Transcatheter closure of atrial septal defect in the elderly: a systematic review and meta-analysis

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ABSTRACT
Objective Despite the establishment of transcatheter closure as the treatment of choice in adults with secundum atrial septal defects (ASDs), the effectiveness of this approach in the elderly is disputed. This systematic review and meta-analysis aims to explore the impact of transcatheter ASD closure in patients ≥60 years old.

Methods We systematically searched four major electronic databases (PubMed, CENTRAL (Cochrane Central Register of Controlled Trials), Scopus and Web of Science), ClinicalTrials.gov, article references and grey literature. Primary outcomes were the right ventricular end-diastolic diameter (RVEDD) and the New York Heart Association functional class change, whereas secondary outcomes included systolic pulmonary arterial pressure (sPAP), left ventricular end-diastolic diameter (LVEDD), brain natriuretic peptide (BNP), tricuspid valve regurgitation (TR) change, as well as the rate of atrial arrhythmias and all-cause mortality.

Results In total, 18 single-arm cohorts comprising 1184 patients were included. RVEDD was reduced after ASD closure (standardised mean difference (SMD) −0.9, 95% CI −1.2 to −0.7). Elderly patients had 9.5 times higher odds of being asymptomatic after ASD closure (95% CI 5.06 to 17.79). Furthermore, ASD closure improved sPAP (mean difference (MD) −10.8, 95% CI −14.6 to −7), LVEDD (SMD 0.8, 95% CI 0.7 to 1.0), TR severity (OR 0.39, 95% CI 0.25 to 0.60) and BNP (MD −68.3, 95% CI −114.4 to −22.1). There was a neutral effect of ASD closure on atrial arrhythmias.

Conclusions Transcatheter ASD closure is beneficial for the elderly population since it improves functional capacity, biventricular dimensions, pulmonary pressures, TR severity and BNP. However, the incidence of atrial arrhythmias did not change significantly after the intervention.

PROSPERO registration number CRD42022378574.

INTRODUCTION
Atrial septal defect (ASD) closure is recommended in patients with right ventricular (RV) volume overload without significant pulmonary arterial hypertension (PAH) and left ventricular (LV) dysfunction, regardless of age,1 to prevent the development of ASD-related complications.2 3 The prognosis is excellent in patients undergoing surgical repair at an early age, whereas, in the elderly, the long-term outcomes appear suboptimal,4 since the operative risk is increased due to the coexisting haemodynamic abnormalities (ie, arrhythmias, heart failure) and comorbidities.5

Transcatheter closure of secundum ASDs has emerged as an attractive alternative to surgery and, when technically feasible, is considered the treatment of choice, especially in the elderly, as it is less invasive with minimal recovery time and lower complications rate.4 5 A recent meta-analysis confirmed the advantages of transcatheter secundum ASD closure in the overall adult population, as it improves functional capacity and ventricular dimensions.6 However, to date, few studies have investigated the effects of transcatheter ASD closure specifically in the elderly population, and the benefits in this subgroup remain uncertain.

Therefore, we aimed to perform a systematic review and meta-analysis and synthesise all available evidence regarding the impact of transcatheter secundum ASD closure on the elderly. This is the first attempt to summarise studies examining the outcomes in the elderly before and after the transcatheter ASD closure.

METHODS
This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (online supplemental appendices 1 and 2).7 8 The prespecified protocol was submitted in the PROSPERO (CRD42022378574).
Search strategy and eligibility criteria

A systematic literature search was conducted in MEDLINE (via PubMed), CENTRAL (Cochrane Central Register of Controlled Trials), Scopus and Web of Science from database inception to July 2022 (online supplemental appendix 3). Prospective and retrospective cohort studies were considered eligible if they reported any of the outcomes of interest before and after transcatheter secundum ASD closure in the elderly (≥60 years old). The primary outcomes were the change in the right ventricular end-diastolic diameter (RVEDD) from baseline as assessed by transthoracic echocardiography (TTE) and the New York Heart Association (NYHA) functional class. Secondary outcomes included the change in systolic pulmonary arterial pressure (sPAP) (estimated from the tricuspid valve regurgitation (TR) jet velocity applying the Bernoulli equation using TTE), left ventricular end-diastolic diameter (LVEDD) (assessed by TTE) and plasma brain natriuretic peptide (BNP) levels from baseline.

Studies reporting right ventricular systolic pressure (RVSP) values were included in the analysis regarding sPAP as RVSP is equivalent to sPAP in the study population of patients with ASD without pulmonary outflow obstruction. Moreover, the incidence of severe TR, atrial arrhythmias and postclosure all-cause mortality were also investigated. Regarding outcomes expressed at different time points after ASD closure, data reported at the longest follow-up time-point were used for all analyses.

Study selection and data collection

The retrieved records from all sources were merged and imported into a reference management software (Mendeley V1.19.8). After the removal of duplicates, two authors (AB and ITF) independently assessed the records’ eligibility against the inclusion criteria initially on a title and abstract level. Subsequently, the full texts of the potentially relevant reports were assessed. All disagreements were resolved by a third author (AA).

A structured pilot-tested Excel spreadsheet, designed according to the Cochrane’s Checklist of items, was used to extract the information on study design, number of participants, follow-up duration, patients’ baseline characteristics and outcomes from full-texts, figures, tables and online supplemental appendices. The process was conducted independently by two authors (AB and ITF), while discrepancies were solved by a third author (AA). Data described with median values and IQRs were converted to mean values and SD. Missing SDs were calculated from relevant statistics, if possible, or otherwise were imputed, according to the Cochrane recommendations. The web-based tool, WebPlotDigitizer, was employed to extract data from figures.

Quality assessment

The quality of the included studies was evaluated by two independent authors (AB and ITF) using the Newcastle-Ottawa Scale (NOS) for cohort studies, with discrepancies resolved by AA. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to evaluate the strength of evidence of the results (high, moderate, low or very low).

Statistical analysis

The effect measure for dichotomous outcomes was the OR with the corresponding 95% CIs. For continuous outcomes, the effect measure was the mean difference (MD) with the 95% CI of the change from baseline to the last follow-up. The standardised mean difference (SMD) was calculated in the case of continuous outcomes expressed in different ways of measurement among individual studies (eg, evaluation of RVEDD in different echocardiographic views). The Freeman-Tukey double arcsine transformation of proportions was used to generate a pooled proportion estimate of mortality. The random effects model was used for all statistical analyses. To report the expected effect estimate of a future study, 95% prediction intervals were also calculated. Study weights were calculated using the inverse variance method.

Statistical heterogeneity among individual studies was evaluated using the Cochran’s Q-test and the I² statistic; values >60% indicated significant heterogeneity. A sensitivity analysis for the primary outcomes was performed, including only studies with a low risk of bias (NOS score ≥7). A subgroup analysis for the primary outcomes was conducted based on the follow-up duration with a cut-off of 1 year after transcatheter ASD closure. Publication bias for the primary outcomes was assessed with a visual inspection of the funnel plot asymmetry, as well as the Egger’s regression test for continuous outcomes and Peters’ test for dichotomous outcomes.

The statistical significance threshold was set at an α-value of 0.05. The ‘meta’ package in the R statistical software (V3.6.3) was used for all statistical analyses.

RESULTS

Search results

A total of 5971 records were initially identified from the combined search (figure 1). After excluding duplicates, 3518 records were screened on a title and abstract level, and 91 records were selected for full-text evaluation. Of these, 73 records were excluded for reasons (online supplemental appendix 4). A total of 18 single-arm cohort studies (n=1184 patients) eventually
fulfilled the eligibility criteria and were included in the qualitative and quantitative synthesis.17–34

Study characteristics
The general characteristics of the individual studies are presented in tables 1 and 2. Reported indications for ASD correction were haemodynamically significant shunts leading to RV volume overload in the absence of PAH or LV dysfunction, based on the current European Society of Cardiology guidelines.1 Exclusion criteria were mainly the presence of PAH, rim insufficiency (except for the anterior rim), large defect diameter (≥36–40 mm), multiple defects and the presence of additional congenital heart disease lesions. In the majority of studies, a balloon occlusion test was performed before ASD closure in haemodynamically high-risk patients, including those with signs of LV diastolic dysfunction (eg, patients with increased LA pressure during haemodynamic assessment). In case of significant LA pressure (>5–10 mm Hg) increase, the procedure was abandoned. Male sex proportion ranged from 17.6% to 68.8%. Comorbidities (eg, patients with increased LA pressure during balloon occlusion) were used in one study.24 Moreover, additional studies. SHSMATM (Shanghai Shape Memory Alloy, Shanghai, Minnesota, USA) device in approximately 78% of the included studies. In the majority of studies, a balloon occlusion test was performed before ASD closure in haemodynamically high-risk patients, including those with signs of LV diastolic dysfunction (eg, patients with increased LA pressure during haemodynamic assessment). In case of significant LA pressure (>5–10 mm Hg) increase, the procedure was abandoned. Male sex proportion ranged from 17.6% to 68.8%. Comorbidities were common; 45.2% of patients had arterial hypertension, and 12.7% had diabetes mellitus. Follow-up duration ranged from 57 days to 4.4 years, with a median value of 27.6 months. Transcatheter ASD closure was accomplished using exclusively the Amplatzer Septal Occluder (AGA Medical, Golden Valley, Minnesota, USA) device in one study.24 Moreover, additional ASD occluders were used to perform transcatheter closure in two studies: StarFlex device (NMT Medical, Boston, Massachusetts, USA) and Cardia (Eagan, Minnesota, USA) occluders in one study28 and the Occlutech Figulla Flex-II and Amplatzer Cribriform Septal Occluder devices in the other one30 (table 2).

Quality assessment of the included studies
The risk of bias of the included studies according to the NOS is presented in online supplemental appendix 5. Due to the prespecified design of the included studies (before–after cohorts), none of them adjusted for potential confounders. Thirteen studies were rated as 7-star (high quality), whereas six studies were rated as 6-star (moderate quality), mainly due to the absence of information regarding losses to follow-up.

Primary outcomes
Effects of transcatheter ASD closure on the RVEDD
A significant improvement in RVEDD after ASD closure was observed (SMD −0.9, 95% CI −1.2 to −0.7) across 12 studies (n=736 patients), with significant between-study heterogeneity (I²=77%, p<0.01; figure 2). The subgroup analysis showed that there was a significant difference in RVEDD change from 57 days to 4.4 years, with a median value of 27.6 months. Transcatheter ASD closure was accomplished using exclusively the Amplatzer Septal Occluder (AGA Medical, Golden Valley, Minnesota, USA) device in one study.24 Moreover, additional ASD occluders were used to perform transcatheter closure in two studies: StarFlex device (NMT Medical, Boston, Massachusetts, USA) and Cardia (Eagan, Minnesota, USA) occluders in one study28 and the Occlutech Figulla Flex-II and Amplatzer Cribriform Septal Occluder devices in the other one30 (table 2).

Secondary outcomes
Effects of transcatheter ASD closure on sPAP, TR, LVEDD and BNP
ASD closure significantly reduced sPAP (eight studies, n=391) by 10.8 mm Hg (95% CI −14.6 to −7, I²=74%, p for heterogeneity<0.01; figure 4A) and improved severe TR (five studies, n=324, OR 0.39, 95% CI 0.25 to 0.60, I²=0%; figure 4B). Furthermore, a significant increase in LVEDD after transcatheter ASD closure was evident when pooling together eight studies with 565 participants (SMD 0.7, 95% CI 0.6 to 0.9, I²=52%, p for heterogeneity=0.04; figure 5A). The findings were similar regardless of the echocardiographic view used for the LVEDD estimation (four-chamber view: SMD 0.5, 95% CI 0.2 to 0.9 vs long-axis view: SMD 0.8, 95% CI 0.7 to 1 vs short-axis view: SMD 0.8, 95% CI 0.5 to 1.4, p=0.19; online supplemental figure S4, appendix 6). Moreover, plasma BNP levels (three studies, n=211) were significantly reduced after transcatheter ASD closure by 68.3 pg/mL (95% CI −114.4 to −22.1, I²=61%, p for heterogeneity=0.05; figure 5B).

Effects of transcatheter ASD closure on atrial arrhythmias and mortality
Across 12 studies including 733 patients, no difference was observed in the incidence of atrial arrhythmias after versus before transcatheter ASD closure (OR 0.88, 95% CI 0.42 to 1.88, I²=76%, p for heterogeneity<0.01; figure 6A). Regarding all-cause mortality after ASD closure (seven studies, n=522 patients), the estimated pooled proportion was 10% (95% CI 6 to 16, I²=72%, p for heterogeneity<0.01; figure 6B) in a median follow-up of 29 months.

GRADE assessment
The strength of evidence was estimated as very low for the primary outcomes. Regarding the RVEDD outcome, the evidence was downgraded due to serious inconsistency, whereas the evidence for the NYHA outcome was downgraded due to serious inconsistency, imprecision and potential publication bias (online supplemental appendix 9).

DISCUSSION
This is the first systematic review and meta-analysis comprehensively exploring the impact of transcatheter ASD closure on the elderly. Overall, our primary analysis demonstrated the favorable effects of ASD closure in RV size, which was significantly reduced after the procedure. The improvement in patients’ functional capacity after closure was also evident, with the elderly having a 9.5-fold higher probability of being asymptomatic after
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Population size</th>
<th>Age (years)</th>
<th>Gender (male %)</th>
<th>Follow-up duration</th>
<th>PAH</th>
<th>Mean PAP</th>
<th>Arterial hypertension</th>
<th>Diabetes mellitus</th>
<th>LA size/LV function</th>
<th>Outcomes of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swan et al</td>
<td>Cohort</td>
<td>50</td>
<td>69±5.8</td>
<td>N/A</td>
<td>57 (44–71) days</td>
<td>N/A</td>
<td>N/A</td>
<td>34%</td>
<td>6%</td>
<td>N/A</td>
<td>RVEDD, sPAP, atrial arrhythmias</td>
</tr>
<tr>
<td>Elshershari et al</td>
<td>Cohort</td>
<td>41</td>
<td>71 (62–87)</td>
<td>41.5</td>
<td>28±23.7 months</td>
<td>23%</td>
<td>26 (11–52)</td>
<td>4.9%</td>
<td>N/A</td>
<td>N/A</td>
<td>NYHA, RVEDD, atrial arrhythmias, mortality</td>
</tr>
<tr>
<td>Jategaonkar et al</td>
<td>Cohort</td>
<td>96</td>
<td>69.9±5.3</td>
<td>68.8</td>
<td>33.6±31.2 months</td>
<td>N/A</td>
<td>25.1±7.8</td>
<td>56.3%</td>
<td>N/A</td>
<td>LA diameter: 49.3±5.9 mm</td>
<td>NYHA, RVEDD, LVEDD, atrial arrhythmias</td>
</tr>
<tr>
<td>Spies and Hijazi</td>
<td>Cohort</td>
<td>55</td>
<td>70 (61–87)</td>
<td>68.8</td>
<td>28 (6–79) months</td>
<td>42%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>NYHA, RVEDD, atrial arrhythmias</td>
</tr>
<tr>
<td>Taniguchi et al</td>
<td>Cohort</td>
<td>9</td>
<td>68.1±7.0</td>
<td>55.6</td>
<td>10.6±4.3 months</td>
<td>3.4%</td>
<td>19.7±4.1</td>
<td>N/A</td>
<td>N/A</td>
<td>LA diameter: 59.8±8.4 mm</td>
<td>NYHA, RVEDD, LVEDD, sPAP, BNP</td>
</tr>
<tr>
<td>Yalonetsky and Lorber</td>
<td>Cohort</td>
<td>23</td>
<td>66.8±5</td>
<td>30.4</td>
<td>12 months</td>
<td>N/A</td>
<td>N/A</td>
<td>82.6%</td>
<td>13%</td>
<td>N/A</td>
<td>sPAP, atrial arrhythmias</td>
</tr>
<tr>
<td>Hanninen et al</td>
<td>Cohort</td>
<td>74</td>
<td>71±6.1</td>
<td>17.6</td>
<td>2.3±1.6 years</td>
<td>N/A</td>
<td>N/A</td>
<td>27%</td>
<td>6.8%</td>
<td>LA pressure: 10 (8–14) mm Hg</td>
<td>NYHA, TR</td>
</tr>
<tr>
<td>Nakagawa et al</td>
<td>Cohort</td>
<td>30</td>
<td>75.8±3.8</td>
<td>33.4</td>
<td>19.1±11.3 months</td>
<td>53%</td>
<td>N/A</td>
<td>40%</td>
<td>N/A</td>
<td>E/e`: 11.0±3.9</td>
<td>NYHA, RVEDD, LVEDD, sPAP, BNP, TR, atrial arrhythmias, mortality</td>
</tr>
<tr>
<td>Woo et al</td>
<td>Cohort</td>
<td>23</td>
<td>66.7±5.25</td>
<td>26.1</td>
<td>21.6±18.5 months</td>
<td>65.2%</td>
<td>28.3±8.5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>NYHA, atrial arrhythmias</td>
</tr>
<tr>
<td>Stroier et al</td>
<td>Cohort</td>
<td>47</td>
<td>69±5</td>
<td>19.1</td>
<td>3.3 (0–10) years</td>
<td>N/A</td>
<td>N/A</td>
<td>70%</td>
<td>N/A</td>
<td>E/A: 0.9±0.22</td>
<td>NYHA, RVEDD, LVEDD, sPAP, TR, atrial arrhythmias, mortality</td>
</tr>
<tr>
<td>Komar et al</td>
<td>Cohort</td>
<td>75</td>
<td>65.3±15.7</td>
<td>40</td>
<td>12 months</td>
<td>16%</td>
<td>N/A</td>
<td>38.6%</td>
<td>5.3%</td>
<td>LVEF: 60.4%</td>
<td>RVEDD</td>
</tr>
<tr>
<td>Jampates and Hengrussamee</td>
<td>Cohort</td>
<td>59</td>
<td>66.0±4.9</td>
<td>22</td>
<td>12 months</td>
<td>N/A</td>
<td>27.7±7.5</td>
<td>52.5%</td>
<td>20.3%</td>
<td>LA diameter: 43.0±7.4 mm LVEF: 66±12.9%</td>
<td>NYHA, LVEDD, sPAP, mortality</td>
</tr>
<tr>
<td>Takaya et al (60–75 years)</td>
<td>Cohort</td>
<td>120</td>
<td>66±4</td>
<td>42</td>
<td>36 (1–104) months</td>
<td>N/A</td>
<td>18±5</td>
<td>41%</td>
<td>17%</td>
<td>E/e<code>: 8.9±2.9 e</code>: 8.6±2.4 LVEF: 70±7%</td>
<td>NYHA, RVEDD, LVEDD, BNP, mortality</td>
</tr>
<tr>
<td>Takaya et al (&gt;75 years)</td>
<td>Cohort</td>
<td>55</td>
<td>78±3</td>
<td>42</td>
<td>36 (1–104) months</td>
<td>N/A</td>
<td>18±5</td>
<td>45%</td>
<td>18%</td>
<td>E/e`: 10.2±3.6 LVEF: 71±6%</td>
<td>NYHA, RVEDD, LVEDD, BNP, mortality</td>
</tr>
<tr>
<td>Thilen and Persson</td>
<td>Cohort</td>
<td>148</td>
<td>72.2±4.9</td>
<td>37.5</td>
<td>4.4±2.6 years</td>
<td>N/A</td>
<td>22±7</td>
<td>56.1%</td>
<td>11.5%</td>
<td>LA pressure: 9±4 (1–19) mm Hg</td>
<td>NYHA, atrial arrhythmias, mortality</td>
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<tr>
<td>Chen et al</td>
<td>Cohort</td>
<td>111</td>
<td>65 (61–80)</td>
<td>37.8</td>
<td>6 months</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>LA diameter: 42.0±9.2 mm LA volume: 86.5±33.1 mL LV volume: 68.8±15.8 mL LVEF: 64.6±4.2%</td>
<td>NYHA, LVEDD, sPAP, TR, atrial arrhythmias</td>
</tr>
</tbody>
</table>

Continued
Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Population size</th>
<th>Age (years)</th>
<th>Gender (male)</th>
<th>Follow-up duration</th>
<th>PHH</th>
<th>Mean PAP</th>
<th>LA size/LV function</th>
<th>Outcomes of interest</th>
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</thead>
<tbody>
<tr>
<td>Giordano et al.</td>
<td>Cohort</td>
<td>68</td>
<td>65.1±3.8</td>
<td>28</td>
<td>4.3±1.5 years</td>
<td>41.2%</td>
<td>24.6±8.9</td>
<td>NYHA, BNP, PAH, TR, atrial arrhythmias</td>
<td>NYHA, RVEDD, sPAP, TR, atrial arrhythmias</td>
</tr>
<tr>
<td>Sun et al.</td>
<td>Cohort</td>
<td>46</td>
<td>64.8±3.7</td>
<td>35</td>
<td>12 months</td>
<td>N/A</td>
<td>40±5.4</td>
<td>LA diameter: 28.7±4.8 mm; E/A: 1.4±0.3; LVEF: 61.3%±5.9%</td>
<td>NYHA, RVEDD, LVEDD, atrial arrhythmias</td>
</tr>
</tbody>
</table>

Regarding haemodynamics, pulmonary pressures have been shown to increase with advancing age.\textsuperscript{19} This increase may be attributed to progressive LV diastolic dysfunction, which leads to elevated filling pressures, impaired LA compliance and backward transmitted elevated pulmonary venous pressure. Age-related systemic vessel stiffness, as well as intrinsic changes in the pulmonary vasculature, may also contribute.\textsuperscript{19} A previous meta-analysis disclosed a beneficial effect of ASD closure on pulmonary pressures in adults irrespective of age, but the magnitude of the postclosure sPAP decrease was lower in patients over 60 years old.\textsuperscript{40} Moreover, accumulating evidence suggests that increased age may obstruct sPAP normalisation after ASD closure.\textsuperscript{13} Our analysis demonstrated that a significant reduction in sPAP is indeed apparent in elderly patients.

Our pooled analysis revealed an improvement in the TR degree after transcatheter ASD closure. This TR improvement results from the RV overload diminution as well as right heart postclosure remodelling.\textsuperscript{25} However, some patients present with persistent severe TR even after closure. Age ≥65 years and sPAP >45 mm Hg before closure have been proposed as independent risk factors for persistent postclosure TR in elderly patients.\textsuperscript{36} From a pathophysiological aspect, long-lasting RV ASD closure. Improvements in RV remodelling and functional status were evident both at short-term (<1 year) and medium- to long-term follow-up (>1 year). Additionally, in secondary analyses, transcatheter ASD closure significantly improved LV size, pulmonary pressures, plasma BNP levels and the degree of TR in the elderly. No significant differences were found in the incidence of atrial arrhythmias after transcatheter ASD closure. Finally, the pooled proportion of postclosure all-cause mortality was estimated to be 10% (95% CI 6% to 16%) in a median follow-up of 29 months.

A previous systematic review and meta-analysis which explored the benefits of ASD closure in adults showed a mean RVEDD decrease of 7 mm after closure, with the reduction being more pronounced in patients <50 years old.\textsuperscript{4} Our results indicate that a significant reduction in RV size is also present in patients ≥60 years old, suggesting that right heart remodelling occurs irrespective of age and should also be anticipated in elderly patients. Existing evidence supports that cardiac remodelling occurs early after ASD closure in adults and is, to a great degree, accomplished within a period of 6 months.\textsuperscript{35} Interestingly, this remodelling, when occurring at early stages after closure, may be attributed to the overload decrease subsequent to the left-to-right shunt elimination; late remodelling, though, is owed to myocardial structural changes.\textsuperscript{13} \textsuperscript{36} In some cases, however, dilated RVs persist after ASD closure. Chronic RV overload, typically encountered in older patients, is presumably responsible for the incapability of the RV to normalise its size completely after closure.\textsuperscript{17} Age at the time of correction and follow-up duration >1 year have been associated with RV dilation persistence after ASD correction, whereas preclosure RV dilation, pre- and postclosure RV pressures and the size of ASD were not found to affect the postclosure RV size.\textsuperscript{17}

ASD closure improves functional capacity in adults. Indeed, a recent meta-analysis demonstrated a 14-fold higher chance of being asymptomatic (NYHA I) after ASD closure compared with symptomatic status before ASD closure.\textsuperscript{4} Our analysis expands these findings, demonstrating that even patients ≥60 years old benefit from an ASD closure in terms of functional capacity. Notably, this functional improvement is partially explained by the RV overload relief following ASD closure, which in turn results in an increase in LV size, LV preload and subsequently in augmentation of LV stroke volume.\textsuperscript{13} \textsuperscript{38}
Systematic review

overload impedes not only cardiac remodelling and, therefore, TR improvement but also causes irreversible changes in the pulmonary vasculature, perpetuating pulmonary hypertension and leading to secondary TR after ASD closure.24 43

Previously published systematic reviews have investigated the occurrence of atrial arrhythmias after ASD closure in adulthood.6 44–47 Only one of them provided data regarding the incidence of new-onset postprocedural atrial arrhythmias in patients >60 years old, reporting an incidence rate of 5.21 patients per 100 patient-years. The chronic volume overload in patients with haemodynamically significant ASDs leads to atrial structural and electrophysiological remodelling and therefore predisposes to atrial arrhythmias.47 Our pooled analysis could not show a significant decrease in the occurrence of atrial arrhythmias after ASD closure. One could hypothesise that elderly patients present inadequate postclosure electromechanical improvement, even though reserve structural remodelling with reduction of RV dimensions is present.48 Furthermore, atrial septum stretching and inflammation produced by implemented ASD occluders may constitute additional predisposing factors for atrial arrhythmias after closure.46

Our pooled analysis revealed a low proportion of all-cause mortality after ASD closure. According to current data, midterm and long-term survival after ASD correction in adults is nowadays normal and similar to that of the general population irrespective of age.49 This could be possibly explained by the advancements in the closure techniques as well in the follow-up surveillance of these patients which result in the earlier detection

Table 2 Periprocedural characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>ASD size (mm)</th>
<th>Qp/Qs</th>
<th>Type of device</th>
<th>Device size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swan et al27</td>
<td>17.5±5.6 (TEE)</td>
<td>N/A</td>
<td>Amplatzer Septal Occluder</td>
<td>21.5±6.6</td>
</tr>
<tr>
<td>Elshenawey et al31</td>
<td>18.9 (8–40) (TEE)</td>
<td>2.3 (1–7.5)</td>
<td>Amplatzer Septal Occluder</td>
<td>24 (12–40)</td>
</tr>
<tr>
<td>Jategaonkar et al36</td>
<td>14.8±5.8 (TEE)</td>
<td>N/A</td>
<td>Amplatzer Septal Occluder</td>
<td>21.9 (5.7)</td>
</tr>
<tr>
<td>Spies and Hijazi38</td>
<td>17.8 (TEE/ICE)</td>
<td>2.1</td>
<td>Amplatzer Septal Occluder</td>
<td>24</td>
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<tr>
<td>Tangirala et al39</td>
<td>25.8±7.0 (TEE)</td>
<td>2.6±0.3</td>
<td>Amplatz Septal Occluder</td>
<td>27.3 (6.3)</td>
</tr>
<tr>
<td>Yalonetsky and Lorber24</td>
<td>17.7±5.1 (TEE)</td>
<td>2.28±0.65</td>
<td>Amplatz Septal Occluder</td>
<td>24.6 (6.1)</td>
</tr>
<tr>
<td>Hanninen et al40</td>
<td>17 (7–30) (TEE)</td>
<td>1.7 (0.4–3.5)</td>
<td>Amplatz Septal Occluder</td>
<td>24 (10–40)</td>
</tr>
<tr>
<td>Humenberger et al45</td>
<td>22.5 (20–28) (TEE)</td>
<td>2.45 (2.75–3.1)</td>
<td>Amplatz Septal Occluder</td>
<td>26 (22.30)</td>
</tr>
<tr>
<td>Nakagawa et al46</td>
<td>20.3±6.4 (TEE)</td>
<td>2.4±0.7</td>
<td>Amplatz Septal Occluder</td>
<td>23.3 (6.0)</td>
</tr>
<tr>
<td>Woo et al47</td>
<td>16.5±6.30 (TEE)</td>
<td>2.28 (1.4–4.3)</td>
<td>Amplatz Septal Occluder</td>
<td>19.9 (12–32)</td>
</tr>
<tr>
<td>Stroker et al47</td>
<td>18±5 (TEE)</td>
<td>N/A</td>
<td>Amplatz Septal Occluder</td>
<td>22±6</td>
</tr>
<tr>
<td>Komar et al48</td>
<td>17.7±15.8 (TEE)</td>
<td>2.84±1.9</td>
<td>Amplatz Septal Occluder</td>
<td>Starflex device</td>
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<td></td>
<td></td>
<td></td>
<td>Cardia ASD device</td>
</tr>
<tr>
<td>Jampates and Hengrussamer49</td>
<td>20.6±7.5 (TEE)</td>
<td>2.6 (1.4–28)</td>
<td>Amplatz Septal Occluder</td>
<td>27.1±5.6</td>
</tr>
<tr>
<td>Takaya et al (60–75 years)46</td>
<td>19±7 (TEE)</td>
<td>2.5±0.8</td>
<td>Amplatz Septal Occluder</td>
<td>22±6</td>
</tr>
<tr>
<td>Takaya et al (&gt;75 years)46</td>
<td>19±8 (TEE)</td>
<td>2.6±0.8</td>
<td>Amplatz Septal Occluder</td>
<td>23±7</td>
</tr>
<tr>
<td>Thilén et al48</td>
<td>16±6 (TEE)</td>
<td>2.3±0.9</td>
<td>Amplatz ASD Occluder</td>
<td>22±6</td>
</tr>
<tr>
<td>Chen et al49</td>
<td>20.4±6.6 (TEE)</td>
<td>N/A</td>
<td>SHSMATM ASD closure device</td>
<td>28.2±8</td>
</tr>
<tr>
<td>Giordano et al41</td>
<td>18.5±5.6 (TEE)</td>
<td>1.8±0.9</td>
<td>Amplatz Septal Occluder</td>
<td>Oclutech Figulla Flex-II ASD Amplatzer Cribriform MF Septal Occluder</td>
</tr>
<tr>
<td>Sun et al42</td>
<td>17.5±4.4 (TEE)</td>
<td>N/A</td>
<td>N/A</td>
<td>22.4±10.6</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; ICE, intracardiac echocardiography; N/A, non-applicable; Qp/Qs, pulmonary-to-systemic flow ratio; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Figure 2 Forest plot of the SMD in RVEDD after transcatheter ASD closure. ASD, atrial septal defect; RVEDD, right ventricular end-diastolic diameter; SMD, standardised mean difference.
and management of the postclosure complications. Therefore, although more data about the safety of ASD closure are needed, it seems to be a promising option for adult patients of advanced age.

In older patients, LV compliance is usually impaired due to cardiac comorbidities (eg, hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease); subsequently, an abrupt ASD closure may increase acutely left-sided filling pressures due to the occlusion of a decompression mechanism through the ASD and trigger acute heart failure and pulmonary oedema. Therefore, a balloon occlusion test is highly recommended before permanent ASD correction in the elderly to assess haemodynamic response. In case of considerable elevation (>10 mm Hg) of LA or LV end-diastolic pressure or significant systolic arterial pressure decrease, medical treatment before ASD correction or implantation of a fenestrated ASD device should be considered.

Limitations
Certain limitations should be acknowledged. First, the present systematic review included only observational (both prospective and retrospective) cohort studies, which were unadjusted for clinically relevant parameters and may were subject to selection bias. Moreover, the lack of a comparator group may reduce the validity of our results. The included studies did not report all the prespecified outcomes of interest; therefore, any study that described any outcome of interest was included in the analysis. Furthermore, high statistical heterogeneity was observed among the included studies, which downgraded the overall strength of evidence of our results. We tried to elucidate the heterogeneity using the random effects model and performing subgroup and sensitivity analyses. Heterogeneity in the analyses could be attributed to the difference in the coexisting comorbidities in the elderly, such as haemodynamically confirmed pulmonary hypertension or the presence and severity of LV diastolic dysfunction. Most studies did not provide information on these possible confounders, and therefore subgroup analyses based on these factors were impossible. Moreover, we cannot exclude the possibility that a minority of patients may have experienced more symptoms after ASD closure, due to insufficient data regarding the postclosure transition from one NYHA class to another (other than NYHA I). Besides, as atrial arrhythmias were not included in the primary outcomes of the individual studies, we cannot draw certain conclusions on their true rate before and after ASD closure, as well as the incidence of new-onset postclosure arrhythmias. Finally, since unpaired analyses were performed for all outcomes, we cannot exclude that 95% CI may have been misestimated.

Figure 3 Forest plot of NYHA I functional class after versus before ASD closure. ASD, atrial septal defect; NYHA, New York Heart Association.

Figure 4 (A) Forest plot of the mean difference in sPAP after transcatheter ASD closure. (B) Forest plot of TR after versus before transcatheter ASD closure. ASD, atrial septal defect; MD, mean difference; sPAP, systolic pulmonary arterial pressure; TR, tricuspid valve regurgitation.
**Figure 5**  (A) Forest plot of the SMD in LVEDD after transcatheter ASD closure. (B) Forest plot of the mean difference in plasma BNP levels after transcatheter ASD closure. ASD, atrial septal defect; BNP, brain natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; MD, mean difference; SMD, standardised mean difference.

**Figure 6**  (A) Forest plot of atrial arrhythmias after versus before transcatheter ASD closure. (B) Forest plot of all-cause mortality after transcatheter ASD closure. ASD, atrial septal defect.
CONCLUSIONS
The present systematic review and meta-analysis suggests potential beneficial effects of transcatheter ASD closure in the elderly in terms of improvement in functional capacity, biventricular remodelling, pulmonary pressures and BNP levels, with a neutral effect on the occurrence of atrial arrhythmias. Our results reinforce the hypothesis that ASD closure may be beneficial and, therefore, may be considered as a treatment option in patients aged 60 years or older. Further well-designed prospective cohort studies and potentially randomised controlled trials are needed to confirm our findings and establish transcatheter ASD closure as a first-line therapeutic option in the elderly.

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Author note The present systematic review and meta-analysis was based on first author’s MSc thesis.

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Systematic review


