MitraClip NT System

Post-marketing Surveillance Protocol

Protocol # 17-519

Abbott Vascular Japan Co., Ltd.

Result of this post-marketing surveillance shall be reported to the Ministry of Health, Labour and Welfare as a condition to marketing approval of the MitraClip System. Your cooperation in this surveillance would be highly appreciated.

Surveillance Device Approval Number	22900BZX00358000
Surveillance Device Approval Date	October 31, 2017
Generic Name of the Surveillance Device	MitraClip NT System
Brand Name of the Surveillance Device	MitraClip NT System
Surveillance Period (Registration Period)	From October, 2017 to October, 2023. (From April 1, 2018 to March 31, 2020)
Post-marketing Surveillance Sponsor	Abbott Vascular Japan Co., Ltd.
Post-marketing Surveillance General Manager	Director, Clinical Strategy and Execution

Table of Contents

1. PURPOSE

The purpose of this post-marketing clinical use surveillance (hereinafter referred to as "Surveillance") is to observe the frequency, type and degree of adverse device effects and adverse events in order to assure the safety of the new medical device, and to collect safety and efficacy information for evaluating the results of the clinical use. The Surveillance will be conducted per the standards required by the Minster of Health, Labour and Welfare (MHLW) and in the standards for post-marketing surveillances and studies [except for those defined in the Ministerial Ordinance on Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)] based on Paragraph 4, Article 23-2-9 (including application *mutatis mutandis* per Article 23-2-19 of Revised PAL) of the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices, etc. (Law No. 145, 1960, hereinafter referred to as "Revised PAL") by the Marketing Authorization Holder or accredited foreign manufacturer of a medical device defined in Paragraph 1, Article 23-2-5 of Revised PAL.

2. SURVEILLANCE METHOD

2.1 Patients

Based on the Ministerial Ordinance on Good Post-marketing Study Practice for Medical Device, the Surveillance will **consecutively register** patients with moderate to severe and severe mitral regurgitation (3+ and 4+ MR) in whom a MitraClip implant was attempted (Marketing Approval No. 22900BZX00358000, October 31, 2017, hereinafter referred to as "MitraClip"). Patients registered in the AVJ-514 clinical trial who received additional MitraClip procedures will be excluded from the Surveillance.

2.2 Registration Method

- Patient registration will occur consecutively when treatment with MitraClip is attempted. Patients registered in the AVJ-514 clinical trial who received additional MitraClip procedures will be excluded from the Surveillance.
    - Patients will be considered registered upon femoral vein puncture for transseptal access in preparation for MitraClip System insertion.
    - If an attempt of MitraClip implantation failed with subsequent treatment done with other device(s) or surgical repair, only the information on the attempted MitraClip implant will be recorded. For this patient, follow-up is not required unless any adverse event occurred in relation to the attempted MitraClip implantation.
- It is not recommended that patients registered in the Surveillance participate in any other therapeutic clinical study. Registered patients can participate in non-therapeutic clinical studies, such as non-invasive cardiac imaging study.

2.3 Planned Sample Size

The target sample size of this surveillance is up to patients at up to Japanese sites.

3. SURVEILLANCE PERIOD

Information will be collected for up to 3 years post procedure. The target registration period will be from the date that patient registration is allowed upon execution of study agreement with each site to the last patient registered into the PMS. Shown below are specific details associated with the surveillance period.

- Approximate preparation period: 6 months
- Registration period: the estimate of the registration period for the PMS is about 2 years
- Follow-up period: 3 years
- Final re-examination report: 6 months
- Total PMS period: Approximately 6 years

Primary analysis data will be collected until all patients complete 30 days follow-up. Annual progress reports (up to 3 years) will be submitted to the regulatory authority at each time point accordingly.

Data will be collected at the following time points:

- Baseline (pre-procedure)
- Procedure
- Discharge
- 30 days（30 days+14 days）(by visit)
- 1 year（365 days±28 days）(by visit)
- 2 years（730 days±28 days）(by visit)
- 3 years（1095 days±28 days）(by visit)

4. TREATMENT OF PATIENTS

The MitraClip NT will be implanted per the current approved instructions for use (IFU). Physicians should refer to the warnings, contraindications, and precautions in the most current version of product IFU for optimal treatment of each patient.

5. INFORMATION TO BE COLLECTED FOR THE SURVEILLANCE

5.1 Baseline

1) Basic Patient Information

- Registration date
- Date of birth or age at procedure
- Gender
- Height
- Weight

2) Cardiac Status at Registration

- Mitral regurgitation severity and etiology, as reported by site
  - Functional mitral regurgitation (FMR)
  - Degenerative mitral regurgitation (DMR)
- Ischemic status at registration, especially previous interventions
- New York Heart Association (NYHA) functional class
- Atrial fibrillation: paroxysmal, persistent, permanent
- Previous cardiac resynchronization therapy
- Previous percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)
- Previous heart valve surgery or other cardiothoracic surgeries
- Left ventricular function and anatomy as reported by site
  - Left ventricular ejection fraction (LVEF)
  - Left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV), left ventricular end systolic dimension (LVESD), left ventricular end diastolic dimension (LVEDD).

3) Risk Factors and Medical History

- General heart disease risk factors
  - Smoking status
  - Diabetes
  - Hypertension
  - Dyslipidemia
- Renal failure
  - Currently on dialysis
- Previous cerebrovascular accident (CVA)/ transient ischemic attack (TIA)
- Previous peripheral disease and intervention
- Chronic pulmonary disease
- Previous major bleeding
- Cirrhosis
- Cancer

- Subject is deemed difficult for mitral valve surgery due to either STS surgical mortality risk for mitral valve replacement of ≥ 8% OR due to the presence of one of the following risk factors:
  - Porcelain aorta or mobile ascending aortic atheroma
  - Post-radiation mediastinum
  - Previous mediastinitis
  - Functional MR with LVEF<40%
  - Over 75 years old with LVEF<40%
  - Re-operation with patent grafts
  - Two or more prior cardiothoracic surgeries
  - Hepatic cirrhosis
  - Other surgical risk factor(s)

4) Classes of Cardiovascular and Heart Failure Medications

- Angiotensin converting enzyme (ACE) inhibitor
- Angiotensin II receptor blocker
- Aldosterone receptor blocker
- Beta-blocker
- Diuretics
- Calcium channel blocker
- Anti-Platelets
- Anticoagulants
- Antiarrhythmics
- Cardiac glycosis (Digitalis)
- Statins
- Other vasodilators
- Other cardiac medication

5) Transthoracic and Transesophageal Echocardiography

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) shall be performed at baseline. TTE and TEE will be used to assess the severity of mitral regurgitation, mitral valve anatomy, and left ventricular function and dimensions.

6) Pre-procedure ECG

A 12-lead electrocardiogram will be performed at baseline or prior to the procedure.

7) Pre-procedure Laboratory Tests

Standard pre-procedure lab tests, including but not limited complete blood count (CBC), cardiac biomarkers, real function, and liver function will be performed.

8) Pre-procedure Antiplatelet Medications

Pre-procedure anticoagulation and/or antiplatelet medications will be administered per institutional standard-of-care.

5.2 MitraClip Procedure Information

1) General Information

- MitraClip Procedure date
- Operator's name
- Procedure start time (time guiding catheter inserted)
- Procedure end time (time guiding catheter removed)
- Radiation time

2) MitraClip NT Used

- Number of clips used
- Successful implantation in intended location
- Device deficiency
- Product information (Lot/Serial #)

3) Final Outcome Result

- MR severity post MitraClip NT procedure
- Procedural complications

5.3 Post-procedure (In-hospital) Information

1) Post-procedure ECG

A 12-lead electrocardiogram will be performed post-procedure.

2) Post-procedure Anticoagulation and Antiplatelet Medications

Post-procedure anticoagulation and/or antiplatelet medications will be administered per institutional standard-of-care.

3) Hospitalization Information

- Post procedure Post-Anesthesia Care Unit (PACU)/Intensive Care Unit (ICU)/ Critical Care Unit (CCU) stay (hours)
- Total hospital stay (days)

4) In-hospital Adverse Events Reported by Site

- In-hospital death
- Cardiogenic shock
- Heart failure
- CVA
- Cardiac tamponade
- Pericardial effusion
- New requirement of dialysis
- Mitral valve re-intervention, MitraClip or surgery
- Vascular complication (requiring prolongation of existing hospitalization)
- Bleeding complication within 72 hours (requiring blood transfusion or Hb drop of > 3g/dL)
  - Access site
  - Non-access site
- Device embolization
- Other adverse events

5.4 Discharge Information

- Discharge date
- Discharge TTE findings, including MR severity and LV measurements
- Heart failure condition, including NYHA class
- Discharge medications
  - Angiotensin converting enzyme (ACE) inhibitor
  - Angiotensin II receptor blocker
  - Aldosterone receptor blocker
  - Beta-blocker
  - Diuretics
  - Calcium channel blocker
  - Anti-Platelets
  - Anticoagulants
  - Antiarrhythmics
  - Cardiac glycosis (Digitalis)
  - Statins
  - Other vasodilators

- Other cardiac medication

5.5 Scheduled Follow-up

Scheduled follow-ups include 30-day, 1-, 2- and 3-year post procedure. Record the following information at each follow-up time point:

- Type of contact (visit)
- Date of contact
- TTE
- NYHA class
- Adverse event occurred or change in symptoms from previous follow-up
- Changes on cardiac medications (started/changed/stopped)
- Device Deficiency

5.6 TTE Follow-up

TTE is required at discharge and each annual follow-up visit.

5.7 Unscheduled Follow-up (only in case of reportable adverse event)

Complete Adverse Event form.

5.8 Device Deficiency during Follow-up Period

- Date device deficiency occurred
- Event occurred
- Adverse event (health hazard) relating to the device deficiency
- Background information/comment on the device deficiency
- Product information (Lot/Serial #)

5.9 Adverse Events (reportable events)

- Record the following adverse events in case report:
  - All heart failure and heart failure hospitalization adverse events
  - All other serious adverse events*
  - Events reported as relating to MitraClip or relationship to the device is unknown

* A serious adverse event is defined as an event: lead to death; potentially leading to death; required in-patient hospitalization or prolongation of existing hospitalization for treatment; potentially leading to a persistent or significant disability or incapacity; led to a congenital disease or anomaly; or other event considered serious per physician's judgment.

Record whether each adverse event defined as above is related to MitraClip and/or the procedure, as well as outcome of the event. For serious adverse events, also record reason for the judgment as serious.

6. ENDPOINTS

6.1 Primary Endpoints

The primary endpoints of this study are single leaflet device attachment (SLDA) rate at 30 days and acute procedural success (APS) assessed at discharge. In the Surveillance, SLDA will be site reported. APS is defined as resulting MR reduction to ≤ 2+ per echocardiographic assessment. If echocardiographic data at discharge was not available or unevaluable, echocardiographic data at 30 days will be used for evaluation. APS will not be achieved if a patient expired or received mitral valve surgery before discharge. Achievement of MR reduction to ≤ 2+ as result of additional MitraClip implantation during index procedure will be considered as APS.

6.2 Other Endpoints

Other endpoints will be evaluated at the specific follow-up timepoints per typical mitral regurgitation intervention clinical studies, including but not limited to, mitral regurgitation severity score, NYHA class, LV function and anatomy, cardiac medication, adverse events, device deficiency. Rate of heart failure hospitalizations in the 1 year post-procedure will be compared to the 1 year prior to the index procedure.

7. Statistical Analysis

7.1 Analysis Populations

All patients registered in the surveillance with MitraClip treatment attempted will be included in the analysis.

7.2 Rationale for Sample Size Setting and the Assumptions

To establish an appropriate sample size for the Surveillance, SLDA, a low-occurrence event of (3%), was used as the event rate of interest. Table 1 presents SLDA rates through 1 year in the MitraClip clinical trials. SLDA was reported most frequently in the E-II RCT, the earliest clinical trial. SLDA

rates in the subsequent clinical trials consistently maintained at around 3% as investigators gained further experience with the MitraClip procedure.

Table 1: SLDA Rates through 1 Year in MitraClip Clinical Trials

	Successful MitraClip Implantation	SLDA	SLDA Rate
E-II RCT	158	10	6.3%
E-II HRR	75	1	1.3%
Realism HR (First 273 patients)	261	6*	2.3%
Realism HR (Subsequent 355 pts)	342	6	1.8%
AVJ-514 Clinical Trial	30	1**	3.3%

* One additional SLDA was reported after 1-year follow up (at 18-months follow-up), resulting in total number of the events of 7.
** SLDA was adjudicated by the core laboratory: not adjudicated by the site.

If the SLDA rate in the Surveillance is 3%, the upper limit of one-sided 95% confidence interval of the SLDA rate for a sample size of 250 patients would be 5.4%, which is lower than 6.3%, the SLDA rate in E-II RCT, the earliest MitraClip clinical trial. In other words, if the true SLDA rate is 3%, the SLDA rate in the Surveillance would be 5.4% or lower with a probability of approximately 95%.

7.3 Statistical Analyses

No pre-specified hypothesis tests are planned for this surveillance. Descriptive analysis will be performed to summarize baseline, procedural, clinical and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in this section below will be used.

For continuous variables such as age, results will be summarized with the numbers of observations, means, standard deviations, and 95% confidence intervals for the mean. These calculations will be done under the assumption that the data are approximately normal in distribution.

For time to event data such as all-cause mortality, Kaplan-Meier analyses will be used.

For recurrent event data such as recurrent heart failure hospitalizations post-procedure, data will be analyzed using a generalized linear model, such as Poisson regression model.

8. ANALYSIS AND REPORTING