

RESEARCH LETTER

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

Guidelines recommend the use of neuro-hormonal 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, Abbott Park, IL, USA) system. Although 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 guideline 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 regurgitation in Suficiency 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

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 ± SD	71.6 ± 8.8	71.2 ± 9.5	71.8 ± 8.4	0.846
Male sex, 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
Dyslipidaemia, n (%)	180 (59)	64 (54)	116 (62)	0.153
Current smoker, n (%)	30 (10)	10 (8)	20 (11)	0.511
Previous smoker, n (%)	118 (39)	40 (34)	78 (42)	0.156
Atrial fibrillation, n (%)	139 (46)	46 (39)	93 (50)	0.066
Body mass index (kg/m ²), mean ± SD	26.0 ± 3.9	26.2 ± 3.9	25.9 ± 4.0	0.387
EuroSCORE II, median (IQR)	6.3 (3.6–11.4)	5.6 (3.3–10.5)	6.7 (4.2–12.0)	0.025
STS risk score, median (IQR)	3.6 (1.9–7.0)	3.2 (1.7–5.7)	4.0 (1.9–7.9)	0.063
Systolic BP (mmHg), mean ± SD	114 ± 16	116 ± 17	112 ± 15	0.127
Diastolic BP (mmHg), mean ± SD	68 ± 12	69 ± 12	67 ± 12	0.194
Creatinine (mg/dL), median (IQR)	1.27 (1.00–1.70)	1.14 (0.93–1.53)	1.35 (1.05–1.84)	0.002
Patients on dialysis, n (%)	9 (3)	1 (1)	8 (4)	0.083
Patients with CKD, n (%)	194 (67)	67 (59)	127 (72)	0.040
6MWT (m), median (IQR)	271 (187–345)	276 (182–368)	253 (194–322)	0.397
NYHA class, n (%)				
II	47 (15)	21 (17)	26 (14)	0.654
III	220 (72)	88 (74)	132 (71)	0.276
IV	39 (13)	10 (9)	29 (15)	0.076
LV ejection fraction (%), mean ± SD	30 ± 8	30 ± 8	30 ± 8	0.361
LV ejection fraction 40–50%, n (%)	48 (16)	23 (19)	25 (13)	0.162
Grade III MR, n (%)	103 (34)	47 (39)	56 (30)	0.085
Grade IV MR, n (%)	203 (66)	72 (61)	131 (70)	0.085
Ischaemic aetiology of MR, n (%)	169 (55)	55 (46)	114 (61)	0.011
NT-proBNP (pg/mL), median (IQR)	1065 (365–2772)	1087 (380–3737)	1042 (354–2707)	0.541
ICD, n (%)	88 (29)	34 (29)	54 (29)	0.954
CRT, n (%)	38 (12)	19 (16)	19 (10)	0.133

6MWT, six-minute walk test; BP, blood pressure; CKD, chronic kidney disease, defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m²; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LV, left ventricular; MR, mitral regurgitation; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation; STS, Society of Thoracic Surgeons.

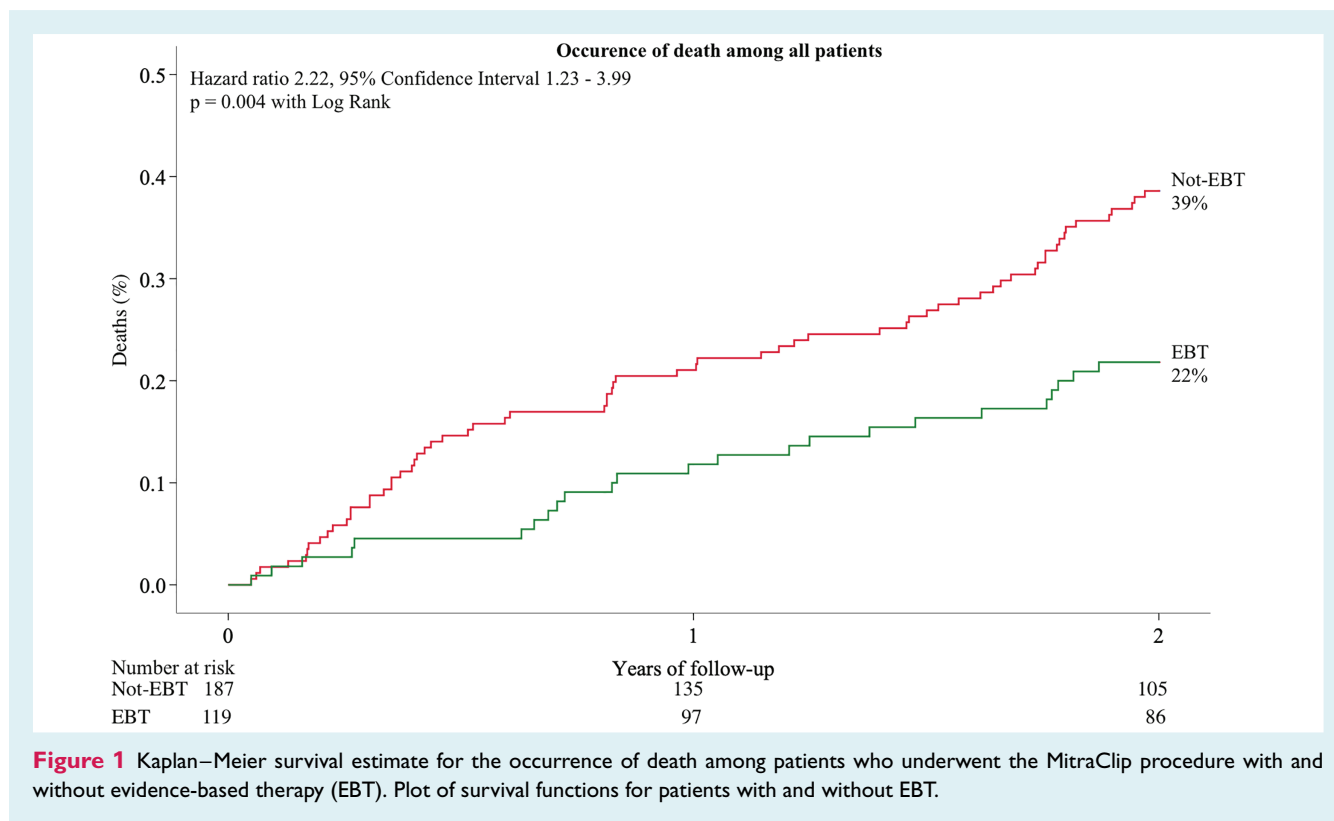


Figure 1 Kaplan–Meier survival estimate for the occurrence of death among patients who underwent the MitraClip procedure with and without evidence-based therapy (EBT). Plot of survival functions for patients with and without EBT.

(online supplementary *Figure S1*). Secondary (functional) MR was defined as MR resulting from left atrial or left ventricular dilatation, causing the mitral valve annulus also to dilate, thus preventing the mitral valve leaflets from properly coapting and a left ventricular ejection fraction of $<50\%$. All outcomes of interest for this study were defined according to the 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 $\leq 35\%$, 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 analyse 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 class, the Society of Thoracic Surgeons risk score for 30-day mortality, ischaemic aetiology of MR and pre-procedure measurement of creatinine and N-terminal pro B-type natriuretic peptide. Statistical analyses were performed using Statistical Package for Social Sciences, version 25 (IBM Corp., Armonk, NY, USA).

Complete data on medication were available for 306 (97%) of the patients (online supplementary *Figure S2*). The baseline characteristics of the study population are presented in *Table 1*. The discharge medication is presented in online supplementary *Table S1*. 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 reduction in MR, prevention of left ventricular adverse remodelling, 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 these data.

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

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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