

# Journal Pre-proof

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

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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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146

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148

149 **Abbreviations**

150	ACE	Acute cerebrovascular events
151	AF	Atrial fibrillation
152	CI	Confidence interval
153	$I^2$	Heterogeneity
154	MAC	Mitral annular calcification
155	MS	Mitral stenosis
156	NOAC	Non-vitamin K oral anticoagulant
157	NOS	Newcastle Ottawa Scale
158	RHD	Rheumatic heart disease
159	TEE	Thromboembolic event
160	TIA	Transient ischaemic accident
161		

162 **Abstract**

163 **Background**

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

170

171 **Methods**

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

176

177 **Results**

178 We included 16 and 9 papers, respectively, in our qualitative and quantitative  
179 analyses. The MS cohort with AF had the highest incidence of composite  
180 ACE (31.55%; 95%CI 3.60-85.03;  $I^2=99\%$ ), followed by the MAC (14.85%; 95%CI  
181 7.21-28.11;  $I^2=98\%$ ), overall MS (8.30%; 95%CI 3.45-18.63;  $I^2=96\%$ ) and rheumatic  
182 MS population (4.92%; 95%CI 3.53-6.83;  $I^2=38\%$ ). Stroke/TIA were reported in  
183 29.62% of the concomitant AF subgroup (95%CI 2.91-85.51;  $I^2=99\%$ ) and in 7.11%  
184 of the overall MS patients (95%CI 1.91-23.16;  $I^2=97\%$ ). However, the heterogeneity  
185 of the pooled incidence of clinical outcomes in all groups, except the rheumatic MS  
186 group, were substantial and significant. The logit-transformed proportion of  
187 composite ACE increased by 0.0141 (95% CI 0.0111-0.0171;  $p<0.01$ ) per year of  
188 follow-up.

189

190 **Conclusion**

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

194

195 **Keywords:** mitral stenosis, ischaemic stroke, incidence

## 196 **1. Introduction**

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

205

## 206 **2. Methods**

### 207 *2.1 Study Protocol & Search Strategy*

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

215

### 216 *2.2 Assessment of Study Quality and Risk of Bias*

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

219

### 220 *2.3 Data Analysis*

221 The included studies were analysed using *R* software version 4.2.0 (*R Core Team*  
222 (2021). *R: A language and environment for statistical computing. R Foundation for*  
223 *Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>) to assess  
224 effect size (ES), its associated 95% confidence intervals (CI), the between-study  
225 variance ( $\tau^2$ ) and the appropriateness of combining studies ( $I^2$  statistic). Packages  
226 used for the analyses included *dplyr*, *meta* and *metafor*. Random effects model was  
227 employed, and forest plots were plotted. A cut-off of >50% heterogeneity with  
228 the  $I^2$  statistic was deemed to be significant. A *p-value* of <0.05 was considered*

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

232

### 233 **3. Results**

#### 234 *3.1 Study Selection*

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

238

#### 239 *3.2 Quantitative Analysis*

##### 240 *3.2.1 Acute cerebrovascular events in the overall MS population*

241 Seven studies[4–8,11,16] with a pooled population of 43,522 patients reported 7,085  
242 composite ACE events, with an incidence of 8.30% (95%CI 3.45-18.63). The  
243 included studies were of considerable heterogeneity with an  $I^2$  of 96% (*Fig 2a*). The  
244 pooled incidence of stroke/TIA (*Fig 2b*) across five studies was 7.11% (95%CI 1.91-  
245 23.16).[4,7,8,11,16], with significant and substantial heterogeneity ( $I^2=97%$ ). There  
246 were only three articles[6,8,16] (n=927) which studied peripheral TEE as an outcome  
247 within the MS population (*Fig 2c*), with an overall incidence of 1.86% (95%CI 0.81-  
248 4.24;  $I^2=74%$ ) and significant heterogeneity.

249

##### 250 *3.2.2 Acute cerebrovascular events in the MS population with AF*

251 In terms of composite ACE (*Supplemental Fig S1a*), two studies[11,16] which  
252 consisted of 566 MS patients with AF reported a pooled incidence of 31.55% (95%CI  
253 3.60-85.03). However, considerable heterogeneity was noted with an  $I^2$  of 99%. The  
254 incidence of stroke/TIA was 29.62% (95%CI 2.91-85.51) with an  $I^2$  of 99%.

255

##### 256 *3.2.3 Acute cerebrovascular events in the MAC subgroup*

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

260

##### 261 *3.2.4 Acute cerebrovascular events in the rheumatic MS subgroup*

262 Three studies[4,6,7] described a total of 36 composite ACE events in 730 patients  
263 with rheumatic MS (*Supplemental Fig S1c*). The pooled incidence rate was 4.92%  
264 (95%CI 3.53-6.83), with low heterogeneity ( $I^2=38\%$ ;  $p=0.20$ ). The analysis of the  
265 outcome of stroke/TIA (*Supplemental Fig S1d*) in two relevant studies[4,7] revealed  
266 the overall incidence was 5.45% (95%CI 3.51-8.36;  $I^2=56\%$ ;  $p=0.13$ ).

267

### 268 3.3 Sensitivity Analysis & Meta-regression

269 We performed a sensitivity analysis by excluding low-quality studies such as Aronow  
270 1998[11] and Pengo 2003[8]. After the removal of these two papers (*Supplemental*  
271 *Figure S2*), the incidence of composite ACE in the overall MS population ( $n=43,332$ )  
272 was down to 7.00% (95% CI 4.16-11.53), but the heterogeneity remained significant  
273 ( $I^2$  of 96%;  $p<0.01$ ). [4–7,16] Exclusion of low-quality studies in the MAC population  
274 ( $n=817$ ) revealed a composite ACE pooled incidence of 9.32% (95% CI 6.21-13.76),  
275 with reduced but still significant heterogeneity ( $I^2=81\%$ ; *Supplemental Figure*  
276 *S3*). [12,13]

277

278 A meta-regression analysis was conducted to further explore the source of high  
279 heterogeneity in the overall MS population among the five studies[4–7,16]. The logit-  
280 transformed proportion of composite ACE increased by 0.0141 (95% CI 0.0111-  
281 0.0171;  $p<0.01$ ) per year of follow-up (*Supplemental Fig S4*).

282

## 283 4. Discussion

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

289

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

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

298

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

303

## 304 **5. Conclusion**

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

309

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311

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313 study conception and design: **QZS, BYP, TTSY, JSYH, BYQT, LLLY, CHS**; data  
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319

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321

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326 publication.

327 **References**

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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;  $\tau^2$ : between-study variance;  $p$ :  $p$ -value



