

Supplementary material

Risk of Infective Endocarditis in patients with Mitral Valve Prolapse: Systematic review with meta-analysis

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Supplementary material 1 - Databases and search strategies

EBM Reviews - **Cochrane Central Register of Controlled Trials January 2022**, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 14, 2022

#	Searches
1	exp mitral valve prolapse/
2	(mitral adj4 prolapse).af.
3	(mitral adj4 floppy).af.
4	mitral AJD4 myxomatous.af.
5	1 or 2 or 3 or 4
6	endocarditis.af.
7	exp endocarditis/
8	6 or 7
9	5 and 8

Web of Science Core Collection

Mitral (all fields) and prolapse (all fields) and endocarditis

SciELO Citation Index

Mitral (topic) and prolapse (topic) and endocarditis (topic)

Supplementary material 2 – Main characteristics of the included case-control studies

Author, year	Cases demographic data	Cases characteristics	IE criteria	Confounding factors for IE	Control selection	MVP criteria
Clemens, 1982	Yale – New Haven Hospital (November 1976 – November 1980)	32 men, 41 women Mean age: 47 ± 18 years	<ul style="list-style-type: none"> Pathological documentation Clinical criteria (heart murmur + 2 positive blood cultures + peripheral stigmata / laboratory evidence) 	<ul style="list-style-type: none"> Exclusion of patients with HD antecedents No exclusion of patients with previous dental work Posterior analysis of IDUs 	Adult inpatients undergoing echocardiography	Systolic leaflet displacement ≥2mm
Danchin, 1989	CHRU de Nancy – Brabois (January 1981 – January 1986)	33 men, 14 women Mean age: 55.0 years	<ul style="list-style-type: none"> Pathological documentation Fever + 2 major clinical criteria Fever + 1 major + 3 minor clinical criteria <p>(major criteria: 2 positive blood cultures, new heart murmur, vegetation on echocardiography; minor criteria: arterial embolism, immunologic disorders, splenomegaly, regurgitation murmur, clinical signs of vasculitis, CHF, pre-existing HD)</p>	No exclusion of patients with HD antecedents, patients with previous dental work or IDUs	Subjects < 60 years undergoing routine echo + patients admitted for surgery of the limb	Abnormal arc of one / both mitral leaflets above the level of the mitral valve annulus into the left atrium
Devereux, 1986	New York Hospital – Cornell Medical Center (November 1978 – December 1982)	49 men, 18 women Mean age: 38 ± 14 years	<ul style="list-style-type: none"> Positive blood cultures <p>(one patient only had clinical criteria – fever, arthralgias, rash, anemia, hematuria, elevated ESR)</p>	No exclusion of patients with previous dental work Posterior analysis of patients with HD antecedents or IDUs	Randomly selected subjects + Patients undergoing echocardiography + Unselected subjects with MVP	Systolic leaflet displacement ≥2mm
Hickey, 1985	Prince Henry and Prince of Wales Hospital Group (January 1976 – January 1984)	32 men (51 ± 15 years) 24 women (45 ± 21 years)	<ul style="list-style-type: none"> Heart murmur + two positive blood cultures Pathological documentation + evidence of infection (pyrexia, embolism, immune complexes) 	<ul style="list-style-type: none"> Exclusion of patients with HD antecedents No exclusion of patients with previous dental work Posterior analysis of IDUs 	Inpatients undergoing echocardiography	Leaflet displacement ≥2mm or pansystolic posterior displacement ≥ 3mm with mitral leaflet echoes
Strom, 1998	Delaware Valley Case-Control Network (August 1988 – November 1990)	Sex: N/A Mean age: 59.1 ± 17.1 years	<ul style="list-style-type: none"> Clinical judgment per review of medical records 	No exclusion of patients with HD antecedents, patients with previous dental work or IDUs	Community control using the Waksberg random-digit dialing method	N/A (interview)

CHF – congestive heart failure; ESR – Erythrocyte Sedimentation Rate; HD – heart disease; IDUs – intravenous drug users; IE – infective endocarditis; MVP – mitral valve prolapse

Supplementary material 3 - Main characteristics of the included cohort studies

Author, year	Demographic data	Characteristics of MVP cohort	MVP criteria	Characteristics of IE cases	IE criteria	Confounding factors for IE
Katan, 2016	Olmsted County residents with MVP (January 1989 – December 1998)	331 men, 565 women Mean age: 53 ± 21 years Follow-up period: 11 ± 5 years	Systolic leaflet displacement ≥2mm	3 men, 5 women Mean age: 62 ± 22 years	Modified Duke criteria	No exclusion of patients with HD antecedents, patients with previous dental work or IDUs

HD – heart disease; IDUs – intravenous drug users; IE – infective endocarditis; MVP – mitral valve prolapse

Supplementary material 4 – Risk of Bias assessment

Newcastle – Ottawa Scale	Selection				Comparability	Exposure / Outcome			Total
	1	2	3	4	1	1	2	3	
Clemens, 1982	0	1	0	1	1	1	1	1	6
Danchin, 1989	1	1	1	1	1	1	1	1	8
Devereux, 1986	1	1	1	1	1	1	1	1	8
Katan, 2016	1	1	1	1	2	0	1	1	8
Hickey, 1985	1	1	0	1	1	1	1	1	7
Strom, 1998	0	1	1	1	2	0	1	0	6

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE: CASE CONTROL STUDIES

Selection:

- 1) Case definition adequate: 1 point if IE diagnosis confirmed with echocardiographic or pathologic findings; 0 points if only based on medical records
- 2) Representativeness of the cases: 1 point if representative case series; 0 if potential for selection bias
- 3) Selection of controls: 1 point if community controls; 0 points if hospital controls or no description
- 4) Definition of controls: 1 point if no history of IE

Comparability: 1 point if study adjusted for age and sex; 1 more point if study adjusted for any other important risk factors

Exposure:

- 1) Ascertainment of exposure: 1 point if validation of MVP with echocardiography based on current criteria; 0 points if medical record only or self report
- 2) Same method of ascertainment for cases and controls: 1 point if yes
- 3) Non-response rate: 1 point if same rate for both groups

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE: COHORT STUDIES

Selection:

- 1) Representativeness of exposed cohort: 1 point if study population truly or somewhat representative of a community/population-based study; 0 if study population was sampled from a special population or not described
- 2) Selection of non-exposed cohort: 1 point if drawn from the same community as the exposed cohort; 0 if different community or not described
- 3) Ascertainment of exposure: 1 point if validation of MVP with echocardiography based on current criteria
- 4) Demonstration that outcome was not present at start of study: 1 point if IE diagnosis followed the MVP diagnosis

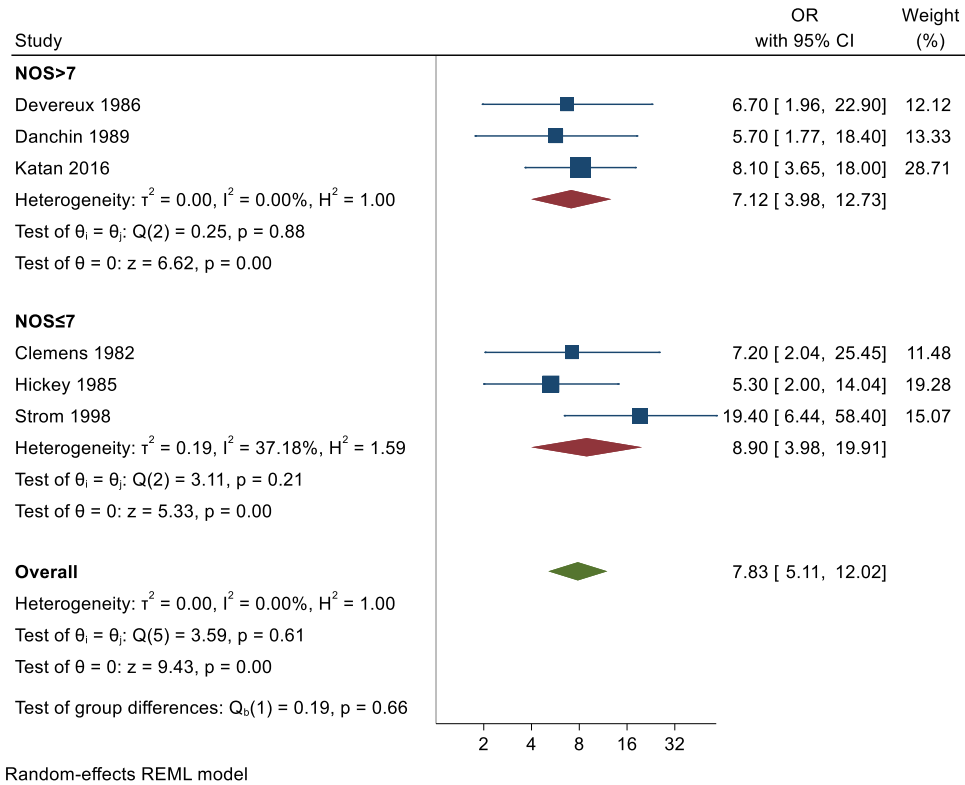
Comparability: 1 point if study adjusted for age and sex; 1 more point if study adjusted for any other important risk factors

Outcome:

- 1) Assessment of outcome: 1 point if IE diagnosis confirmed by echocardiographic or pathologic findings; 0 if only based on medical

Supplementary material 5 – Forest plot for NOS subgroups

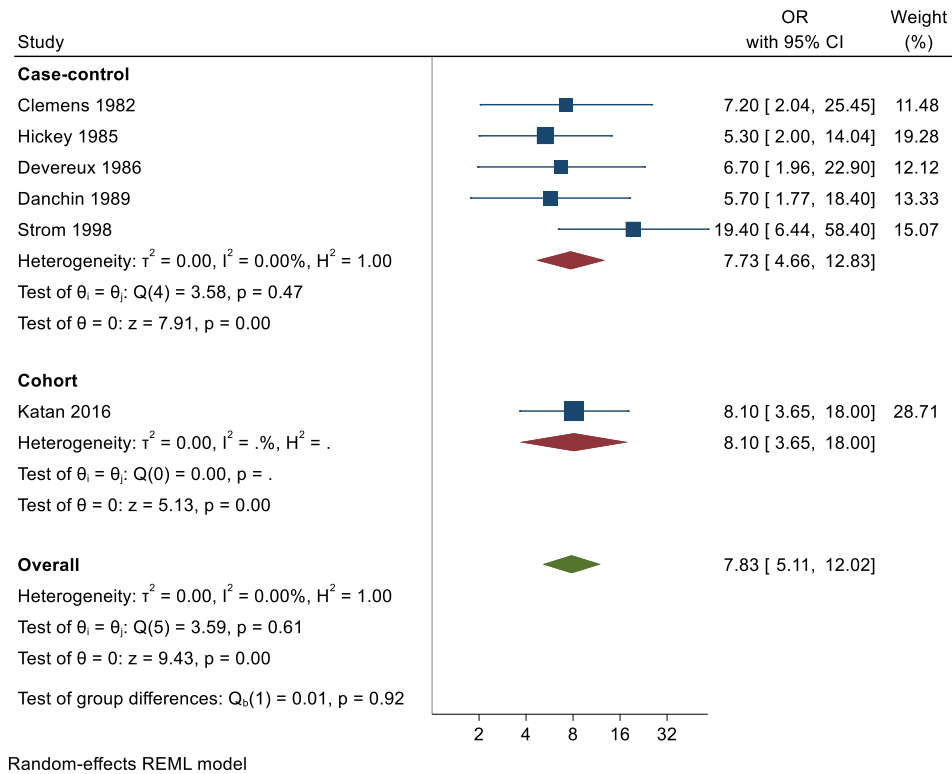
Considering the risk of bias, an analysis based on the NOS scale was conducted. When comparing studies with NOS ≤ 7 (OR 8.09, 95% CI 3.98, 19.91; I2 = 37.18%) and NOS > 7 (OR 7.12, 95% CI 3.98, 12.73; I2 = 0%), there was a small difference on the values obtained, as seen below.



Forest plot with odds ratio and 95% CI for the studies with a NOS > 7 and for the studies with a NOS ≤ 7.

Supplementary material 6 – Forest plot for study design subgroups

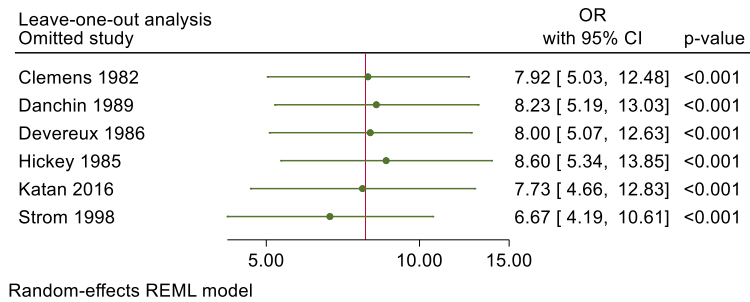
An analysis was conducted to see possible differences regarding the study design. Both the case control (OR 7.73, 95% CI 4.66, 12.83; I2 = 0%) and the cohort (OR 8.10, 95% CI 3.65, 18.00; I2 = 0%) subgroups obtained a similar OR, as can be seen below.



Forest plot with odds ratio and 95% CI for the case-control studies and the cohort study

Supplementary material 7 – Sensitivity analysis

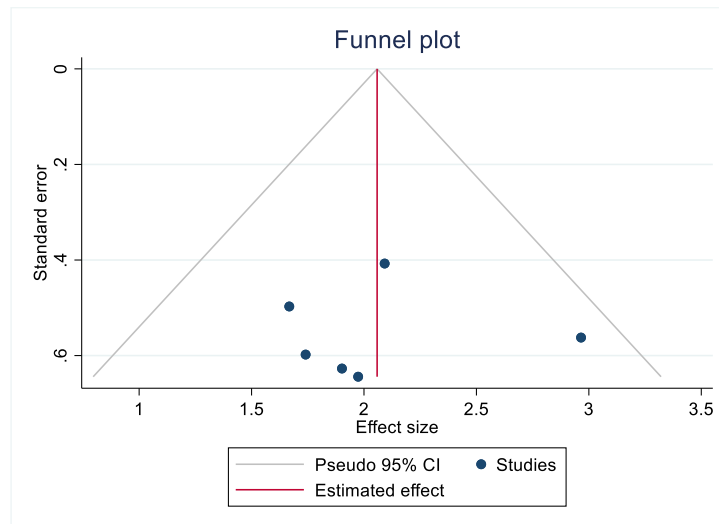
Sensitivity analysis revealed that no studies were causing significant changes in the obtained OR. Regarding the studies with a higher risk of bias, analysis excluding Clemens et. al, revealed an OR 7.92 (95% CI 5.03, 12.48), similar to the values obtained in the overall analysis; however, exclusion of Strom et. al revealed an OR 6.67 (95% CI 4.19, 10.61), slightly inferior to the value obtained.



Forest plot with odds ratios and 95% CI obtained in the sensitivity analysis (leave-one-out analysis)

Supplementary material 8 - Publication bias

The funnel plot and the Egger test results ($p=0.99$) do not support publication bias.



Funnel plot of the publication bias analysis