic volume — ml/m^2	136.2±37.4	134.5±33.1
Effective regurgitant orifice area — mm^2	31±10	31±11
Regurgitant volume — ml	45±13	45±14
Median NT-proBNP (IQR) — ng/liter‡	3407 (1948–6790)	3292 (1937–6343)
Median brain natriuretic peptide (IQR) — ng/liter‡	765 (417–1281)	835 (496–1258)
Glomerular filtration rate — ml/min	48.8±19.7	50.2±20.1

Obadia J, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1805374

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Device Group (N=302)	Control Group (N=312)
Clinical		
Age — yr	71.7±11.8	72.8±10.5
Male sex — no. (%)	201 (66.6)	192 (61.5)
Diabetes — no. (%)	106 (35.1)	123 (39.4)
Hypertension — no. (%)	243 (80.5)	251 (80.4)
Hypercholesterolemia — no. (%)	166 (55.0)	163 (52.2)
Previous myocardial infarction — no. (%)	156 (51.7)	160 (51.3)
Previous percutaneous coronary intervention — no. (%)	130 (43.0)	153 (49.0)
Previous coronary-artery bypass grafting — no. (%)	121 (40.1)	126 (40.4)
Previous stroke or transient ischemic attack — no. (%)	56 (18.5)	49 (15.7)
Peripheral vascular disease — no. (%)	52 (17.2)	57 (18.3)
Chronic obstructive pulmonary disease — no. (%)	71 (23.5)	72 (23.1)
History of atrial fibrillation or flutter — no. (%)	173 (57.3)	166 (53.2)
Body-mass index†	27.0±5.8	27.1±5.9
Creatinine clearance		
Mean — ml/min‡	50.9±28.5	47.8±25.0
≤60 ml/min — no./total no. (%)	214/299 (71.6)	227/302 (75.2)
Anemia — no./total no. (%)§	180/301 (59.8)	192/306 (62.7)
STS risk score¶		
Mean — %	7.8±5.5	8.5±6.2
≥8% — no. (%)	126 (41.7)	136 (43.6)
Risk of surgery-related complications or death — no./total no (%)‖		
High	205/299 (68.6)	218/312 (69.9)
Not high	94/299 (31.4)	94/312 (30.1)
Related to heart failure		
Cause of cardiomyopathy — no. (%)		
Ischemic	184 (60.9)	189 (60.6)
Nonischemic	118 (39.1)	123 (39.4)
NYHA class — no./total no. (%)		
I	1/302 (0.3)	0/311 (0)
II	129/302 (42.7)	110/311 (35.4)
III	154/302 (51.0)	168/311 (54.0)
IVa, ambulatory	18/302 (6.0)	33/311 (10.6)
Hospitalization for heart failure within previous 1 yr — no. (%)	176 (58.3)	175 (56.1)
Previous cardiac resynchronization therapy — no. (%)	115 (38.1)	109 (34.9)
Previous implantation of defibrillator — no. (%)	91 (30.1)	101 (32.4)
B-type natriuretic peptide level — pg/ml	1014.8±1086.0	1017.1±1212.8
N-terminal pro–B-type natriuretic peptide level — pg/ml	5174.3±6566.6	5943.9±8437.6
Assessed at the echocardiographic core laboratory		
Severity of mitral regurgitation — no./total no. (%)		
Moderate-to-severe, grade 3+	148/302 (49.0)	172/311 (55.3)
Severe, grade 4+	154/302 (51.0)	139/311 (44.7)

Stone GW, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1806640