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Incidence of Acute Cerebrovascular Events in Patients with Rheumatic or Calcific Mitral Stenosis: A Systematic Review and Meta-analysis

Short Title: *Thromboembolic Events in Mitral Stenosis*

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Incidence of Acute Cerebrovascular Events in Patients with Rheumatic or Calcific Mitral Stenosis: A Systematic Review and Meta-analysis

POPULATION

Systematic search for patients with **mitral stenosis** (**MS**) or **mitral annular calcification** (**MAC**), with or without **atrial fibrillation** (**AF**)

16 studies included
43,986 **MS** patients; 2,296 **MAC** patients

OUTCOMES OF INTEREST

Incidence of:

- **Stroke/ transient ischaemic attack** (**TIA**)
- **Peripheral thromboembolic events** (**TEE**)
- **Composite acute cerebrovascular events** (**ACE**) which includes Stroke/ TIA and peripheral TEE

in **rheumatic MS (rMS)**, **calcific MS** & **MAC**

RESULTS

ACE: Pooled incidence of **8.30%** (95% CI 3.45-18.63; I^2=96%) among **MS** patients

Incidence of **ACE** in **MAC** patients **14.85%** (95% CI 7.21-28.11; I^2=98%)

Incidence of **ACE** in **MS** patients **4.92%** (95% CI 3.53-6.83; I^2=38%)

Incidence of **ACE** in **MS** patients with **AF** **31.55%** (95% CI 3.60-85.03; I^2=99%)

The logit-transformed proportion of ACE increased by **0.0141** per **year of follow-up**

CONCLUSION

- High **stroke/ TIA** (7.11%) and composite **ACE** (8.30%) incidences were reported in **MS** patients
- Concomitant **AF** and **MAC** are risk factors for the development of **ACE** in the **MS** population
- Further research is needed to investigate the thromboembolic risks in **rheumatic** and **calcific MS** subtypes

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Abbreviations

ACE	Acute cerebrovascular events
AF	Atrial fibrillation
CI	Confidence interval
I^2	Heterogeneity
MAC	Mitral annular calcification
MS	Mitral stenosis
NOAC	Non-vitamin K oral anticoagulant
NOS	Newcastle Ottawa Scale
RHD	Rheumatic heart disease
TEE	Thromboembolic event
TIA	Transient ischaemic accident

Abstract

Background

Patients with mitral stenosis (MS) may be predisposed to acute cerebrovascular events (ACE) and peripheral thromboembolic events (TEE). Concomitant atrial fibrillation (AF), mitral annular calcification (MAC) and rheumatic heart disease (RHD) are independent risk factors. Our aim was to evaluate the incidence of ACEs in MS patients and the implications of AF, MAC, and RHD on thromboembolic risks.

Methods

This systematic review was registered on PROSPERO (*CRD42021291316*). Six databases were searched from inception to 19th December 2021. The clinical outcomes were composite ACE, ischaemic stroke/transient ischaemic attack (TIA), and peripheral TEE.

Results

We included 16 and 9 papers, respectively, in our qualitative and quantitative analyses. The MS cohort with AF had the highest incidence of composite ACE (31.55%; 95%CI 3.60-85.03; I^2=99%), followed by the MAC (14.85%; 95%CI 7.21-28.11; I^2=98%), overall MS (8.30%; 95%CI 3.45-18.63; I^2=96%) and rheumatic MS population (4.92%; 95%CI 3.53-6.83; I^2=38%). Stroke/TIA were reported in 29.62% of the concomitant AF subgroup (95%CI 2.91-85.51; I^2=99%) and in 7.11% of the overall MS patients (95%CI 1.91-23.16; I^2=97%). However, the heterogeneity of the pooled incidence of clinical outcomes in all groups, except the rheumatic MS group, were substantial and significant. The logit-transformed proportion of composite ACE increased by 0.0141 (95% CI 0.0111-0.0171; $p<0.01$) per year of follow-up.

Conclusion

In the MS population, MAC and concomitant AF are risk factors for the development of ACE. The scarcity of data in our systematic review reflects the need for further studies to explore thromboembolic risks in all MS subtypes.

Keywords: mitral stenosis, ischaemic stroke, incidence

1. Introduction

Patients with mitral stenosis (MS) may be predisposed to acute cerebrovascular events (ACE). Concomitant atrial fibrillation (AF), mitral annular calcification (MAC) and rheumatic heart disease (RHD) are independent risk factors.[1–3] Our study aimed to evaluate the incidence of of ACE in MS patients and the implications of AF, MAC, and RHD on thromboembolic risks. We also aimed to compare the risk of ACE between the different subtypes of MS (calcific and rheumatic). Our secondary objective was to examine non-stroke clinical event such as peripheral thromboembolic events (TEE) in this population.

2. Methods

2.1 Study Protocol & Search Strategy

The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; *CRD42021291316*). A systematic search of PubMed, Scopus, Embase, Medline, Web of Science, and Cochrane Library databases was performed from inception to 19th December 2021. *Supplemental Methods* details our search strategy. Baseline characteristics of all patients in the included studies are presented in *Supplemental Tables S1* and *S2*.

2.2 Assessment of Study Quality and Risk of Bias

The quality of the included studies was evaluated using Newcastle-Ottawa Scale (NOS) (*Supplemental Tables S4, S5 and S6)*.

2.3 Data Analysis

The included studies were analysed using *R* software *version 4.2.0* (*R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/*) to assess effect size (ES), its associated 95% confidence intervals (CI), the between-study variance (τ2) and the appropriateness of combining studies (I^2 statistic). Packages used for the analyses included *dplyr*, *meta* and *metafor*. Random effects model was employed, and forest plots were plotted. A cut-off of >50% heterogeneity with the I^2 statistic was deemed to be significant. A *p-value* of <0.05 was considered

statistically significant. A sensitivity analysis was performed to explore the source of high heterogeneities by excluding low-quality studies. We also performed meta-regression analyses to adjust our results to the follow-up period in each study.

3. Results

3.1 Study Selection

We included 16 and 9 papers, respectively, in our qualitative and quantitative analyses. The detailed study selection process is depicted in a preferred reporting items for systematic reviews and meta-analysis (*PRISMA*) diagram *(Fig 1).*

3.2 Quantitative Analysis

3.2.1 Acute cerebrovascular events in the overall MS population

Seven studies[4–8,11,16] with a pooled population of 43,522 patients reported 7,085 composite ACE events, with an incidence of 8.30% (95%CI 3.45-18.63). The included studies were of considerable heterogeneity with an I^2 of 96% (*Fig 2a*). The pooled incidence of stroke/TIA (*Fig 2b)* across five studies was 7.11% (95%CI 1.91-23.16).[4,7,8,11,16], with significant and substantial heterogeneity (I^2=97%). There were only three articles[6,8,16] (n=927) which studied peripheral TEE as an outcome within the MS population *(Fig 2c)*, with an overall incidence of 1.86% (95%CI 0.81-4.24; I^2=74%) and significant heterogeneity.

3.2.2 Acute cerebrovascular events in the MS population with AF

In terms of composite ACE (Supplemental *Fig S1a*), two studies[11,16] which consisted of 566 MS patients with AF reported a pooled incidence of 31.55% (95%CI 3.60-85.03). However, considerable heterogeneity was noted with an I^2 of 99%. The incidence of stroke/TIA was 29.62% (95%CI 2.91-85.51) with an I^2 of 99%.

3.2.3 Acute cerebrovascular events in the MAC subgroup

Three studies[11–13] investigated the outcomes of stroke/TIA in patients with MAC (n=1,762) and reported a pooled incidence of 14.85% (95%CI 7.21-28.11*; I^2*=98%), illustrated in *Supplemental Fig S1b*.

3.2.4 Acute cerebrovascular events in the rheumatic MS subgroup

Three studies[4,6,7] described a total of 36 composite ACE events in 730 patients with rheumatic MS (*Supplemental Fig S1c*). The pooled incidence rate was 4.92% (95%CI 3.53-6.83), with low heterogeneity (I^2=38%; p=0.20). The analysis of the outcome of stroke/TIA (*Supplemental Fig S1d)* in two relevant studies[4,7] revealed the overall incidence was 5.45% (95%CI 3.51-8.36; I^2=56%; p=0.13).

3.3 Sensitivity Analysis & Meta-regression

We performed a sensitivity analysis by excluding low-quality studies such as Aronow 1998[11] and Pengo 2003[8]. After the removal of these two papers (*Supplemental Figure S2)*, the incidence of composite ACE in the overall MS population (n=43,332) was down to 7.00% (95% CI 4.16-11.53), but the heterogeneity remained significant (I^2 of 96%; *p<0.01)*.[4–7,16] Exclusion of low-quality studies in the MAC population (n=817) revealed a composite ACE pooled incidence of 9.32% (95% CI 6.21-13.76), with reduced but still significant heterogeneity (I^2= 81%; *Supplemental Figure S3)*.[12,13]

A meta-regression analysis was conducted to further explore the source of high heterogeneity in the overall MS population among the five studies[4–7,16]. The logit-transformed proportion of composite ACE increased by 0.0141 (95% CI 0.0111-0.0171; *p<0.01*) per year of follow-up (*Supplemental Fig S4*).

4. Discussion

Our meta-analysis revealed high stroke/TIA (7.11%) and composite ACE (8.30%) incidences in MS patients. The pooled incidence of stroke/TIA in MS patients with concomitant AF was 29.62%, and that in MAC (without MS) patients was 14.85%. The incidence of stroke/TIA in rheumatic MS was 5.45%, similar to the overall MS population.

In our study, we found a similar incidence (14.85%) of stroke/TIA in our pooled MAC population, whilst only 7.11% of the overall MS cohort experienced stroke/TIA. However, similar to the previous studies[3,17], our study did not directly compare the incidence of ischaemic events between both MAC and the overall MS populations. Therefore, our results could only suggest that MAC may confer a higher risk for

ischaemic events than the overall MS cohort but were unable to quantify the actual risk difference. Prospective studies directly comparing the incidence in both groups are needed to verify this claim.

Limitations of our systematic review include the high heterogeneities across our results where we ran sensitivity and meta-regression analyses to explore their source and the underreporting of anticoagulation usage within the patient populations.

5. Conclusion

MAC and concomitant AF in the MS population are significant risk factors for the development of ACE. The scarcity of data in our systematic review reflects the need for further studies to explore thromboembolic risks in the rheumatic and calcific subtypes of MS.

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[INSERT FIGURE 1]

Fig 1 PRISMA diagram of the systematic literature search

[INSERT FIGURE 2a-c]

Fig 2a-c Summary data and pooled effect size of **cerebrovascular outcomes** in the overall mitral stenosis population (a: composite acute cerebrovascular events; b: ischaemic stroke/ transient ischaemic attack; c: peripheral thromboembolic event) CI: Confidence interval; I^2: I-squared of statistic of heterogeneity; τ2: between-study variance; *p*: *p*-value