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**DOI:** 10.4244/EIJ-D-19-00602

**Citation:** Barros da Silva P, Sousa JP, Oliveiros B, Donato H, Costa M, Gonçalves L, Teixeira R. Stroke after MitraClip: Systematic Review and Meta-Analysis. *EuroIntervention* 2019; Jaa-697 2019, doi: 10.4244/EIJ-D-19-00602

**Manuscript submission date:** 26 June 2019

**Revisions received:** 26 September 2019, 28 October 2019, 25 November 2019

**Accepted date:** 04 December 2019

**Online publication date:** 10 December 2019

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# Stroke after MitraClip: Systematic Review and Meta-Analysis

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**Short running title:** Stroke after MitraClip

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The authors have no conflicts of interest to declare.



**Abstract:**

**Aims:** To assess stroke rate after transcatheter mitral valve repair (TMVR) with MitraClip, comparing it with surgical mitral valve repair (SMVR) and optimal medical treatment (OMT).

**Methods and Results:** We systematically searched PubMed, Embase and Cochrane Controlled Register of Trials, in December 2018, 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 1881 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],  $P=0.19$ ). Cumulative meta-analysis showed a significantly lower stroke rate in TMVR, compared to SMVR (OR 0.4 [0.24, 0.67],  $P<0.01$ ). 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:**

Although with a low number of pooled events, there was a trend for a lower post-procedure stroke in TMVR when compared with SMVR and a similar one between TMVR and OMT alone.

**Classifications:** mitral valve repair, stroke, atrial fibrillation, anticoagulant therapy

**Condensed abstract:** A systematic review assessed stroke rate after transcatheter mitral valve repair (TMVR) with MitraClip, comparing it with surgical mitral valve repair (SMVR) and optimal medical treatment (OMT). Ten studies were included providing a total of 1881 patients. Post-procedure TMVR stroke rate was similar to that of patients managed with OMT only. For the same outcome, results favoured TMVR compared with SMVR. A lower incidence of post-procedure *de novo* atrial fibrillation was recorded for TMVR compared to SMVR patients.

**Abbreviations:**

TMVR transcatheter mitral valve repair

SMVR surgical mitral valve repair

OMT optimal medical treatment

MR mitral regurgitation

AF atrial fibrillation

RCTs Randomised Controlled Trials

CI confidence intervals

LVEF left ventricular ejection fraction

## **Introduction:**

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

The MitraClip is inspired by the surgical Alfieri technique, which creates a double orifice mitral area<sup>3</sup>. As a result, physiology of diastolic transmitral flow is modified, leading to some restriction in left ventricle filling. Thus, this hemodynamic profile could result in blood stasis, an increased risk of left atrial thrombosis and, consequently, the risk of thromboembolic events<sup>4-7</sup>. Additionally, atrial fibrillation (AF) complicates the course of MR and is itself a risk factor for stroke and peripheral embolic events<sup>8</sup>. 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<sup>9</sup>. Despite this, no strict peri and post-MitraClip procedure antithrombotic therapies have been defined so far and distinct protocols are currently being applied<sup>10, 11</sup>.

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<sup>12, 13</sup>. Recent meta-analysis demonstrated that, compared with conservative treatment alone, TMVR is associated with significant relative risk reduction of death from any cause and heart failure in high-risk patients with left ventricular dysfunction<sup>14, 15</sup>. However, none of these reviews specifically analysed stroke incidence. In 2018, the COAPT trial<sup>16</sup> reinforced the increased safety of the edge-to-edge repair technique compared to optimal medical treatment (OMT) while the MITRA-FR trial<sup>17</sup> reported no significant difference in adverse effects between the two groups. We aim to systematically review the published literature on the comparison between the TMVR with the MitraClip device and both SMVR and OMT groups of patients, analysing stroke incidence among these therapeutic options for MR.

## **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 Preferred Reporting Items for Systematic Reviews and Meta-analysis we systematically searched PubMed, Embase, and Cochrane Controlled Register of Trials (CENTRAL) on 5<sup>th</sup> 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 1 shows the search strategy of this review. Additional data were

collected from randomised controlled trial (RCT) protocols. Different publications from the same patients' cohort 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 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 less 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 (PBS and JPS) systematically screened titles and abstracts of publications retrieved using the search strategy in order to select studies that met the inclusion criteria outlined above. The full text of the eligible studies was, 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 involving a third author (RT), 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) vs 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 bleeding events incidence, we included major bleeding and need for blood transfusions (>1 unit) in postoperative care.

### **Risk of bias assessment**

Two authors (PBS, JPS) independently assessed the risk of bias of the included articles, following the Cochrane Collaboration's 'Risk of bias' tool for RCTs and 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 vs 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).

## 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 by Egger's Test and both Galbraith and normalized 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 (CI) and overall standardised mean differences were recalculated, enabling us to evaluate the outcome evolution over time. Impact for both age and left ventricular ejection fraction (LVEF) in stroke incidence between TMVR and SMVR was analyzed 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, and the traditional meta-analysis using RevMan 5.3.

## Results

### Search results

Literature search identified 1447 articles, and two cited RCTs (MITRA-FR and COAPT) were added. After duplication removal, we excluded a total of 1194 publications based on title and abstract evaluation, study type (RCTs or observational studies comparing 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 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 RCTs' design studies, three used data from the Everest trial for a different analysis and three RCTs did not yet included any published results; Taramasso was chosen among 4 studies based on the same institutional population, as it included a wider number of participants<sup>18-21</sup>. Finally, 12 publications met all the inclusion criteria for the qualitative review and 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 1881 patients and 61 pooled strokes (16 in TMVR versus SMVR and 45 in TMVR versus OMT). Baseline characteristics of included studies are shown in Table 1.

### MitraClip versus Surgery

We identified seven studies comparing TMVR using MitraClip with surgical repair/replacement. TMVR patients were older and had higher surgical risk scores than SMVR patients. 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). The cumulative meta-analysis showed a significantly lower stroke rate in TMVR compared with SMVR (OR 0.4 [0.24, 0.67],  $P<0.01$ , Figure 7). This result was evident from 2013, after adding Conradi<sup>22</sup> to the previous studies (OR 0.46 [0.22, 0.98],  $P=0.044$ ).

Studies were homogeneous and no selection or publication bias were identified by funnel plots, which was confirmed by the Galbraith or the normalized Galbraith plots (Supplementary figures 2 to 4). Moreover, the Egger test confirmed that the normalized effects were independent from the precision ( $b = 0.38$ ,  $P = 0.82$ ,  $t$  value = 0.24;  $R^2 = 0.013$ , Supplementary figure 5). Also, 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 MitraClip plus OMT with OMT exclusively. However, only three of these provided data on stroke incidence during follow-up in both TMVR and OMT groups and 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).

### Discussion and Limitations

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 for 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 patients.

The decision to deny surgery for patients with MR is mostly based on impaired LVEF, age, and comorbidity<sup>1</sup>. For this reason, MitraClip patients are theoretically at increased risk for AF and stroke. However, our results indicate the opposite. 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 TMVR group<sup>23</sup>. However, to the best of our knowledge, this is the first and only meta-analysis to specifically examine stroke and *de novo* AF rate after mitral valve repair with MitraClip, comparing it with both surgery and OMT.

### OMT

In patients who are not candidates for surgery, the option between TMVR with MitraClip and OMT alone is still debated: MITRA-FR trial<sup>17</sup> showed that both treatments were similar regarding adverse effects, but the COAPT trial<sup>16</sup> results favoured the MitraClip for the same outcome. For stroke incidence, our analysis showed that post-TMVR with MitraClip stroke rate 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 for paradoxical embolism, which has already been described for catheter ablation of arrhythmia<sup>24</sup>. 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<sup>25</sup>.

### **Mitral Valve surgery**

Although regular meta-analysis suggested no significant difference in stroke incidence between TMVR and SMVR, a cumulative meta-analysis, added by year of publication, showed a significantly lower stroke rate in TMVR, compared to SMVR, suggesting a temporal trend in this direction<sup>26</sup>. 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<sup>27, 28</sup>. A 2018 meta-analysis reported a negative effect of previous AF in TMVR 1-year survival rate, but did not address specific post-procedure adverse events or *de novo* AF<sup>13</sup>. However, 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<sup>29</sup>. The lower stroke rate for TMVR compared with SMVR might therefore be related to its lower incidence of post-procedure *de novo* AF.

### **Antithrombotic therapy**

Only six of the 12 studies described post-procedure antithrombotic strategy, and only three were similar, hindering a comprehensive analysis of the used protocols. 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 biomechanical similarity, there is the possibility of a contraindication to direct oral anticoagulants in MitraClip, as in mitral stenosis and mitral prosthesis<sup>9</sup>. Nevertheless, 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 hemodynamics within the left atrium<sup>4-7</sup>.

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 is a low number of pooled events. We tried to overcome this limitation by applying a continuity correction and a cumulative meta-analysis<sup>28</sup>. One could argue that low event rate is the justification for the statistical homogeneity found ( $I^2 = 0\%$ ), despite numerically heterogeneity (odds ratios range from 0.1 to 2.43), that enabled the performance of a cumulative meta-analysis. However, by combining study events and sample sizes, the 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 was not available for fatal versus non-fatal stroke, haemorrhagic stroke and transient ischemic attack.

### **Conclusion**

Although with a low number of pooled events, our methodology showed a trend for 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**

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

### **Funding**

No funding was provided for this research.

### **Conflict of interest**

The authors declare that they have no conflict of interests that could prejudice the impartiality of this review.

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**Figure legends:**

Figure 1- Risk of Bias Summary

Figure 2- Newcastle-Ottawa Scale summary

Figure 3- Flow diagram of literature search

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






















Figure 8- TMVR vs. MV Surgery – Bleeding events

Figure 9- TMVR vs. OMT - All stroke incidence

Table 1- Characteristics of included studies

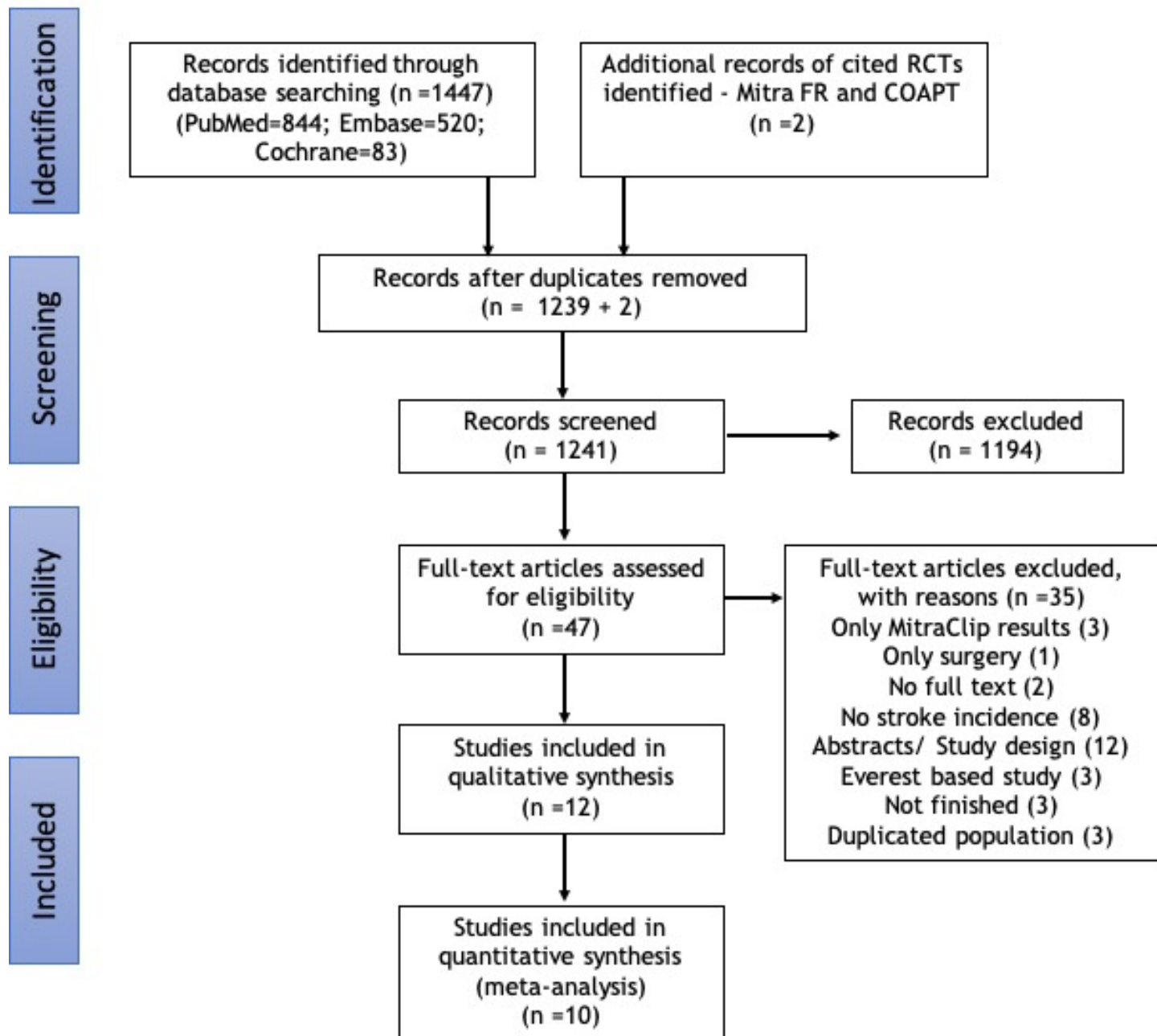
Author	Publication	Design	Control	Patients no.		Mean age-years (SD)		Duration of follow up (months)		Post MitraClip antithrombotic protocol
				MitraClip	Control	MitraClip	Control	MitraClip	Control	
Alozie, A <sup>30</sup>	2017	Retrospective	SMV repair or replacement	42	42	82.2 (1.65)	81.7 (1.35)	9	24	3 months DAPT, followed by SAPT indefinitely
Anwer, LA <sup>31</sup>	2018	Retrospective	SMV repair	56	75	75.7 (8.6)	68.6 (13.1)	11	11	-
Conradi, L <sup>22</sup>	2013	Retrospective	SMV repair	95	76	72.4 (8.1)	64.5 (11.4)	5	6	-
Feldman, T <sup>32</sup>	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 SAP
Geis, N <sup>33</sup>	2017	Retrospective	OMT	86	69	68.2 (11)	53.4 (13)	24	24	Coumadin for at least 4 weeks post implantation
Giannini, C <sup>34</sup>	2016	Retrospective	OMT	60	60	74 (8)	76 (8)	17	17	-
Krawczyk-Ozog, A <sup>35</sup>	2018	Retrospective	OMT	10	23	71.8 (7.8)	73.0 (11.5)	4	4	-
Obadia, J-F <sup>17</sup>	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, T <sup>36</sup>	2016	Retrospective	Minimally invasive MV repair	24	48	75 (9)	76 (4)	34	30	-
Paranskaya, L <sup>37</sup>	2013	Retrospective	SMV repair	24	26	80 (5)	63 (12)	12	12	3 months DAPT, followed by SAPT indefinitely
Stone, GW <sup>16</sup>	2018	RCT-COAPT	OMT	302	312	71.7 (11.8)	72.8 (10.5)	22.7	16.5	6 months DAPT
Taramasso, M <sup>18</sup>	2012	Retrospective	SMV repair	52	91	68.4 (9.2)	64.9 (9.8)	8.5	18	-

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Feldman 2011 EVEREST Trial							
Obadia 2018 Mitra-FR Trial							
Stone 2018 COAPT Trial							

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





Study or Subgroup	TMVR		SMVR		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
Feldman 2011 – EVEREST Trial	59	175	35	89	17.4%	0.78 [0.46, 1.33]	2011
Taramasso 2012	37	52	29	91	15.2%	5.27 [2.50, 11.10]	2012
Conradi 2013	55	95	35	76	16.6%	1.61 [0.88, 2.96]	2013
Paranskaya 2013	15	24	14	26	11.3%	1.43 [0.46, 4.42]	2013
Ondrus 2016	18	24	33	48	11.5%	1.36 [0.45, 4.13]	2016
Alozie 2017	29	42	23	42	13.6%	1.84 [0.75, 4.50]	2017
Anwer 2018	40	56	61	75	14.4%	0.57 [0.25, 1.30]	2018

**Total (95% CI)**

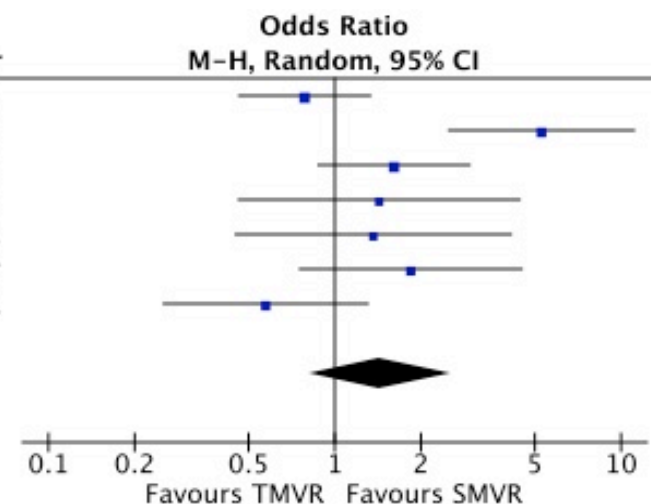
**468 447 100.0% 1.45 [0.82, 2.55]**

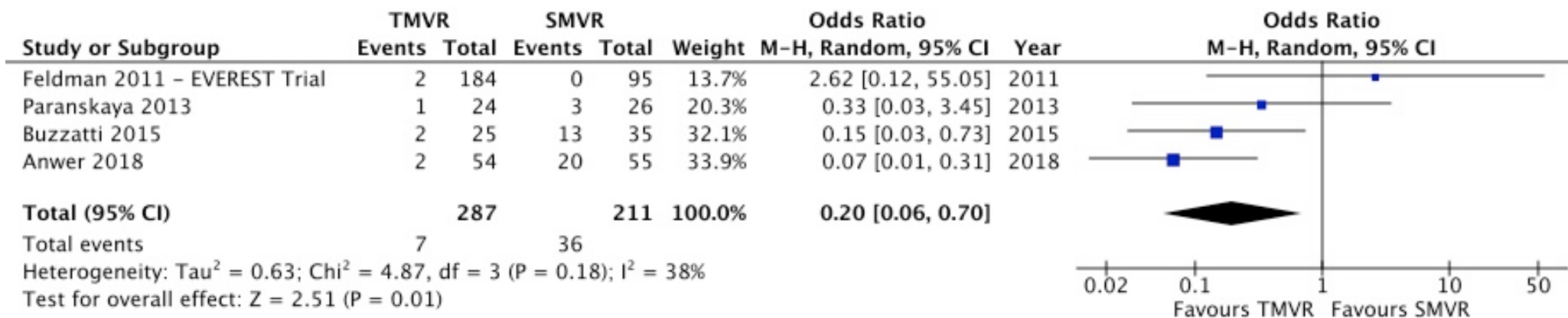
Total events

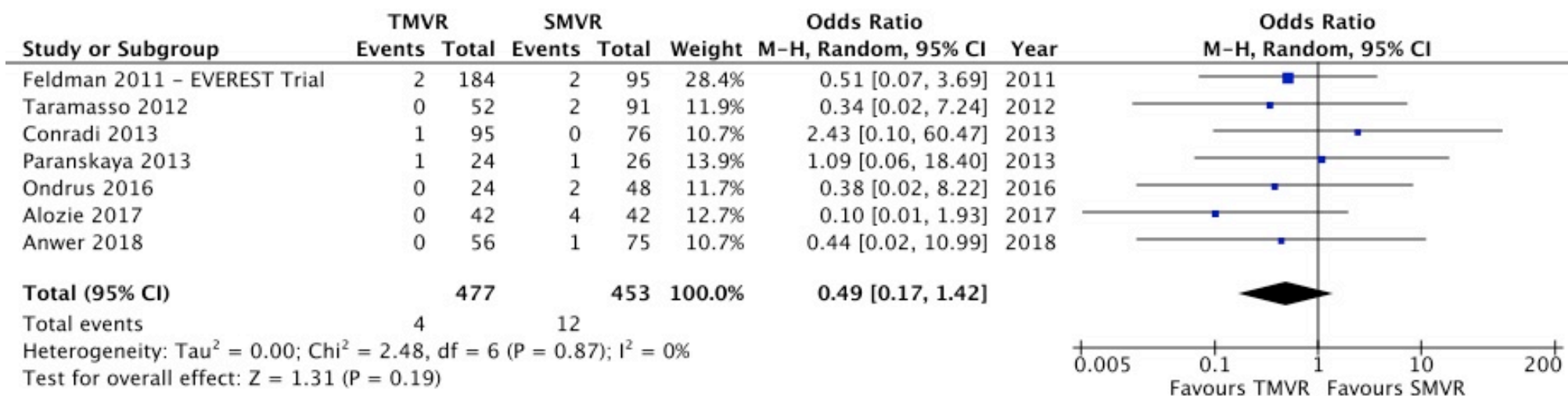
253 230

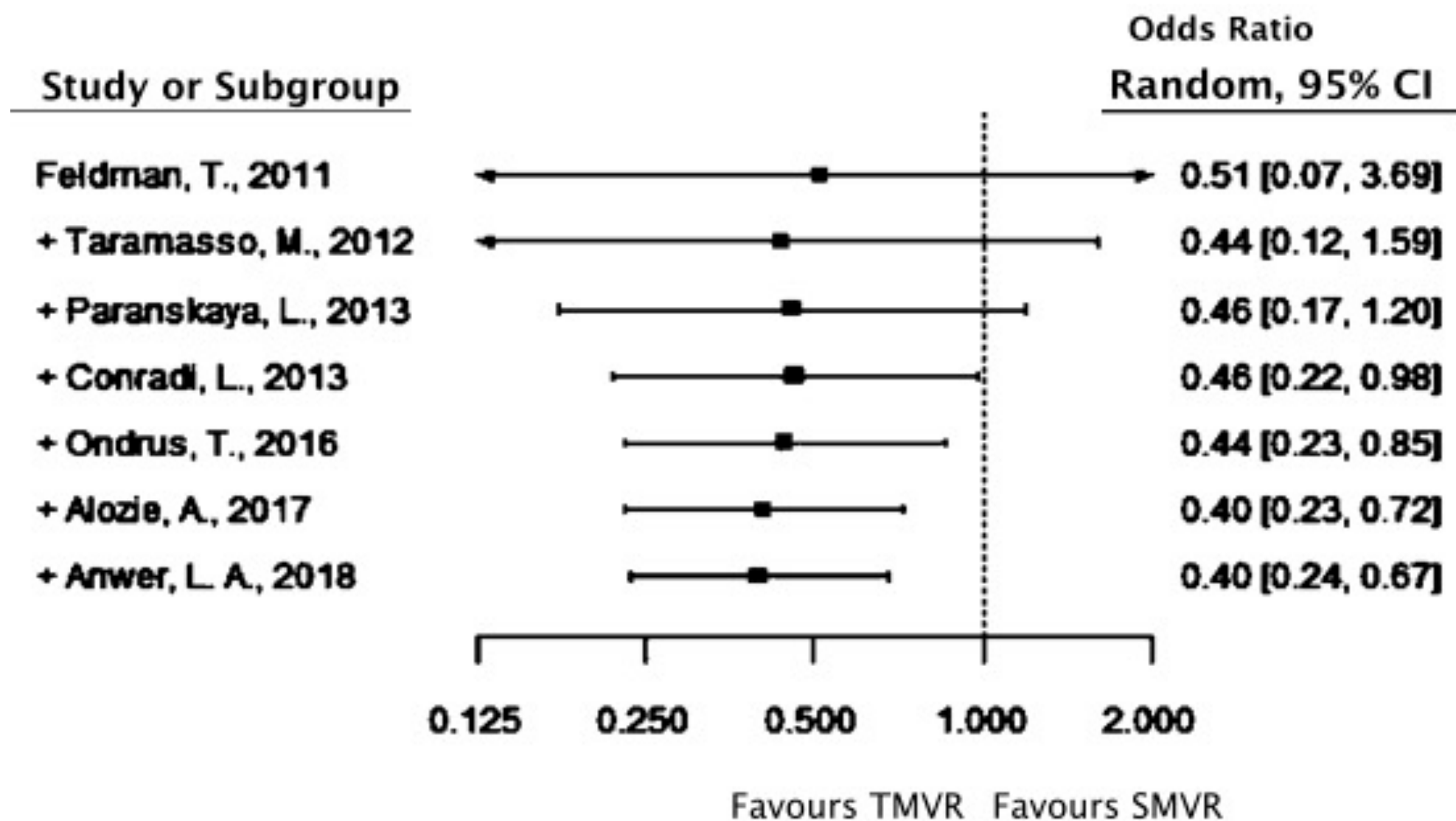
Heterogeneity:  $\tau^2 = 0.41$ ;  $\chi^2 = 21.89$ ,  $df = 6$  ( $P = 0.001$ );  $I^2 = 73\%$

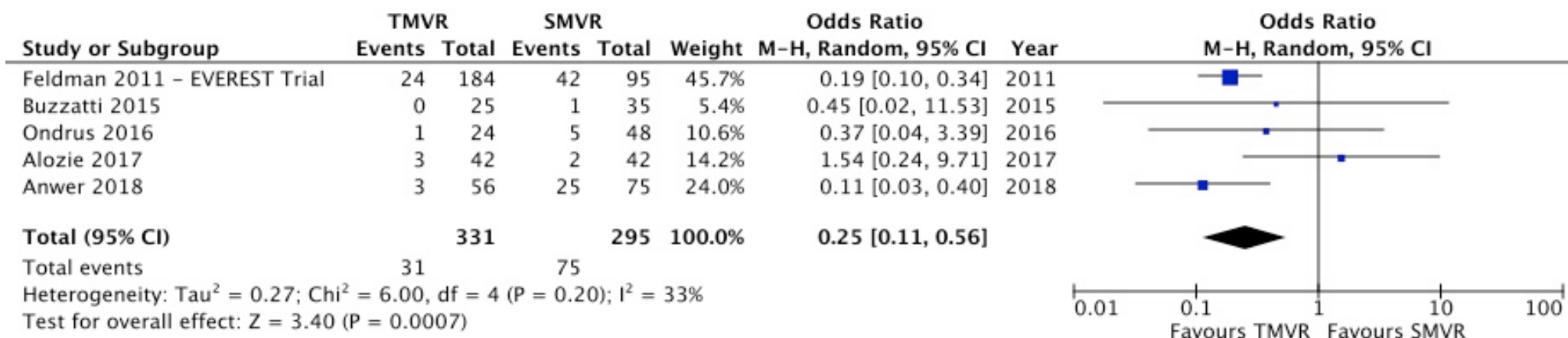
Test for overall effect:  $Z = 1.27$  ( $P = 0.20$ )











Study or Subgroup	TMVR		OMT		Weight	Odds Ratio	Year
	Events	Total	Events	Total		M-H, Random, 95% CI	
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:  $\tau^2 = 0.00$ ;  $\chi^2 = 1.36$ ,  $df = 2$  ( $P = 0.51$ );  $I^2 = 0\%$

Test for overall effect:  $Z = 0.27$  ( $P = 0.79$ )

