MitralClip in Patients With Mitral Regurgitation and Left Ventricular Ejection Fraction <30% — Potential Implications for the Treatment of Patients in Japan —

Hidehiro Kaneko, MD, PhD; Mitsunobu Kitamura, MD; Michael Neuss, MD; Maki Okamoto, MD; Tobias Schmidt, MD; Hannes Alessandrini, MD; Karl-Heinz Kuck, MD; Issei Komuro, MD, PhD; Christian Frerker, MD; Christian Butter, MD

Background: The effect of the unique Japanese indication for MitraClip based on left ventricular ejection fraction (LVEF) is unclear.

Methods and Results: We analyzed 874 patients who underwent MitraClip because of mitral regurgitation (MR) and compared the characteristics and outcomes between patients with LVEF <30% and ≥30%. Patients with LVEF <30% accounted for 33% of the study population and had a higher prevalence of functional MR. Severity of MR after MitraClip was comparable, and LVEF <30% did not independently affect survival.

Conclusions: Japanese unique indication based on LVEF may exclude one third of patients who were treated with MitraClip in Europe.

Key Words: Left ventricular ejection fraction; MitraClip; Mitral regurgitation

Since April 2018, MitraClip® (Abbott, Menlo Park, CA, USA) has been commercially available for the treatment of mitral regurgitation (MR) in Japan. MitraClip had already obtained CE mark in 2008, and was approved (for degenerative MR) by the US Food and Drug Administration in 2013.

In Japan, patients with left ventricular ejection fraction (LVEF) <30% are not indicated for MitraClip according to the inclusion criteria of the Pharmaceuticals and Medical Devices Agency-approved trial (AVJ-514). In contrast, there is no limitation concerning LVEF for the indication of MitraClip in Europe and the USA. Therefore, the Japanese indication of MitraClip is unique. In this study, we sought to clarify the effect of this indication of MitraClip according to baseline LVEF.

Methods

Data Collection

This study had a 2-center design, representing a collaboration between Asklepios Klinik St. Georg (Hamburg, Germany) and Heart Center Brandenburg (Bernau, Germany). Of 1,022 consecutive patients who underwent MitraClip, we excluded patients with redo procedure (n=52), no LVEF data (n=29), and undermined etiology (n=67). Finally, 874 patients were included. The median follow-up period was 531±510 days.

Ethics

This retrospective study was performed according to the ethical guidelines of each institution in accordance with the Declaration of Helsinki. All patients were informed about specific risks and alternative treatments before the procedure, and they provided informed consent.

MitraClip Procedure

We performed percutaneous mitral valve (MV) repair using MitraClip. The procedure was carried out under general anesthesia under fluoroscopic and transesophageal echocardiographic guidance as previously described. MR at baseline and after MitraClip was graded according to the American Society of Echocardiography guidelines and the technique reported by Foster et al.

Statistical Analysis

Categorical and consecutive data are presented as number (percentage) or mean±standard deviation. The chi-square test was used for comparisons of categorical data, and the
MitraClip in MR and LVEF <30%

**Discussion**

Epidemiological data show that MV surgery, which is the standard treatment for severe MR, is denied in half of patients with severe symptomatic MR, and impaired ventricular function was the common reason for avoiding surgery. Furthermore, MV surgery is performed in only 16% of patients with functional MR. Thus there is unmet medical need.

Percutaneous MV repair using the MitraClip has developed as a novel treatment for surgically high-risk patients. To date, more than 60,000 patients have been treated with the MitraClip, and approximately 70% of the patients had functional MR etiology. Because functional MR is commonly complicated by advanced heart failure (HF), MitraClip is also considered as a novel therapeutic option for MR and HF. However, the Japanese indication excludes these subjects because of their reduced LVEF.

This unique indication may arise from the fact that preoperative LV dysfunction is a prognostic factor after MV surgery, and MV surgery is not strongly recommended (Class IIb) for severe primary MR with LVEF ≤ 30%.

In contrast, previous studies have shown that MitraClip has clinical benefits even in patients with reduced LVEF. Furthermore, the efficacy of MitraClip has been confirmed even in cardiac resynchronization therapy nonresponders and end-stage HF patients. Our multivariable Cox regression analysis suggested that clinical factors other than LVEF, such as older age, HF status, renal function, and right ventricular function, are more important for the outcome after the MitraClip procedure.

With regard to the current status of HF treatment in Japan, the waiting period for heart transplantation is still long and ventricular assist device use as destination therapy has not been approved yet. Thus, the practical therapeutic options for advanced HF are still limited in Japan. From this view point, MitraClip is a novel option for MR with advanced HF, and therefore, the indication of MitraClip

**Results**

**Characteristics of the Patients**

Patients with LVEF ≤30% accounted for 33% of study population (Figure A). In particular, half of the patients with functional MR etiology had baseline LVEF <30% (Figure B). Patients with LVEF <30% were more likely to be male, younger, and have a higher prevalence of functional MR and CKD. Severity of baseline MR was not different between groups. TAPSE was lower in patients with LVEF <30% (Table).

**Outcomes of MitraClip**

The number of implanted clips and the severity of MR after MitraClip were not different between groups (Table).

**Determinants of Survival**

Univariate Cox regression analysis showed that LVEF <30% was associated with higher mortality (P=0.012, hazard ratio (HR) 1.4). The mortality of patients at both 30 days and 12 months was 5.5%, and 18% in patients with LVEF ≥30%, whereas it was 6.5%, and 26% in those with LVEF <30%. However, multivariable Cox regression analysis showed that age ≥75 years (P=0.002, HR 1.8), NT-proBNP ≥10,000 pg/mL (P=0.005, HR=1.8), CKD (P=0.032, HR 1.6), and TAPSE <15 mm (P=0.001, HR=1.8) were independent determinants of mortality, but LVEF <30% was not a prognostic determinant (P=0.73).
number of participating institutions was limited. Therefore, it might not be possible to generalize these findings simply to Japan.

**Study Limitation**

Although our retrospective study had one of the largest sample of patients undergoing MitraClip application, the number of participating institutions was limited. Therefore, it might not be possible to generalize these findings simply to Japan.
Conclusions
LVEF <30% accounted for one third of patients with MR undergoing MitraClip in German high-volume centers. LVEF <30% did not affect neither acute MR improvement nor long-term survival after MitraClip.

Disclosure
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