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Long-Term Outcome After Transcatheter Closure of Atrial Septal Defect in Older Patients

Impact of Age at Procedure

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ABSTRACT

OBJECTIVES This study assessed long-term outcome after transcatheter atrial septal defect (ASD) closure in older patients, especially those older than 75 years of age.

BACKGROUND The clinical benefits of transcatheter ASD closure in this aged population are controversial.

METHODS A total of 244 patients older than 50 years of age were divided into 3 groups according to age at procedure (50 to 59 years: n = 69; 60 to 74 years: n = 120; 75 years and older: 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 patients (7%). Among patients older than 75 years of age, 2 died of noncardiovascular disease, 2 were hospitalized due to heart failure, and 1 had a stroke. More than 90% of patients older than 75 years of age did not experience these events. Kaplan-Meier analysis showed that the event-free survival rate was not different among the 3 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 of age, similar to the other age groups.

CONCLUSIONS Long-term outcome after transcatheter ASD closure in patients older than 75 years of age 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 of age. (J Am Coll Cardiol Intv 2015;8:600–6)

An atrial septal defect (ASD) of the secundum type is one of the most common congenital heart diseases. ASD is often diagnosed at an advanced age because younger ASD patients have less recognized symptoms and can survive. Older patients with ASD frequently experience complications of 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 of surgery.

Transcatheter ASD closure has been established as an effective and safe treatment for secundum-type ASDs (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 it is less invasive with fewer complications and shorter hospital stay compared with surgical closure (5-7), limited information is available

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regarding the clinical benefits in this aged population. A few studies have shown the short-term benefits of improvement in functional capacity and cardiac remodeling after transcatheter ASD closure in older patients (1,2,8–11). With regard to long-term outcome, Kotowycz et al. (12) reported that transcatheter closure was equivalent to surgical closure in adult patients younger than 75 years of age. However, little is known about the long-term outcome, defined as mortality and hospitalization due to heart failure, in older patients, especially those older than 75 years of age. Therefore, this study aimed to focus on older patients, especially those older than 75 years of age, and to assess the benefits of transcatheter ASD closure for the long-term outcome.

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METHODS

STUDY POPULATION. The study population consisted of 244 consecutive patients older than 50 years of age (range 50 to 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 of age in the present study. To assess the benefits of transcatheter ASD closure for the long-term outcome in older patients, especially patients older than 75 years of age, compared with those in patients between 50 and 59 years of age who were a relatively younger age group, patients were divided into 3 groups according to age at the procedure: 69 were patients between 50 and 59 years of age, 120 patients were between 60 and 74 years of age, and 55 patients older than 75 years of age.

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 ethics 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, Minnesota). Before the procedure, the 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 of aspirin at least 48 h before the procedure, which was continued for 6 months after the procedure. Clopidogrel was also administered at a dose of 50 to 75 mg/day for 1 month after the procedure. Other medications, such as diuretic and antihypertension 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. Improvement in functional capacity and cardiac remodeling evaluated by transthoracic echocardiography at the latest follow-up was 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 and 3, 6, 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 2-dimensional parasternal long-axis views. LV ejection fraction was derived using Teichholz's formula. Early E (diastolic mitral valve flow velocity) and e′ (early diastolic septal mitral annular velocity) were measured by pulsed wave Doppler and tissue Doppler imaging, respectively. An average of more than 5 determinations of each variable was assessed by 2 independent cardiologists.

STATISTICAL ANALYSIS. Data are presented as mean ± SD for continuous variables and as number and percentage for categorical variables. Continuous variables were compared among the 3 age groups by 1-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 exact test. Differences between baseline and follow-up in

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

each age group were analyzed by the paired Student *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, North Carolina), and significance was defined as $p < 0.05$.

RESULTS

BASELINE CHARACTERISTICS. Comparison of baseline characteristics among the 3 age groups is shown in Table 1. As expected, patients older than 75 years of age had more comorbidities, such as hypertension, permanent atrial fibrillation, and stroke. Among patients older than 75 years or age, 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 diuretic agents for heart failure before the procedure. The severity of heart failure was greater in patients older than 75 years of age. Lower e′ and higher E/e′ were observed in patients older than 75 years of age.

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

TABLE 1 Comparison of Baseline Characteristics Among Age Groups

	All (N = 244)	50–59 Yrs (n = 69)	60–74 Yrs (n = 120)	≥75 Yrs (n = 55)	p Value
Age, yrs	66 ± 9	55 ± 3	66 ± 4	78 ± 3	<0.001
Female	151 (62)	49 (71)	70 (58)	32 (58)	0.175
ASD diameter, mm	19 ± 7 (4–38)	20 ± 8 (5–38)	19 ± 7 (4–38)	19 ± 8 (4–38)	0.777
Device size, mm	22 ± 7 (8–38)	23 ± 7 (8–38)	22 ± 6 (8–38)	23 ± 7 (11–38)	0.366
Pulmonary-to-systemic blood flow ratio	2.6 ± 0.8	2.7 ± 0.9	2.5 ± 0.8	2.6 ± 0.8	0.347
Pulmonary artery pressure, mm Hg	17 ± 6	16 ± 8	18 ± 5	18 ± 5	0.146
Hypertension	91 (37)	17 (25)	49 (41)	25 (45)	0.028
Diabetes mellitus	35 (14)	5 (7)	20 (17)	10 (18)	0.106
Permanent atrial fibrillation	42 (17)	2 (3)	17 (14)	23 (42)	<0.001
Stroke	19 (8)	3 (4)	7 (6)	9 (16)	0.040
Coronary artery disease	15 (6)	1 (1)	8 (7)	6 (11)	0.061
Smoking	36 (15)	11 (16)	17 (14)	8 (15)	0.946
NYHA functional class I/II	217 (89)	68 (99)	108 (90)	41 (75)	<0.001
NYHA functional class III/IV	27 (11)	1 (1)	12 (10)	14 (25)	
Hospitalization due to heart failure	37 (15)	4 (6)	12 (10)	21 (38)	<0.001
Diuretic agent use	87 (36)	17 (25)	38 (32)	32 (58)	<0.001
B-type natriuretic peptide, pg/ml	119 ± 166	53 ± 76	94 ± 88	255 ± 271	<0.001
LV end-diastolic diameter, mm	41 ± 5	41 ± 5	42 ± 5	41 ± 5	0.175
LV end-systolic diameter, mm	25 ± 4	25 ± 4	25 ± 5	24 ± 3	0.442
LV ejection fraction, %	70 ± 6	69 ± 6	70 ± 7	71 ± 6	0.472
RV end-diastolic diameter, mm	38 ± 6	37 ± 6	38 ± 5	40 ± 6	0.024
RV/LV end-diastolic diameter ratio	0.93 ± 0.19	0.91 ± 0.19	0.92 ± 0.17	0.98 ± 0.22	0.086
e′, cm/s	8.6 ± 2.4	9.7 ± 2.1	8.2 ± 2.3	8.0 ± 2.6	<0.001
E/e′ ratio	8.9 ± 3.0	8.0 ± 2.2	8.9 ± 2.9	10.2 ± 3.6	<0.001
Hospital stay after the procedure, days	3 ± 2	3 ± 3	3 ± 2	4 ± 3	0.004
Median follow-up period, months	34	39	30	36	0.381

Values are mean ± SD, n (%), or mean ± SD (range).

ASD = atrial septal defect; 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.

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 of age was equal to that in the other age groups (log-rank test, p = 0.938) (Figure 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 treatment, such as intravenous administration of inotropes and mechanical support, did not occur in patients older than 75 years of age.

FUNCTIONAL CAPACITY AND CARDIAC REMODELING. After the procedure, NYHA functional class improved in 28 (62%) of 45 patients older than 75 years of age of NYHA functional class II or III. No patients had deterioration of NYHA functional class (Figure 3). Plasma BNP levels significantly decreased, even in patients older than 75 years of age. 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 of age, similar to the other age groups (Table 3). A small residual shunt evaluated by transthoracic echocardiography was observed in 3 patients (4%) between 50 and 59 years of age, in 7 (6%) patients between 60 and 75 years of age, and in 4 patients (7%) older than 75 years of age. However, no patients had moderate or severe residual shunt.

TABLE 2 All-Cause Mortality and Hospitalization Due to Heart Failure or Stroke After Transcatheter Atrial Septal Defect Closure

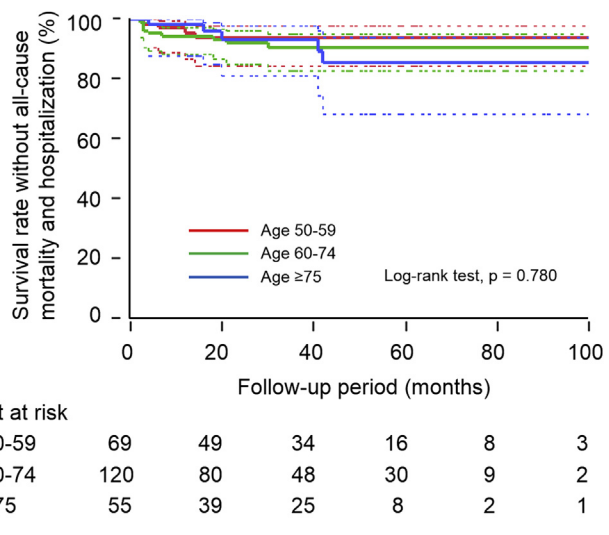
Age, yrs	Sex	Follow-Up, months	All-Cause Mortality and Hospitalization Due to Heart Failure or Stroke
52	F	14	Heart failure
55	F	3	Stroke
56	F	12	Stroke
59	M	6	Heart failure
63	M	3	Death (stroke)
63	M	18	Death (amyotrophic lateral sclerosis)
65	F	4	Heart failure
66	F	2	Heart failure
66	F	3	Heart failure
68	M	21	Death (lung cancer)
68	F	30	Death (hepatic cancer)
71	F	3	Death (unknown)
71	M	7	Death (hepatic cancer)
76	M	4	Heart failure
77	M	42	Death (chronic obstructive pulmonary disease)
78	M	16	Heart failure
82	M	20	Death (prostatic cancer)
83	F	41	Stroke

DISCUSSION

The major findings of the present study are as follows: 1) more than 90% of patients older than 75 years of age 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 of age was not different from that in the other age groups; and 3) functional capacity and cardiac remodeling improved in patients older than 75 years of age, 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.

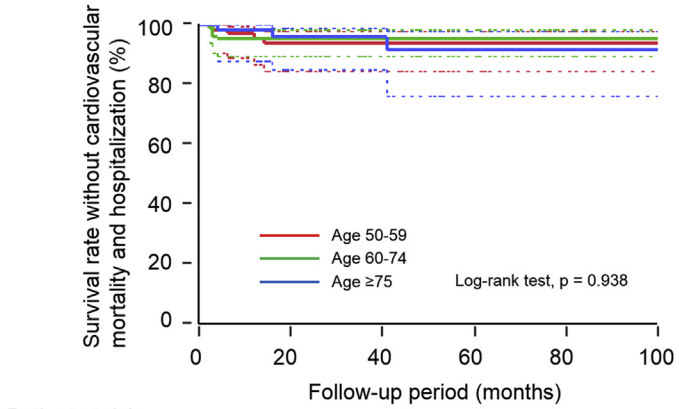
Because older patients are at high risk of mortality and morbidity, their outcome is considered to be inferior compared with that in young adult patients in whom the survival rate after ASD closure is similar to that in age-matched controls (13). Therefore, the present study included patients older than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

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.

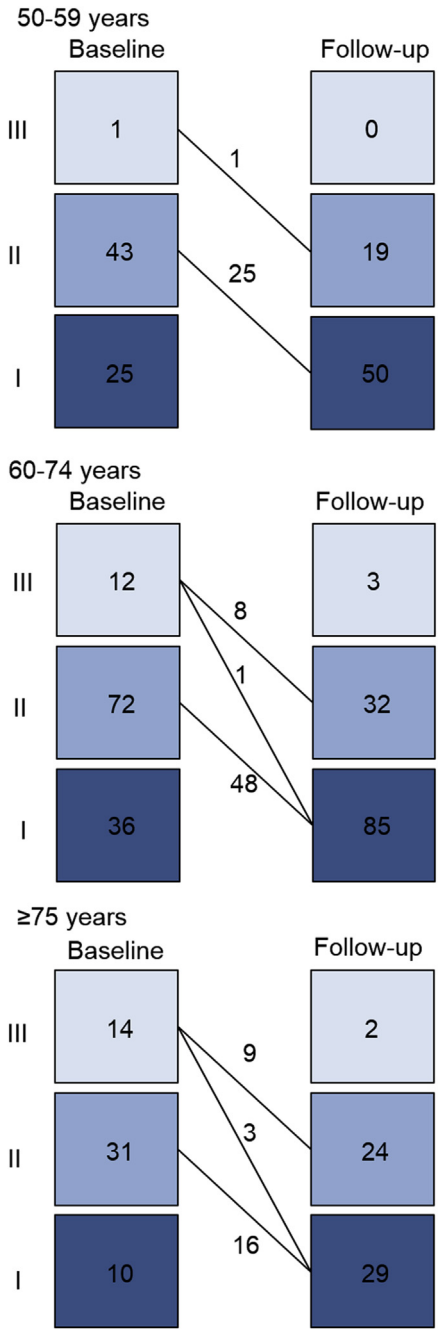
FIGURE 2 Cardiovascular Mortality and Hospitalization



Patient at risk						
Age 50-59	69	49	34	16	8	3
Age 60-74	120	80	48	30	9	2
Age ≥75	55	39	25	8	2	1

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.

endpoint of the present study included noncardiovascular 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 limited experience in older patients, ASD closure may be considered as nonbeneficial in this older population. More recently, a few studies have shown the short-term benefits of transcatheter ASD closure in older patients, including improvement in functional 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 older population.

The present study showed that the survival rate without all-cause mortality and hospitalization in patients older than 75 years of age was not equal to that in the other age groups. However, 2 patients died of noncardiovascular events related to age, and the cause of stroke in 1 patient was considered to be arteriosclerosis, but not related to the procedure or the device, as was diagnosed by neurologists using magnetic resonance imaging. The difference in the survival rate was probably caused by the age-related events. Furthermore, although ~40% of patients older than 75 years of age had a history of hospitalization due to heart failure before the procedure, only 2 were hospitalized after the procedure. Therefore, our findings suggest that transcatheter ASD closure is effective for preventing

TABLE 3 Clinical Assessments Before and After Transcatheter Atrial Septal Defect Closure

	50–59 yrs (n = 69)			60–74 yrs (n = 120)			≥75 yrs (n = 55)		
	Before	After	p Value	Before	After	p Value	Before	After	p Value
B-type natriuretic peptide, pg/ml	53 ± 76	33 ± 27	0.055	94 ± 88	64 ± 55	0.003	255 ± 271	135 ± 123	0.005
LV end-diastolic diameter, mm	41 ± 5	44 ± 4	<0.001	42 ± 5	46 ± 4	<0.001	41 ± 5	45 ± 4	<0.001
RV end-diastolic diameter, mm	37 ± 6	30 ± 6	<0.001	38 ± 5	31 ± 5	<0.001	40 ± 6	33 ± 5	<0.001
RV/LV end-diastolic diameter ratio	0.91 ± 0.19	0.68 ± 0.16	<0.001	0.92 ± 0.17	0.68 ± 0.13	<0.001	0.98 ± 0.22	0.75 ± 0.13	<0.001

Values are mean ± SD.
Abbreviations as in Table 1.

cardiovascular events related to ASD, even in patients older than 75 years of age. In addition, NYHA functional class and RV/LV end-diastolic diameter ratio improved, even in these patients, despite long-standing volume overload. Improvement 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 requires a prolonged hospital stay and may cause psychological trauma, both of which are related to a decrease in 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 routinely in older patients (13,16,17). However, the present study showed that in patients older than 75 years of age, neither death nor major complications were related to transcatheter ASD closure. Furthermore, NYHA functional class improved in these patients. Therefore, our findings suggest that transcatheter ASD closure is safe and contributes to improvement of quality of life, even in patients older than 75 years of age.

LV diastolic dysfunction, which is common in older patients, often causes the development of acute congestive heart failure immediately after ASD closure because of an abrupt increase 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 of age, although they had LV diastolic dysfunction as estimated by a decrease in e′ (20). Anticongestive medications were reported to be effective for preventing acute congestive heart failure after ASD closure (19). In our series, more than one-half of patients older than 75 years of age were being treated with diuretic agents before ASD closure, indicating that strict volume management before the procedure might contribute to the prevention of acute congestive heart failure in this older population.

CLINICAL IMPLICATIONS. At the time when surgical closure was the only approach for ASD, older patients tended to refuse or hesitate to undergo 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 one-half of patients older than 75 years of age had previously had a diagnosis of 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 being less invasive with 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 because of the lack of scientific evidence. Therefore, ASD closure is often delayed or withheld in this older population, despite the development of congestive heart failure. The present study showed that transcatheter ASD closure can be safety performed and contributes to long-term clinical benefits in patients older than 75 years of age. 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 evidence that transcatheter ASD closure can be a valuable therapeutic option, even in patients older than 75 years of age.

STUDY LIMITATIONS. The major limitation of this study is relatively small number of patients. This was a retrospective cohort study with no 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 of 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 as evaluated by cardiopulmonary exercise testing. However, performance on cardiopulmonary exercise testing is affected by lower extremity muscle weakness in older patients, and, therefore, the improvement in NYHA functional class was regarded as an improvement in functional capacity in the present study.

CONCLUSIONS

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

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PERSPECTIVES

The clinical benefits of transcatheter closure of ASD in older patients are still unclear. This study demonstrated that the long-term outcome after transcatheter ASD closure in patients older than 75 years of age is similar to that in the other relatively younger age groups. Our data suggest that transcatheter ASD closure is a valuable therapeutic option, even in older patients.

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