

Effect of post-procedural evidence-based therapy on 2-year prognosis after transcatheter mitral valve repair

Magnus J Hagnäs^{a,b,*}, Carmelo Grasso^b, Maria Elena Di Salvo^b, Andrea Sardone^b, Paola Rapisarda^b, Matteo Pelliccia^b, Francesco Dipasquale^b, Giuseppe Castania^b, Sarah Mangiafico^b, Piera Capranzano^b, Marco Barbanti^b, Alessandro Denaro^b, Salvatore Scandura^b, Timo Mäkikallio^c, Davide Capodanno^b and Corrado Tamburino^b

^aDepartment of Internal Medicine, Heart smithy, Lapland Central Hospital, Rovaniemi, Finland

^bCardiac-Thoracic-Vascular and Transplant Department, Azienda Ospedaliero-Universitaria “Policlinico-Vittorio Emanuele”, Catania, Italy

^cDivision of Cardiology, Department of Internal Medicine, Oulu University Hospital, Oulu, Finland

*** Corresponding author:**

Magnus J Hagnäs

Telephone number: +358505722985

Email address: m.hagnas@gmail.com

Mailing address: C.A.S.T., A.O.U. “Policlinico-Vittorio Emanuele”, P.O. Rodolico, Ed. 8, Via Santa Sofia 78, Catania, Italy.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.2002

Guidelines recommend the use of neurohormonal antagonists for all patients with heart failure and mitral regurgitation (MR) as an initial treatment strategy.^{1,2} Patients with symptoms despite maximally tolerated neurohormonal antagonist treatment, evidence-based therapy (EBT), and moderate-to-severe MR who are surgery-ineligible may undergo transcatheter mitral valve repair with the MitraClip (Abbott Vascular) system. Although the MR has been treated mechanically, these patients still have underlying heart failure and should stay on EBT. Adherence to EBT has been shown to improve clinical outcomes in patients with heart failure.³ However, in clinical practice, a sizeable proportion of patients is not treated according to guidelines recommendations.³ We sought to examine the long-term effect of EBT in patients who underwent a MitraClip procedure for secondary MR.

The Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation (GRASP) registry is a retrospective, observational registry of patients who underwent MitraClip implantation at the division of Cardiology, A.O.U. “Policlinico-Vittorio Emanuele”, University of Catania, Catania, Italy.⁴ Between October 2008 and the end of December 2017 444 patients underwent a MitraClip procedure, of those 316 had secondary MR, hence representing the population of interest for this study. Secondary (functional) MR was defined as MR resulting from left atrium or left ventricle dilation, causing the mitral valve annulus also to dilate, thus preventing the mitral valve leaflets from properly coapting and a left ventricular ejection fraction of less than 50%. All outcomes of interest for this study were defined according to Mitral Valve Academic Research Consortium criteria.⁵ The medication was evaluated at discharge after the procedure. The definition of EBT used in this study was adopted from the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, as the use of appropriate classes of neurohormonal antagonists for heart failure or not; either angiotensin-converting enzyme inhibitors (ACEi)

or angiotensin receptor blockers (ARB), beta-blockers (BB) and, in patients with a left ventricular ejection fraction of 35% and less, mineralocorticoid receptor antagonist (MRA) at discharge.⁶ Follow-up data were prospectively collected by scheduled clinical evaluations and phone interviews. A multivariable Cox proportional hazards survival model was used to analyze the risk of 2-year mortality in patients with and without EBT. Covariates were selected according to clinical plausibility and statistical significance in univariate analysis, which included age, gender, ejection fraction, heart failure symptoms according to the New York Heart Association (NYHA)-class, the Society of Thoracic Surgery Risk (STS) score for 30-day mortality, ischemic etiology of MR and pre-procedure measurement of creatinine and NT-pro B-type natriuretic peptide. Statistical analyses were performed using Statistical Package for Social Sciences, version 25 (IBM Corp., Armonk, NY).

Complete data on medication was available for 306 (97%) of the patients (Supplementary Figure 1). The baseline characteristics of the study population are presented in Table 1. The discharge medication is presented in Supplementary Table 1. The majority of patients were not on EBT (N=187, 61%) according to the study definition. A complete 2-year follow-up was available in 281 patients (92% of the eligible), with death reported in 90 (29%). The cumulative incidence of all-cause death among patients with or without EBT is shown in Figure 1. After adjusting for confounding factors, the hazard ratio of all-cause death among patients without EBT was 2.2 (95% Confidence Interval 1.23–3.99, P=0.008) compared to patients with EBT.

The main findings of this study, conducted in a real-world population of patients with heart failure undergoing mitral valve repair with the MitraClip system, may be summarized as

follows. About two-thirds of the patients were discharged without EBT. Patients with EBT had better survival rates compared to those without.

Although guidelines recommend the use of multiple state-of-the-art medications in patients with heart failure,^{1,2} the adherence to these guidelines seems to vary.³ The long-term benefits of ACEi, ARB, BB and MRA on clinical outcomes in patients with heart failure are well established, which places these therapies as first-line options in the treatment of heart failure.⁶ It has also been shown that treating severe secondary MR with maximal tolerable doses of heart failure medications may result in MR reduction, prevention of left ventricular adverse remodeling, and improved long-term prognosis.⁷ While the individual merit of heart failure medications to prevent adverse events has been demonstrated repeatedly, the extent of the advantage of using their combination for patients with heart failure undergoing the MitraClip procedure is largely unknown. The underuse of EBT observed in our study is consistent with prior studies suggesting that a sizeable proportion of patients with heart failure undergoing a MitraClip procedure is discharged without prognostically important medications.⁸ The patients' and physicians' non-adherence to the EBT might be partly explained by low blood pressure, renal problems, and problems that are related to the healthcare system. Although these patients possibly experience transient relief in symptoms after the procedure, their non-adherence to EBT may lead to progressive heart failure, clinical deterioration, and adverse clinical outcomes. In the era of surgical and transcatheter treatment options, the importance of medications may be neglected when severe MR is present in a patient with heart failure. We speculate that the benefits of the MitraClip procedure might be amplified by the use of EBT.

Our results should be interpreted in view of several potential limitations. Firstly, patients were not randomized to EBT, and therefore, as in any observational registry, selection bias could be at play. However, our findings are clinically plausible, and they were

consistent according to multiple adjustment methodologies. Secondly, we do not have data on the dosage or follow-up changes of medication. However, our findings are significant even without this data.

Patients undergoing MitraClip procedure for secondary MR with EBT are at a lower risk of death compared to patients without EBT. The long-term outcomes of MitraClip procedures may benefit from better adherence to EBT.

Funding: This work was supported by the Finnish Foundation of Cardiovascular Research to MJH; Finland and the Medical Society of Finland to MJH; the Päivikki and Sakari Sohlberg foundation to TM and VTR grant (Finnish government research funding) to MJH and TM.

Conflict of interest: Carmelo Grasso is a proctor for Abbott vascular. Corrado Tamburino has received speaker's honoraria from Abbott Vascular. Davide Capodanno has received consulting honoraria from Abbott Vascular. None of the other authors have any conflicts of interest to disclose.

References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O’Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2017;**70**:252–289.
3. Komajda M, Schöpe J, Wagenpfeil S, Tavazzi L, Böhm M, Ponikowski P, Anker SD, Filippatos GS, Cowie MR, QUALIFY Investigators. Physicians’ guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2019;**21**:921–929.
4. Buccheri S, Capodanno D, Barbanti M, Popolo Rubbio A, Di Salvo ME, Scandura S, Mangiafico S, Ronsivalle G, Chiarandà M, Capranzano P, Grasso C, Tamburino C. A Risk Model for Prediction of 1-Year Mortality in Patients Undergoing MitraClip Implantation. *Am J Cardiol* 2017;**119**:1443–1449.
5. Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, Mehran R, Kuck K-H, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and

replacement: part 2: endpoint definitionsA consensus document from the Mitral Valve Academic Research Consortium. *Eur Heart J* 2015;**36**:1878–1891.

6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
7. Nasser R, Van Assche L, Vorlat A, Vermeulen T, Van Craenenbroeck E, Conraads V, Van der Meiren V, Shivalkar B, Van Herck P, Claeys MJ. Evolution of Functional Mitral Regurgitation and Prognosis in Medically Managed Heart Failure Patients With Reduced Ejection Fraction. *JACC Heart Fail* 2017;**5**:652–659.
8. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, Tavazzi L, QUALIFY Investigators. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. *Eur J Heart Fail* 2016;**18**:514–522.

Legends

Figure 1. Title: Kaplan-Meier survival estimate for the occurrence of death among patients who underwent MitraClip procedure with and without evidence-based therapy. Legend: Plot of survival functions for patients with and without evidence-based therapy (EBT).

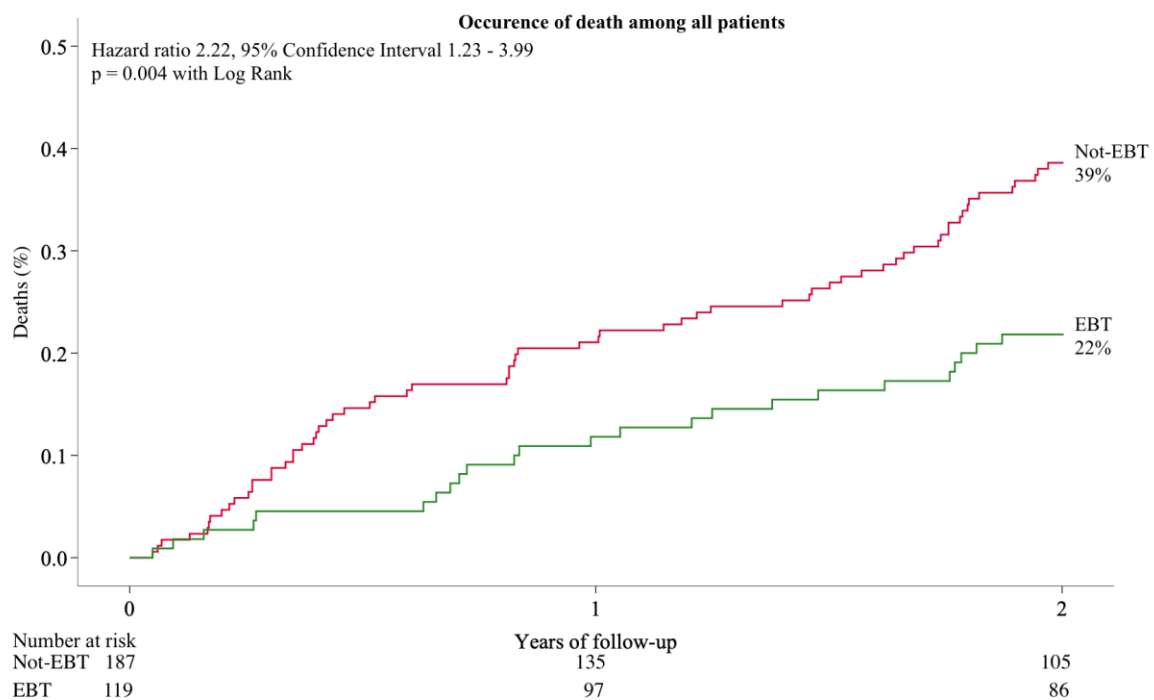


Table 1. Baseline characteristics of all patients, patients with and without evidence-based therapy at discharge

Variable	All patients n=306	Evidence-based therapy		p Value
		YES n=119	NO n=187	
Age (years), mean \pm SD	71.6 \pm 8.8	71.2 \pm 9.5	71.8 \pm 8.4	0.846
Sex (male), n (%)	199 (65)	70 (59)	129 (69)	0.069
Hypertension, n (%)	241 (79)	100 (84)	141 (75)	0.072
Diabetes, n (%)	122 (40)	42 (35)	80 (43)	0.371
Dyslipidemia, n (%)	180 (59)	64 (54)	116 (62)	0.153

Current smoker, n (%)	30 (10)	10 (8)	20 (11)	0.51 1
Previous smoker, n (%)	118 (39)	40 (34)	78 (42)	0.15 6
Atrial fibrillation, n (%)	139 (46)	46 (39)	93 (50)	0.06 6
Body mass index (kg/m ²), mean ±SD	26.0 ±3.9	26.2 ±3.9	25.9 ±4.0	0.38 7
EuroSCORE II, median (IQR)	6.3 (3.6-11.4)	5.6 (3.3-10.5)	6.7 (4.2-12.0)	0.02 5
STS risk score, median (IQR)	3.6 (1.9-7.0)	3.2 (1.7-5.7)	4.0 (1.9-7.9)	0.06 3
Systolic BP, mean ±SD (mmHg)	114 ±16	116 ±17	112 ±15	0.12 7
Diastolic BP, mean ±SD (mmHg)	68 ±12	69 ±12	67 ±12	0.19 4
Creatinine (mg/dL), median (IQR)	1.27 (1.00- 1.70)	1.14 (0.93- 1.53)	1.35 (1.05- 1.84)	0.00 2
Patients on dialysis, n (%)	9 (3)	1 (1)	8 (4)	0.08 3
Patients with CKD, n (%)	194 (67)	67 (59)	127 (72)	0.04 0
6MWT (meter), median (IQR)	271 (187-345)	276 (182-368)	253 (194-322)	0.39 7
NYHA Class II, n (%)	47 (15)	21 (17)	26 (14)	0.65 4
NYHA Class III, n (%)	220 (72)	88 (74)	132 (71)	0.27 6
NYHA Class IV, n (%)	39 (13)	10 (9)	29 (15)	0.07 6
LV Ejection fraction (%), mean ±SD	30 ±8	30 ±8	30 ±8	0.36 1
LV Ejection fraction 40-50%, n (%)	48 (16)	23 (19)	25 (13)	0.16 2
Grade III MR, n (%)	103 (34)	47 (39)	56 (30)	0.08 5
Grade IV MR, n (%)	203 (66)	72 (61)	131 (70)	0.08 5
Ischemic etiology of MR, n (%)	169 (55)	55 (46)	114 (61)	0.01 1
ProBNP (pg/ml), median (IQR)	1065 (365- 2772)	1087 (380- 3737)	1042 (354- 2707)	0.54 1
ICD-pacemaker, n (%)	88 (29)	34 (29)	54 (29)	0.95 4
CRT-pacemaker, n (%)	38 (12)	19 (16)	19 (10)	0.13 3

SD, standard deviation; STS, The Society of Thoracic Surgery Risk Score for mortality; BP, Blood pressure; NYHA, New York Heart Association; LV, Left ventricle; 6MWT, Six-minute walk test; MR, Mitral regurgitation; ProBNP, NT-Pro B-type natriuretic peptide; IQR, interquartile range; CKD, Chronic kidney disease, defined as an estimated glomerular filtration rate of less than 60 ml/min/1.73m²; ICD, Implantable cardioverter defibrillator; CRT, Cardiac resynchronization therapy