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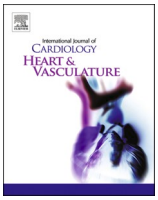

Left atrial volume index: A predictor of atrial fibrillation recurrence following direct current cardioversion – A systematic review and meta-analysis

Dipesh Raniga [a], Mina Goda [a], Laetitia Hattingh [b,c,d,*], Sarah Thorning [e], Matthew Rowe [a], Laurie Howes [a,f,g]

[a] Department of Cardiology, Division of Specialist Medical Services, Gold Coast Hospital and Health Services, Southport, QLD 4215, Australia
[b] Allied Health Research, Gold Coast Hospital and Health Services, Southport, QLD 4215, Australia
[c] School of Pharmacy, The University of Queensland, QLD 4102, Australia
[d] School of Pharmacy and Medical Sciences, Griffith University, QLD 4222, Australia
[e] Office of Research, Gold Coast Hospital and Health Services, Southport, QLD 4215, Australia
[f] School of Medicine, Griffith University, QLD 4222, Australia
[g] School of Medicine, Bond University, QLD 4226, Australia

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ABSTRACT

This systematic review and *meta*-analysis was conducted to determine the clinical relevance of echocardiographically measured left atrial (LA) size to predict the recurrence of atrial fibrillation (AF) after direct current cardioversion (DCCV). A search was performed on Medline (Ovid), Embase (Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL) in Cochrane Library, Wiley and Web of Science (Clarivate) to identify relevant studies. Amongst the initial 4066 citations identified, 31 fulfilled the criteria for inclusion in the data analysis incorporating 2725 patients with a mean follow-up period of 6.5 months. The weighted mean left atrial volume index (LAVI) was 40.56 ml/m^2 (95 %CI:37.24–43.88) in the sinus rhythm (SR) maintenance group versus 48.69 ml/m^2 (95 % CI: 44.42–52.97) in the AF recurrence group with P value of < 0.001, left atrial diameter (LAD) was 42.06 mm (95 %CI: 41.08–43.05) in the SR maintenance group versus 45.13 mm (95 %CI: 44.09–46.16) in the AF recurrence group, P value < 0.001. Effect size analysis of LAVI showed that each unit increase in LAVI resulted in an increase in the risk of AF recurrence by 6 % (95 % CI: 3 %–10 %). Age and AF duration were also statistically significant between the two groups however comorbidities, use of beta blockers or amiodarone were not significantly different. This *meta*-analysis shows that AF duration, LAVI, LAD and age predict the risk of recurrence of atrial fibrillation post electrical cardioversion with LAVI being the most clinically relevant echocardiographic feature.

1. Introduction

The worldwide prevalence of AF is estimated at 4,977 cases per million inhabitants and has increased substantially over the last 20 years) [1]. It is expected that, due to the ageing population, the number of patients living with AF will continue to increase, in turn contributing to rising healthcare costs [1].

The recommended management of AF is the Atrial Fibrillation Better Care (ABC) holistic pathway which involves A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular and Comorbidity optimisation [2]. One aspect of 'B' Better symptom management is rhythm control which attempts to restore and maintain sinus rhythm (SR) by engaging one or a combination of treatment approaches including synchronised direct current cardioversion (DCCV), anti-arrhythmic medications, and/or catheter ablation [2]. Current evidence dictates that the primary indication for rhythm control is to reduce AF-related symptoms and improve quality of life (QoL) [2]. AF ablation should be considered in those with HFrEF who have been selected for rhythm control to reduce heart failure (HF) hospitalization and, potentially, mortality [2]. Performing DCCV is the recommended management of AF in hemodynamically compromised AF patients, it is more effective than chemical cardioversion and results in immediate

* Corresponding author at: Laetitia Hattingh Allied Health Research, Gold Coast Health, QLD 4215, Australia.
E-mail address: laetitia.hattingh@health.qld.gov.au (L. Hattingh).

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restoration of SR [2]. Pharmacological cardioversion or DCCV are both effective management options in stable patients [2].

The advantages of DCCV include a high initial success rate of 68–98 %, however, sustaining SR long-term is not reliably achieved [3]. A multi-centre double-blind, placebo-controlled study that assessed the efficacy and safety of two anti-arrhythmic medications in preventing the recurrence of AF after successful DCCV in 848 patients showed that 83 % of patients receiving placebo had recurrence within 1 year [4]. Relapse of AF following DCCV is associated with increased mortality. [3] It is therefore imperative to identify appropriate patient cohorts for DCCV and manage reversible factors related to recurrence [2–4].

Several factors in individual studies have been associated with an increased risk of AF recurrence after elective cardioversion including older age, female gender, obesity, previous cardioversion, chronic obstructive pulmonary disease (COPD), renal impairment, structural heart disease, left atrium (LA) dimensions, and heart failure (HF) [3].

Evidence from several studies supports an association between LA size before or immediately after DCCV and the risk of AF recurrence [5–9]; however, other studies have failed to observe a relationship [10,11]. These original studies were all performed in single centres, had small numbers and used different modalities of determining LA size, limiting the conclusions that can be drawn. A systematic review and *meta*-analysis of these studies would provide insights into whether SR maintenance after successful elective DCCV may be influenced by LA size measured by transthoracic echocardiogram. The purpose of this review was to determine the clinical relevance of echocardiographically measured left atrial size to predict the recurrence of atrial fibrillation after DCCV.

2. Protocol registration

A protocol registered with PROSPERO International Prospective Register of Systematic Reviews outlines the methods for this systematic review (CRD42022308169) [12]. The Preferred Reporting Items for Systematic Reviews (PRISMA) and Synthesis guidelines were followed throughout the review and reporting of the findings [13].

3. Search strategy and screening

Searches were conducted on the 14th December 2021 in Medline (Ovid), Embase (Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL) in Cochrane Library, Wiley (Issue 11, 2021) and Web of Science (Clarivate). We applied no limits for study type, or year of publication. Three investigators (MG, DR, LH) worked alongside ST, an experienced medical librarian, to develop the search strategy. The search used a combination of Medical Subject Headings (MeSH) and key words for the terms “atrial fibrillation”, “electric cardioversion” and “recurrence”. The full search strategies for each database are included in Appendix A.

After removing all duplicates, title and abstract screening was conducted by MG, DR, ST and LH to select studies which met eligibility criteria through the web-based software platform Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, available at https://www.covidence.org). All articles were screened by two investigators with criteria set for either MG or DR to screen each article.

Due to the large volume of studies included from the initial title and abstract screening, the project was divided into parts to focus on specific variables. Consequently, the abstracts of studies that reported on echocardiographic factors were screened. Studies were included that reported on echocardiographic factors which were clinically relevant and widely described.

Reference checks of related systematic reviews, metanalysis and conference articles was done, the resulting studies were included for full text review. Full-text screening was conducted by MG, DR, LH and ST to identify eligible articles which were evaluated before inclusion in the analysis. Disagreements were resolved by consensus.

4. Inclusion and exclusion criteria

Studies were eligible for inclusion if they were primary research articles, published in English language from January 1980 onwards, RCTs, non-RCTs and cohort studies and incorporated:

- adult patients > 18 years,
- patients with both AF and external electrical cardioversion,
- outcomes at least 30 days post external electrical cardioversion

Exclusion criteria were 1) case studies, cross-sectional studies, 2) follow up less than 30 days 3) animal studies, 4) non-English studies, 5) only report pharmacological cardioversion, 6) abstracts with insufficient data e.g., conference proceedings, and 7) trial protocols.

5. Data extraction and synthesis

Two authors (MG, DR) performed data extraction with a purpose-built data extraction template, which was verified by LH and ST. Data extracted included article characteristics (e.g., title, year, author, country, journal and type of study), study characteristics (e.g., number of participants, number of lost to follow up, mean age, demographic factors, AF duration, comorbidities and medications), and primary and secondary outcomes of interest from the article.

6. Statistical analysis

Quantitative data related to outcomes for studies investigating AF following DCCV was analysed, and a *t*-test was conducted to compare patients who maintained sinus rhythm (SR) and those who reverted to AF for demographic details, co-morbidities and medications used to manage AF before DCCV. Efficacy outcomes related to age, body mass index, AF duration and echocardiographic findings were *meta*-analysed. Forest plots were presented alongside the I^2 statistic to evaluate heterogeneity for LAVI and LAD. A p-value of < 0.05 was considered to represent statistical significance. All analyses were performed using Stata 17 (Stat Corp., College Station, Tx, USA).

7. Quality assessment

Two unblinded reviewers independently evaluated the quality of each of the included studies using the JBI Critical Appraisal Tool. Discrepancies between reviewers were solved by consensus. The percentage for each feature was independently evaluated among the studies.

Regression-based Egger’s test and the non-parametric trim-and-fill method were used to assess for publication bias.

8. Study selection and patient characteristics

At initial screening, 4066 studies were identified. After the exclusion of nonrelevant studies, case reports, and reviews by title and abstracts, 74 studies were retrieved for full-text screening of which 12 were obtained from reference checks (Fig. 1). Thirty-one studies were included in the final analysis after meeting the eligibility criteria (Table 1). Out of the 31 studies included, 3 studies were retrospective cohort studies and 28 were prospective cohort studies. The total number of patients from the 31 studies was 2830; 105 patients were lost to follow-up resulting in 2725 patients being analysed. The mean period of follow-up was 6.5 months, and 12 studies had a mean follow-up duration of $< \underline{3}$ months.

9. Baseline characteristics of patients

The total population consisted of 1447 patients in the SR-maintaining group and 1278 patients in the AF-recurrence group. The

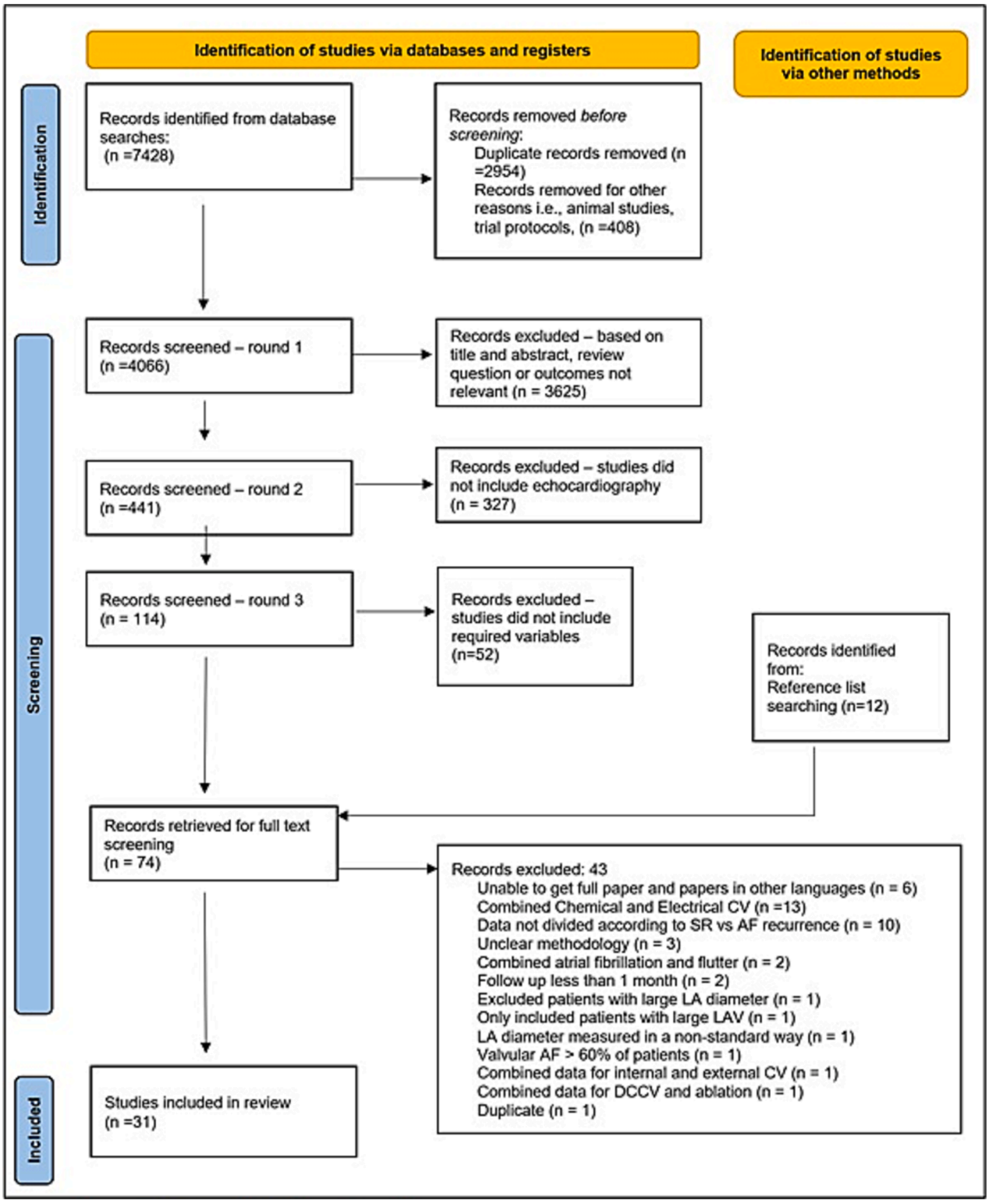

Fig. 1. Flow chart of the systematic review and reasons for exclusion of studies.

baseline clinical and echocardiographic characteristics of these patients are summarised in Table 2. Overall, 61.7 % of patients were male in the SR- maintenance group and 59.7 % in the AF-recurrence group. There was no statistically significant differences between other factors including demographics, comorbidities, or use of beta blockers or amiodarone.

10. Association of patient characteristics with recurrence of AF after DCCV

Table 3 provides a summary of *meta*-analysis data. Patients with recurrence of AF were older compared to patients who maintained SR (weighted mean 64.94 [95 % CI: 63.22–66.66] versus 63.20 years [95 % CI: 61.45–64.94], p = 0.016, respectively). AF duration was significantly different with mean duration of 197.82 days (95 %CI:

Table 1
Summary of the characteristics of the included studies.

Study	Country	Study Design	Patients (N)	Duration of follow-up (Mean, months)	Lost to follow up (N)
Akdemir et al. 2013 [5]	Turkey	Prospective Cohort	50	1	0
Altun et al. 2015 [23]	Turkey	Prospective Cohort	32	6	0
Ari et al. 2008 [24]	Turkey	Prospective Cohort	58	6	0
Aribas et al. 2013 [25]	Turkey	Prospective Cohort	156	6	7
Bernard- Brunet et al. 2014 [26]	France	Prospective Cohort	29	1	9
Besli et al. 2015 [27]	Turkey	Prospective Cohort	75	1	0
Budeus et al. 2006 [28]	Germany	Prospective Cohort	151	9	33
Cho et al. 2015 [29]	Korea	Prospective Cohort	163	12	0
Caputo et al. 2011 [30]	Italy	Prospective Cohort	51	12	0
Degiovanni et al. 2018 [31]	Italy	Prospective Cohort	96	1	0
Gurses et al. 2019 [32]	Turkey	Prospective Cohort	90	3	0
Kim et al. 2014 [33]	Korea	Retrospective Cohort	171	5	34
Lin et al. 2002 [10]	Taiwan	Prospective Cohort	36	7	0
Luong et al. 2015 [6]	Canada	Retrospective Cohort	95	6	13
Luong et al. 2016 [7]	Canada	Retrospective Cohort	95	6	0
Meurling et al. 2006 [34]	Sweden	Prospective Cohort	32	2	0
Mukherjee et al. 2013 [35]	USA	Prospective Cohort	82	3	0
Naji et al. 2011 [36]	Slovenia	Prospective Cohort	85	24	6
Park et al. 2010 [11]	Korea	Prospective Cohort	53	6	0
Roijer et al. 2001 [37]	Sweden	Prospective Cohort	62	1	0
Rondano et al. 2010 [38]	Italy	Prospective Cohort	130	12	0
Toufan et al. 2017 [8]	Iran	Prospective Cohort	51	3	0
Verhorst et al. 1997 [39]	Netherlands	Prospective Cohort	50	12	0
Walek et al. 2020 [9]	Poland	Prospective Cohort	117	12	0
Watanabe et al. 2006 [40]	Japan	Prospective Cohort	84	12	0
Eren et al. 2020 [41]	Turkey	Prospective Cohort	306	7	0
Fujimoto et al. 2018 [42]	Japan	Prospective Cohort	141	1	0
Maffe et al. 2015 [43]	Italy	Prospective Cohort	104	14	0
Moreno-Ruiz et al 2019 [44]	Mexico	Prospective Cohort	81	6	0
Muller et al. 2014 [45]	Germany	Prospective Cohort	54	3	3
Weijs et al. 2018 [46]	Netherlands	Prospective Cohort	50	1	0

Table 2
Summary of baseline characteristics of patients who maintained SR compared to patients with AF recurrence.

	Maintaining SR N = 1447	Recurrent AF N: 1278	P value	No of studies
Demographics				
Males/Females	721/447	667/450		25
Co-morbidities Mean (SD)				
Patients with CAD	10.78 (13.48)	8.94 (10.03)	0.193	18
Patients with heart failure/ cardiomyopathy	8.36 (8.24)	10.54 (12.36)	0.282	11
Patients with hypertension	27.25 (20.43)	26.91 (20.56)	0.918	24
Patients with diabetes	7.46 (4.98)	7.7 (6.63)	0.844	20
Medications Mean (SD)				
Patients on beta blockers	25.38 (19.26)	22.2 (16.85)	0.230	15
Patients on amiodarone	21.28 (11.88)	18.2 (12.46)	0.301	10

AF: atrial fibrillation; CAD: coronary artery disease; SR: sinus rhythm.
SD and p-values at 95% confidence interval.

153.88–241.75) in the SR group versus 223.1 days (95 %CI: 176.73–269.46) in the AF recurrence group, p = 0.019.

There was no statistically significant difference between other factors including demographics, comorbidities, or use of beta blockers or amiodarone.

11. Association of echocardiographic LA measurements with recurrence of AF after DCCV

A summary of differences in LA size amongst the patients maintaining SR and patients with AF recurrence is presented in Table 3. The weighted mean LA diameter was 42.06 mm (95 %CI: 41.08–43.05) in the SR maintenance group versus 45.13 mm (95 %CI: 44.09–46.16) in the AF recurrence group, p < 0.001.

Patients with recurrence of AF had larger LA area compared to those

Table 3
Metanalysis of demographic and echocardiogram variables of patients who maintained SR compared to patients with AF recurrence.

	Maintaining SR N = 1447	Recurrent AF N = 1278	P value	No of studies
Demographic factors				
Mean (95 % confidence interval)				
Age years	63.20 (61.45–64.94)	64.94 (63.22–66.66)	0.016	28
BMI kg/m^2	27.17 (26.08–28.25)	27.73 (26.49–28.96)	0.239	12
AF duration days	197.82 (153.88–241.75)	223.1 (176.73–269.46)	0.019	20
Echocardiographic findings				
Mean (95 % confidence interval)				
LA area cm^2	17.55 (3.98–31.11)	20.74 (5.19–36.28)	0.034	4
LA volume ml	70.23 (55.66–84.81)	77.70 (65.60–89.82)	0.268	4
LA volume indexed mL/ m^2	40.56 (37.24–43.88)	48.69 (44.42–52.97)	<0.001	18
LA diameter mm	42.06 (41.08–43.05)	45.13 (44.09–46.16)	<0.001	23
LVEF %	57.11 (55.17–59.05)	56.49 (54.64–58.33)	0.194	28

Data presented as weighted means and SD at 95% confidence interval in parenthesis.
BMI; body mass index, AF; atrial fibrillation, LA; left atrium, LVEF; left ventricular ejection fraction, SR; sinus rhythm.

who maintained SR (weighted mean 20.74 cm2; 95 %CI: 5.19–36.28 versus 17.55 cm2; 95 % CI: 3.98–31.11), respectively; p = 0.034. The weighted mean LAVI was 40.56 ml/m^2 (95 %CI:37.24–43.88) in the SR maintenance group versus 48.69 ml/m^2 (95 % CI: 44.42–52.97) in the AF recurrence group with p < 0.001. There were no significant differences in LV ejection fraction and non-indexed LA volume between patients with and without AF recurrence.

There were 18 studies that reported on LAVI of which 9 studies reported data in a format appropriate for *meta*-analysis. Fig. 2 provides a summary result for LAVI. Random effects *meta*-analysis showed a high level of heterogeneity ($I^2 = 78$ %) with findings suggesting that for each 1 unit increase in LAVI, the odds of AF relapse is higher by 6 % (95 % confidence interval 3 % to 10 %).

12. Quality assessment

Results of the quality assessment of included studies are summarised in Fig. 3. The details of quality assessment for individual studies can be found in the supplementary material [Supplementary Table 1]. Almost 30 % of the studies did not report on confounding factors. Amongst the studies which identified confounding factors, less than 25 % reported strategies to mitigate the risk of bias. More than 90 % of the studies included details of the inclusion criteria.

Funnel plot and Egger's test show strong evidence of a small studies effect, possibly publication bias. When the trim-and-fill method is used to account for the bias the overall summary effect is reduced from 0.06 (95 % CI 0.03 to 1.0) to 0.05 (95 % CI 0.01 to 0.08) (Fig. 4).

This systematic review and *meta*-analysis was conducted to determine the association between echocardiographic measurement of LA size and the recurrence of AF post successful elective DCCV. To our knowledge, there has not been a similar study published that assessed the correlation between LA size and recurrence of AF after successful DCCV.

The most important finding of our systematic review and *meta*-analysis is that patients with larger LAVI, LA area and LAD were more likely to have a recurrence of AF after successful DCCV. For example, an increase in LAVI by 1 ml/m2 increases the risk of overall recurrence of AF post DCCV by 6 %. Another vital finding is the importance of indexation of LA volume measurements as LA volume alone was not predictive, supporting contemporary society recommendations for reporting LAVI on echocardiogram [14].

Additionally, LAD and LA area measurements were significant for predicting AF recurrence without being indexed for body surface area. However, the narrow difference in the weighted mean of LA diameter (42.06 mm vs 45.13 mm) and LA Area (17.55 cm^2 vs 20.72 cm^2) between the two groups, raises questions as to whether these measurements would be clinically relevant. Interestingly, the mean values for LA area in both the groups were within normal reference limit (≤20 cm^2) [14].

In patients with AF, the LA usually enlarges in the superior-inferior or medial–lateral axis since it is constrained posteriorly by the tracheal bifurcation and anteriorly by the aortic root and right ventricular outflow tract [15]. Therefore, measurement of the antero-posterior (AP) diameter may often neglect the changes in other LA dimensions which are better captured with LA volume [16].

There was no significant difference in LVEF between the two groups, which may have been expected given most of the included studies excluded patients with moderate to severely reduced ejection fraction. Moreover, medication usage was a not a factor associated with in maintenance of SR, although only beta blockers and amiodarone were reported frequently enough to be analysed. This lack of association may also be due to heterogeneity in dosage, timing of initiation and cessation of these medications.

Our analysis also shows that more advanced age is a significant predictor of recurrence of AF. Age has also been associated with recurrence of AF post cardioversion in multiple studies with variable methodologies and definitions of age groups [17–20]; additionally, in clinical practice, older patients are less likely to be offered DCCV. [47].

It is well known from previous studies that prolonged AF duration is associated with lower rates of successful cardioversion and higher recurrence post successful cardioversion [17,18,21]. Our analysis also reiterates that longer AF duration is associated with higher likelihood of

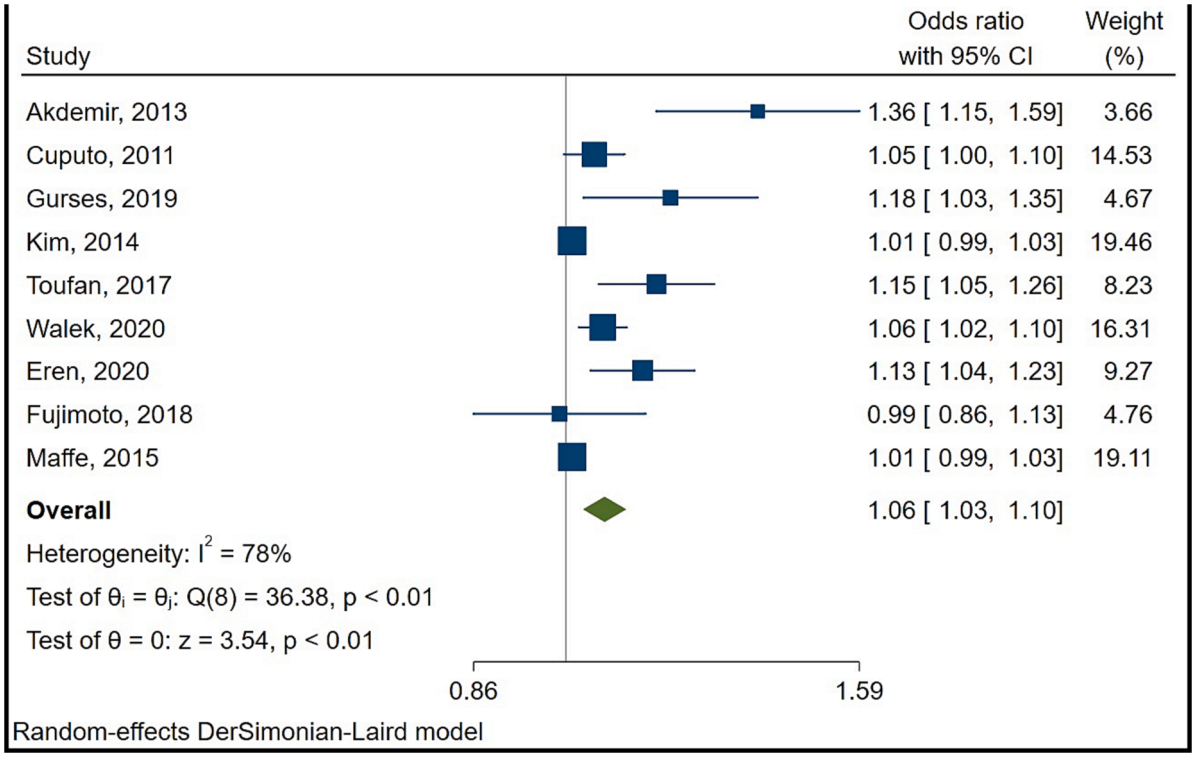

Fig. 2. Forest plot of the effect metanalysis of left atrial volume indexed (LAVI) on risk of atrial fibrillation recurrence post electrical cardioversion.

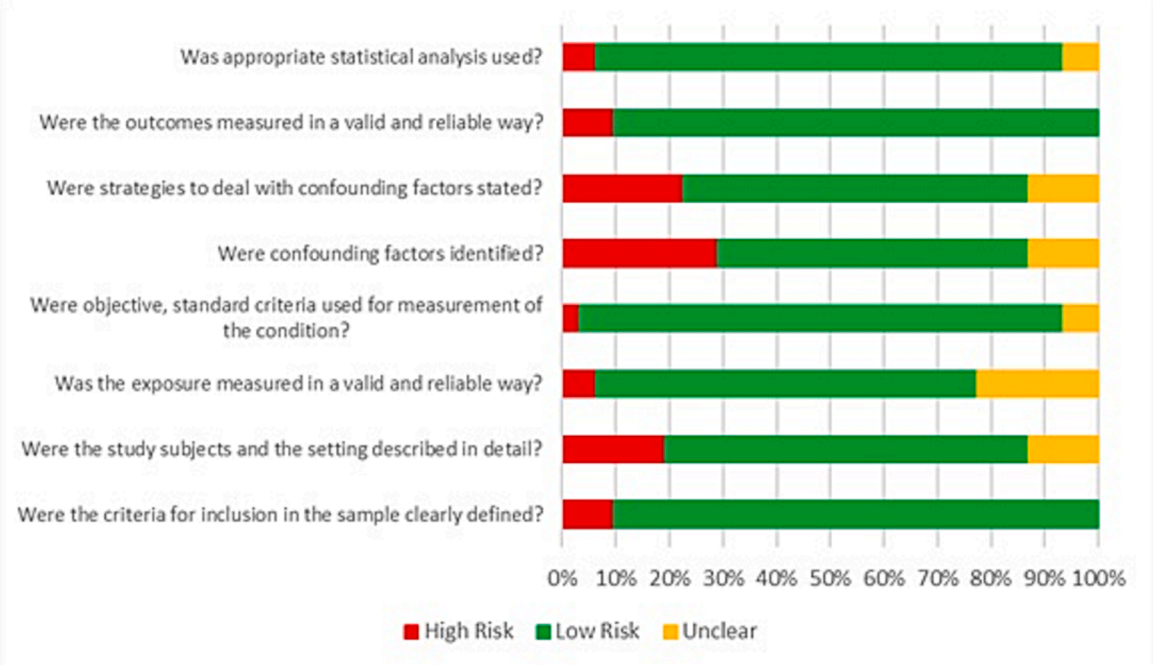

Fig. 3. Assessment of the methodological quality of the studies using the JBI Critical Appraisal Tool.

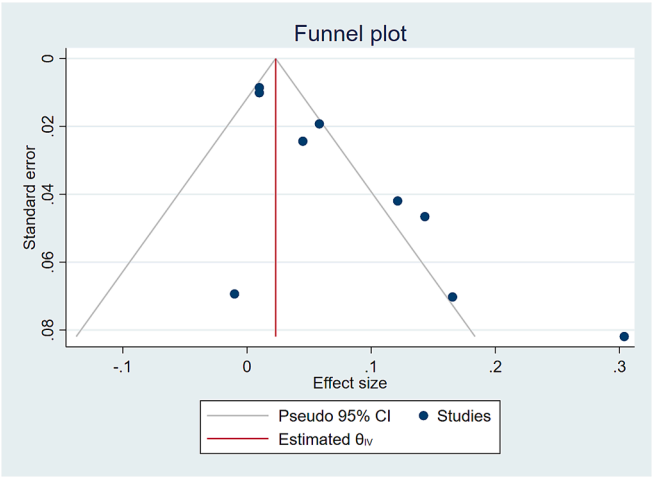

Fig. 4. Funnel plot on study results to assess risk of bias.

AF recurrence post successful DCCV. Chronic AF promotes electrical and structural remodelling so that patients with chronic AF appear to have larger atria and are more resistant to DCCV [22].

Based on the findings we suggest AF patients with normal (16-34 ml/m^2) or mildly enlarged LAVI (35-41 ml/m^2) proceed to DCCV if rhythm control is decided upon. In those with moderate (42–48 ml/m^2) to severely (>48 ml/m^2) enlarged LA, given recurrence is more likely, we suggest they should undergo appropriate risk and benefit discussion with shared decision making prior to DCCV.

Future studies areas of study may include more complex measurements of LA function such as strain and reservoir function and their impact on maintenance of SR. The identified echocardiographic variables could be incorporated into selecting cohorts in future randomised trials of rhythm control strategies.

13. Limitations

A few considerations must be taken into account in this systematic review and metanalysis. The studies did not segregate patients with short duration AF, for example < 7 days, which may have different patterns of AF recurrence. Independent predictors of recurrence could not be determined by further statistical analysis such as *meta*-regression since individual patient data and supplementary data could not be accessed for the included studies. The studies included had a high degree of heterogeneity with variable duration of follow-up. Incomplete information regarding some variables such as smoking habits, alcohol intake, and use of medications such as angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARB) and statins could have a role in recurrence of AF. Moreover, patient variables used in adjustment of confounders were not uniform or clearly mentioned in the studies included. Furthermore, three of the studies included were retrospective thus bias related to incomplete data reporting cannot be excluded. Additionally, patients may have undetected recurrences of AF however continuous patient monitoring for long durations may not be practical. We did not adjust the analysis for contributing factors such as age and AF duration as we did not have access to the original data from the various studies.

14. Conclusion

In this systematic and *meta*-analysis of patients undergoing elective DCCV for AF, significant predictors of AF recurrence include age, AF duration, LA area, diameter and indexed volume. In particular LA volume, when indexed for BSA, appears to be a strong and clinically relevant predictor of AF recurrence after successful cardioversion. These findings suggest LAVI should be factored into decision making around utility of DCCV in patients with AF.

CRediT authorship contribution statement

Dipesh Raniga: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Mina Goda:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Laetitia Hattingh:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sarah Thorning:** Writing – review & editing, Formal analysis, Data

curation. **Matthew Rowe:** Writing – review & editing, Supervision, Resources. **Laurie Howes:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101364.

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