Effect of Endothelial Adhesion Molecules on Atrial Fibrillation: A Systematic Review and Meta-analysis

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Background: Endothelial adhesion molecules (EAMs), and more specifically vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), belong to a family of immunoglobulin-like molecules and are found to have increased expression in inflamed microvessels. Due to the growing evidence regarding EAM effects on cardiovascular diseases, we aimed to investigate the link between EAMs and atrial fibrillation (AF) to discover the efficacy of EAMs assessment as predictive markers in high-risk patients. **Methods**: We searched for articles published from January 1990 to April 2022. Two independent researchers selected studies that examined the relationship between VCAM-1 and ICAM-1 levels and AF. Study design, patient characteristics, VCAM-1 and ICAM-1 levels, and measurement methods were extracted from the selected articles. **Results**: Of 181 records, 22 studies were finally included in the systematic review. Meta-analyses showed a significant difference in serum levels of EAMs in patients with AF compared with patients with sinus rhythms (VCAM-1: mean difference [MD] 86.782, 95% CI 22.805–150.758, p=0.008; ICAM-1: MD 28.439 ng/mL, 95% CI 12.540–44.338, p<0.001). In subgroup analysis of persistent AF, the differences were still significant (VCAM-1: MD 98.046, 95% CI 26.582–169.510, p=0.007; ICAM-1: MD 25.091, 95% CI 12.952–37.230, p<0.001). We also found the mean ranges of VCAM-1 (95% CI 661.394–927.984 ng/mL) and ICAM-1 (95% CI 190.101–318.169 ng/mL) in patients with AF. **Conclusion**: This study suggests a positive association between serum levels of VCAM-1 and ICAM-1 with AF, but there is a need for further large-scale studies.

Keywords

Atrial fibrillation, intercellular adhesion molecule-1, postoperative atrial fibrillation, tissue expression, vascular cell adhesion molecule-1

Disclosures: Mehran Rahimi, Leili Faridi, Leila Nikniaz, Sara Daneshvar, Amirreza Naseri, Mohammadreza Taban-Sadeghi, Hesam Manaflouyan, Javad Shahabi and Nizal Sarrafzadegan have no financial or non-financial relationships or activities to declare in relation to this article.

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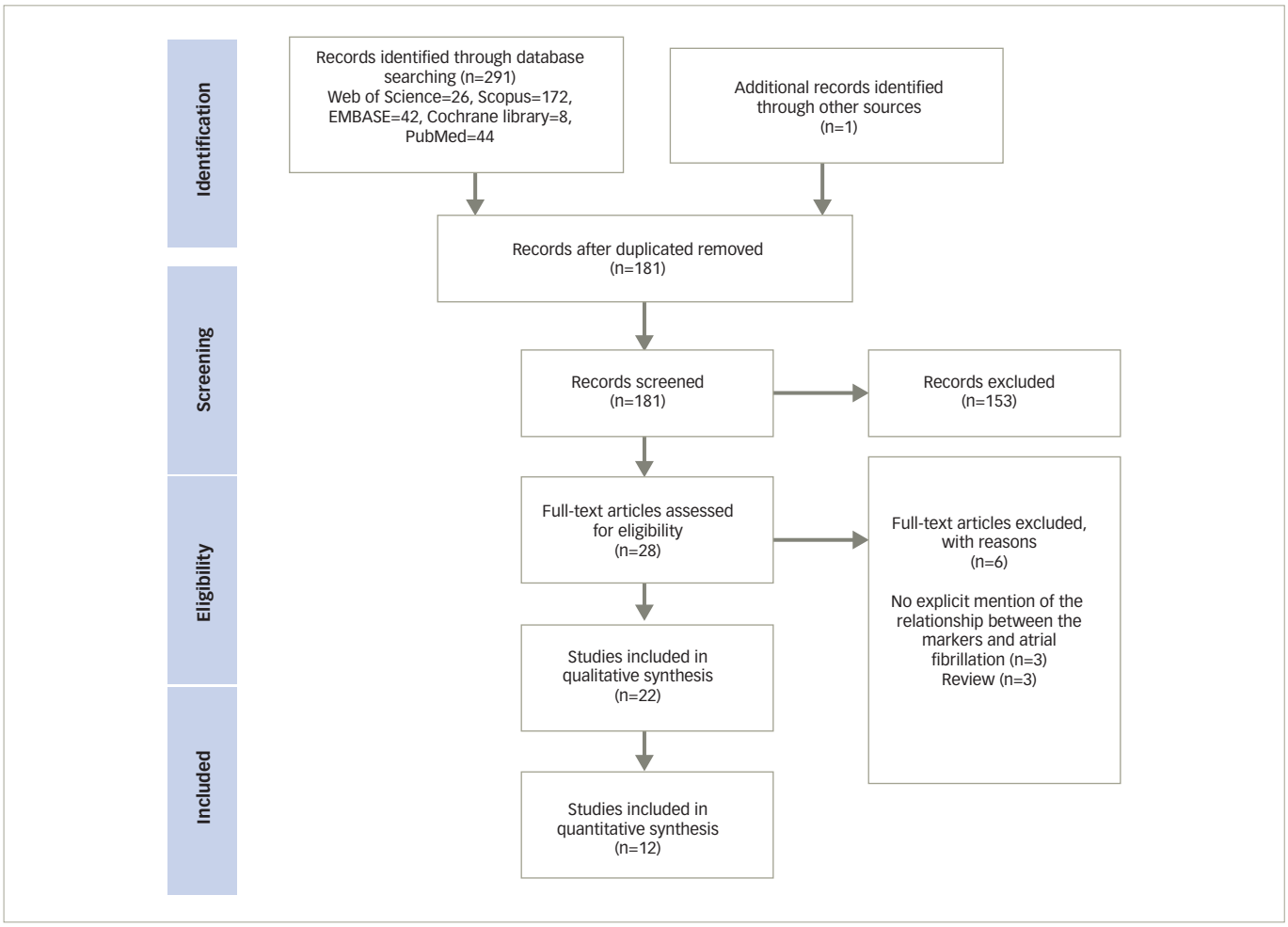
Atrial fibrillation (AF), one of the most common cardiac arrhythmias, is considered to be a significant risk factor for cardiovascular disease, stroke and mortality. The prevalence of AF increases with age, and patients with AF are at risk of atrial thrombosis and its consequences.[1] The pathogenesis of AF consists of inflammatory activity, structural remodelling and endothelial dysfunction.[2] It is estimated that more than 10% of patients with AF in the USA are undiagnosed,[3] and this shows the importance of finding predictive markers for AF.

Inflammation that occurs in the atrium is due to the infiltration of inflammatory cells and is associated with an increase in inflammatory markers such as C-reactive protein, osteoprotegerin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).[4] VCAM-1 and ICAM-1 are endothelial adhesion molecules (EAMs) expressed on the activated endothelial cells, belonging to a family of immunoglobulin-like molecules. These two EAMs have increased expression in inflamed microvessels and are responsible for the adhesion and migration of monocytes and lymphocytes.[5]

VCAM-1 expression is associated with various cardiac diseases, such as heart failure, and rheumatic and ischaemic heart diseases.[6,7] Reactive oxygen species and haemodynamic factors enhance cardiac VCAM-1 expression, which causes sustained cardiac remodelling, fibrosis and dysfunction.[8,9] Atrial upregulation and increase in VCAM-1 expression has been reported in patients with AF.[10] It has been demonstrated that blockade of angiotensin II receptor reduces the occurrence of AF, and the proposed mechanism is the downregulation of adhesion molecules within the atrium.[11] Two studies have reported high levels of serum VCAM-1 in patients with AF compared with sinus rhythm (SR);[4,12] however,

Figure 1: PRISMA 2009 flow diagram



another study showed no difference in this regard.[13] In addition, there are conflicting findings in studies regarding the correlation between the increased expression of VCAM-1 and the promotion of thrombogenic factors and left atrial appendage clot formation.[14–16] ICAM-1 expression has been detected in the blood vessels of the atrium and the atrial endocardium.[17] On the other hand, similar vascular and muscular expressions of VCAM-1 and ICAM-1 have been seen in patients with postoperative atrial fibrillation (POAF) and patients without arrhythmia, such as those with coronary artery disease.[18] Furthermore, higher ICAM-1 levels have been found to be linked to hypertension.[19]

To the best of our knowledge, no systematic review and meta-analysis has been conducted to summarize the relationship between VCAM-1/ICAM-1 and AF; therefore, we aimed to assess the effect of VCAM-I and ICAM-1 on AF and whether these EAMs could be used as biomarkers to identify patients at high risk of AF, including after cardiac surgery.

Methods

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO).[21]

Eligibility criteria

The inclusion criteria for this study were: (1) patients with AF as the study population; (2) reports of VCAM-1 and ICAM-1 serum levels. The exclusion criteria were: (1) other types of articles such as case reports, review articles, letters, comments; (2) languages other than English; (3) conference abstracts; (4) studies conducted on animals.

Search

Two independent researchers (M.R. and S.D.) conducted the search. The literature search was performed through PubMed, Scopus, EMBASE and Web of Science for studies published from January 1990 until April 2022. Search terms in PubMed included: ("vascular cell adhesion molecule-1" [Mesh] OR vascular cell adhesion molecule-1 OR [title/abstract], "intercellular adhesion molecule-1" [Mesh] OR intercellular adhesion molecule-1 [title/abstract]) AND ("atrial fibrillation" [Mesh] OR atrial fibrillation [title/abstract]). Grey or unpublished literature was identified manually by searching bibliographies.

Study selection and data extraction

We used Endnote X6 for organizing the studies. After removing duplicate records, studies were selected based on titles and abstracts by two independent researchers (M.T. and H.M.). Studies were then assessed for inclusion based on the full text, and data were extracted using a table in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Information was collected regarding study design, studied tissue, tissue staining, number of cases and controls, serum levels of VCAM-1 and ICAM-1, measurement methods, and the type of surgery that preceded the occurrence of AF.

Quality appraisal

We evaluated the quality of the included studies based on the Joanna Briggs Institute (JBI) checklists.[22] Two authors (L.N. and M.R.) completed

Table 1: Expression of endothelial adhesion molecules in patients with atrial fibrillation

Author, year, country	Study type	Purpose	No. of participants (AF/ non-AF)	Tissue	Methods (staining)	VCAM-1 expression changes	ICAM-1 expression changes
Begieneman et al.[26] 2015 Netherlands	Case–control	CML presence in the myocardium and fat tissue (AF)	AF: 33 Non-AF: 9	Left atrial appendage	Immunohistochemistry	Significant increased VCAM-1 blood vessels in the myocardium of patients with AF	Not specified
Yamashita et al.[17] 2010 Japan	Case–control	Local immunological responses in human atria during AF	11 persistent AF 5 SR with history of paroxysmal AF	Left atrial appendage	Immunostaining	VCAM-1 expression was observed more prominently in the vasculature and endocardium in AF VCAM-1 was not significantly different between SR and AF	ICAM-1 was observed in the vasculatures and atrial endocardium Endocardial expression was more evident in AF ICAM-1 was not significantly different between SR and AF
Breitenstein et al.[14] 2015 Switzerland	Cohort	Prothrombotic profile in the left atrial appendage of AF	5	Left atrial appendage	Immunoblotting / stimulated with TNF-α	Induction of VCAM-1 was more pronounced	Not specified
Bukowska et al.[27] 2008 Germany	Case–control	Mitochondrial function and Redox signalling in AF	AF: 13 Non-AF: 13	Atrial tissue	PCR and Western blotting	Not specified	Protein levels were significantly elevated during AF mRNA levels of ICAM-1 were only slightly elevated in AF
Goette et al.[10] 2008 Germany	Case–control	Angiotensin II receptor blockade effect on tachycardia-induced atrial adhesion molecule expression	AF: 61 Non-AF: 259	Right atrial appendage	PCR and Western blotting	VCAM-1 was increased in patients with AF compared with patients in SR	Not specified
Verdejo et al.[18] 2011 Chile	Prospective case–control	Role of systemic and tissue biomarkers in development of POAF	AF: 31 Non-AF: 112	Right atrial appendage	Immunohistochemistry	Tissue expression similar to control	Tissue expression similar to control

AF = atrial fibrillation; CML = (carboxymethyl)lysine; ICAM-1 = intercellular adhesion molecule-1; PCR = polymerase chain reaction; POAF = postoperative atrial fibrillation; SR = sinus rhythm; TNF = tumour necrosis factor; VCAM-1 = vascular cell adhesion molecule-1.

the quality assessments. Any disagreement during the process was resolved by consensus-based discussion or another researcher's comment (S.D.).

Data synthesis and analysis

The meta-analysis was performed following the Cochrane Collaboration recommendations, and the results were reported following the PRISMA statement.[20,23] The data were expressed as mean and standard deviation (SD). We used the formula by Hozo et al. to estimate the mean and SD for the data reported as median (min–max).[24] For estimating the SD in articles that reported data as median (Q1–Q3), we used the formula by Wan et al., and the median was considered to be equivalent to the mean.[25] The meta-analysis was conducted using Open Meta-Analyst® software (Brown University, RI, USA). We used the mean difference (MD) between patients with AF and those with normal SR to conduct the meta-analysis. A subgroup analysis of studies including only patients with persistent AF was also conducted. In addition, the range of EAMs in patients with AF was calculated using 95% confidence intervals (CIs). Heterogeneity was evaluated by I^2 statistics. Significant heterogeneity of results was acknowledged when an $I^2 \geq 50\%$. A p-value of <0.05 was considered statistically significant.

Results

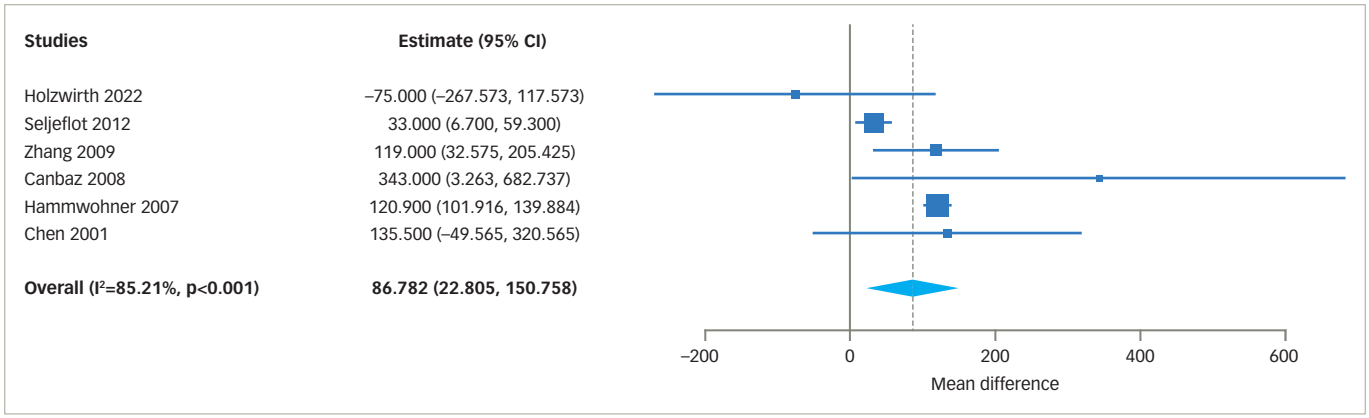
We identified 291 articles through the search from four databases. In addition, one article was found manually through references of other studies. After duplicates were removed, the titles and abstracts of 181 articles were analysed for eligibility. Eventually, 28 articles went through full-text screening, and six articles were excluded because they did not meet our eligibility criteria. The reasons for the exclusion of articles are presented in *Figure 1*. Finally, we included 22 studies in the systematic review.[4,6,10,12–15,17,18,26–38]

Table 2: Levels of endothelial adhesion molecules in patients with atrial fibrillation

Author, year, country	Study type	AF type	Sample size	Female % (AF)	Kit	ICAM-1 ng/mL (AF)	ICAM-1 ng/mL (non-AF)	p	VCAM-1 ng/mL (AF)	VCAM-1 ng/mL (non-AF)	p
Holzwirth et al.[32] 2022 Germany	Case–control	Both types	154	AF: 43.2% Non-AF: 53.8%	Luminex multiplex screening assay (R&D Systems/ bio-techne, Minneapolis, MN, USA)	n=21 Median: 330 (IQR: 273–412) SD: 152.94	n=13 Median: 294 (IQR: 254–362) SD: 120.28	0.330	n=21 Median: 840 (IQR: 699–1031) SD: 365.29	n=13 Median: 915 (IQR: 860–1116) SD: 207.11	0.208
Mendez et al.[29] 2021 USA	Cohort	Not specified	2504	Not specified	Quantitative sandwich ELISA	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Willeit et al.[28] 2017 Austria	Cohort	Both types	909	Not specified	ELISA kit (Bender MedSystems)	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Seljeflot et al.[13] 2012 Norway	Case–control	Persistent	186	AF: 29.0% Non-AF: 29.8%	R & D Systems Europe, Abingdon, UK	Not specified	Not specified	Not specified	Median: 865 (745–1067)	Median: 832 (734–980)	0.162
Scridon et al.[31] 2012 France	Case–control	Paroxysmal	48	AF: 17.9% Non-AF: 33.3%	Human sICAM-1/ CD54 Quantikine ELISA kits (R&D Systems/bio-techne)	178.5 ± 8.3	161.4 ± 15.8	0.36	Not specified	Not specified	Not specified
Scridon et al.[31] 2012 France	Case–control	Persistent	42	AF: 15.1% Non-AF: 33.33%	Human sICAM-1/ CD54 Quantikine ELISA kits (R&D Systems/bio-techne)	179.7 ± 7.0	161.4 ± 15.8	0.25	Not specified	Not specified	Not specified
Zhang et al.[4] 2009 China	Case–control	Paroxysmal	72	AF: 47.6% Non-AF: 43.3%	Human VCAM-1 ELISA kit (BioSource, Carlsbad, CA, USA)	Not specified	Not specified	Not specified	337 ± 250	218 ± 117	0.018
Canbaz et al.[30] 2008 Turkey	Prosp. case–control	Persistent	64	AF: 33.3% Non-AF: 20.6%	Standard ELISA	Not specified	Not specified	Not specified	1140 ± 414	797 ± 293	>0.05
Hammwöhner et al.[12] 2007 Germany	Case–control	Persistent	40	AF: 35.0% Non-AF: 40.0%	R&D Systems, Wiesbaden, Germany	232 ± 12.6	196.4 ± 7.65	≤0.05	800.0 ± 21.1	679.1 ± 37.83	≤0.05
Chen et al.[6] 2004 Taiwan	Case–control	Persistent	22	AF: 50.0% Non-AF: 37.5%	Diaclone; Besancon, France	670.8 ± 103.7	609.6 ± 111.9	>0.05	716.4 ± 221.6	580.9 ± 208.0	>0.05

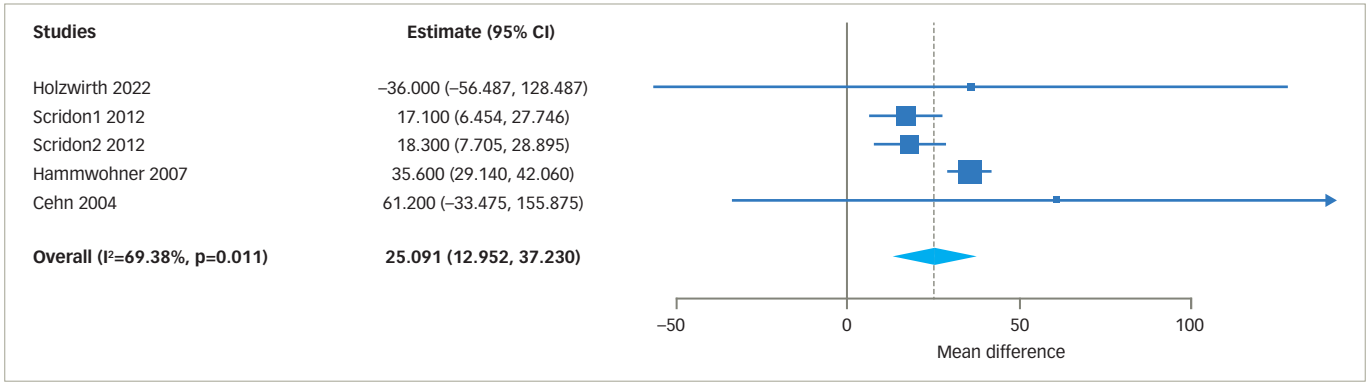
AF = atrial fibrillation; ELISA = enzyme-linked immunosorbent assay; ICAM-1 = intercellular adhesion molecule-1; IQR = interquartile range; Prosp. = prospective; SD = standard deviation; VCAM-1 = vascular cell adhesion molecule-1.

Figure 2: Forest plot for vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 levels were higher in patients with atrial fibrillation (mean difference 86.782; 95% CI 22.805–150.758; p=0.008)[4,6,12,13,30,32]



CI = confidence interval.

Figure 3: Forest plot for intercellular adhesion molecule-1 (ICAM-1). ICAM-1 levels were higher in patients with atrial fibrillation (mean difference 25.091; 95% CI 12.952–37.230; p<0.001)[6,12,31,32]



CI = confidence interval.

Tissue expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in patients with atrial fibrillation

Five articles discussed the changes in expression of VCAM-1 in atrial tissue of patients with AF (*Table 1*). Three studies[14,17,26] found an increase in VCAM-1 tissue expression in the left atrial appendage, while Goette et al.[10] found an increase in its tissue expression in the right atrial appendage and Verdejo et al.[18] reported similar tissue expression of VCAM-1 in right atrial appendage between patients with AF and the control group. Only three out of six articles reported alterations in ICAM-1 tissue expression in patients with AF. Two studies[17,27] reported increased ICAM-1 tissue expression in atrial tissue, and one study[18] did not find any increase in ICAM-1 tissue expression in the right atrial appendage.

Serum levels of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in patients with atrial fibrillation

Seven studies assessed serum levels of VCAM-1 and/or ICAM-1 in patients with AF compared with individuals with normal SR (*Table 2*). Two cohort studies[28,29] reported significantly higher levels of VCAM-1 in individuals who developed AF; however, levels of VCAM-1 in these two studies were only reported at baseline and were not specified for AF and SR cases separately. Six studies reported serum levels of VCAM-1 in both groups.[4,6,12,13,30,32]

A meta-analysis was carried out, and VCAM-1 levels were higher in patients with AF, with an MD of 86.782 (95% CI 22.805–150.758; p=0.008). The forest plot is depicted in *Figure 2*. In addition, the analysis revealed significant statistical heterogeneity among studies (p<0.001, I^2=85.208); the continuous random-effects model was therefore used. Four studies included persistent AF.[6,12,13,30] We performed a subgroup analysis for persistent AF, which revealed a significant difference between serum VCAM-1 levels in AF and SR groups (MD 98.046, 95% CI 26.582–169.510; p=0.007).

Four studies reported and compared serum levels of ICAM-1 between AF and SR groups. Two of them reported serum levels of ICAM-1 in persistent AF and paroxysmal AF.[31,32] Due to the identification of statistical heterogeneity (tau²=96.394, Q=13.063, df (4), p=0.011, I^2=69.379%) the continuous random-effects model was used. The results of meta-analysis were as follows: MD 25.091, 95% CI 12.952–37.230; p<0.001 (*Figure 3*). Subgroup meta-analysis comparing the level of ICAM-1 between persistent AF and SR groups was also associated with a significant difference (MD 28.439, 95% CI 12.540–44.338; p<0.001).

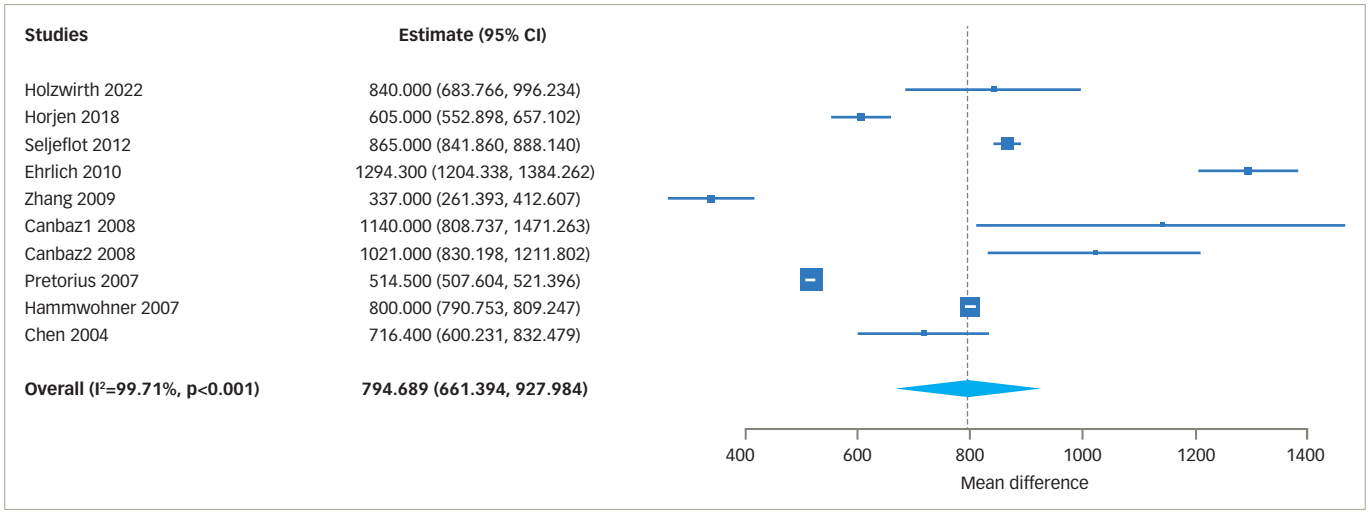
Five articles focused on the relationship of VCAM-1 and/or ICAM-1 with the generation of POAF (*Table 3*).[18,30,33–35] Only two or three reported levels for each of our variables, and because of the great diversity (preoperative and postoperative levels), we decided not to perform a meta-analysis.

Table 3: Levels of endothelial adhesion molecules in patients with postoperative atrial fibrillation

Author, year, country	Study type	Sample size	Female (AF/Non-AF)	Male (AF/Non-AF)	Kit	Sampling time	ICAM-1 ng/mL (AF/Non-AF)	p	VCAM-1 ng/mL (AF/Non-AF)	p
Harling et al.[34] 2017 UK	Prosp. case–control	34	AF: 4 Non-AF: 6	AF: 9 Non-AF: 15	Abcam® VCAM-1 (CD106) Human ELISA Kit (ab46118)	Preoperative	Not specified	Not specified	Not specified	0.022
Antoniades et al.[33] 2009 England	Prosp. case–control	144	AF: 9 Non-AF: 14	AF: 34 Non-AF: 87	R&D Systems, Wiesbaden, Germany	Preoperative	AF: Median: 324 (IQR 217–468) SD: 271.274 Non-AF: Median: 298 (IQR 225–514) SD: 313.0295	0.7	Not specified	Not specified
Verdejo et al.[18] 2011 Chile	Prosp. case–control	144	AF: 9 Non-AF: 23	AF: 23 Non-AF: 89	R&D Systems, Minneapolis, MN, USA	Preoperative	Not specified	Not specified	AF: 1135 ± 116 Non-AF: 785 ± 63	<0.05
Canbaz et al.[30] 2008 Turkey	Prosp. case–control	77	AF: 2 Non-AF: 12	AF: 11 Non-AF: 46	Standard ELISA	Preoperative and postoperative	Not specified	Not specified	AF: Preop: 902 ± 320 Postop: 1021 ± 351 Non-AF: Pre-op: 797 ± 293 Postop: 924 ± 424	>0.05
Pretorius et al.[35] 2007 USA	Prosp. case–control	253	AF: 19 Non-AF: 68	AF: 48 Non-AF: 118	LINCO Research, Inc.	Postoperative	AF: 55.5 ± 5.7 Non-AF: 52.8 ± 1.5	0.557	AF: 514.5 ± 28.8 Non-AF: 476.4 ± 12.4	0.164

AF = atrial fibrillation; ELISA = enzyme-linked immunosorbent assay; ICAM-1 = intercellular adhesion molecule-1; IQR = interquartile range; Prosp. = prospective; SD = standard deviation; VCAM-1 = vascular cell adhesion molecule-1.

Figure 4: Forest plot for vascular cell adhesion molecule-1 range (95% CI 661.394–927.984 ng/mL)[4,6,12,13,15,30,32,35,36]



CI = confidence interval.

Table 4: Levels of endothelial adhesion molecules in atrial fibrillation and postoperative atrial fibrillation patients

Author, year, country	Study type	Kit	AF type	No. of cases	ICAM-1 ng/mL in AF patients	VCAM-1 ng/mL in AF patients
Holzwirth et al.[32] 2022 Germany	Case–control	Luminex multiplex screening assay (R&D Systems/bio-techne, Minneapolis, MN, USA)	Both types	21	Median: 330 (IQR 273–412) SD: 152.94	Median: 840 (IQR 699–1031) SD: 365.29
Horjen et al.[36] 2018 Norway	Double-blind, placebo-controlled study	R&D System, Abingdon, Oxon, UK	Persistent	129	Not specified	Median 605 (IQR 497–776) SD: 301.9276541
Seljeflot et al.[13] 2012 Norway	Cross-sectional	R & D Systems Europe, Abingdon UK	Persistent	62	Not specified	Median: 865 (IQR 745–1067)
Scridon et al.[31] 2012 France	Case–control	Human sICAM-1/CD54 Quantikine ELISA kits (R&D Systems, Inc., Minneapolis, MN, USA)	Paroxysmal	39	178.5 ± 8.3	Not specified
Scridon et al.[31] 2012 France	Case–control	Human sICAM-1/CD54 Quantikine ELISA kits (R&D Systems, Inc., Minneapolis, MN, USA)	Persistent	33	179.7 ± 7.0	Not specified
Ehrlich et al.[15] 2011 Germany	Cohort	DRG Instruments GmbH, Marburg, Germany	Both types	278	Not specified	Mean: 1294.3 (SEM 45.9) SD: 765.30594
Conen et al.[37] 2010 USA	Cohort	R&D Systems, Minneapolis, MN, USA	Paroxysmal	747	Median: 342 (IQR 300–393) SD: 100.3741	Not specified
Zhang et al.[4] 2009 China	Case–control	Human VCAM-1 ELISA kit (BioSource, Carlsbad, CA, USA)	Paroxysmal	42	Not specified	337 ± 250
Girerd et al.[38] 2013 France	Cohort	Human sICAM-1/CD54Quantikine ELISA kits (R&D Systems, Inc., Minneapolis, MN, USA)	Paroxysmal	25	Median: 160.0 (IQR 137.5–207.5) SD: 76.39509	Not specified
Girerd et al.[38] 2013 France	Cohort	Human sICAM-1/CD54Quantikine ELISA kits (R&D Systems, Inc., Minneapolis, MN, USA)	Persistent	24	Median 174.0 (IQR 141.0–213.0) SD: 79.0234	Not specified
Canbaz et al.[30] 2008 Turkey	Prosp. case–control	Standard ELISA	Persistent	6	Not specified	1140 ± 414
Canbaz et al.[30] 2008 Turkey	Prosp. case–control	Standard ELISA	Paroxysmal	13	Not specified	1021 ± 351
Pretorius et al.[35] 2007 USA	Prosp. case–control	LINCO Research, Inc.	Paroxysmal	67	55.5 ± 5.7	514.5 ± 28.8
Hammwöhner et al.[12] 2007 Germany	Case–control	R&D Systems, Wiesbaden, Germany	Persistent	20	232 ± 12.6	800.0 ± 21.1
Chen et al.[6] 2004 Taiwan	Case–control	Diaclone; Besancon, France	Persistent	14	670.8 ± 103.7	716.4 ± 221.6

AF = atrial fibrillation; ELISA = enzyme-linked immunosorbent assay; ICAM-1 = intercellular adhesion molecule-1; IQR = interquartile range; Prosp. = prospective; SD = standard deviation; SEM = standard error or the mean; VCAM-1 = vascular cell adhesion molecule-1.

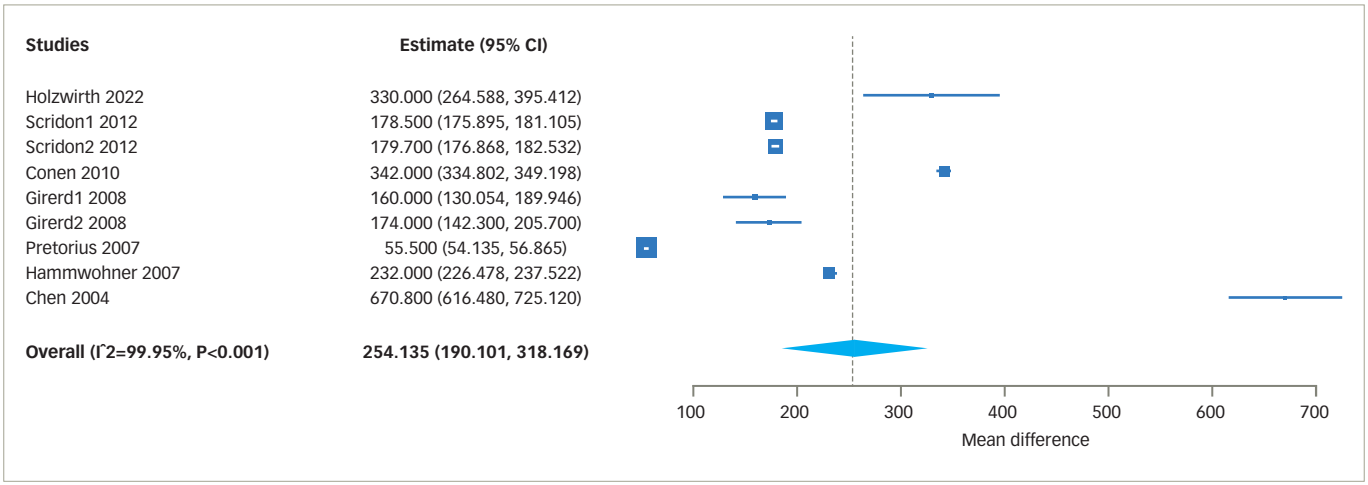
Only Harling et al. and Verdejo et al. reported a significant difference in serum levels of VCAM-1 between the SR group and the POAF group.[18,34] The remaining studies did not report a statistically significant difference between the two groups in terms of serum levels of VCAM-1 and/or ICAM-1.

Range of serum levels of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in patients with atrial fibrillation

We found 12 articles reporting levels of VCAM-1 and/or ICAM-1 in patients with AF (*Table 4*). We did not include the studies by Antoniades et al. and Verdejo et al. because their blood sampling for two markers was done preoperatively.[18,33] Across nine studies, the 95% CI of VCAM-1 in patients with AF was 661.394 to 927.984 ng/mL (*Figure 4*). The studies by Ehrlich et al.[15] and Holwirth et al.[32] did not specify the VCAM-1 levels for persistent and paroxysmal AF patients separately, and they could not be included in the subgroup analysis. The subgroup analysis for persistent AF resulted in a VCAM-1 range of 694.260 to 847.743 ng/mL.

We also determined the 95% CI of the serum levels of ICAM-1 in patients with AF, which was 190.101 to 318.169 ng/mL (*Figure 5*). We

Figure 5: Forest plot for intercellular adhesion molecule-1 range (95% CI 190.101–318.169 ng/mL)[6,12,31,32,35,37,38]



CI = confidence interval.

also conducted a subgroup analysis of studies including only patients with persistent AF, which showed a much narrower range of ICAM-1 (95% CI 242.945–349.817 ng/mL).

Bias risk within studies

All of the studies were of good quality according to JBI checklists. The results of the quality analysis are presented in *Tables 5–7*. The mean score for cohort studies was 10.5 (maximum score=11). In addition, 9.18 (maximum score=10) was the mean score for included case–control studies. The study by Horjen et al. was a derivation of the trial, and it was assessed by checklist for randomized controlled trials and scored 12 out of 13.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating VCAM-1 and ICAM-1 serum levels and tissue expression in patients with AF. In addition, we aimed to examine the effect of these markers in the development of AF in different situations. Our study showed a statistically significant difference between serum levels of the two markers in patients with AF and SR. These results point out that if the cause–effect relationship is proven in future studies, it may be helpful to assess the serum levels of these markers in patients at high risk for AF development, in order to consider the pharmacological and non-pharmacological actions for prevention. We also analysed the serum levels of ICAM-1 and VCAM-1 and reported an estimated range of these markers in patients with AF. In order to do this, we did not include preoperative levels in studies conducted by Antoniades et al.[33] and Verdejo et al.[18] as these levels were reported when AF diagnosis had not been confirmed.

AF has a high economic burden, which imposes a high cost on patients and the healthcare system. Numerous conditions such as increased age, alcohol consumption, heart failure and low vitamin D levels have been linked to AF. VCAM-1 and ICAM-1 have increased endocardial expression, and this may be the link between the inflammation and prothrombotic states responsible for the development of thrombus in the atrium.[39,40]

VCAM-1 and ICAM-1 are parts of the immunoglobulin superfamily that are associated with the inflammatory process. These molecules are responsible for cell adhesion and trans-endothelial migration of macrophage-like and dendritic cells.[41] In contrast to ICAM-1, studies have suggested non-constitutive expression of VCAM-1 (i.e. it is only induced in the activated endothelium).[42] VCAM-1 is upregulated whenever there is inflammation, mediating the adhesion of immune cells to the endothelium.[36] Their role in different cardiac diseases is now under research. VCAM-1 is linked to congestive heart failure, coronary artery disease and rheumatic heart disease, and ICAM-1 is associated with hypertension.[6,7,19] VCAM-1 has been reported to have an increased expression in patients with AF[10,17,26] and is more pronounced when induced by tumour necrosis factor-α (TNF-α).[14] Increased levels of inflammatory markers in AF suggest inflammation as one of the major bases of the development and perpetuation of this condition.[43] The adhesion of circulating leukocytes to the vascular endothelium leads to leukocyte extravasation during inflammation. This process depends on an interaction between VCAM-1 and ICAM-1 and the leukocytes;[40,44] therefore, increased levels of these endothelial factors in inflammatory responses such as AF is not unexpected.

There is controversy regarding the link between EAMs and AF. While Seljeflot et al. reported no association between VCAM-1 and AF in a case–control study consisting of 62 AF cases and 124 SR individuals,[13] Zhang et al. found a statistically significant difference between the two groups in serum levels of VCAM-1.[4] The study by Holzwirth et al. found lower levels of VCAM-1 but higher levels of ICAM-1 in the AF group compared with the SR group; however, these results were not statistically significant.[32] Two studies found a significant difference between AF and SR groups in serum levels of VCAM-1.[4,12] Multivariate analysis in the studies by Zhang et al. and Conen et al. found VCAM-1 and ICAM-1, respectively, to be independent factors in AF generation.[4,37] One study reported VCAM-1 as an independent predictor for atrial thrombi.[12] Ehrlich et al. showed that VCAM-1 is independently associated with myocardial infarction, stroke, peripheral embolism or mortality.[15] The high heterogeneity seen in the current meta-analysis may be due to different commercial enzyme-linked immunosorbent assay kits used in included studies.

As shown in *Table 6*, in some of the included case–control studies, cases and controls did not match appropriately. This was the main point that should be considered when analysing the results of the study conducted by Chen et al.[6] This study consisted of three groups. The main group included 19 patients with symptomatic mitral stenosis going through mitral valvuloplasty (four patients with SR and 15 patients with chronic AF), and the authors compared this group with two other groups (22 control patients: 14 healthy individuals with SR and eight patients with chronic lone AF). The first group was a heterogeneous group regarding

Table 5: Risk of bias in cohort studies, based on Joanna Briggs Institute's critical appraisal tool for cohort studies

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Sum
Mendez et al.[29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Willeit et al.[28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Harling et al.[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Canbaz et al.[30]	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Antoniades et al.[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Conen et al.[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Ehrlich et al.[15]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
Verdejo et al.[18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Breitenstein et al.[14]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
Pretorius et al.[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Table 6: Risk of bias in case–control studies, based on Joanna Briggs Institute's critical appraisal tool for case–control studies

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Sum
Holzwirth et al.[32]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
Seljeflot et al.[13]	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	9
Scridon et al.[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Zhang et al.[4]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Hammwöhner et al.[12]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Girerd et al.[38]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Chen et al.[6]	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8
Begieneman et al.[26]	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8
Bukowska et al.[27]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
Yamashita et al.[17]	Y	U	Y	Y	Y	Y	N	Y	Y	Y	8
Goette et al.[10]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

the serum levels of ICAM-1 and VCAM-1, and they should not have been considered in one group.

Regarding POAF, two studies reported a significant difference in serum levels of VCAM-1 between patients with POAF and the SR group.[18,34] Canbaz et al.[30] found a difference in VCAM-1 levels in preoperative and postoperative samplings in the SR group, and Harling et al. reported a significant reduction in VCAM-1 levels in both AF and POAF groups 48 hours after surgery. Nevertheless, the interesting point is that Canbaz et al. reported a significant increase, whereas Harling et al. found a reduction in VCAM-1 levels after surgery.[30,34] It has been shown that VCAM-1 levels significantly correlate with age and white blood cell count.[12,18] These data suggest a complicated mechanism in cardiac surgery that involves inflammation cascades and is closely related to the most important risk factor in the development of AF: age.[45] Harling et al. and Verdejo et al. found VCAM-1 to be an independent factor in the generation of POAF.[18,34]

To our knowledge, a range for VCAM-1 and ICAM-1 has not previously been reported in patients with AF. We analysed all of the studies that reported serum VCAM-1 and ICAM-1 levels in patients with AF (without considering the type of AF) and reported the 95% CIs for serum levels of the markers. The highest levels of VCAM-1 and ICAM-1 were reported by Canbaz et al.[30] and Chen et al.,[6] respectively, whereas the lowest levels of VCAM-1 and ICAM-1 were reported by Zhang et al.[4] and Pretorius et al.,[35] respectively.

Table 7: Risk of bias in randomized clinical trial study, based on Joanna Briggs Institute's critical appraisal tool for randomized clinical trial studies

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Sum
Horjen et al.[36]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomized?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

There are some limitations to our study. First, observational studies cannot prove a causative relationship, and all included studies were observational. Second, the possibility of publication bias was not evaluated because of the small number of studies. Third, only studies in the English language were included; therefore, some valuable sources of evidence may have been missed. Fourth, we could not perform a meta-analysis to assess the relationship of VCAM-1 and ICAM-1 with POAF. Finally, differences in the kits utilized for VCAM-1 and ICAM-1 level assessment were not considered in our final analyses. Several homogeneous studies that have a similar sampling pattern are needed to assess this relationship. Despite these limitations, we were able to conduct this study, and we believe this meta-analysis draws attention to the importance of serum VCAM-1 and ICAM-1 levels in predicting and preventing AF, especially POAF.

Conclusion

This systematic review and meta-analysis suggested a positive relationship between serum VCAM-1 and ICAM-1 levels and AF, especially persistent AF. Furthermore, the expression of these markers is increased in human cardiac tissue. The relationship between these markers and POAF needs to be evaluated with large-scale studies that use the same methodology. ❑

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