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Atrial tachyarrhythmias following percutaneous device closure of secundum atrial septal defects



Vishal Vyas^{a,b,*}, Amit Kaura^c, Vinit Sawhney^b, Martin Lowe^b, Vivienne Ezzat^b

^a William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, UK

^b Department of Cardiac Electrophysiology, Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, UK

^c Department of Cardiology, Hammersmith Hospital Campus, Imperial College London, London, UK

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ABSTRACT

Background: Atrial tachyarrhythmias (ATs) are a major source of morbidity in the atrial septal defect (ASD) patient cohort. The optimal timing and approach of anti-arrhythmic intervention is currently unclear. Here, we sought to determine the overall rate of ATs following percutaneous ASD closure and risk factors that may predict this.

Methods: A systematic search of the literature was performed using the search terms '(Secundum Atrial Septal Defects AND Atrial arrhythmias) AND (transcatheter closure or percutaneous closure or device closure)'. All studies in English reporting the rate of ATs following percutaneous closure of secundum ASDs in adult patients were included. The primary outcome was documented AT detection during follow-up ECG monitoring. A meta-regression was then performed to test for an interaction between demographic/procedural characteristics and the primary outcome.

Results: 13 observational studies including 2366 patients were analysed. The overall post-procedure AT event detection rate was 8.6%. Multivariate meta-regression analysis revealed that only male gender was associated with a higher rate of post-procedure AT detection while utilisation of the Amplatzer Septal Occluder device was associated with a lower AT detection rate and comprised 96.2% of all devices used. A high level of heterogeneity was observed (I^2 -statistic 92.3%, Q value 156.8).

Conclusions: Our study illustrates that despite percutaneous ASD closure, a high proportion of adult patients have ATs with male gender correlating with higher AT rates. While the Amplatzer Septal Occluder device correlated with lower AT rates, this was the overwhelmingly the predominant device used hence comparison to other devices remains challenging.

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1. Introduction

Atrial septal defects (ASDs) are one of the most common form of congenital heart disease in adults, accounting for approximately 6% of heart defects diagnosed after birth [1]. The three major types of ASDs are the ostium secundum (most common, typically involving the fossa ovalis), ostium primum and sinus venosus defects. Asymptomatic ASDs may be detected in children typically through physical examination or echocardiographic screening in infancy. Defects less than 6 mm will typically close spontaneously [2] in the first few months to years of life. One of the major sources of

morbidity in the ASD patient population are atrial tachyarrhythmias (ATs). Here, we define ATs as atrial fibrillation, atrial flutter and supraventricular tachycardias. In patients above the age of 40 with unrepaired ASDs, the rate of ATs is even higher, with one study reporting the prevalence as high as 19% [3], which itself may be an underestimation. This is not surprising given the development of right heart volume and pressure overload with time, alongside increases in pulmonary artery pressure, worsening tricuspid regurgitation and resultant atrial electrical remodelling.

Closure, with either a percutaneous or surgical strategy, is indicated when signs of volume overload are evident and the pulmonary vascular resistance <5 Wood units (European Society of Cardiology [ESC] recommendations [4]) or if there is evidence of paradoxical embolism. The most recent ESC guidelines [4] indicate that where there is favourable anatomy, percutaneous closure is the preferred approach for the secundum type defect. Importantly, while there is some degree of reverse remodelling following ASD

* Corresponding author at: William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK.

E-mail addresses: vishal.vyas@doctors.org.uk (V. Vyas), a.kaura@imperial.ac.uk (A. Kaura), sawhneyvin@googlemail.com (V. Sawhney), martin.lowe@bartshealth.nhs.uk (M. Lowe).

closure, the substrate for ATs remains [5] with the associated complications of ATs, especially stroke, persisting. The timing of anti-arrhythmic interventions to prevent and manage ATs is unclear given the limited evidence available to guide decision-making. Here, we sought to determine the overall rate of ATs following percutaneous ASD closure and risk factors that may predict this. We then review the argument for a pre-emptive ablation strategy in patients who are suitable for device closure of their ASDs.

2. Methods

2.1. Search strategy

A systematic search of MEDLINE and EMBASE was performed for the published literature using the search terms '(Secundum Atrial Septal Defects AND Atrial arrhythmias) AND (transcatheter closure or percutaneous closure or device closure)'. All studies in English between 1990 and April 2018 that reported the rate of ATs following percutaneous closure of secundum ASDs in adult patients were included. The bibliographies of relevant selected studies and reviews were also hand-searched to identify additional eligible studies. Abstracts were reviewed for suitability by two independent reviewers and disputes resolved by consensus.

2.2. Inclusion and exclusion criteria

All studies reporting the AT event rate in adults following percutaneous closure of secundum ASDs were considered. Case reports, reviews, meta-analyses and animal studies were excluded. See Fig. 1 for PRISMA flow chart.

2.3. Analysis

The primary outcome was documented AT during follow-up ECG monitoring. Secondary outcomes included event rates for new diagnosis of AT, all-cause mortality and stroke/transient ischaemic attack (TIA). The data was analysed on an intention-to-treat basis. Results were analysed using the Comprehensive Meta-Analysis software (version 3, BioStat Inc). Summary estimates for each variable were calculated using the random effects model. This was chosen as a more conservative method in view of the significant methodological heterogeneity observed between studies. The I^2 -statistic was used to investigate heterogeneity. Meta-regression analysis was performed to test for an interaction between baseline and post-ASD closure clinical factors and primary outcome.

3. Results

A total of 2366 patients in 13 studies [6–18] were identified as suitable for inclusion (Fig. 2) with the type of monitoring utilised for AT detection and duration of follow-up summarised in Fig. 3. The mean age was 41.3 years with 29.3% patients male and an average follow-up time of 38.4 months. The overwhelming majority of the patients (96.2%) had an Amplatzer Septal Occluder device deployed with a mean device diameter of 24.1 mm.

3.1. Meta-analysis

The overall post-procedure AT detection rate was 8.6% (95% CI 4.8–14.9%). A high level of heterogeneity was observed (I^2 -statistic 92.3, Q value 156.8, $P < 0.001$). The Forest plot in Fig. 4 illustrates the overall AT detection rate and the relative relevance from each study included in the summated rate. The event rate for a new diagnosis of AT was 2.2% ($n = 10$, 95% CI 1.0–5.0%, supple-

mental Fig. 1), all-cause mortality was 2.7% ($n = 12$, 95% CI 1.4–5.4%, supplemental Fig. 2) and stroke/TIA was 1.5% ($n = 8$, 95% CI 0.6–4.1%, supplemental Fig. 3).

3.2. Meta-regression

Multivariate meta-regression was performed using post-procedure AT detection rate as a continuous moderator and study as a random effect. Meta-regression demonstrated that male gender (supplemental Fig. 4, $n = 12$, β coefficient 0.06, 95% CI 0.03–0.08, $P < 0.001$) was associated with higher rate of post-procedure AT detection. A higher percentage usage of the Amplatzer Septal Occluder device was associated with a lower AT event rate (supplemental Fig. 5, $n = 9$, β coefficient -0.07 , 95% CI -0.08 to -0.05 , $P < 0.001$).

There was no evidence of publication bias as indicated by the Funnel plot symmetry (supplemental Fig. 6) and Egger test (Egger's regression intercept -2.01 (95% CI -6.48 to 2.46), $P = 0.34$).

4. Discussion

4.1. ATs in the adult ASD population

Atrial tachyarrhythmias remain a persistent problem in the ASD patient cohort despite closure. For patients with documented atrial flutter or fibrillation undergoing surgical ASD repair, the modified Maze procedure is recommended at the time of surgery [4]. However, these guidelines do not extend to atrial arrhythmia intervention in the context of device closure, even though percutaneous closure is the mainstay of treatment in the majority of patients. There is a paucity of arrhythmia recommendations in this cohort, despite the observation that patients who have an ASD closed (surgically or percutaneously) continue to suffer arrhythmias, and AF particularly becomes more problematic with advancing age. The incidence of ATs was noted to be one-third in patients above 60 and as much as 50% in those above 70 in a Japanese cohort [19]. Gatzoulis and colleagues in a surgical ASD cohort [20] reported that 40 years of age was a key cut-off in identifying the likelihood of patients at risk of late post-operative AF or atrial flutter. Furthermore, the authors noted that of the patients who had pre-operative ATs but failed to convert to sinus rhythm post-operatively, all patients were aged above 40 years.

Although significant in univariate analysis, age was not a significant independent risk factor for ATs in our multi-variate analysis. One reason for this may be that the mean age in our study population was 41.3 years, with the highest percentage of post-procedure ATs being seen in the cohort of patients with a mean age of 47 years, which also had one of the larger sample sizes of 240 patients [16]. The two studies with the oldest populations had much smaller samples sizes with lower AT detection rates which is likely to have contributed to age not emerging as a significant risk factor for ATs. Additionally, male gender was a major risk factor which is an established independent risk factor for ATs.

Given the improved haemodynamics and reduced atrial scarring associated with percutaneous closure, one may have been anticipated a lower risk of ATs. A single centre study analysis of 200 patients found 16% adult patients developed ATs in a mean follow-up of 1.9 years [21]. The risk factors predisposing to a higher risk of arrhythmias were prior AT and age over 40 years [21]. Wi et al. (2013) [22] looked at the fate of post-operative atrial fibrillation in patients undergoing either device or surgical ASD closure. They too found that increasing proportion of male patients was a predictor of pre-operative AF. Additionally, left atrial size was an independent predictor of pre-operative AF. Unfortunately, in the cohort studied here left atrial size was not reported consis-

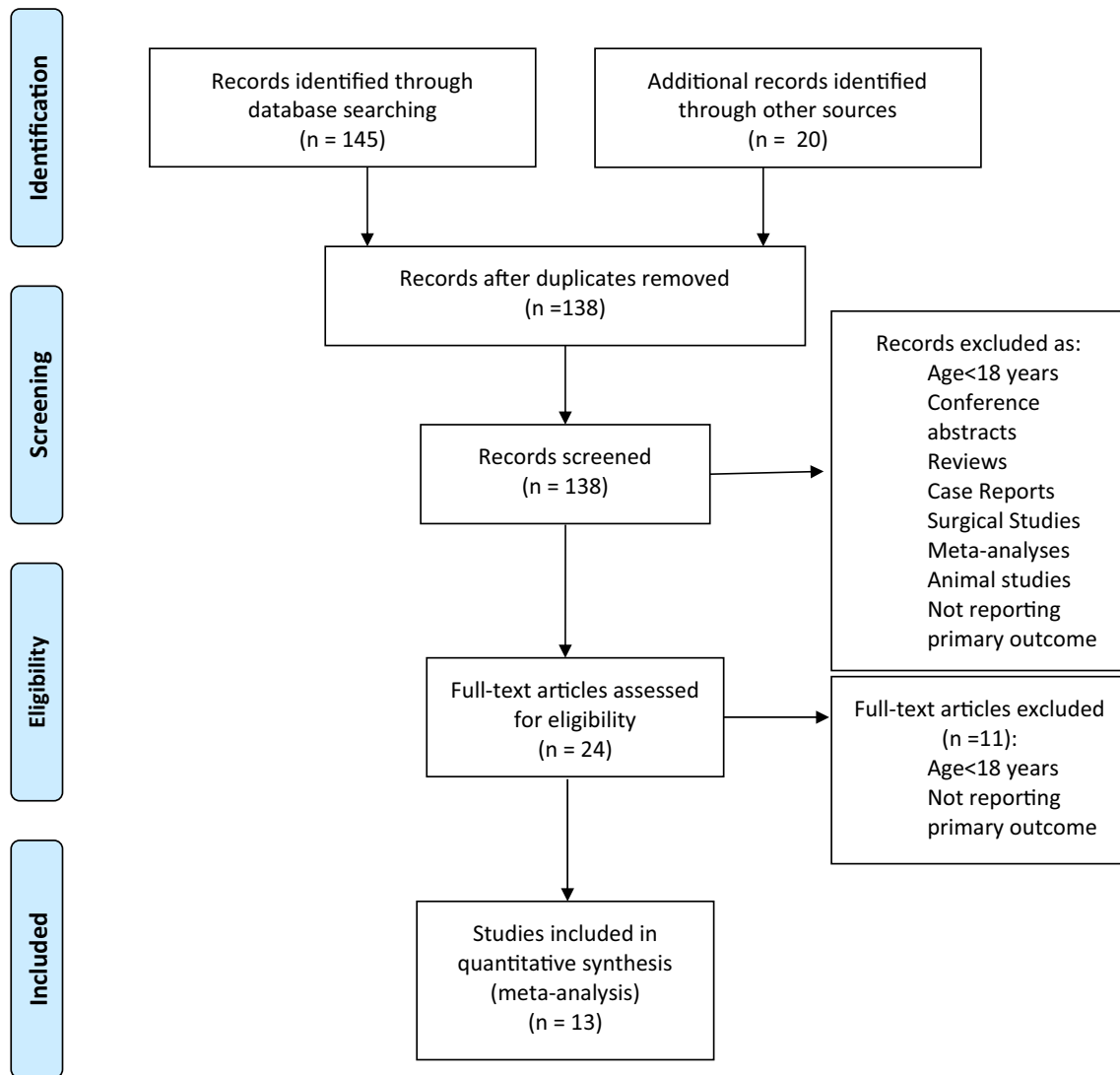


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing the search strategy for the systematic review, meta-analysis and meta-regression.

tently enough to make it suitable to study as a potential independent predictor of AT risk in multivariate analyses. Moreover, in the context of a left-to-right atrial shunt, right atrial size is likely to also be an important risk factor for AT given right atrial dilatation and stretch, exacerbated by tricuspid regurgitation and increased pulmonary pressures, in the context of secundum ASDs likely altering right heart haemodynamics.

Co-morbidities such as hypertension, diabetes, ischaemic heart disease and previous strokes [19] are major risk factors for thromboembolism as well the likely risk of developing ATs. Nyboe et al. [23] used the Danish National Patient Registry of 1168 patients undergoing ASD closure between 1977 and 2007, the cumulative incidence of developing AF was 11% at 10 years in patients with no prior documented AF. This was 5-times higher than the comparison cohort. At 5 years post-device closure, 60% of those with AF were on anti-arrhythmic drugs and 93% on oral anticoagulation. All study patients with an ASD showed a two-fold greater risk of stroke and were more likely to suffer a stroke at an earlier age (mean age 55 vs 68 years). This lends further support to the concept that ASD closure does not prevent or remove the substrate for ATs. The overall AT rate in our study was 8.6%, similar to the 11% observed in the Danish registry, albeit at a mean follow-up

time of just 38.4 months and including all patients with ATs (rather than only those with documented AT). While the post-closure stroke rate in our study was relatively low at 1.5%, this is still eight-fold higher than that seen in the general UK population [24] and clearly illustrates that thromboembolism is a major complicating factor for this cohort. Furthermore, the elevated stroke rate highlights the importance of AT persistence post-device closure alongside the potential for the inter-atrial shunt to remain and thrombus formation to occur on the device disks, which all predispose to stroke.

All-cause mortality in our study population was 2.7% which can be at least partly explained by a number of studies having a much older population cohort with Stroker [10] and Elshershari [15] studies having a mean age of 69 and 71 respectively. The authors go on to explain that coronary artery disease is of course a major cause of mortality in the older age group and such co-morbidities can account for the higher mortality rate in this cohort.

4.2. Approach and timing of arrhythmia intervention

In view of the high post-procedure rate of ATs and the rate of de novo ATs (2.2%) in patients with closed ASDs, one possible manage-

Study	n	Mean Age (Years)	Male Gender (%)	Average Follow-up Period (months)	Amplatzer Septal Occluder Device (%)	Mean Device Diameter (mm)	Pre-existing AT (%)
Chiu ⁶	517	41.5	24.6	44	100	26	6.9
Park ⁷	427	37	28.8	11.4	100	22	0
Chen ⁸	595	40	30.3	46.8	NR	NR	0
Van De Bruaene ⁹	27	55.7	40.7	28	55.6	23.8	NR
Stroker ¹⁰	47	69	19.1	39.6	NR	22	NR
Kutty ¹¹	84	NR	19	NR	NR	NR	25
Knepp ¹²	42	49.9	NR	NR	100	NR	23.8
Suchon ¹³	45	42.4	37.8	23	100	NR	NR
Giardini ¹⁴	134	39	39.6	57.6	93.3	NR	9.7
Elsershari ¹⁵	41	71	41.5	28	100	24	58.5
Spies ¹⁶	240	47	35	20	83.75	NR	22.1
Patel ¹⁷	113	57.9	30.1	36	100	24	NR
Rosas ¹⁸	54	34.3	18.5	25.2	NR	NR	5.56
	2366	41.3	29.3	38.4	96.2	24.1	9.8

NR= Not recorded AT = Atrial tachyarrhythmia

Fig. 2. Baseline characteristics of study population.

ment strategy would be to couple ASD closure with catheter ablation.

While anti-arrhythmic drugs may control symptoms and anti-coagulants reduce their thromboembolic risk, patients are committed to lifelong therapy and their associated side-effects from a young age. There is a wealth of data to support the use of catheter ablation as a definitive therapy for symptomatic AF in patients with structurally normal hearts [25]. Surgical data based on a concurrent Maze procedure in patients undergoing surgical ASD closure indicate that the Maze was effective in maintaining SR in patients with both paroxysmal AF (PAF) and permanent AF [19]. Nie et al. (2015) [27] looked at catheter ablation of AF in 18 consecutive patients with medically refractory AF and unrepaired ASDs. They found that compared to controls without ASDs (matched on age, gender, type of AF and left atrial diameter), there were no statistically significant differences in maintenance of SR (56% vs 64%) at follow-up of approximately 4 years. The authors thus concluded that it was reasonable to perform ablation prior to ASD device closure.

In a larger cohort of patients, Duong et al. [27] looked at arrhythmia outcomes at 1 year in patients aged ≥ 40 with pre-existing paroxysmal or persistent AF undergoing transcatheter ASD closure. They reviewed those who had undergone catheter ablation for AF (specifically pulmonary vein isolation) and compared these to patients with no documented arrhythmia pre-closure. They found that of the 15 patients with paroxysmal/persistent AF, 9 remained in sinus rhythm (60%) while the others

reverted back to AF. This is similar to observations made in the Nie et al. study [26]. Duong and colleagues [27] report 5/114 patients (4.4%) had de novo AF, consistent with the rate we observed in our meta-analysis. Moreover, they acknowledge that asymptomatic arrhythmias may have also occurred and hence one possibility would be to perform a prolonged period of monitoring (e.g. via an implantable loop recorder) to identify asymptomatic AF in the ASD cohort prior to device closure.

Left atrial access is likely to be significantly easier in an unrepaired ASD compared with the need for *trans*-septal puncture. Additionally, *trans*-septal access following previous percutaneous device closure may be technically feasible but typically more difficult and resulting in longer procedure times [28], increased fluoroscopy time and greater risk [25] lending weight to the argument for a pre-emptive ablation strategy in patients who are planned for device closure.

Given the identified risk factor (gender) and potential benefit of the Amplatzer Septal Occluder device for ATs (further comparison to other devices is needed), one possibility would be to perform a randomised controlled trial of catheter ablation in these patients to determine if this reduces the longer-term incidence of ATs compared to the matched control group.

One area of controversy is the optimal catheter ablation strategy given there is very little data comparing different approaches to ablation and their comparative outcomes. While pulmonary vein isolation has emerged as the choice of treatment in AF patients without inter-atrial shunts, the substrate for ATs is likely to be dif-

ferent in the context of the haemodynamic changes associated with left-to-right atrial shunting. Pulmonary vein triggers may not necessarily account for the high burden of ATs observed in

the ASD cohort and given the volume and pressure overload of the right heart with time, it is likely the right atrial substrate plays a greater role in the genesis of ATs. Clearly, given the lack of cur-

Study	n	Method for AT detection	Timing of New-Onset AT Post-ASD Closure (months)	Duration of Monitoring/Follow-Up (months) Mean/Median indicated where directed.
Chiu⁶	517	12-lead ECG/24-hour Holter monitoring records through review of clinical charts	Not available	54 (median)
Park⁷	427	12-lead ECG Holter monitoring at 1 week, 3 months, 6 months, 1 year and 2 years after closure. 24-hour Holter monitoring in some cases.	2.6 (IQR 1.2-4.1)	11.4 (median)
Chen⁸	595	Clinical chart review and 12-lead ECG data to determine 4 year clinical outcomes.	Not available	46.8 (mean)
Van De Bruaene⁹	27	12-lead ECG/ 24-hour Holter monitoring through ongoing clinical chart review.	Not available	28 (mean)
Stroker¹⁰	47	Clinical chart review/12-lead ECG data available from outpatient visits. Unclear intervals.	Not available	39.6 (median)
Kutty¹¹	84	Clinical chart review and telephone survey (for symptoms)	Not available	120 (median)
Knepp¹²	42	12-lead ECG at 6 months and further outpatient review at different intervals.	<1 month to 60 months	73 (median)
Suchon¹³	45	12-lead ECG/24-hour Holter monitoring at 1 month and 1 year follow-up	Not available	12 (all)
Giardini¹⁴	134	12-lead ECG/ 24-hour Holter monitoring at 1, 6 12 months and then yearly where possible.	Not available	57.6 (mean)
Elshershari¹⁵	41	12-lead ECG at 24 hours, 6 months and then yearly.	Not available	24 (median)

Fig. 3. Table outlining study monitoring methodology and follow-up duration in the detection of atrial tachyarrhythmias. AT, atrial tachyarrhythmias; ASD, atrial septal defects; ECG, electrocardiogram.

Spies¹⁶	240	12-lead ECG/ 24-hour Holter monitoring at follow-up. Unclear follow-up intervals.	Not available	20 (median)
Patel¹⁷	113	Clinical chart review and follow-up at 24 hours, 6 months and annually	Not available	36 (median)
Rosas¹⁸	54	Clinical chart review and follow-up at 6-8 monthly intervals	Not available	30 (mean)
	2366			

Fig. 3 (continued)

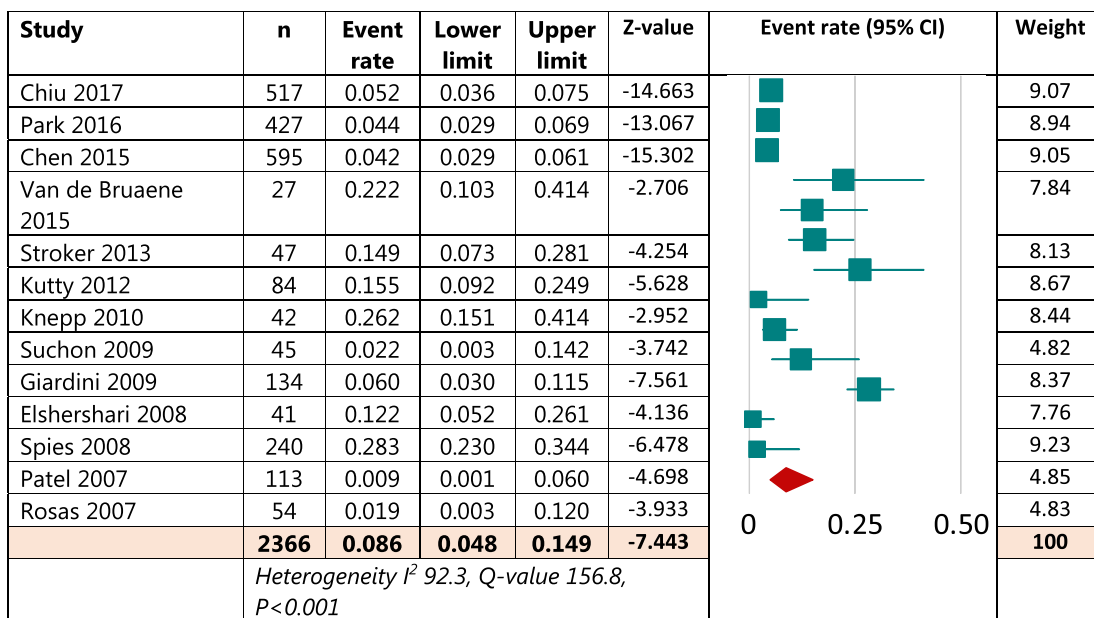


Fig. 4. Forest Plot of the included studies concerning the AT detection rate at follow-up, highlighting the statistical relevance of the results from each individual study. CI, confidence interval.

rently available data to guide catheter ablation strategy, further studies are urgently required to help answer whether left vs right atrial vs bi-atrial ablation akin to the Cox Maze procedure is the arrhythmia treatment of choice.

Finally, while symptomatic patients should clearly be considered for AT catheter ablation either at the time of or prior to ASD device closure, the asymptomatic AT population also need careful consideration. A prolonged period of monitoring in the asymptomatic population being considered for device closure, for instance through the insertion of an implantable loop recorder, would be a rational strategy to try and ensure that patients are offered the best treatment strategy to manage arrhythmia alongside the ASD.

5. Limitations

One of the main limitations of our study is the high degree of statistical heterogeneity observed. In addition to gender and type of ASD device being potential confounders, sample size, duration of follow-up and the retrospective nature of the studies are all relevant contributing factors. Importantly, cardiac cavity dimensions were not consistently reported across studies making it difficult to report on their overall relationship to AT risk. We anticipate that

there is a likely relationship between atrial dimensions and AT risk and having this data available would undoubtedly add to the conclusions we can draw from this meta-analysis. Well-designed, prospective registries are necessary to evaluate the incidence and long-term risk of ATs. This should help to guide the optimal timing of anti-arrhythmic intervention.

Given the Amplatzer Septal Occluder device made up over 95% of the ASD closure devices used, we do recognise any comparison to other devices is of course limited and of course the association between Amplatzer Septal Occluder usage and lower AT risk must be made with caution. Finally, there is a definite need for a new ASD closure device in the future with less material to reduce the risk of thrombus formation, the possibility to cross the device post-implantation e.g. through a membrane or small hole facilitating left atrial access if needed (e.g. for electrophysiological procedures).

6. Conclusion

In the vast majority of patients with secundum-type ASD defects, percutaneous closure with the Amplatzer Septal Occluder will be the therapy of choice. However, given patients with ASDs are often asymptomatic and do not present to medical services

until later in adult life, most adult ASD closure occurs in older patients. Our data indicates that male patients are at a higher risk of ATs that do not abate with device closure.

Catheter ablation is a rational strategy to improve symptoms, reduce morbidity (i.e. stroke) associated with ATs and reduce the need for long-term anti-arrhythmic therapy and their associated side-effects. Given that trans-septal access is technically easier in the vast majority of patients with unrepaired ASDs, with the additional benefit of shorter procedure times, reduced radiation exposure and lower overall risk, ablation prior to ASD device closure may be a favourable treatment approach. Finally, the optimal ablation strategy remains an area of debate with the need for long-term data outcome data to guide the best ablation approach.

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CRedit authorship contribution statement

Vishal Vyas: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Project administration. **Amit Kaura:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization. **Vinit Sawhney:** Supervision, Project administration. **Martin Lowe:** Supervision, Project administration. **Vivienne Ezzat:** Conceptualization, Validation, Resources, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest. No sources of financial or industry support given for this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100490>.

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