# Novel aspects of optimization the efficiency of cardiac resynchronizaton therapy

PhD thesis

**Peter Bogyi MD**

Basic and Translational Medicine Doctoral School
Semmelweis University



Supervisor: Gabor Zoltan Duray, MD, Ph.D.
Mate Vamos, MD, Ph.D.
Official reviewers: Gabor Bencsik MD, Ph.D.
Peter Perge MD, Ph.D

Head of the Final Examination Committee:
Tivadar Tulassay MD, Ph.D, DSc

Members of the Final Examination Committee:
Attila Patocs, MD, Ph.D.
Peter Andreka MD, Ph.D.

Budapest

2020

## 1. INTRODUCTION

Effectivity of cardiac resynchronization therapy (CRT) in treating heart failure with reduced ejection fraction is proven by numerous randomized clinical trials, so according to current guideline recommendations it has class one indication under fulfillment of several circumstances. However, despite proper application of this treatment modality, up to one third of patients are non-responders, so knowledge of exact details to reach appropriate efficiency is essential. Most beneficial treatment effect and survival gain can be expected in case of wide QRS complex, left bundle branch block, and long PR interval.

The technical evolution have helped in achieving the theoretically defined optimal left ventricular electrode position by development of quadripolar leads. Through its four different pole applicable to excitation the proper vector can be determined by the combined aspects of the electrically latest activated segment, lowest treshold and avoiding phrenic nerve stimulation and can be changed later by programming. Safety and effectivity of quadripolar leads was verified by several studies, however, conflicting data was published on the effect on survival.

At the beginning of defibrillator therapy, lower defibrillation threshold and reduced defibrillation energy requirement have contributed to widespread of dual coil electrodes. However, dual coil leads not only can be characterized by lower defibrillation threshold, but are also more vulnerable, due to its complex structure, and have higher complication rate in case of transvenous extraction, so use of single coil leads can lead to net clinical benefit.

There are conflicting scientific results was published about the exact role of right ventricular lead position in efficiency of

cardiac resynchronization therapy even electro- even echocardiographic parameters was set as treatment success.

Remote monitoring systems for follow-up patients with cardiac implantable electronic devices are available since the last two decades.

Implanted devices are able to send stored data through an imbebbed antenna to a local communication unit, which can provide the information to a central data server that can be accessed by clinicians.

Early studies proved, that remote monitoring feasible for identify technical issues automatically, and therefore improve safely patient care and at the same time reduce the burden of health care systems. Randomized clinical trials showed that remote monitoring is able to reduce the time between onset and perception of arrhythmias, shortens the mean duration of hospitalization and prevents appropriate and inappropriate shocks with less frequent in-office visits.

Observational studies reported mortality benefit also, however, randomized clinical trials published conflicting data about the effect of remote monitoring on survival.

## 2. AIMS

*Detailed objectives of our study on quadripolar leads:*

Effect of use quadripolar compared to bipolar leads for cardiac resynchronization therapy on;

- implantation and fluoroscopy time
- QRS duration
- echocardiographic parameters
- clinical response
- long-term survival

*Detailed objectives of our study on defibrillation lead type and position in CRT-D recipients:*

Effect of single or dual coil ICD leads on:

- clinical response
- all-cause mortality
- change of QRS duration
- echocardiographic parameters

Effect of ICD lead position (apical versus non-apical) on:

- clinical response
- all-cause mortality
- change of QRS duration
- echocardiographic parameters

*Detailed objectives of our study on remote monitoring:*

Effect of remote monitoring on:

- survival
- echocardiographic response to cardiac resynchronization therapy

Compare in-office visits between patients on conventional follow-up and on remote monitoring.

## 3. METHODS

*Study on quadripolar left ventricular leads*

Our dual center observational retrospective study involved 536 consecutive CRT-D recipient (Hungarian Defence Forces Medical Centre, Hungary; 227 patient, J.W. Goethe University, Frankfurt; 309 patient). Implantations was performed between 2005 and 2016, the indications was

established according to contemporary guidelines of European Society of Cardiology.

Study endpoints was clinical response to cardiac resynchronization therapy, defined as at least one NYHA class improvement 6 months after implantation, and all-cause mortality.

Kolmogorov-Smirnov test was used to determine normal distribution of variables. The Chi-square test was used for categorical variables and the two-sample t test or the Mann-Whitney U test for continuous variables among patient groups. The effects of baseline parameters on CRT response rate were assessed by the Chi-square test and by a multivariate logistic regression model. Survival curves were constructed according to the Kaplan-Meier method and compared with the Cox proportional hazard model and the Wald test for multivariate analysis.

*Study on ICD lead type and position in CRT-D recipients*

Our dual center observational retrospective study involved 563 consecutive CRT-D recipient (Hungarian Defence Forces Medical Centre, Hungary; 196 patient, J.W. Goethe University, Frankfurt; 367 patient). ICD lead type and final right ventricular electrode position was left to physician discretion. RV lead position was classified as either non-apical or apical according to the postoperatively performed chest X-rays and surgical reports.

Primary end point was clinical response to cardiac resynchronization therapy, defined as at least one NYHA class improvement 6 months after implantation, and all-cause mortality. Changes from baseline to 6 months of echo- and electrocardiographic parameters, and cardiovascular mortality constituted secondary study outcome measures.

The Chi-square test was used to test for categorical variables and the two-sample t test or the Mann–Whitney U test for continuous variables among patients groups. Survival plots are presented as Kaplan–Meier curves. To assess the impact of ICD lead type and RV lead position on all-cause mortality and cardiovascular death, we used the Cox proportional hazards regression model. To assess the impact of right ventricular lead position on changes in left ventricular ejection fraction, left ventricular end diastolis diameter and QRS duration, nonparametric tests and a multivariate linear regression model were used.

*Study on remote monitoring*

The population of this single-center, retrospective, observational study was formed of 231 consecutive patients receiving CRT-D devices in the Medical Centre of the Hungarian Defence Forces (Budapest, Hungary) between 2011 and 2016. The possibility of remote monitoring was offered to every patient implanted with a wireless telemetry-capable CRT-D device. Patients who consented to remote monitoring formed the remote monitoring group. The control group consisted of CRT-D recipients, who were conventionally followed up in our outpatient device clinic without remote monitoring. In-office visits were recommended to patients on remote monitoring without symptoms once a year. Remote transmissions were evaluated every day by a team consisting of cardiology trainees and consultant electrophysiologists. In the case of suspected heart failure progression, a heart failure specialist was involved additionally.

The primary end point was all-cause mortality. Mortality data were retrieved using the Hungarian National Health Fund Death Registry in case of lack of any detailed information. The

secondary endpoint was the response to resynchronization therapy at the visit at 6 to 12 months, defined as 5% absolute increase in left ventricular ejection fraction. The number of all ambulant visits, device clinic visits, and heart failure outpatient clinic visits were also analyzed and compared between the two patient groups.

The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous data. The Chi-square test was applied to test for categorical variables; the two-sample t test or the Mann-Whitney U test was used for continuous variables among patient groups.

## 4. RESULTS

*Study on quadripolar left ventricular lead*

A total of 536 CRT-D recipients were included in the analysis of whom 123 (23%) received a quadripolar and 413 (77%) a bipolar left ventricular lead. Mean age was 66 ± 11 years and 65% (n = 421) were male. The majority of patients had ischemic cardiomyopathy as the underlying heart disease (n=302; 56%) and underwent CRT-D implantation for primary prevention of sudden cardiac death (n=423; 79%). Almost one third CRT implantation was an upgrade procedure (n=180; 28%). About two third of patients had hypertension (n=381; 59%), one thirds had permanent atrial fibrillation (n=185; 35%) and diabetes (n=188; 35%).

Implantation of quadripolar leads was associated with shorter fluoroscopy times (14 min vs. 20 min; $p < 0.001$) and doses (23 Gy/cm$^2$ vs. 29 Gy/cm$^2$; p=0.03). Aiming for a lateral lead position, a lateral/posterolateral/anterolateral branch of the coronary sinus could be reached as the final target vein in 72%

of patients implanted with quadripolar leads and in 71% of patients implanted with bipolar leads (p = 0.15). There was no difference in the rate of non-apical positions between the two groups (73% vs 78%, p = 0.18).

Patients implanted with a quadripolar lead were more likely to respond to CRT compared with patients implanted with bipolar lead (77% vs. 63%; p<0.001). After adjusting for potential baseline confounders, better NYHA response rates persisted in patients receiving quadripolar leads (OR=2.30; 95% CI 1.37–3.85; p=0.002).

Six months after implantation, changes of left ventricular ejection fraction and left ventricular end diastolic diameter was comparable between patients with different left ventricular leads (LVEF: p=0.13, LVEDD: p=0.57). Regarding QRS width and morphology, 76% of the patients (n=407) had an intrinsic left bundle branch block (mean QRS duration 159±29ms) at CRT-D implantation. Six months after CRT implantation the use of quadripolar leads was associated with greater reduction in QRS duration compared with patients implanted with bipolar leads (21±30 vs. 8±35 ms, p univariate = 0.004; p multivariate < 0.0001). Mean biventricular pacing percentage was 92% at six months after CRT-D implantation and did not significantly differ between patient groups (quadripolar 93% vs. bipolar 91%; p=0.20).

Within a follow-up period of 39±31 months, 172 patients (27%) died. More patients implanted with bipolar leads died (37% vs. 16%) but this difference was not statistically significant on a time-to-event analysis (HR = 0.81; 95% CI 0.51–1.31). After adjusting for potential clinical confounders, the adjusted HR was 0.71 (95% C I 0.44–1.15). Independent predictors of mortality were age, chronic kidney disease, peripherial artery disease, and an upgrade procedure to CRT-D.

Cause-specific mortality was similar between patient groups with different electrodes.

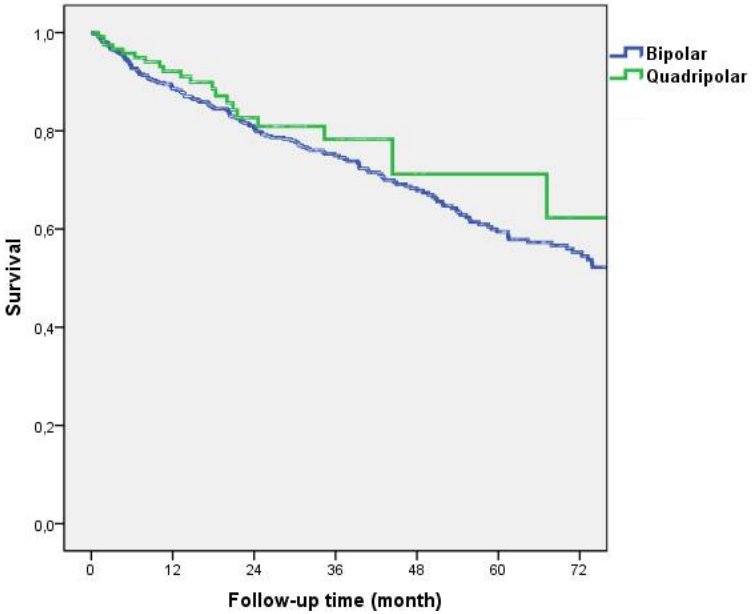


Figure 1. Survival curves by quadripolar and bipolar left ventricular lead

*Study on ICD lead type and position in CRT-D recipients*

A total of 563 consecutive patients were included in the study. More than half of the patients (313 out of 563, 55.6%) received a dual-coil ICD lead, whereas, in 250 patients, a single-coil lead was implanted (44.4%). Patients receiving dual-coil ICD leads had higher hemoglobin levels, a wider QRS and lower left ventricular ejection fraction. Dual-coil lead position were apical in more cases, in the same time left ventricular lead position were more likely basal/mid. Patients with single-coil

lead had more often lateral or posterolateral left ventricular lead position.

The RV lead was implanted in a non-apical position in 262 patients 296 patients received an apical lead. Patients with non-apical RV leads had a slightly lower NYHA class, and received their device more often for primary prevention of sudden cardiac death, and less often as an upgrade procedure. They also had a higher estimated glomerular filtration rate, shorter QRS and better left ventricular ejection fraction, and there were differences regarding ICD lead type and left ventricular lead position.

Six months after CRT-D implantation, NYHA class had improved by at least one class in 365 patients (68.0%). There was no difference in clinical response for patients receiving a dual-coil ICD lead (66.7%) as compared to single-coil lead (69.7%). ICD lead type did not have impact on either echo- or electrocardiographic parameters [left ventricular ejection fraction change (6.0±9.3 vs. 5.4±9.9%), left ventricular end diastolic diameter change (2.9±9.8 vs. 0.9±13.6 mm) reduction in QRS duration (9.5±31.5 vs. 8.0±36.7 ms), respectively].

There was no significant difference in clinical response when comparing patients with right ventricular lead in a non-apical position (70%) to those with right ventricular lead in an apical position (66%). Both non-apical and apical right ventricular lead position had similar impact on changes in left ventricular ejection fraction (increase of 5.8±8.0 vs. 5.7±10.5%) and left ventricular end diastolic diameter (decrease of 1.6±8.9 vs. 1.2±13.4 mm). Non-apical right ventricular lead position was associated with a greater reduction in QRS duration on both uni- and multivariate analyses (decrease of 14.4±32.1ms vs. 4.3±34.3ms, $p = 0.005$, $p < 0.001$ uni- and multivariate analyses, respectively).

During a mean follow-up time of 41±34 months, 201 (35.7%) patients died. In the majority of patients (42%), the cause of death was cardiovascular in nature, whereas 22% of deaths were of non-cardiovascular origin. Dual-coil ICD lead type was not associated with all-cause mortality, when compared to single-coil ICD lead type (hazard ratio: 0.79, 95% confidence interval: 0.57–1.10, p=0.15; adjusted hazard ratio: 0.81, 95% confidence interval:0.58–1.12, p=0.2). (Figure 2.) There was no difference in cardiovascular mortality according to lead type (hazard ratio: 1.02, 95% confidence interval: 0.62–1.68, p=0.95; adjusted hazard ratio: 1.22, 95% confidence interval: 0.73–2.04, p=0.46).

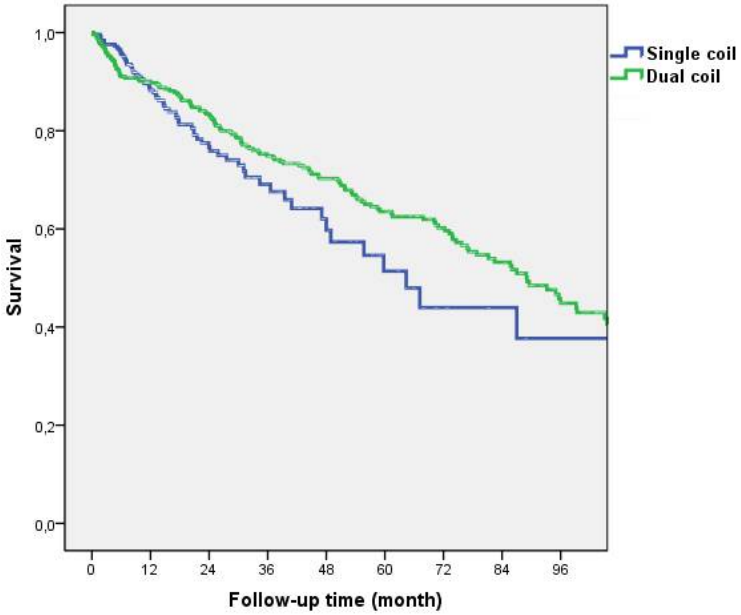


Figure 2. Survival curves by single- or dual-coil ICD lead

There was a trend for a beneficial effect on all-cause mortality in favour of non-apical compared to apical right ventricular lead position (hazard ratio:0.78, 95% confidence interval:0.57–1.10, p=0.11) on univariate analysis. However, after adjusting for possible confounders, non-apical position was not associated with a beneficial effect on survival (adjusted hazard ratio: 0.98, 95% confidence interval: 0.71–1.36, p=0.92). (Figure 3.) Likewise, non-apical RV lead positioning was not significantly associated with a lower risk for cardiovascular mortality on multivariate analysis (hazard ratio: 0.51, 95% confidence interval: 0.31–0.86, p=0.01, adjusted hazard ratio: 0.76, 95% confidence interval: 0.44–1.31, p=0.33).

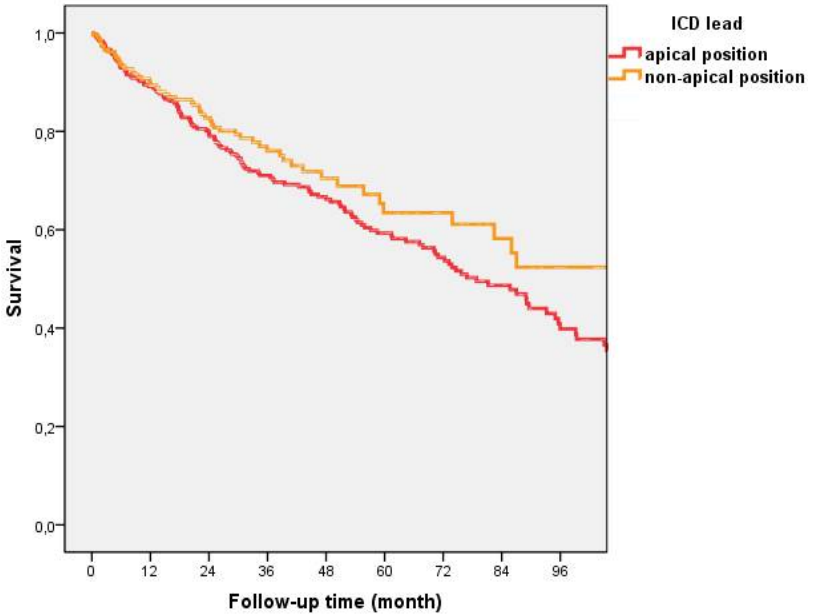


Figure 3. Survival curves by apical and non-apical right ventricular lead position

*Study on remote monitoring*

A total of 231 CRT-D recipients were included in this study. Of the 90 patients implanted with remote monitoring-capable devices, 62 consented to receive a remote monitor (41 of 56 patients with Medtronic and 21 of 34 with Biotronik devices). Patients on remote monitoring were more likely to have atrial fibrillation and have received heart failure management more often at our dedicated heart failure outpatient clinic. They also had a slightly lower NYHA functional class.

During the average follow-up time of 28.4±18.1 months, 63 patients died, 2 underwent heart transplantation, 2 received a left ventricular assist device, and in 1 case device explantation was performed due to infection. Crude all-cause mortality of remote-monitored patients was significantly lower (16.6% vs. 31.3%) compared with patients followed conventionally (hazard ratio: 0.368, 95% confidence interval: 0.186-0.727, p=0.004) (Figure 4.)

The survival benefit remained statistically significant after adjustment for important baseline parameters (adjusted hazard ratio: 0.361, 95% confidence interval: 0.181-0.722, p=0.004). The survival benefit did not differ between the remote monitoring systems (ie, CareLink vs Home Monitoring; p=0.79).

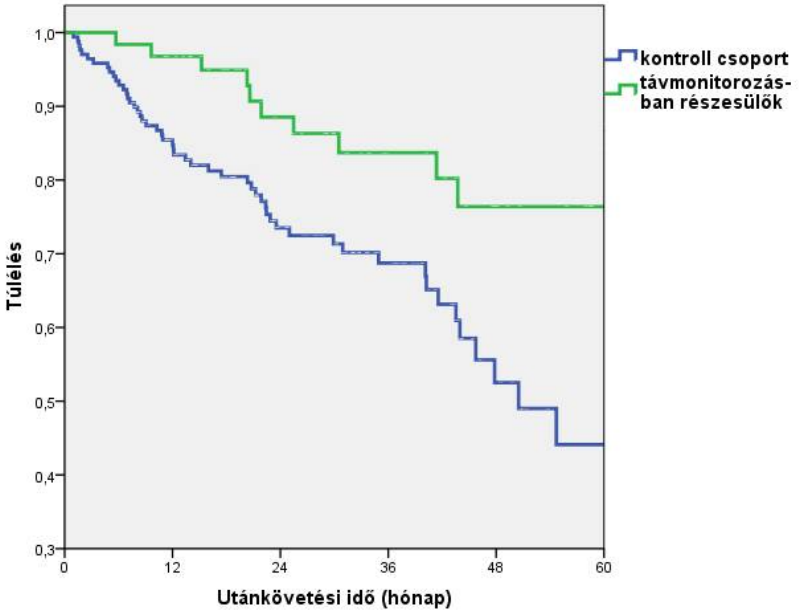


Figure 4. Survival curves by remote monitoring and conventional follow-up

Echocardiographic response to cardiac resynchronization therapy at 6 to 12 months was more often observed in patients on remote monitoring (41.9%, vs 31.9%); however, this difference was statistically nonsignificant.

The total number of follow-up controls tended to be higher in the remote monitoring group compared with patients undergoing conventional follow-up (4.6 visits per patient per year vs 3.9 visits per patient per year, p=0.08). This was because patients on remote monitoring presented at our specialized heart failure outpatient clinic more often (1.9 visits per patient per year vs. 1.1 visits per patient per year, p=0.003).

## 5. CONCLUSIONS

*Study on quadripolar left ventricular lead*

With the use of quadripolar left ventricular lead compared to bipolar electrode in cardiac resynchronization therapy patients:

1) Time of procedure and fluoroscopy duration can be significantly reduced.

2) At least one NYHA functional class improvement can be observed more often.

3) The shortening of QRS duration is more pronounced.

4) Change of left ventricular ejection fraction and left ventricular end diastolis diameter is comparable.

5) Long-term survival of patients did not differ.

*Study on ICD lead type and position in CRT-D recipients*

1) In patients with cardiac resynchronization therapy, different type of shock electrodes (ie. single-coil or dual-coil) and different position of the defibrillator lead (ie. apical vs. non-apical) offer similar:

- At least one NYHA functional class improvement
- change in left ventricular ejection fraction
- reduction in left ventricular end diastolis diameter
- long-term survival.

2) Shortening of QRS duration was more pronounced in patients with non-apical right ventricular lead position.

*Study on remote monitoring*

1) Among patients on optimal pharmacological treatment, after CRT-D implantation, use of remote monitoring was associated with better survival compared with conventional follow-up.

2) Survival gain is independent from the type of remote monitoring system.

3) Changes of echocardiographic parameters were comparable among patient groups.

4) However, total number of follow-up visits did not differ depending on follow-up type, patients on remote monitoring presented more often at heart failure outpatient clinic.

## 6. LIST OF PUBLICATIONS

*Related to the thesis*

Erath JW, Vamos M, Domokos D, Benz AP, Bari Z, **Bogyi P**, Duray GZ, Hohnloser SH. (2019) Effects of implantation of quadripolar left ventricular leads on CRT response. J Interv Card Electrophysiol, 55: 73-81. **IF:1,277**

Benz AP, Vamos M, Erath JW, **Bogyi P**, Duray GZ, Hohnloser SH. (2018) ICD lead type and RV lead position in CRT-D recipients.
Clin Res Cardiol, 107: 1122-1130. **IF: 4,907**

**Bogyi P**, Vamos M, Bari Z, Polgar B, Muk B, Nyolczas N, Kiss RG, Duray GZ. (2019) Association of Remote Monitoring With Survival in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy: Retrospective Observational Study. J Med Internet Res, 21: e14142. **IF: 5,034**

*Not related to the thesis*

Domokos D, Szabo A, Banhegyi G, Polgar B, Bari Z, **Bogyi P**, Marczell I, Papp L, Kiss RG, Duray GZ, Merkely B, Hizoh I. (2020) Needle aspiration for treating iatrogenic pneumothorax after cardiac electronic device implantation: a pilot study. J Interv Card Electrophysiol, 57: 295-301. **IF:1,277**

Pilecky D, Vamos M, **Bogyi P**, Muk B, Stauder D, Racz H, Nyolczas N, Duray GZ, Zacher G, Zima E. (2019) Risk of cardiac arrhythmias after electrical accident: a single-center study of 480 patients. Clin Res Cardiol, 108: 901-908. **IF: 5,268**

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Bohm A, Kiss RG, **Bogyi P**, Duray GZ. (2016) Temporary severe bradycardia due to pacemaker programming. Neth Heart J, 24: 491. **IF: 1,013**

Kutyifa V, Geller L, **Bogyi P**, Zima E, Aktas MK, Ozcan EE, Becker D, Nagy VK, Kosztin A, Szilagyi S, Merkely B. (2014) Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: results of a high-volume, single-centre experience. Eur J Heart Fail, 16: 1323-1330. **IF: 7,181**