EuroIntervention 2020;15:1401-1408 published online jAA December 2019

Stroke after transcatheter edge-to-edge mitral valve repair: a systematic review and meta-analysis

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00602

KEYWORDS

- anticoagulant therapy
- atrial fibrillation
- mitral valve repair
- stroke

Abstract

Aims: The aim of this study was to assess the stroke rate after transcatheter mitral valve repair (TMVR) with the MitraClip, comparing it with surgical mitral valve repair (SMVR) and optimal medical treatment (OMT).

Methods and results: In December 2018, we systematically searched PubMed, Embase and Cochrane Controlled Register of Trials for studies comparing TMVR with SMVR and/or OMT for the treatment of severe mitral regurgitation. Random-effects and cumulative meta-analysis was performed. Ten studies were included (seven of TMVR versus SMVR and three of TMVR versus OMT), providing a total of 1,881 patients and 61 pooled strokes (16 in TMVR versus SMVR and 45 in TMVR versus OMT). There was no difference in stroke incidence between TMVR and SMVR (pooled OR 0.49 [0.17, 1.42], p=0.19). However, there was a trend towards a lower stroke risk in TMVR. For TMVR versus OMT, no difference in stroke rate was identified (pooled OR 1.09 [0.60, 1.97], p=0.79). Post-procedure *de novo* atrial fibrillation was more frequent in SMVR when compared with TMVR.

Conclusions: Despite both a low number of pooled stroke events and the failure to reach the pre-specified statistical significance, there was a trend for a lower post-procedure stroke rate in TMVR when compared with SMVR and a similar one between TMVR and OMT alone.

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SUBMITTED ON 26/06/2019 - REVISION RECEIVED ON 1st 26/09/2019 / 2nd 28/10/2019 / 3rd 25/11/2019 - ACCEPTED ON 04/12/2019

DOI: 10.4244/EIJ-D-19-00602

Abbreviations

AF	atrial fibrillation
CI	confidence interval
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
OMT	optimal medical treatment
RCT	randomised controlled trial
SMVR	surgical mitral valve repair
TMVR	transcatheter mitral valve repair

Introduction

It is well established that surgical mitral valve repair (SMVR) is the optimal treatment for severe mitral regurgitation (MR). However, a large proportion of patients is deemed unsuitable for surgical treatment, thus representing a striking unmet need in cardiovascular medicine[1]. So far, in patients with both primary and secondary symptomatic MR who are judged inoperable, only the edge-to-edge repair technique with the MitraClip® device (Abbott Vascular, Santa Clara, CA, USA) is globally used (class IIb indication in the most recent European Society of Cardiology guidelines)[2].

The MitraClip is inspired by the surgical Alfieri technique, which creates a double orifice mitral area[3]. As a result, the physiology of diastolic transmitral flow is modified, leading to some restriction in left ventricle filling. Thus, this haemodynamic profile could result in blood stasis, an increased risk of left atrial thrombosis and, consequently, the risk of thromboembolic events[4-7]. Additionally, atrial fibrillation (AF) complicates the course of MR and is itself a risk factor for stroke and peripheral embolic events[8]. Although this rationale might seem insufficient to offset cardiac surgery stroke risk, it may embody the recommendation for anticoagulation, particularly with vitamin K antagonists, which are the only oral anticoagulants indicated in both mitral prosthesis and mitral stenosis[9]. Despite this, no strict peri- and post-MitraClip procedure antithrombotic therapies have been defined so far; distinct protocols are currently being applied[10,11].

Systematic reviews support the long-term safety of transcatheter mitral valve repair (TMVR) with the MitraClip for degenerative and functional MR plus the durability of MR reduction[12,13]. Recent meta-analyses have demonstrated that, compared with conservative treatment alone, TMVR is associated with a significant relative risk reduction of death from any cause and heart failure in high-risk patients with left ventricular dysfunction[14,15]. However, none of these reviews specifically analysed stroke incidence. In 2018, the COAPT trial[16] reinforced the increased safety of the edge-to-edge repair technique compared to optimal medical treatment (OMT), while the MITRA-FR trial[17] reported no significant difference in adverse effects between the two groups.

We aimed to carry out a systematic review of the published literature on the comparison between TMVR with the MitraClip device and both SMVR and OMT groups of patients, analysing stroke incidence among these therapeutic options for MR.

Editorial, see page 1387

Methods

PROTOCOL AND REGISTRATION

This study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A registration (CRD42018117614) in the PROSPERO database was made at inception.

LITERATURE SEARCH

Based on the PRISMA statement, we systematically searched PubMed, Embase, and Cochrane Controlled Register of Trials (CENTRAL) in December 2018, for both interventional and observational studies comparing TMVR with SMVR and/or OMT for the treatment of severe MR. The search was limited by language (English, French, Portuguese, or Spanish) and type of subjects (human). No date publication limits were imposed. **Supplementary Figure 1** shows the search strategy of this review. Additional data were collected from randomised controlled trial (RCT) protocols. Different publications from the same patient cohorts were considered as a single study for the purpose of this review.

ELIGIBILITY CRITERIA

The following criteria were used to define study eligibility: 1) RCTs or observational studies comparing the MitraClip procedure with mitral valve surgery and/or OMT; 2) participants with severe MR; and 3) information on stroke incidence after procedure. We excluded series with fewer than 20 patients or without full-text article publications.

PRIMARY AND SECONDARY OUTCOMES

Primary outcomes were early (<30 days) and late (>30 days) post-procedural stroke rate. Secondary endpoints were *de novo* AF and bleeding events.

DATA COLLECTION AND MANAGEMENT

Two authors (P. Barros da Silva and J.P. Sousa) systematically screened the titles and abstracts of publications retrieved using the search strategy in order to select studies which met the inclusion criteria outlined above. The full texts of the eligible studies were, again, independently assessed for eligibility by the two review team members. Any disagreement between them over the eligibility of particular studies was resolved through discussion and involvement of a third author (R. Teixeira), when necessary. Data extraction concerned the study population, main demographics and baseline characteristics, interventions, and the outcomes described above. We analysed studies with multiple sequenced publications, ensuring no duplication of results and the collection of the most recent data.

Some studies did not break down information on early (<30 days) versus late (>30 days) post-procedural stroke incidence. For this reason, and to increase statistical power, we joined both outcomes, creating an all-stroke post-procedural rate. Post-procedural stroke incidence included both ischaemic and haemorrhagic cerebrovascular events, due to the lack of separate outcomes in the majority of studies.

To compare the incidence of bleeding events, we included major bleeding and need for blood transfusions (>1 unit) in post-operative care.

RISK OF BIAS ASSESSMENT

Two authors (P. Barros da Silva, J.P. Sousa) independently assessed the risk of bias of the included articles, following the Cochrane Collaboration's "Risk of bias" tool for RCTs and the Newcastle-Ottawa Scale for observational studies. RCTs were assessed as "low", "high" or "unclear" risk for the following biases: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. None of the included studies had a blinding strategy, which resulted in a high risk for performance and detection bias. This assessment was expected, because the MitraClip device is visible on imaging studies, most studies were retrospective, and in the two RCTs on TMVR versus OMT there was no sham procedure. The quality assessment for each study is presented in the "risk of bias summary" **(Figure 1)** and Newcastle-Ottawa Scale summary **(Figure 2)**.

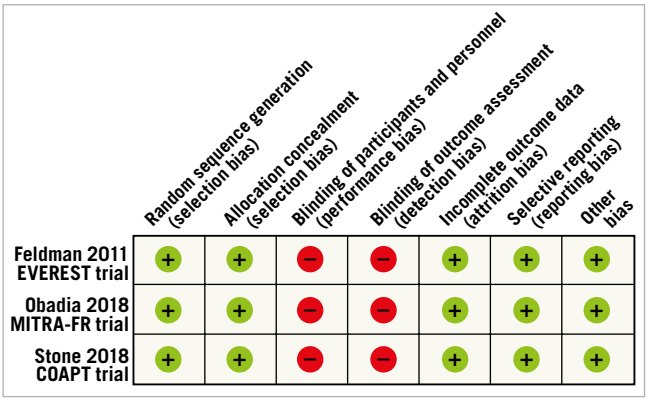

Figure 1. *Risk of bias summary.*

	Selection	Comparability	Outcome
Alozie 2017	****	*	**
Anwer 2018	***	**	*
Conradi 2013	****	*	*
Geis 2018	***	–	*
Giannini 2016	****	–	*
Krawczyk-Ozog 2018	***	*	*
Ondrus 2016	****	*	**
Paranskaya 2013	****	**	**
Taramasso 2012	****	*	**

Figure 2. *Newcastle-Ottawa Scale summary.*

STATISTICAL ANALYSIS

We pooled dichotomous non-adjusted data using odds ratios (OR) to describe effect sizes using the Mantel-Haenszel procedure in a random effects model. We also performed a continuity correction for the individual odds ratios and the overall measure, which considers adding the quantity 0.5 to all cells whenever relative effect measures are undefined due to the presence of zeros. Study heterogeneity was evaluated by funnel plots while publication bias was evaluated using Egger's test and both Galbraith and normalised Galbraith plots. To evaluate temporal trends on stroke incidence, a cumulative meta-analysis was performed according to date of publication, following a usual meta-analysis. In the cumulative analysis, studies were successively added by year of publication and the 95% confidence intervals (CIs) and overall cumulative odds ratios were recalculated, enabling us to evaluate the outcome evolution over time. The impact of both age and left ventricular ejection fraction (LVEF) on stroke incidence between TMVR and SMVR was analysed by meta-regression based on the mixed-effects model.

The mean effect was considered significant if its 95% CI did not include zero. Heterogeneity was assessed using the I^2 statistic and assumed to be relevant if it exceeded 50%.

The cumulative meta-analysis and the meta-regression was performed using R software through R Studio, version 1.1.463 (R Foundation for Statistical Computing, Vienna, Austria), and the traditional meta-analysis using RevMan 5.3 (Cochrane Community, London, UK).

Results

SEARCH RESULTS

The literature search identified 1,447 articles. Two cited RCTs (MITRA-FR and COAPT) were added. After duplication removal, we excluded a total of 1,194 publications based on title and abstract evaluation, study type (RCTs or observational studies comparing the MitraClip procedure with SMVR and/or OMT) and study population (participants with severe MR). The full text of the remaining 47 studies was then screened, leading to the exclusion of 35 publications: three studies only included outcomes of MitraClip populations, one study only reported stroke rates on the mitral valve surgical arm, two full texts could not be accessed, eight did not specifically refer to post-procedure stroke incidence, 12 were conference abstracts or RCT design studies, three used data from the EVEREST trial for a different analysis and three RCTs did not yet include any published results; the study by Taramasso et al was chosen among four studies based on the same institutional population, as it included a wider number of participants[18-21]. Finally, 12 publications met all the inclusion criteria for the qualitative review; 10 of these were suitable for the quantitative synthesis with meta-analysis **(Figure 3)**. Seven studies compared TMVR versus SMVR and three TMVR versus OMT, providing a total of 1,881 patients and 61 pooled strokes (16 in TMVR versus SMVR and 45 in TMVR versus OMT). Baseline characteristics of the included studies are shown in **Table 1**.

MITRACLIP VERSUS SURGERY

We identified seven studies comparing TMVR using the MitraClip with surgical repair/replacement. TMVR patients were older and had higher surgical risk scores than SMVR patients. The

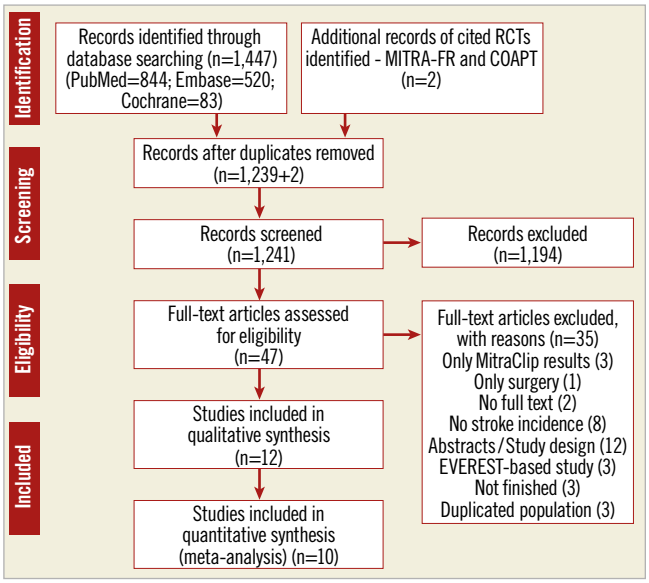

Figure 3. *Flow diagram of literature search.*

groups were homogeneous regarding previous AF rate (pooled OR 1.45 [0.82-2.55]) **(Figure 4)**, whereas post-procedure *de novo* AF was more frequent in SMVR compared with TMVR (pooled OR 0.20 [0.06-0.7]) **(Figure 5)** in the four studies that reported data on 30-day post-procedural AF.

There was no significant difference in stroke incidence between TMVR and SMVR (pooled OR 0.49 [0.17, 1.42], p=0.19, I^2= 0%) **(Figure 6, Figure 7)**. However, by approximating this OR's confidence interval distribution to a standard normal one, we found that the interval between 0.17 and 1 is responsible for 77.5% of the distribution. In other words, obtaining a definitive OR favouring TMVR is 3.435 times more likely than obtaining a definitive OR favouring SMVR.

The studies were homogeneous. No selection or publication bias was identified by funnel plots, which was confirmed by the Galbraith or the normalised Galbraith plots **(Supplementary Figure 2-Supplementary Figure 4)**. Moreover, the Egger test confirmed that the normalised effects were independent from the precision (b=0.38, p=0.82, t value=0.24; R^2=0.013) **(Supplementary Figure 5)**. Also, the Begg and Mazumdar test confirmed that the effects were not related to their variance (Kendall's tau=0.14; p=0.77).

Meta-regression for age and LVEF had small effect sizes with no statistically significant p-values (respectively Z=–0.61, p=0.54 and Z=0.038, p=0.97).

Bleeding events were less frequent in TMVR compared to SMVR (pooled OR 0.25 [0.11, 0.56], p<0.05, I^2=33%) **(Figure 8)**.

MITRACLIP VERSUS OMT

There were five studies comparing TMVR using the MitraClip plus OMT with OMT alone. However, only three of these provided data on stroke incidence during follow-up in both the TMVR and OMT groups and these were used for meta-analysis. No difference in stroke rate was identified (pooled OR 1.09 [0.60, 1.97], p=0.79, I^2=0%) **(Figure 9)**.

Table 1. Characteristics of included studies.

Author	Publication	Design	Control	No. of patients		Mean age, years (SD)		Duration of follow-up, months		Post MitraClip antithrombotic protocol
				MitraClip	Control	MitraClip	Control	MitraClip	Control	
Alozie et al[30]	2017	Retrospective	SMV repair or replacement	42	42	82.2 (1.65)	81.7 (1.35)	9	24	3 months DAPT, followed by SAPT indefinitely
Anwer et al[31]	2018	Retrospective	SMV repair	56	75	75.7 (8.6)	68.6 (13.1)	11	11	–
Conradi et al[22]	2013	Retrospective	SMV repair	95	76	72.4 (8.1)	64.5 (11.4)	5	6	–
Feldman et al[32]	2011	RCT - EVEREST	SMV repair or replacement	184	95	67.3 (12.8)	65.7 (12.9)	60	60	Heparin during procedure, 30 days DAPT, 6 months SAPT
Geis et al[33]	2017	Retrospective	OMT	86	69	68.2 (11)	53.4 (13)	24	24	Coumadin for at least 4 weeks post implantation
Giannini et al[34]	2016	Retrospective	OMT	60	60	74 (8)	76 (8)	17	17	–
Krawczyk-Ozog et al[35]	2018	Retrospective	OMT	10	23	71.8 (7.8)	73.0 (11.5)	4	4	–
Obadia et al[17]	2018	RCT - MITRA-FR	OMT	152	152	70.1 (10.1)	70.6 (9.9)	12	12	3 months DAPT, followed by SAPT indefinitely
Ondrus et al[36]	2016	Retrospective	Minimally invasive MV repair	24	48	75 (9)	76 (4)	34	30	–
Paranskaya et al[37]	2013	Retrospective	SMV repair	24	26	80 (5)	63 (12)	12	12	3 months DAPT, followed by SAPT indefinitely
Stone et al[16]	2018	RCT - COAPT	OMT	302	312	71.7 (11.8)	72.8 (10.5)	22.7	16.5	6 months DAPT
Taramasso et al[18]	2012	Retrospective	SMV repair	52	91	68.4 (9.2)	64.9 (9.8)	8.5	18	–

DAPT: dual antiplatelet therapy; OMT: optimal medical treatment; SAPT: single antiplatelet therapy; SMV: surgical mitral valve

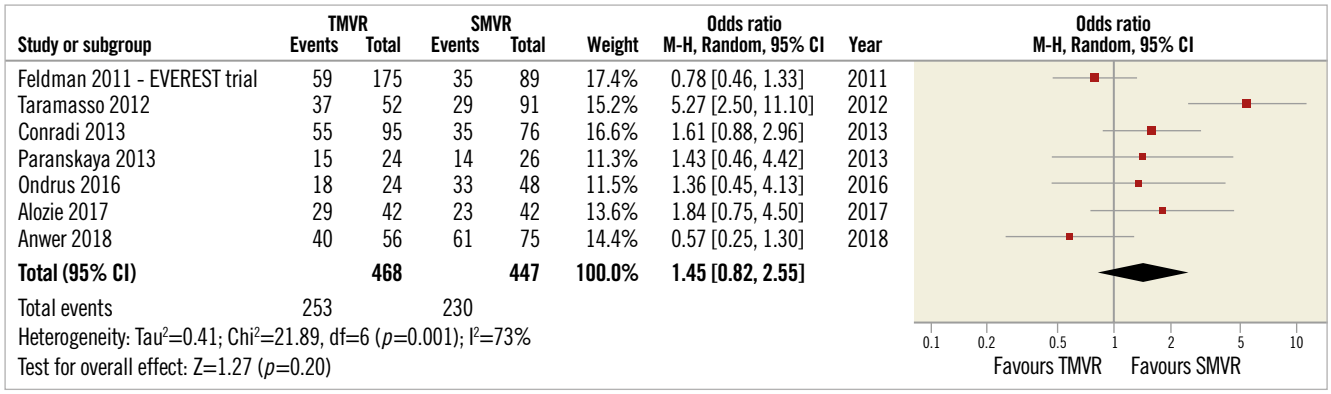

Figure 4. *TMVR vs SMVR – previous atrial fibrillation.*

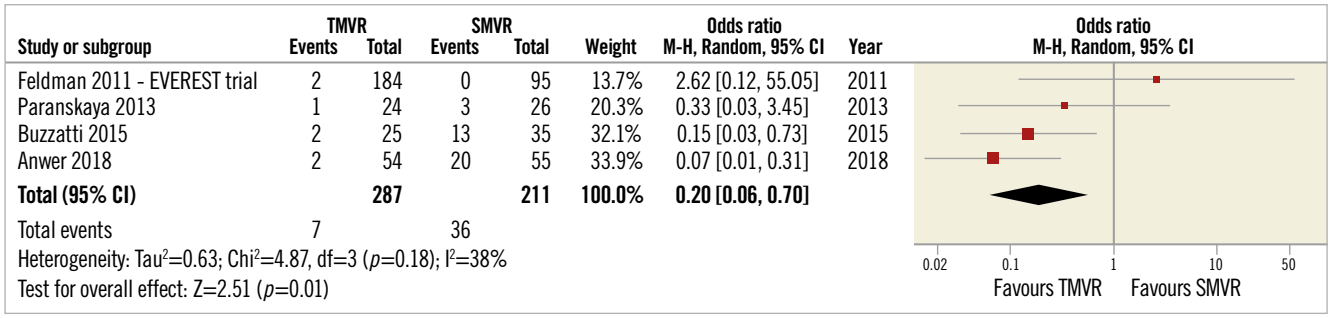

Figure 5. *TMVR vs SMVR – de novo atrial fibrillation.*

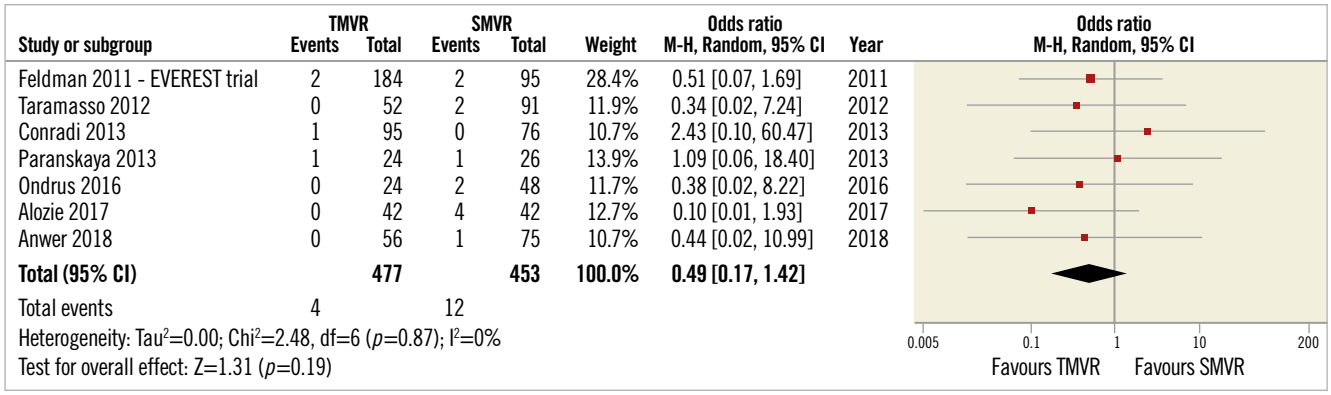

Figure 6. *TMVR vs SMVR – all stroke incidence.*

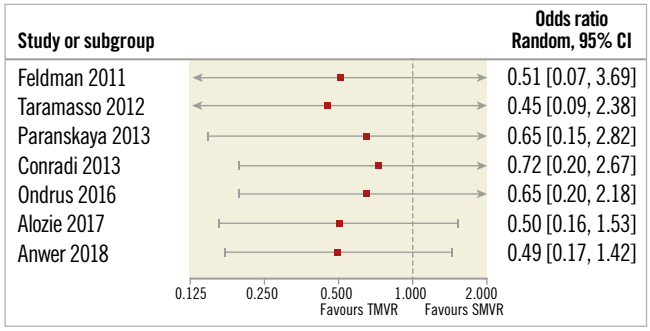

Figure 7. *TMVR vs SMVR – all stroke incidence, cumulative meta-analysis.*

Discussion

According to our meta-analysis in the context of MR treatment, (i) the pooled stroke rate after TMVR, SMVR and OMT for MR patients had a low number of events, (ii) there was a trend towards a lower stroke rate for patients submitted to TMVR compared to SMVR, (iii) there was a similar stroke rate for patients treated with TMVR when compared to patients allocated to OMT, and (iv) post-procedure AF was more frequent after SMVR when compared to TMVR.

The decision to deny surgery for patients with MR is mostly based on impaired LVEF, age, and comorbidity[1]. For this reason, MitraClip patients are theoretically at increased risk for AF and

Study or subgroup	TMVR Events	TMVR Total	SMVR Events	SMVR Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Feldman 2011 - EVEREST trial	24	184	42	95	45.7%	0.19 [0.10, 0.34]	2011
Buzzatti 2015	0	25	1	35	5.4%	0.45 [0.02, 11.53]	2015
Ondrus 2016	1	24	5	48	10.6%	0.37 [0.04, 3.39]	2016
Alozie 2017	3	42	2	42	14.2%	1.54 [0.24, 9.71]	2017
Anwer 2018	3	56	25	75	24.0%	0.11 [0.03, 0.40]	2018
Total (95% CI)		**331**		**295**	**100.0%**	**0.25 [0.11, 0.56]**	
Total events	31		75				

Heterogeneity: Tau²=0.27; Chi²=6.00, df=4 (*p*=0.20); I²=33%
Test for overall effect: Z=3.40 (*p*=0.0007)

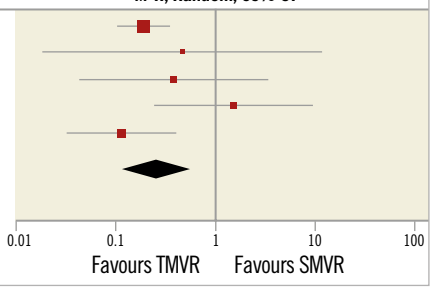

Figure 8. *TMVR vs SMVR – bleeding events.*

Study or subgroup	TMVR Events	TMVR Total	OMT Events	OMT Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Stone 2018 - COAPT trial	11	302	11	312	49.3%	1.03 [0.44, 2.42]	2018
Obadia 2018 - MITRA-FR trial	11	152	11	152	47.4%	1.00 [0.42, 2.38]	2018
Krawczyk-Ozog 2018	1	10	0	23	3.3%	7.42 [0.28, 198.83]	2018
Total (95% CI)		**464**		**487**	**100.0%**	**1.09 [0.60, 1.97]**	
Total events	23		22				

Heterogeneity: Tau²=0.00; Chi²=1.36, df=2 (*p*=0.51); I²=0%
Test for overall effect: Z=0.27 (*p*=0.79)

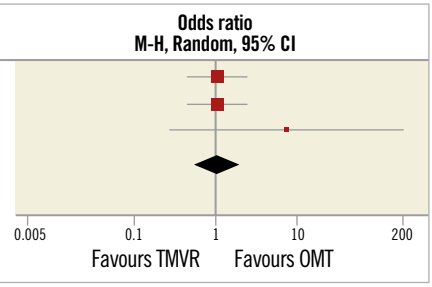

Figure 9. *TMVR vs OMT – all stroke incidence.*

stroke. However, our results do not confirm that hypothesis. In addition, they support the most recent systematic review that reported similar survival for TMVR with MitraClip and surgery, despite patients' higher risk profiles in the TMVR group[23]. However, to the best of our knowledge, this is the first and only meta-analysis specifically to examine stroke and *de novo* AF rates after mitral valve repair with the MitraClip, comparing it with both surgery and OMT.

OMT

In patients who are not candidates for surgery, the option between TMVR with the MitraClip and OMT alone is still debated: the MITRA-FR trial[17] showed that both treatments were similar regarding adverse effects, but the results of the COAPT trial[16] favoured the MitraClip for the same outcome. In terms of stroke incidence, our analysis showed that the stroke rate post TMVR with the MitraClip was similar to that of patients managed with OMT alone. This finding is unexpected, as, for instance, transseptal puncture for catheter ablation poses a risk of paradoxical embolism, which has already been described for catheter ablation of arrhythmia[24]. Selecting patients for percutaneous treatment with optimal risk–benefit balance is still subject to ongoing research. Hopefully, the RESHAPE-HF trial may solve the present controversy regarding MitraClip safety compared to conservative treatment, allowing a more sustained clinical decision[25].

MITRAL VALVE SURGERY

Even though our meta-analyses disclosed no statistically significant difference in stroke incidence between TMVR and SMVR, a trend towards a lower stroke risk in post-TMVR patients was identified. For instance, the cumulative meta-analysis demonstrated this finding at all times[26]. Cumulative meta-analysis is still not a widely used statistical tool, but this chronological combination of studies has been proposed as a valuable method to decide when to stop ongoing trials or to adopt or reject an investigated treatment by different authors[27,28].

A 2018 meta-analysis reported a negative effect of previous AF in the TMVR one-year survival rate; however, it did not address specific post-procedure adverse events or *de novo* AF[13]. On the other hand, a recent retrospective study comparing TMVR with MitraClip in patients with and without previous AF reported no significant difference in stroke incidence during follow-up[29]. The lower stroke rate for TMVR compared with SMVR might therefore be related to the lower incidence of post-procedure *de novo* AF in TMVR.

ANTITHROMBOTIC THERAPY

Only six of the 12 studies described post-procedure antithrombotic strategy, and only three were similar, hindering a comprehensive analysis of the protocols used. Antithrombotic therapy has never been formally evaluated in terms of outcome events in this setting. Both direct oral anticoagulants and vitamin K antagonists are currently used. However, considering their biomechanical similarity, there is the possibility of a contraindication to direct oral anticoagulants in MitraClip, as in mitral stenosis and mitral prostheses[9]. Nevertheless, the similar stroke incidence for TMVR and OMT indicates no concern regarding the use of direct oral anticoagulants after the MitraClip procedure.

FUTURE PERSPECTIVES

The call for a specific antithrombotic strategy is justified not only by the high prevalence of AF in TMVR with MitraClip candidates but also by the increased risk of left atrial thrombus formation after the procedure, caused by acute reduction of MR and changes in haemodynamics within the left atrium[4-7].

Our findings suggest the need for RCTs on different post-MitraClip procedure antithrombotic treatments, in order to define a strict protocol, particularly for patients with AF. This is of major interest, because AF is highly prevalent in TMVR with MitraClip candidates, and the choice of antithrombotic treatment has a high impact on both quality of life and health costs.

Limitations

The most important limitation of our meta-analysis is the paucity of RCTs on this issue. In fact, the majority of studies included were observational and not randomised, increasing the risk of bias and therefore limiting the strength of our results. Furthermore, for our primary outcome there were only 16 events among the 930 patients included in the comparison between TMVR and SMVR, which may have single-handedly reduced the odds of unveiling a significant difference in stroke rates. We tried to overcome this limitation by applying a continuity correction and a cumulative meta-analysis[28]. One could argue that the low event rate is the justification for the statistical homogeneity found (I^2=0%), despite numerical heterogeneity (odds ratios ranging from 0.1 to 2.43), that enabled the performance of a cumulative meta-analysis. However, by combining study events and sample sizes, cumulative meta-analysis may improve the statistical power as similar results are combined cumulatively. This method reduces the problem caused by the low event rate and especially by the presence of zero values in study groups. Regarding pooled stroke, data were not available for fatal versus non-fatal stroke, haemorragic stroke or transient ischaemic attack.

Conclusions

Although there was a low number of pooled events, our methodology showed a trend towards a lower post-procedure stroke rate for TMVR when compared with SMVR, possibly related to a lower incidence of *de novo* AF found in the percutaneous group. For the same outcome, rates were similar between TMVR and OMT alone. A clinical trial comparing MitraClip patients with and without previous AF, with and without anticoagulant therapy in the first group, is still needed to resolve this dilemma.

Impact on daily practice

Our findings may prove insightful for future recommendations regarding the conundrum of the best antithrombotic strategy, particularly for patients with AF.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Search strategy.
Supplementary Figure 2. Funnel plot.
Supplementary Figure 3. Galbraith plot.
Supplementary Figure 4. Normalised Galbraith plot.
Supplementary Figure 5. Egger test.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00602

Supplementary data

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#16	Search "Stroke"[Mesh]	118083	
#15	Search "mitral clip"	23	
#14	Search "mitral valve clip"	488	
#13	Search mitraclip	893	

Cochrane Central Register of Controlled Trials			Date: 5/12/2018
#1	Mitraclip OR "mitral clip" OR "mitral valve clip" Filters: RCT	83	

Embase search			Date: 5/12/2018
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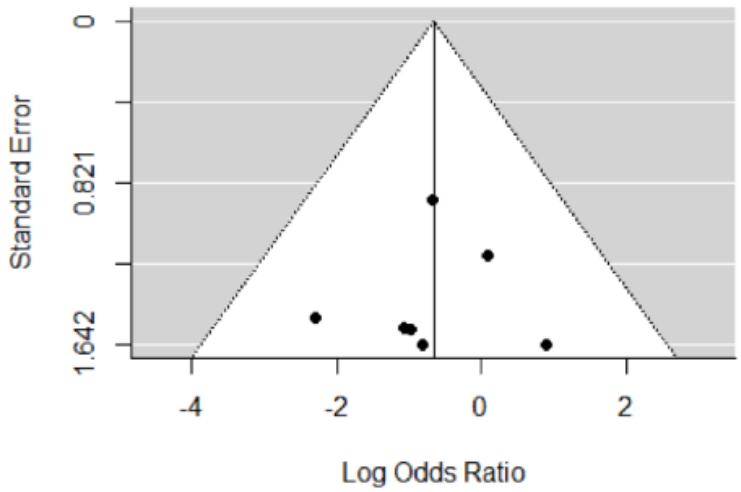
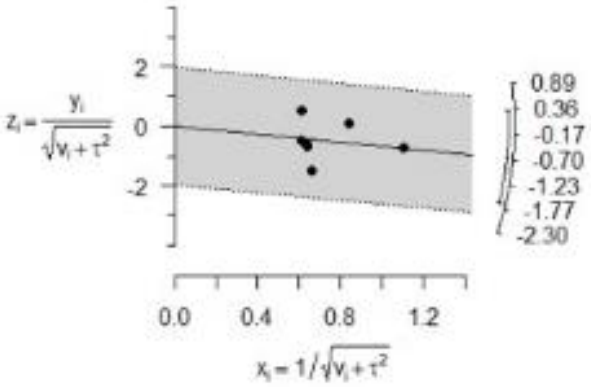
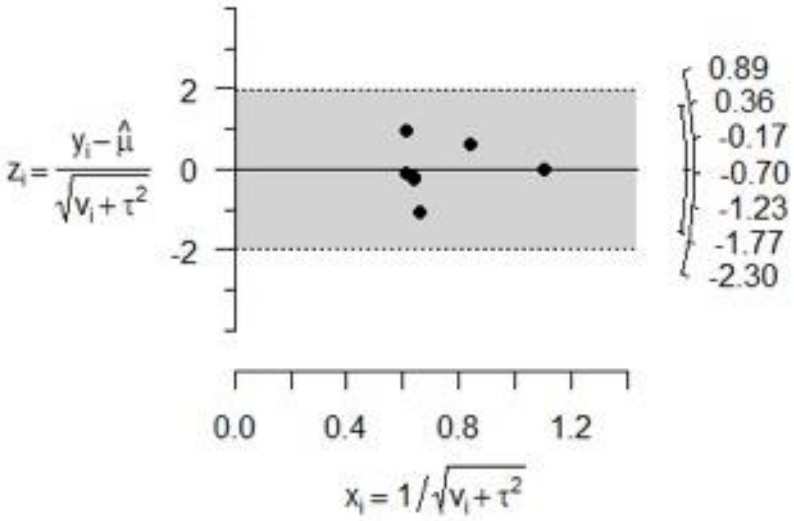
Supplementary Figure 1. Search strategy.



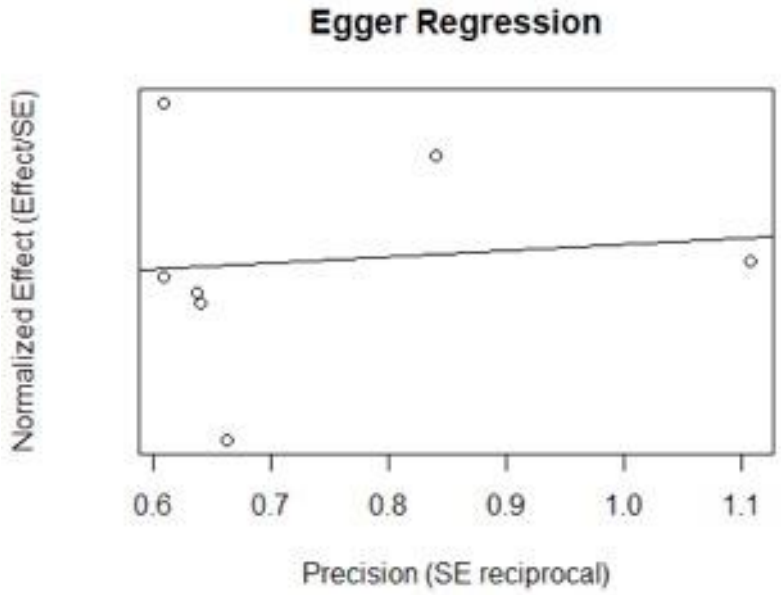
Supplementary Figure 2. Funnel plot.



Supplementary Figure 3. Galbraith plot.



Supplementary Figure 4. Normalised Galbraith plot.



Supplementary Figure 5. Egger test.