

## **Long-term Outcome After Transcatheter Closure of Atrial Septal Defect in Older Patients:**

### **Impact of Age at the Procedure**

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Word count: 3249

Short title: Atrial Septal Defect in Older Patients

Dr. Akagi is a consultant for St. Jude Medical, Inc. The other authors have no relationships relevant to the contents of this paper to disclose.

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## Abstract

**Objectives:** This study aimed to assess long-term outcome after transcatheter atrial septal defect (ASD) closure in older patients, especially those older than 75 years.

**Background:** The clinical benefits of transcatheter ASD closure in this aged population are controversial.

**Methods:** Two hundred forty-four patients older than 50 years were divided into three groups according to age at the procedure (50-59 years: n = 69, 60-74 years: n = 120,  $\geq 75$  years: n = 55). The primary endpoint was defined as all-cause mortality and hospitalization due to heart failure or stroke. Improvements in functional capacity and cardiac remodeling after the procedure were also assessed.

**Results:** During a median follow-up of 36 months, mortality and hospitalization due to heart failure or stroke occurred in 18 (7%) patients. Among patients older than 75 years, two died from non-cardiovascular disease, two were hospitalized due to heart failure, and one had stroke. More than 90% of patients older than 75 years did not have these events. Kaplan-Meier analysis showed that the event-free survival rate was not different among the three age groups (log-rank test, p = 0.780). New York Heart Association functional class and right ventricular/left ventricular end-diastolic diameter ratio improved in patients older than 75 years, similar to the other age groups.

**Conclusions:** Long-term outcome after transcatheter ASD closure in patients older than 75 years is similar to that in the other relatively younger age groups. This suggests that transcatheter ASD closure can be considered a valuable therapeutic option in patients older than 75 years.

**Key Words:** atrial septal defect, older patients, outcome, transcatheter closure

### **Condensed Abstract**

Limited information is available regarding the benefits of atrial septal defect (ASD) closure in older patients. The present study showed that more than 90% of patients older than 75 years did not have all-cause mortality and hospitalization due to heart failure or stroke at least 3 years follow-up period after the procedure, and that long-term outcome in patients older than 75 years was not different from that in the other relatively younger age groups. Our findings suggest that transcatheter ASD closure can be considered a valuable therapeutic option even in patients older than 75 years.

**Abbreviations and Acronyms**

ASD = atrial septal defect

BNP = B-type natriuretic peptide

E = early diastolic mitral valve flow velocity

e' = early diastolic septal mitral annular velocity

LV = left ventricular

NYHA = New York Heart Association

RV = right ventricular

## Introduction

Atrial septal defect (ASD) of secundum-type is one of the most common congenital heart diseases. ASD is often diagnosed at an advanced age because ASD patients are less recognized symptoms and can survive. Older patients with ASD are frequently complicated with hemodynamic abnormalities, including heart failure, pulmonary artery hypertension, and atrial arrhythmias, as well as various comorbidities, including hypertension, diabetes mellitus, left ventricular (LV) dysfunction, and chronic kidney disease (1,2), which are at high risk for surgery.

Transcatheter ASD closure has been established as an effective and secure treatment for secundum-type ASD (3,4), and has become an alternative to surgical closure. Although transcatheter ASD closure can be considered an effective therapeutic option for older patients because of less invasive, fewer complications, and shorter hospital stay compared with surgical closure (5-7), limited information is available regarding the clinical benefits in this aged population. A few studies have shown the short-term benefits of improvements in functional capacity and cardiac remodeling after transcatheter ASD closure in older patients (1,2,8-11). With regard to long-term outcome, Kotowycz and colleagues reported that transcatheter closure was equivalent to surgical closure in adult patients, aged younger than 75 years (12). However, little is known about the long-term outcome, defined as mortality and hospitalization due to

heart failure, only in older patients, especially those older than 75 years. Therefore, this study aimed to focus on older patients, especially those older than 75 years, and assess the benefits of transcatheter ASD closure on the long-term outcome.

## **Methods**

### **Study population**

The study population consisted of 244 consecutive patients older than 50 years (range 50-84 years, 151 females) who underwent transcatheter ASD closure between April 2005 and November 2013. Because the survival rate in young adult patients was similar to that in age-matched controls (13), we included patients older than 50 years in the present study. To assess the benefits of transcatheter ASD closure on the long-term outcome in older patients, especially patients older than 75 years, compared with those in patients between 50 and 59 years that were a relative younger age group, patients were divided into three groups according to age at the procedure: 69 patients between 50 and 59 years, 120 patients between 60 and 74 years, and 55 patients older than 75 years.

Indications for transcatheter ASD closure were a significant left-to-right shunt, right ventricular (RV) volume overload, and/or clinical symptoms of heart failure or paradoxical embolism. Exclusion criteria included pulmonary hypertension with pulmonary vascular

resistance  $>8$  Wood units in the reversibility test using 100% oxygen and other concomitant congenital heart disease. All of the patients gave written informed consent for the procedure. The study was approved by the ethical committee of our institution.

### **Transcatheter ASD closure**

Transcatheter ASD closure was performed as described previously (14), using the Amplatzer Septal Occluder (St. Jude Medical, St. Paul, MN, USA). Before the procedure, pulmonary to systemic blood flow ratio and pulmonary artery pressure were evaluated with cardiac catheterization. For patients who were considered to be hemodynamically high-risk, such as those with pulmonary artery hypertension or heart failure, pulmonary artery wedge pressure was monitored just before the release of the device. All of the patients received 100 mg/day aspirin at least 48 hours before the procedure, and was continued for 6 months after the procedure. Clopidogrel was also administered at a dose of 50-75 mg/day for 1 month after the procedure. Other medications, such as diuretics and anti-hypertension drugs, were continued.

### **Study design**

This was a retrospective cohort study. The primary endpoint was defined as all-cause mortality and hospitalization due to heart failure or stroke. The secondary endpoint was defined as cardiovascular mortality and hospitalization due to heart failure or stroke. Improvements in functional capacity and cardiac remodeling evaluated by transthoracic echocardiography at the

latest follow-up were also assessed. Patients were followed from the date of the procedure until the date of first documentation of mortality and hospitalization or the end of follow-up, whichever occurred first. Follow-up information was obtained by medical records, contact with the patient's physicians, or telephone interview with the patient or, if deceased, with family members.

### **Clinical assessments**

Clinical assessments were scheduled at 1 month, 3 months, 6 months, and 12 months after the procedure, and annually thereafter. New York Heart Association (NYHA) functional class and plasma B-type natriuretic peptide (BNP) levels were assessed. Transthoracic echocardiography was also performed. LV end-diastolic and end-systolic diameters and RV end-diastolic diameter were measured by two-dimensional parasternal long-axis views. LV ejection fraction was derived using Teichholz's formula. Early diastolic mitral valve flow velocity (E) and early diastolic septal mitral annular velocity (e') were measured by pulse wave Doppler and tissue Doppler imaging, respectively. An average of more than five determinations of each variable was assessed by two independent cardiologists.

### **Statistical analysis**

Data are presented as mean  $\pm$  standard deviation for continuous variables and as number and percentage for categorical variables. Continuous variables were compared between the three age

groups by the one-way analysis of variance for normal distribution variables and by the Kruskal-Wallis test for non-normal distribution variables. Categorical variables were compared by the chi-square test and Fisher's exact test. Differences between baseline and follow-up in each age group were analyzed by the paired *t* test and the Wilcoxon signed-rank test. The event-free survival rate was estimated by Kaplan-Meier analysis, and the difference was compared by the log-rank test. Statistical analysis was performed with JMP version 8.0 (SAS Institute Inc., Cary, NC, USA), and significance was defined as a value of  $p < 0.05$ .

## **Results**

### **Baseline characteristics**

Comparison of baseline characteristics between the three age groups is shown in Table 1. As expected, patients older than 75 years had more comorbidities, such as hypertension, permanent atrial fibrillation, and stroke. Among patients older than 75 years, 14 (25%) were in NYHA functional class III/IV, 21 (38%) had a history of hospitalization due to heart failure, and 32 (58%) were being treated with diuretics for heart failure before the procedure. The severity of heart failure was greater in patients older than 75 years. Lower  $e'$  and higher  $E/e'$  were observed in patients older than 75 years.

### **Mortality and hospitalization**

During a median follow-up of 36 months (range 1 to 104 months), mortality and hospitalization due to heart failure or stroke occurred in 18 (7%) patients (Table 2). Among patients between 50 and 59 years, two were hospitalized due to heart failure, and two had stroke. Among patients between 60 and 74 years, one died from stroke, three died from cancer, one died from amyotrophic lateral sclerosis, and one died from an unknown cause at home at 3 months after the procedure. In the patient who died from an unknown cause, a history of transient cerebral ischemic attack was reported at 1 week before the death. The remaining three patients were hospitalized due to heart failure. Among patients older than 75 years, one died from cancer, one died from chronic obstructive pulmonary disease, two were hospitalized due to heart failure, and one had stroke. The incidence of mortality and hospitalization was not different among the three age groups (6%, 8%, and 9%,  $p = 0.781$ ). More than 90% of patients older than 75 years did not have these events. Kaplan-Meier analysis showed that the event-free survival rate was not different among the three age groups (log-rank test,  $p = 0.780$ , Fig. 1).

When the secondary endpoint defined as cardiovascular mortality and hospitalization due to heart failure or stroke was assessed, Kaplan-Meier analysis showed that the event-free survival rate in patients older than 75 years was equal to that in the other age groups (log-rank test,  $p = 0.938$ , Fig. 2).

No deaths related to transcatheter ASD closure were observed. There were no major

complications related to the procedure. Erosion, device embolization, or thrombus formation was not observed during the follow-up period. Acute congestive heart failure immediately after the procedure, which required additional treatments, such as intravenous administration of inotropes and mechanical supports, did not occur in patients older than 75 years.

### **Functional capacity and cardiac remodeling**

After the procedure, NYHA functional class improved in 28 (62%) of 45 patients older than 75 years with NYHA functional class II or III. No patients had deterioration of NYHA functional class (Fig. 3). Plasma BNP levels significantly decreased even in patients older than 75 years. RV end-diastolic diameter decreased, LV end-diastolic diameter increased, and RV/LV end-diastolic diameter ratio significantly improved in patients older than 75 years, similar to the other age groups (Table 3). A small residual shunt evaluated by transthoracic echocardiography was observed in three (4%) patients between 50 and 59 years, in seven (6%) patients between 60 and 75 years, and in four (7%) patients older than 75 years. However, no patients had moderate or severe residual shunt.

## **Discussion**

The major findings of the present study are as follows: 1) more than 90% of patients older than 75 years did not have all-cause mortality and hospitalization due to heart failure or stroke

during the follow-up period; 2) the long-term outcome in patients older than 75 years was not different from that in the other age groups; and 3) functional capacity and cardiac remodeling improved even in patients older than 75 years, similar to the other age groups. To the best of our knowledge, this is the first study to show the long-term outcome, defined as mortality and hospitalization, after transcatheter ASD closure in older patients.

Because older patients themselves are at high risk for mortality and morbidity, their outcome is considered to be inferior, when compared with that in young adult patients in whom the survival rate after ASD closure is similar to age-matched controls (13). Therefore, the present study included patients over 50 years of age except for young adult patients, and assessed the outcome in patients older than 75 years compared with that in the other relatively younger age groups. In addition, the primary endpoint of the present study included non-cardiovascular death, to assess the benefits of transcatheter ASD closure in the real-world setting.

## **Outcome**

Although most studies have shown the benefits of transcatheter ASD closure (3-7,15), the data for older patients are limited. Because not only surgical closure but also transcatheter closure have been reported but with very limited experience in older patients, ASD closure may be considered as non-beneficial in this aged population. More recently, a few studies have shown the short-term benefits of transcatheter ASD closure in older patients, including

improvements in fractional capacity and cardiac remodeling (1,2,8-11). However, limited information is available regarding the long-term outcome, defined as mortality and hospitalization, in this age population.

The present study showed that the survival rate without all-cause mortality and hospitalization in patients older than 75 years was not equal to that in the other age groups. However, two patients died from non-cardiovascular events related to age, and the cause of stroke in one patient was considered to be arteriosclerosis, but not the procedure or the device, that was diagnosed by neurologists using magnetic resonance imaging. The difference in the survival rate was probably caused by the age-related events. Furthermore, although approximately 40% of patients older than 75 years had a history of hospitalization due to heart failure before the procedure, only two were hospitalized after the procedure. Therefore, our findings suggest that transcatheter ASD closure is effective for preventing cardiovascular events related to ASD even in patients older than 75 years. In addition, NYHA functional class and RV/LV end-diastolic diameter ratio improved even in these patients, despite long-standing volume overload. Improvements in functional capacity and cardiac remodeling can be expected irrespective of age.

### **Complications related to ASD closure**

Surgical ASD closure has a low risk, but is obviously associated with perioperative

mortality (13). Surgical ASD closure also causes prolonged hospital stay and psychological trauma, which are related to a reduction of functional capacity in older patients. Because age is found to be a predictor of surgical mortality and complications, it is likely that surgical closure should not be performed as a routine in older patients (13,16,17). However, the present study showed that patients with older than 75 years had neither death nor major complications related to transcatheter ASD closure. Furthermore, NYHA functional class improved and did not deteriorate in these patients. Therefore, our findings suggest that transcatheter ASD closure is safe and contributes to the improvement in quality of life even in patients older than 75 years.

LV diastolic dysfunction, which is common in older patients, often cause the development of acute congestive heart failure immediately after ASD closure because of abrupt elevation in LV preload (18,19). However, in the present study, acute congestive heart failure immediately after the procedure was not observed in any of patients older than 75 years, although they had LV diastolic dysfunction as estimated by a decrease in  $e'$  (20). Anti-congestive medications were reported to be effective for preventing acute congestive heart failure after ASD closure (19). In our series, more than half of patients older than 75 years were being treated with diuretics prior to ASD closure, indicating that strict volume management before the procedure might contribute to the prevention of acute congestive heart failure in this aged population.

### **Clinical implications**

At the time when surgical closure was the only approach for ASD, older patients tended to refuse or hesitate to receive ASD closure. This was considered to be mainly because of the risk of open heart surgery with cardiopulmonary bypass. Indeed, in the present study, approximately half of patients older than 75 years had previously been diagnosed with ASD, but they had refused surgical closure. From this point of view, transcatheter ASD closure may be more acceptable for older patients because it has therapeutic advantages, including less invasive, fewer complications, and shorter hospital stay (5-7). However, in the clinical setting, even attending physicians cannot decide whether transcatheter ASD closure should be performed in older patients or not, because of the lack of scientific evidence. Therefore, ASD closure is often delayed or withheld in this aged population, despite the development of congestive heart failure. The present study showed that transcatheter ASD closure can be safely performed and contributes to long-term clinical benefits in patients older than 75 years. Our findings suggest that transcatheter ASD closure should be performed without age limitation, and that age should not be a factor to exclude candidates. The present study provides one piece of evidence that transcatheter ASD closure can be a valuable therapeutic option even in patients older than 75 years.

### **Study limitations**

The major limitation of this study is relatively small number of patients. This was a

retrospective cohort study and the lack of a control group. A large randomized prospective study is required to confirm the benefits of transcatheter ASD closure in older patients. In addition, this study excluded young adult patients. The long-term outcome in older patients was not compared with that in young adult patients. Another limitation is that the assessment of functional capacity was made on the basis of the patient's subjective impression, but not oxygen uptake evaluated by cardiopulmonary exercise testing. However, performance in cardiopulmonary exercise testing is affected by lower-extremity muscle weakness in older patients, and therefore, the improvement in NYHA functional class was regarded as the improvement in functional capacity in the present study.

### **Conclusion**

Long-term outcome after transcatheter ASD closure in patients older than 75 years is similar to that in the other relatively younger age groups. Improvements in functional capacity and cardiac remodeling occur even in patients older than 75 years, similar to the other age groups. Our findings suggest that transcatheter ASD closure can be considered a valuable therapeutic option even in patients older than 75 years.

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### **Figure legends**

#### Figure 1. All-cause Mortality and Hospitalization

Survival rate without all-cause mortality and hospitalization due to heart failure or stroke after transcatheter atrial septal defect closure according to age.

Dashed lines represent the 95% confidence interval of survival rate.

#### Figure 2. Cardiovascular Mortality and Hospitalization

Survival rate without cardiovascular mortality and hospitalization due to heart failure or stroke after transcatheter atrial septal defect closure according to age.

Dashed lines represent the 95% confidence interval of survival rate.

#### Figure 3. Functional Capacity

New York Heart Association functional class according to age.