SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Transcatheter Septal Occluder

Device Trade Name: AMPLATZER™ Post-Infarct Muscular VSD Occluder

Device Procode: MLV

Applicant's Name and Address:

AGA Medical Corporation
5050 Nathan Lane North
Plymouth, MN 55442
USA

(AGA Medical Corporation is an indirectly wholly-owned subsidiary of St. Jude Medical, Inc.)

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H070005

Humanitarian Use Device (HUD) Designation Number: HUD # 07-0178

Date of HUD Designation: April 4, 2007

Date of Notice of Approval to Applicant: 1/10/2017

II. INDICATIONS FOR USE

The AMPLATZER™ Post-Infarct Muscular VSD Occluder is a percutaneous transcatheter occlusion device intended for closure of post myocardial infarct muscular ventricular septal defects in patients who are not satisfactory surgical candidates.

The indication for use statement is identical to that which was granted for the HUD designation.

III. CONTRAINDICATIONS

The AMPLATZER™ Post-Infarct Muscular VSD Occluder is contraindicated for the following:

- Patients with perimembranous VSD or a VSD close to the aortic or mitral valve;
- Patients with congenital muscular VSD;
- Patients with the presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to

the defect is gained;

- Patients with active endocarditis or other infections producing bacteremia;
- Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate sheath size;
- Patients known to have active sepsis or any systemic infection that cannot be successfully treated prior to device placement; or
- Any patient known to have a bleeding disorder, untreated ulcer, or any other contraindications to aspirin therapy, unless another antiplatelet agent can be administered for 6 months.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the AMPLATZER Post-Infarct Muscular VSD Occluder labeling.

V. DEVICE DESCRIPTION

The AMPLATZER Post-Infarct Muscular VSD Occluder is a self-expanding, double-disc device made from nitinol wire mesh and designed to facilitate occlusion of muscular ventricular septal defects (VSDs) that occur post-myocardial infarction. The discs are linked together by a waist corresponding to the size of the VSD. To increase its closing ability, the discs and waist are filled with polyester fabric that is sewn securely to the device with polyester thread. Radiopaque marker bands at each end of the device provide visualization under fluoroscopy.

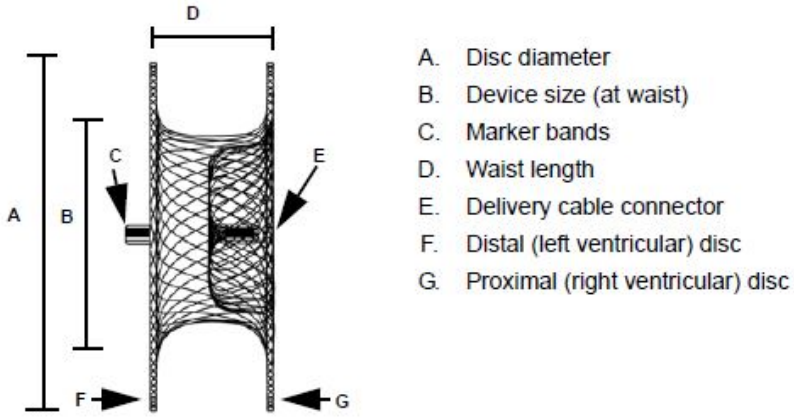

Figure 1. AMPLATZER™ Muscular VSD Occluder.

The 510(k) cleared AMPLATZER TorqVue™ Delivery System or AMPLATZER TorqVue Exchange system is used to deliver the device.

The AMPLATZER Post-Infarct Muscular VSD Occluder is available in sizes 16, 18, 20, 22 and 24mm which correspond to the central waist diameter designed to fill the defect.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of a post-infarct ventricular septal defect include:

1. Medical Therapy – Use of intravenous inotropic medications in combination with intravenous diuretics and mechanical respiratory support. The 30-day mortality rate using this approach exceeds 90%.

2. Mechanical Circulatory Support – Use of an intra-aortic balloon pump or a temporary ventricular assist device to support the circulatory system to recovery or as a bridge to additional therapy, such as a longer term mechanical circulatory support device or cardiac transplantation. These strategies are less common, and the data detailing their success is limited.

3. Surgical Repair – Use of open cardiac surgery under cardiopulmonary bypass to repair the ventricular septal defect. Operative mortality rate ranges between 18% and 54%.

VII. MARKETING HISTORY

The AMPLATZER Post-Infarct Muscular VSD Occluder has been marketed in the following countries:

Albania
Algeria
Andorra
Argentina
Armenia
Australia
Austria
Azerbaijan
Bahrain
Belarus
Belgium
Bulgaria
Canada
Chile
China
Colombia
Costa Rica
Croatia
Curacao
Cyprus
Czech Republic
Denmark
Dominican Republic
Estonia
Ethiopia
Finland
France & Monaco
Georgia
Germany
Greece
Guatemala
Hong Kong
Hungary
Iceland
India Indonesia
Iraq
Ireland
Israel
Italy
Jordan
Kenya
Kuwait
Latvia
Lebanon
Libya
Liechtenstein
Lithuania
Luxembourg
Malaysia
Malta
Mauritius
Mexico
Morocco
Netherlands
New Zealand
Norway
Oman
Palestine
Peru
Poland Portugal
Qatar
Russia
Rwanda
Saudi Arabia
Senegal
Serbia
Slovakia
Slovenia
South Africa
Spain
Sweden
Switzerland
Trinidad/Tobago
Tunisia
Turkey
Uganda
United Kingdom
Uruguay
Venezuela
Vietnam
Yemen

The device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

- Air embolus
- Allergic reaction
- Anesthesia reaction
- Anemia
- Apnea
- Arrhythmia
- Arterial pulse loss
- Atelectasis
- Bacterial endocarditis
- Bleeding
- Brachial plexus injury
- Cardiac Arrest
- Cardiomyopathy
- Cyanosis
- Chest pain
- Death
- Device embolization
- Device fracture
- Fever
- Headache/migraine
- Heart block
- Heart failure
- Hemolysis
- Hypertension
- Hypotension
- Left ventricular aneurysm
- Myocardial infarction
- Perforation of vessel or myocardium
- Peripheral embolism
- Renal insufficiency
- Respiratory arrest
- Sepsis
- Stridor
- Stroke/TIA
- Sub-aortic stenosis
- Thrombocytopenia
- Thrombus
- Valvular regurgitation/insufficiency
- Vascular access site complications
- Venous thrombosis
- Vomiting

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

A series of non-clinical studies were performed to evaluate the AMPLATZER Post Infarct Muscular VSD Occluder.

1. Biocompatibility Studies on the Implant

Biocompatibility testing for the AMPLATZER Post Infarct Muscular VSD Occluder was conducted. In addition, chemical characterization and nickel leach studies were conducted to support the overall biocompatibility profile of the device.

All biocompatibility testing was conducted in accordance with:

- ISO 10993-1: "Biological evaluation of medical devices – Part 1: Evaluation and testing" and
- Good Laboratory Practices Regulations (21 CFR § 58).

A summary of the biocompatibility data provided to support this HDE can be found in Table 1. "Pass" denotes that the test results met the product specifications or acceptance criteria.

Table 1. Biocompatibility Test Summary

BIOLOGICAL TEST	DESCRIPTION	RESULTS
Cytotoxicity	Minimum Essential Medium Elution ISO 10993-5 (2009)	PASS Non-cytotoxic
Sensitization	Guinea Pig Maximization ISO 10993-10 (2010)	PASS Non-sensitizer
Intracutaneous Reactivity (Irritation)	ISO 10993-10 (2010)	PASS Non-irritant
Acute Systemic Toxicity	ISO 10993-11 (2006)	PASS No evidence of systemic toxicity
Pyrogenicity	ISO 10993-11 (2006)	PASS Non-pyrogenic
Genotoxicity	In vitro Chromosomal Aberration ISO 10993-3 (2003)	PASS Non-mutagenic
	Mouse Micronucleus Assay ISO 10993-3 (2003)	PASS The test article did not induce micronuclei in mice
	Bacterial reverse mutation assay ISO 10993-3 (2003)	PASS Non-mutagenic
	Mouse Lymphoma Assay ISO 10993-3 (2003)	PASS Non-mutagenic
Implantation	1 & 4 Week Muscular Implantation ISO 10993-11(2006)	PASS Non-irritant, macroscopic reactions not significant compared to control
Sub-Chronic Toxicity	13 week Systemic Toxicity Study in Rats Following Subcutaneous Implantation ISO 10993-10 (2010)	PASS Slight irritant compared to control, no signs of systemic toxicity - test requirements met
Hemocompatibility	Hemolysis ASTM Direct Contact and Extract ISO 10993-4 (2002, A2006)	PASS Non-hemolytic
	C3a Complement Activation ISO 10993-4 (2002, A2006)	PASS Not considered a potential activator
	SC5b-9 Complement Activation ISO 10993-4 (2002, A2006)	PASS Not considered a potential activator

BIOLOGICAL TEST	DESCRIPTION	RESULTS
Chemical Characterization	Gas Chromatography - Mass Spectroscopy (GC/MS) for volatile and semi-volatile, organic compounds	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Inductively Coupled Plasma (ICP) Spectroscopy for metallic compounds	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Liquid Chromatography - Mass Spectroscopy (LC/MS) for semi-volatile and non-volatile organic compounds	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
Nickel Leaching	120 day immersion study	Peak release occurred on day 1 with very low release for remainder of study; levels were below the toxicity limit for the adult patient population

The information provided demonstrated that the AMPLATZER Post Infarct VSD Occluder is biocompatible.

2. In Vitro Engineering Testing

The in vitro engineering studies performed are summarized in Table 2. "Pass" denotes that the test result met the product specifications or acceptance criteria.

Table 2: Engineering Testing

Testing Summary			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Recapture Force Testing	Evaluate the force required to recapture the device into the delivery sheath during simulated use testing	The device must be able to be completely recaptured into the recommended delivery sheath.	PASS
Device Tensile Testing	Evaluate the tensile strength of the welded device end screw and marker band	Force must be greater than 12 lbs	PASS
Visual Inspection	To visually assess the device maintains its intended shape and form while deployed	The device must meet the visual inspection requirements as listed in the final inspection manufacturing procedure	PASS

<table>
<tr><th colspan="4">Testing Summary</th></tr>
<tr><th>Test</th><th>Purpose</th><th colspan="2">Acceptance Criteria</th><th>Results</th></tr>
<tr><td>Dimensional Inspection</td><td>To quantitatively assess that the device meets all dimensional requirements</td><td colspan="2"><table><tr><th>Device Size</th><th>DISC Diameter ǿC ± 0.5 mm</th><th>WAIST Diameter ǿA ± 0.5 mm</th></tr><tr><td>16</td><td>26</td><td>16</td></tr><tr><td>18</td><td>28</td><td>18</td></tr><tr><td>20</td><td>30</td><td>20</td></tr><tr><td>22</td><td>32</td><td>22</td></tr><tr><td>24</td><td>34</td><td>24</td></tr></table></td><td>PASS</td></tr>
<tr><td>Advancement / Deployment Test</td><td>To assess the force needed to advance the device through the correct sized sheath.</td><td colspan="2">PASS/FAIL, the device must be able to be advanced through the recommended delivery sheath and deployed into the simulated cardiac defect

Each device tested was advanced, deployed and recaptured 3 times. Advancement and recapture forces were recorded.</td><td>PASS</td></tr>
<tr><td>Deployment into simulated defect</td><td>To verify the device can maintain its structural integrity and properly deploy when delivered and placed in a simulated bench test model.</td><td colspan="2">PASS/FAIL if the device is able to be deployed into the simulated cardiac defect without deforming.</td><td>PASS</td></tr>
<tr><td>Post-Deployment Device Dimensions</td><td>To evaluate the device dimensions both pre- and post-deployment.</td><td colspan="2">The post-deployment dimensional data was compared to pre-deployment specifications (disc diameter, waist diameter and waist length); All post-deployment dimensions should be within pre-deployment specifications.</td><td>PASS</td></tr>
<tr><td>Device Integrity</td><td>To evaluate the effect broken wires have on overall structural integrity of the device.</td><td colspan="2">There should be no statistical difference in pull-out and push-through forces found between the two groups (intact devices and cut-devices)</td><td>PASS</td></tr>
</table>

Particulate Testing	To quantify and characterize particulate matter potentially introduced to the body when implanting the device with the delivery system	USP<788> Guidance	PASS
Potentiodynamic Corrosion Testing	To assess the corrosion susceptibility of the device	ASTM F2129	PASS
Fatigue Testing	To ensure the device is suitable for long term implantation into the human ventricular septum through mechanical simulation	The device must reach 200 million cycles without damage that causes any part of the device to embolize. The device must remain in the implanted location in the test fixture for the entire duration of the test and the device must maintain structural integrity.	PASS

Magnetic Resonance Imaging (MRI) Compatibility:

Non-clinical testing has demonstrated that the AMPLATZER Post-infarct Muscular VSD Occluder is MR Conditional. A patient with this device can be safely scanned immediately after implantation in an MR system meeting the following conditions:

• Static magnetic field of 3T
• Maximum spatial field gradient of 720 gauss/cm
• Maximum MR system reported whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Under the scan conditions defined above, the AMPLATZER Post-Infarct Muscular VSD Occluder is expected to produce a maximum temperature rise of less than 1.7°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 20 mm from the AMPLATZER Post-Infarct Muscular VSD Occluder when imaged with a gradient echo pulse sequence and a 3T MRI system.

3. Sterilization

The AMPLATZER Post Infarct Muscular VSD Occluder is sterilized via ethylene oxide. The sterilization cycle was validated to meet a minimum Sterility Assurance Level (SAL) of 10^{-6}.

4. Shelf Life/Packaging

The shelf life and packaging for the AMPLATZER Post Infarct Muscular VSD Occluder was validated to ensure that both device performance and package integrity were maintained for 5 years. The testing to support the product shelf life included functional performance testing and packaging integrity of test samples accelerated aged to an equivalent of 5 years. A summary of the functional testing was presented above in Table 2 and a summary of packaging integrity testing can be found below in Table 3.

Table 3: Package Integrity Testing Summary

Test	Samples	Specification	Results
Bubble Leak	Inner and outer pouch	No leaks	Pass
Seal Strength	Inner and outer pouch	Equal to or greater than 0.5lbs	Pass

B. Animal Studies

Two chronic GLP studies were performed to evaluate the AMPLATZER Post Infarct Muscular VSD Occluder for device implant safety and performance. Testing was conducted with representative devices of the same Nitinol wire finish. The studies are summarized in Table 4.

Table 4. Animal Studies

Study	No. of Animals and Study Duration; Species	Objective	Results
GLP Study to evaluate Nitinol wire surface	2 animals, 30 days; Canine	To evaluate and compare devices built with different surface finishes.	The occlusion times were similar for the devices built with 2 different surface finishes.
GLP study to evaluate systemic Nickel content	8 animals. 60 days; porcine	To evaluate systemic (serum) nickel content from test animals as compared to sham animals.	There was no difference in nickel levels between the test animals and sham animals.

X. SUMMARY OF CLINICAL INFORMATION

The AMPLATZER Post Infarct Muscular VSD Occluder was studied as part of the AMPLATZER Muscular VSD Occluder Investigational Device Exemption (IDE G990289). The study evaluated the treatment of post-myocardial infarction muscular ventricular septal defects in patients who are not surgical candidates. A total of 44 post-myocardial infarction VSD patients were treated with the AMPLATZER Post Infarct Muscular VSD Occluder.

The patients studied were compiled from three different patient cohorts, consisting of a Registry cohort (15 patients), a High-Risk cohort (6 patients), and an Emergency/Compassionate Use cohort (23 patients). Patients were enrolled at 21 investigational sites or institutions. Effectiveness was evaluated by examining a) the post-myocardial infarction VSD closure rate; and b) the survival rate, through 30 days post-implant.

Additional outcomes presented are technical success, acute procedural success, and 1-month success. The database for this HDE reflects data collected through May 1, 2007.

Inclusion/Exclusion Criteria

Registry Cohort (N=15)

Inclusion and exclusion criteria for the Registry cohort included the following:

Inclusion criteria:

- Muscular VSD following myocardial infarction

Exclusion criteria:

- Less than 4 mm distance from the semilunar (aortic and pulmonary) and atrioventricular valves (mitral and tricuspid)
- Perimembranous (close to the aortic valve) VSD
- Patients < 3 kg
- Patients with sepsis (local/generalized)
- Patients with gastritis, gastric ulcer, duodenal ulcer, bleeding disorder etc. and other contraindications to aspirin therapy unless other anti-platelet agents can be administered for 6 months
- Inability to obtain informed consent.

High-Risk Cohort (N=6)

Inclusion criteria for the High-Risk cohort considered included the following:

Inclusion criteria:

- Post infarct muscular VSD
- High-risk, non-surgical candidate
- Life-threatening condition that needs immediate treatment; or no generally acceptable alternative for treating the patient is available.

Emergency/Compassionate Use Cohort (N=23)

Other than the following, inclusion criteria for patients considered for emergency/compassionate use treatment with the AMPLATZER Post Infarct Muscular VSD Occluder were specified on a case-by-case basis.

- Post infarct muscular VSD
- Life-threatening condition that needs immediate treatment; or no generally acceptable alternative for treating the patient is available.

Patient demographics were collected on the three patient cohorts. Other baseline characteristics such as cardiac history and physical examination/ECG parameters were not collected in Emergency/Compassionate Use patients.

Patient Demographics and Baseline Parameters

Table 5 summarizes the overall demographics of the various patient cohorts. The patients in the High-Risk cohort are approximately 5 years older than those in the other cohorts. The gender distribution and other baseline characteristics were similar across the three cohorts.

Table 5. Baseline Demographics

Baseline Characteristic	Registry N = 15	High-Risk N = 6	Emergency/ Compassionate N = 23	Total N = 44
Age (years)	72.8 ±10.0 (15) [54.1, 86.1]	77.2 ± 10.6 (6) [56.4, 83.1]	72.4 ± 10.7 (23) [49.3, 91.0]	73.2 ± 10.4 (44) [49.3, 91.0]
Gender				
Female	9/15 (60.0%)	3/6 (50.0%)	11/23 (47.8%)	23/44 (52.3%)
Male	6/15 (40.0%)	3/6 (50.0%)	12/23 (52.2%)	21/44 (47.7%)
Height (cm)	169.3 ± 11.5 (14) [155.0, 188.0]	168.2 ± 12.3 (6) [152.0, 185.0]	168.7 ± 11.4 (22) [150.0, 185.0]	168.8 ± 11.3 (42) [150.0, 188.0]
Weight (kg)	76.2 ± 20.2 (15) [50.0, 125.0]	90.5 ± 13.7 (6) [69.2, 106.3]	79.8 ± 22.9 (22) [53.0, 170.0]	80.0 ± 21.0 (43) [50.0, 170.0]

Table 6 summarizes the baseline cardiac history for the Registry and the High-Risk cohort patients. The majority of patients had a history of congestive heart failure (57.1%) and/or shortness of breath (53.3%). Also, a significant proportion of patients had undergone a prior open surgical VSD closure procedure (42.9%).

Table 6. Baseline Cardiac History

Cardiac History	Registry N = 15	High-Risk N = 6	Total N = 21
Congestive heart failure	10/15 (66.7%)	2/6 (33.3%)	12/21 (57.1%)
Cardiac arrhythmia	5/15 (33.3 %)	3/6 (50.0%)	8/21 (38.1%)
Shortness of breath	8/15 (53.3%)	NC	8/15 (53.3%)
Contraindication to aspirin	NC	1/6 (16.7%)	1/6 (16.7%)
Pulmonary hypertension	1/15 (6.7%)	NC	1/15 (6.7%)
Other cardiac anomalies	11/15 (73.3%)	NC	11/15 (73.3%)
Previous cardiac surgery	NC	4/6 (66.7%)	4/6 (66.7%)
Previous surgical VSD closure	6/15 (40.0%)	3/6 (50.0%)	9/21 (42.9%)

NC, not collected.

The Registry and High-Risk cohort patients underwent a baseline physical exam and an ECG. Results are shown in Table 7. All 21 patients showed some signs of heart murmur, with 16 patients (76.2%) having a holosystolic heart murmur.

Table 7. Baseline Physical Examination & ECG Parameters

Parameter	Registry N = 15	High-Risk N = 6	Total N = 21
Heart murmur (not mutually exclusive)			
None	0/15 (0.0%)	0/6 (0.0%)	0/21 (0.0%)
Holosystolic	11/15 (73.3%)	5/6 (83.3%)	16/21 (76.2%)
Mid-diastolic	0/15 (0.0%)	0/6 (0.0%)	0/21 (0.0%)
Systolic	5/15 (33.3%)	NC	5/15 (33.3%)
Continuous	0/15 (0.0%)	NC	0/15 (0.0%)
Other	3/15 (20.0%)	1/6 (16.7%)	4/21 (19.1%)
ECG (not mutually exclusive)			
Left ventricle hypertrophy	2/15 (13.3%)	0/5 (0.0%)	2/20 (10.0%)
Right ventricle hypertrophy	1/15 (6.7%)	0/5 (0.0%)	1/20 (5.0%)
Biventricular hypertrophy	1/15 (6.7%)	0/5 (0.0%)	1/20 (5.0%)
Cardiac arrhythmia	NC	3/6 (50.0%)	3/6 (50.0%)
Right atrial hypertrophy	0/15 (0.0%)	NC	0/15 (0.0%)
Left atrial hypertrophy	1/15 (6.7%)	NC	1/15 (6.7%)

NC, not collected.

Effectiveness Results

The effectiveness endpoint for VSD closure using the AMPLATZER Post-infarct Muscular VSD Occluder was evaluated by the one-month success criteria below. Other outcome success criteria are also presented.

Technical Success

Table 8 displays the technical success results per patient and per procedure. Per-procedure technical success was calculated as procedures during which device placement was attempted and a device was successfully deployed in a defect during a catheterization. Per-patient technical success was calculated as patients in whom device placement was attempted and a device was successfully deployed in a defect during a catheterization at some point during the study. The per-patient technical success rate for the combined Registry and High-Risk cohorts was 90.5% (19/21 patients). Specifically, of the 15 Registry patients in whom deployment of the device was attempted, deployment was technically successful for 13 (86.7%) patients. Deployment was tx nnechnically successful for all 6 (100.0%) High-Risk patients and all 23 (100.0%) Emergency/Compassionate use patients.

Table 8. Technical Success Results

Success Criterion	Registry	High-Risk	Emergency/ Compassionate	Total
Per Procedure Results	**N = 19**	**N = 6**	**N = 26**	**N = 51**
Technical Success	16/19 (84.2%)	6/6 (100.0%)	26/26 (100.0%)	48/51 (94.1%)
95% CI for Success	(60.4%, 96.6%)	(54.1%, 100.0%)	(86.8%, 100.0%)	(83.8%, 98.8%)
Per Patient Results	**N = 15**	**N = 6**	**N = 23**	**N = 44**
Technical Success	13/15 (86.7%)	6/6 (100.0%)	23/23 (100.0%)	42/44 (95.5%)

95% CI for Success	(59.5%, 98.3%)	(54.1%, 100.0%)	(85.2%, 100.0%)	(84.5%, 99.4%)

CI: Confidence Interval

Acute Procedure Success

Residual shunt was evaluated immediately following the implant procedure and used to evaluate acute procedure success. Residual shunt status was evaluated during angiography post device placement following a technically successful procedure. Table 9 displays the distribution of the shunt sizes per patient and per procedure. Post procedure per-patient shunt success, defined as small residual shunt or less, was achieved for 65.0% (26/40) of patients.

Table 9. Post Procedure Shunt Status

Shunt size[a]	Registry	High-Risk	Emergency/ Compassionate	Total
Per-procedure results	N = 16	N = 6	N = 23[b]	N = 45
None/closed	0/16 (0.0%)	1/6 (16.7%)	2/23 (8.7%)	3/45 (6.7%)
Trivial	5/16 (31.3%)	1/6 (16.7%)	5/23 (21.7%)	11/45 (24.4%)
Small	8/16 (50.0%)	2/6 (33.3%)	4/23 (17.4%)	14/45 (31.1%)
Moderate	3/16 (18.8%)	2/6 (33.3%)	10/23 (43.5%)	15/45 (33.3%)
Large	0/16 (0.0%)	0/6 (0.0%)	2/23 (8.7%)	2/45 (4.4%)
Per-patient results	N = 13	N = 6	N = 21[c]	N = 40
None/closed	0/13 (0.0%)	1/6 (16.7%)	2/21 (9.5%)	3/40 (7.5%)
Trivial	5/13 (38.5%)	1/6 (16.7%)	5/21 (23.8%)	11/40 (27.5%)
Small	7/13 (53.9%)	2/6 (33.3%)	3/21 (14.3%)	12/40 (30.0%)
Moderate	1/13 (7.7%)	2/6 (33.3%)	10/21 (47.6%)	13/40 (32.5%)
Large	0/13 (0.0%)	0/6 (0.0%)	1/21 (4.8%)	1/40 (2.5%)

a) Trivial shunt size was less than 1mm; small shunt size was 1.0-2.9mm; moderate shunt size was 2.0-4.0mm; large shunt size was > 4mm
b) Shunt was not evaluated following 3 procedures in the Emergency/Compassionate-use cohort.
c) Shunt was not evaluated following the procedures for 2 patients in the Emergency/Compassionate-use cohort.

Acute procedure success, as determined by the investigator, was based on the echocardiogram results. Per-procedure acute procedure success was calculated as procedures that resulted in a successful closure of the ventricular septal defect immediately following the procedure. For per-procedure acute procedure success, successful closure of the defect was defined as less than or equal to 2.9-mm residual shunt. Technical failure procedures were considered acute procedure failures. Per-patient acute procedure success was calculated as patients who had successful closure of the ventricular septal defect immediately following the procedure. For per-patient acute procedure success, successful closure of the defect was defined as less than or equal to a 2-mm residual shunt. If a patient underwent multiple procedures, acute procedure results were determined by the first successful procedure. Technical failure patients were considered acute procedure failures.

The per-patient acute procedure success rate for the combined Registry and High-Risk cohorts was 76.2% (16/21 patients). Specifically, 12 (80.0%) of the 15 Registry patients and 4 (66.7%) of the 6 High-Risk patients were determined to be acute procedure successes. In addition, 10 (43.5%) of the 23 Emergency/Compassionate use patients were determined to have acute

procedure success. Table 10 summarizes acute procedure success results per procedure and per patient.

Table 10. Acute Procedural Success Results

Success criterion	Registry	High-Risk	Emergency Compassionate	Total
Per-procedure results	N = 19	N = 6	N = 26	N = 51
Acute procedure success	13/19 (68.4%)	4/6 (66.7%)	11/26 (42.3%)	28/51 (54.9%)
95% CI for success	(43.5%, 87.4%)	(22.3%, 95.7%)	(23.4%, 63.1%)	(40.3%, 68.9%)
Per-patient results	N = 15	N = 6	N = 23[a]	N = 44
Acute procedure success	12/15 (80.0%)	4/6 (66.7%)	10/23 (43.5%)	26/44 (59.1%)
95% CI for success	(51.9%, 95.7%)	(22.3%, 95.7%)	(23.2%, 65.5%)	(43.3%, 73.7%)

a) Two patients in the Emergency/Compassionate-use cohort did not have shunt status evaluated post-procedure and were not considered to be successful.

One-month Success

Data from the one-month follow-up visit was available for 8/13 (61.5%) technical success Registry patients, 2/6 (33.3%) High-Risk patients, and 9/23 (39.1%) Emergency/Compassionate use patients. Table 11 presents the results of the available data for tests completed at the 1-month follow-up examination. At one month follow-up there was no evidence of wire breakage or change in device position. In addition, 70% (12/17) of patients with follow-up data had successful closure (shunt considered small, trivial or closed). Results of the physical examination, ECG, and chest x-rays were not collected for the Emergency/Compassionate use patients.

Table 11. One-Month Follow-up Measures

Follow-up measure	Registry N = 8	High-Risk N = 2	Emergency/ compassionate use N = 9	Total N = 17
Heart murmur				
None	0/8 (0.0%)	0/2 (0.0%)	NC	0/10 (0.0%)
Holosystolic	4/8 (50.0%)	1/2 (50.0%)	NC	5/10 (50.0%)
Mid-diastolic	0/8 (0.0%)	0/2 (0.0%)	NC	0/10 (0.0%)
Other	3/8 (37.5%)	1/2 (50.0%)	NC	4/10 (40.0%)
ECG (not mutually exclusive)				
Left ventricular hypertrophy	0/7 (0.0%)	0/2 (0.0%)	NC	0/9 (0.0%)
Right ventricular hypertrophy	1/7 (14.3%)	0/2 (0.0%)	NC	1/9 (11.1%)
Biventricular hypertrophy	0/7 (0.0%)	0/2 (0.0%)	NC	0/9 (0.0%)
Cardiac arrhythmia	3/7 (42.9%)	0/2 (0.0%)	NC	3/9 (33.3%)
Chest x-ray				
Device position changed	0/7 (0.0%)	0/2 (0.0%)	NC	0/9 (0.0%)
Evidence of wire breakage	0/6 (0.0%)	0/2 (0.0%)	NC	0/8 (0.0%)
Residual shunt				
None/closed	2/8 (25.0%)	1/2 (50.0%)	0/7 (0.0%)	3/17 (17.7%)
Trivial	1/8 (12.5%)	0/2 (0.0%)	1/7 (14.3%)	2/17 (11.8%)
Small	3/8 (37.5%)	0/2 (0.0%)	4/7 (57.1%)	7/17 (41.2%)
Moderate	2/8 (25.0%)	1/2 (50.0%)	2/7 (28.6%)	5/17 (29.4%)

Follow-up measure	Registry N = 8	High-Risk N = 2	Emergency/ compassionate use N = 9	Total N = 17
Large	0/8 (0.0%)	0/2 (0.0%)	0/7 (0.0%)	0/17 (0.0%)

NC, not collected

VSD closure success at one-month follow-up was based on the echocardiogram results for the Registry and High-Risk patients. One-month success for patients seen was calculated as patients whose shunt status was evaluated at the 1-month follow-up visit and had successful closure of the ventricular septal defect. Successful closure of the defect was defined as less than or equal to a 2-mm residual shunt. Patients with a residual shunt greater than 2 mm were considered 1-month failures. One-month success for all patients was calculated as patients whose shunt status was evaluated at the 1-month follow-up visit and had successful closure of the ventricular septal defect. Successful closure of the defect was defined as less than or equal to a 2-mm residual shunt. Patients who failed for any reason prior to or at the 1-month follow-up visit (e.g., technical failure, discontinued, or moderate or large shunt at the 1-month follow-up visit) were considered 1-month failures.

In the combined Registry and High-Risk cohort (N=21), 10 patients died and 1 discontinued between implant and the one-month follow-up visit. Of the remaining 10 patients, the VSD residual shunt success rate at one-month was 70.0% (7/10 patients). Table 12 summarizes the one-month success results.

Table 12. One-month Success Results

Success Criterion	Registry	High-Risk	Emergency/ Compassionate	Total
Patients Seen Results	**N = 8**	**N = 2**	**N = 8**	**N = 18**
One-Month Success	6/8 (75.0%)	1/2 (50.0%)	5/8 (62.5%)	12/18 (66.7%)
95% CI for Success	(34.9%, 96.8%)	(1.3%, 98.7%)	(24.5%, 91.5%)	(41.0%, 86.7%)
All Patients Results	**N = 15**	**N = 6**	**N = 23**	**N = 44**
One-Month Success	6/15 (40.0%)	1/6 (16.7%)	5/23 (21.7%)	12/44 (27.3%)
95% CI for Success	(16.3%, 67.7%)	(0.4%, 64.1%)	(7.5%, 43.7%)	(15.0%, 42.8%)

One-month Survival Rate

The 1-month survival among the combined Registry and High-Risk cohort, calculated as 'patients seen' and 'estimated survival,' was found to be 50.0% (10/20 patients) and 47.6% (10/21 patients), respectively. Table 13 displays the 1-month survival rate along with a 95% exact binomial confidence interval.

Table 13. One-month Survival

Survival at 1-month	Registry	High-Risk	Emergency/ Compassionate	Total
Patients seen	N = 14[a] 8/14 (57.1%) [28.9%, 82.3%]	N = 6 2/6 (33.3%) [4.3%, 77.7%]	N = 19 9/19 (47.4%) [24.5%, 71.1%]	N = 39 19/39 (48.7%) [32.4%, 65.2%]
Estimated survival	N = 15 8/15 (53.3%) [26.6%, 78.7%]	N = 6 2/6 (33.3%) [4.3%, 77.7%]	N = 23 8/23 (34.8%) [16.4%, 57.3%]	N = 44 18/44 (40.9%) [26.3%, 56.8%]

a) One patient in the Registry cohort was discontinued prior to the 1-month follow-up, and as such, was excluded from the "patients seen" analysis. The patient was included in the "estimated survival" analysis, with the assumption that the patient did not survive to represent worst-case.

Safety Results

Safety was evaluated by examining the percent of patients who experienced a major adverse event through 30 days post implant. Conclusions regarding safety results are drawn from the Registry and High-Risk cohorts as both were consistently followed under the prospective IDE protocol.

Major Adverse Events**:**

The distribution of reported major adverse events is presented in Table 14 for all patients as well as by cohort. Among the combined Registry and High-Risk cohorts (N=21), 21 major adverse events were reported to occur within 30 days among 47.6% (10/21) of the patients. Among this ill patient population, six of these events were death (28.6%). Only one of the major events was reported as definitely device-related (hemolysis), while eleven of the major adverse events were reported as definitely procedure-related.

Table 14: Major Adverse Events – All Patients

Study Cohort[a]	Event Type	Time to Event (Days)	Device Related	Procedure Related
E/C	Heart failure	7	Yes	Yes
E/C	Death	52	Unknown	Unknown
E/C	Death	21	Unknown	Unknown
E/C	Acute tubular necrosis	4	No	Unknown
E/C	Death	1	Unknown	No
REG	Blood loss	0	No	Yes
REG	Device kinking	0	No	Yes
REG	Cardiac perforation	0	No	Yes
REG	Death	0	No	Yes
REG	Aneurysm	68	No	Yes
REG	Respiratory arrest	1	No	Unknown
REG	Death	4	No	Unknown
REG	Arterial pulse loss	84	No	Yes
REG	Other – thrombocytopenia[b]	0	Unknown	Yes
REG	Bradycardia	0	Unknown	Unknown
HR	Multiple organ failure	2	Unknown	Unknown
HR	Sepsis	7	Unknown	Unknown
HR	Death	16	Unknown	Unknown
HR	Death	3	No	Unknown
HR	Cardiogenic shock	1	Unknown	Unknown

HR	Tricuspid regurgitation/tricuspid insufficiency/valvular	0	No	Yes
HR	Death	10	Unknown	Unknown
HR	Blood loss	0	No	Yes
HR	Death	4	Unknown	Unknown
HR	Tricuspid regurgitation/tricuspid insufficiency/valvular	0	Unknown	Yes
HR	Hypotension	0	Unknown	Yes
HR	Renal insufficiency	2	Unknown	Unknown
HR	Hemolysis	1	Yes	No

a) Study cohorts: E/C – Emergency/Compassionate; REG – Registry; HR – High Risk
b) No event type was reported on the DSMB CRF. Thrombocytopenia was determined by the investigator.

Supplemental Clinical Information

Upon completion of the clinical evaluation summarized above, the AMPLATZER Post-Infarct VSD Occluder continued to be implanted on an emergency and compassionate use basis. Data gathered from these cases was not collected in accordance with the original study protocol, but is summarized here as supplemental information in the interest of providing all available clinical experience regarding use of the AMPLATZER Post-Infarct VSD Occluder. Data for 247 AMPLATZER Post-Infarct VSD Occluder emergency or compassionate use cases performed from March 2002 through July 2016 in 243 patients are summarized in Tables 15 and 16 and Figure 1 below. Four of these patients each had two procedures which results in the number of cases being more than the number of patients. The data provide an overview of case demographics, patient status, and procedural outcomes.

Table 15 provides a demographic summary, as well as incidence rate for myocardial infarction and cardiogenic shock by case type. Requests for emergency use account for 79% (196/247) and requests for compassionate use account for 21% (51/247) of the cases. Patients' ages range from five to ninety-three years and the overall population was evenly divided between female and male patients. Ninety-two percent (92%) of the patient population presented following an acute myocardial infarction and 55% were in cardiogenic shock. Over half (54%) of the patients experienced both acute myocardial infarction and cardiogenic shock.

Table 15: Demographics and Medical History by Case

	Mean ± SD [Min, Max] or n/N (%)		
Variable	**Emergency**	**Compassionate**	**Overall**
Number of Cases	196	51	247
Age (years)	69.2 ± 14.1 [5, 93]	64.5 ± 16.6 [16, 89]	68.2 ± 14.8 [5, 93]
Under 40 years of age	6 (3%)	5 (10%)	11 (4%)
Sex			
Female	97 (49%)	26 (51%)	123 (50%)
Male	99 (51%)	25 (49%)	124 (50%)
Acute Myocardial Infarction (MI)	184 (94%)	43 (84%)	227 (92%)
Cardiogenic Shock	120 (61%)	16 (31%)	136 (55%)
Acute MI and Cardiogenic Shock	118 (60%)	16 (31%)	134 (54%)

Patient Status

The status of the 243 patients is provided in Figure 1 below. One hundred and ninety four (194) patients (80%) were successfully implanted with the device. One hundred and twenty two (63%) of the implanted patients survived and seventy-two (37%) died post-implant. Early death is defined as occurring ≤30 days post procedure and late death is defined as occurring >30 days post procedure. Early death occurred in 67 implanted patients (35%) and late death occurred in 5 patients (3%). Forty-nine (49) patients (20%) underwent an unsuccessful attempt to implant the device. Within this group of patients undergoing an implant attempt, the survival rate was 49%.

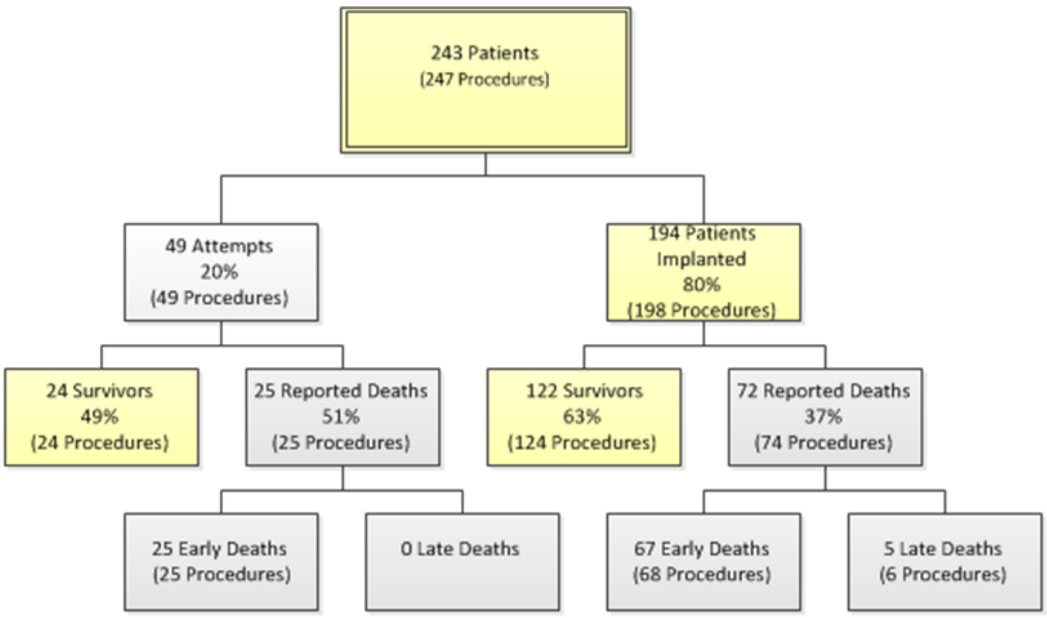

Figure 2: Patient Status

Among patients implanted with the device, there were 16 patients who underwent a device explant. Ten patients (63%) survived following device explant. Device embolization or migration occurred in 5% (9/198) of the cases. All available procedure outcome data are presented in Table 16.

Table 16: Procedure Outcomes (Attempts and Implants)

	n/N (%)		
Variable	**Emergency**	**Compassionate**	**Overall**
Successful Implant[a]	154/196 (79%)	44/51 (86%)	198/247 (80%)
Device Embolization / Migration in Implanted Patients	6/154 (4%)	3/44 (7%)	9/198 (5%)
Deaths[b]	86/193 (45%)	11/51 (22%)	97/243 (40%)
Early Deaths (≤ 30 Days)	83	9	92
Late Deaths (> 30 Days)	3	2	5

a. The successful implant denominator is the number of procedures. Four patients had 2 procedures each.
b. The deaths denominator is the number of patients (243), not the number of procedures (247).

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 22 investigators of which none were full-time or part-time employees of the sponsor and 5 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none;
- Significant payment of other sorts: 5;
- Proprietary interest in the product tested held by the investigator: none; and
- Significant equity interest held by investigator in sponsor of covered study: none.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. BENEFIT-RISK ANALYSIS

A. Probable Benefit Conclusions

The probable benefit of achieving mechanical closure of a post-infarct ventricular septal defect using the AMPLATZER Post-Infarct Muscular VSD Occluder via a minimally invasive transcatheter approach is restoration and stabilization of the patient's hemodynamic status with subsequent reversal of pulmonary congestion and end-organ injury. The minimally invasive transcatheter approach avoids

complications associated with an invasive open heart surgery and allows for a more rapid recovery. Among the combined Registry and High-Risk cohorts, the AMPLATZER Post-Infarct Muscular VSD Occluder was implanted with a technical success of >90% (19/21 patients), and a post-procedure shunt closure success of >80% of patients (16/19 patients). At one month, the VSD residual shunt success rate was found to be 70% (7/10 patients), and the survival calculated based on 'patients seen' was found to be 50% (10/20 patients).

B. Safety Conclusions

The serious risks associated with use of the device include device embolization from the interventricular septum, ventricular rupture, bleeding and injury to the vascular access sites used for delivering the device, valvular regurgitation/insufficiency, arrhythmia and hemolysis [3]. There is also a small risk that the post-infarct ventricular septal defect may not be completely closed or enlarge during the implant, and that additional interventions may be needed to achieve mechanical closure or treat an adverse event. Among the combined Registry and High-Risk cohorts, major adverse events were reported to occur within 30 days among 47.6% (10/21) of the patients. Many of these risks, such as arrhythmia or valvular regurgitation, are similar to risks associated with surgical intervention, and use of the device does not preclude surgical intervention if necessary.

C. Benefit-Risk Conclusions

Patients with a post-infarct ventricular septal defect in cardiogenic shock and end-organ injury frequently are poor candidates for open cardiac surgical repair. For these extremely fragile patients with very high surgical risk, the benefit of rapidly achieving mechanical closure of a post-infarct muscular ventricular septal defect and restoring hemodynamic status via a transcatheter approach, combined with the acceptable incidence of adverse events, support the probable benefit of using the AMPLATZER Post-Infarct Muscular VSD Occluder and outweigh the potential risks. The benefit-risk determination for these patients must take into consideration the potential risks and probable benefits associated with alternative practices and procedures, such as medical therapy, mechanical circulatory support, and surgical repair which are associated with higher complications, recovery and mortality.

Patient Considerations: The AMPLATZER Post-Infarct Muscular VSD Occluder is a less invasive approach to achieving mechanical closure of the ventricular septal defect compared to an open cardiac surgical repair. The less invasive approach is associated with a reduced risk for complications and the potential for a more rapid recovery. This HDE submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. For the population indicated, there is probable benefit of achieving mechanical closure of a post-infarct ventricular septal defect using a minimally invasive transcatheter

approach with the AMPLATZER Post-Infarct Muscular VSD Occluder, with a likely reduced risk for mortality and complications compared to alternative forms of treatment (medical therapy or open cardiac surgical repair).

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee because other marketing applications for transcatheter septal occluders have been reviewed by the panel. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the AMPLATZER Post-Infarct Muscular VSD Occluder will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on 1/10/2017. The final conditions of approval cited in the approval order are described below.

Post-Approval Study - AMPLATZER Post-Infarct Muscular VSD Occluder*:* On July 1, 2016 (S024) AGA Medical Corporation agreed to conduct a study as follows:

The study will evaluate the long-term safety and effectiveness of the AMPLATZER Post-Infarct Muscular VSD Occluder for use in transcatheter closure of muscular ventricular septal defects following a myocardial infarction. The study will be a retrospective, non-randomized, observational study. Data will be collected from previously attempted emergency/compassionate use cases. A random sample of the implant attempts from 2011 to present will be used to identify the potential subjects. Data collection will happen sequentially until data on a minimum of 30 subjects from up to 50 U.S. centers with hemodynamically significant muscular VSDs (demonstrated by echocardiography or angiography) following a myocardial infarction who were implanted with an AMPLATZER Post-Infarct Muscular VSD Occluder are obtained. In the event that data from 30 subjects cannot be obtained retrospectively (due to patient death or inability to obtain consent), data will be collected prospectively until data on a minimum of 30 subjects is obtained. The purpose of the study will be to assess the following endpoints:

- Technical success defined as the ability to successfully place the device in the defect;
- Acute closure defined as the absence of a residual shunt ≥3mm at the post procedure visit;
- Chronic closure defined as the absence of a residual shunt ≥3mm at 6 months post procedure;

- Acute survival defined as survival at 24 hours post procedure; and
- Chronic survival defined as survival at 6 months post procedure.

All echocardiograms will be reviewed and assessed by an Echocardiography Core Laboratory for quantification of shunts. Subjects will have data collected from visits that occurred at baseline, implant, post-procedure, and 6 months post-procedure.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1] Cinq-Mars, Alexandre, Pierre Voisine, François Dagenais, Éric Charbonneau, Frédéric Jacques, Dimitris Kalavrouziotis, Jean Perron et al. "Risk factors of mortality after surgical correction of ventricular septal defect following myocardial infarction: Retrospective analysis and review of the literature." International journal of cardiology 206 (2016): 27-36.

[2] Arnaoutakis, George J., Yue Zhao, Timothy J. George, Christopher M. Sciortino, Patrick M. McCarthy, and John V. Conte. "Surgical repair of ventricular septal defect after myocardial infarction: outcomes from the Society of Thoracic Surgeons National Database." The Annals of thoracic surgery 94, no. 2 (2012): 436-444.

[3] Schlotter, F., S. de Waha, I. Eitel, S. Desch, G. Fuernau, and H. Thiele. "Interventional post-myocardial infarction ventricular septal defect closure: a systematic review of current evidence." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 12, no. 1 (2016): 94-102.