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***IS STROKE AN ISSUE AFTER TRANSCATHETER MITRAL
VALVE REPAIR?
A SYSTEMATIC REVIEW AND META-ANALYSIS***

REVISÃO SISTEMÁTICA
ÁREA CIENTÍFICA DE CARDIOLOGIA

Trabalho realizado sob a orientação de:
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Thesis outline

This Master Thesis in Medicine consists in a Systematic Revision and Meta-analysis, registered at Prospero database with the code number CRD42018117614.

Part of this work has been presented as an Abstract at the European Society of Cardiology Congress in September 2019 in Paris (Supplement 1).

The full text article is under revision process after having already been submitted and reviewed in the EuroIntervention Journal. Therefore, the instructions for the authors of this journal were followed as baseline format for its writing (Supplement 2).

Resumo

Introdução: A reparação percutânea da válvula mitral com o MitraClip é atualmente considerada uma alternativa ao tratamento cirúrgico da regurgitação da válvula mitral, em doentes considerados de alto risco para a abordagem cirúrgica. A referida técnica percutânea cria um duplo orifício na válvula mitral, mimetizando a cirurgia mitral de Alfieri. Tal modifica a fisiologia do fluxo transmitral diastólico, ao condicionar restrição ao enchimento ventricular esquerdo. Desta forma, a transformação da válvula mitral com o MitraClip pode condicionar um aumento do risco de trombose auricular esquerda e conseqüente risco de tromboembolismo sistémico. Para além do referido, o acidente vascular cerebral (AVC) e a fibrilhação auricular são comorbilidades frequentes nos doentes com regurgitação mitral e que podem surgir na sequência do tratamento. Até ao momento, não há recomendações estritas sobre a melhor terapêutica antitrombótica após MitraClip e diferentes protocolos têm sido aplicados.

Objetivos: Avaliar a taxa de AVC após tratamento percutâneo da regurgitação mitral com MitraClip, comparando com as taxas obtidas na reparação cirúrgica e na terapêutica médica otimizada.

Métodos e Resultados: Procedeu-se a uma pesquisa sistemática na *PubMed*, *Embase* e *Cochrane Controlled Register of Trials* (CENTRAL), para selecionar estudos observacionais e aleatorizados, publicados até dezembro de 2018. Esta revisão sistemática foi registada na base de dados Prospero no início do trabalho, com o identificador CRD42018117614. Apenas foram incluídos: (I) estudos observacionais ou ensaios clínicos randomizados que comparassem o tratamento da regurgitação mitral utilizando o MitraClip por via percutânea com tratamento cirúrgico e/ou com tratamento médico otimizado; (II) estudos com doentes com regurgitação mitral severa e (III) artigos que indicassem a taxa de AVC pós procedimento. A seleção e análise dos artigos foi feita por dois autores, recorrendo a um terceiro em caso de desacordo. De 1241 artigos inicialmente identificados, dez estudos foram incluídos: sete que comparavam o tratamento percutâneo com o cirúrgico e três que comparavam o tratamento percutâneo com o tratamento médico otimizado, num universo de 1881 doentes. Realizaram-se uma meta-análise de efeitos aleatórios e uma meta-análise cumulativa. Não foi encontrada diferença estatisticamente significativa entre a incidência de AVC no tratamento percutâneo com o MitraClip e no tratamento cirúrgico (*pooled* OR 0.49 [0.17, 1.42],

P=0.19). Contudo, a meta-análise cumulativa demonstrou uma redução da taxa de AVC no tratamento percutâneo quando comparado com a alternativa cirúrgica, com significância estatística (OR 0.4 [0.40, 0.67], P<0.05). Não foi identificada diferença estatística na taxa de AVC ao comparar o tratamento percutâneo com o tratamento medicamente otimizado (*pooled* OR 1.09 [0.60, 1.97], P=0.79). A fibrilhação auricular *de novo* pós-procedimento foi mais frequente no tratamento cirúrgico, quando comparada com o tratamento percutâneo da regurgitação mitral com o MitraClip (*pooled* OR 0.20 [0.06-0.7]).

Conclusões: De acordo com a metodologia utilizada, a incidência de AVC pós-procedimento foi menor no tratamento percutâneo com o MitraClip comparativamente ao tratamento cirúrgico. Para o mesmo *outcome*, não se identificaram diferenças entre o tratamento percutâneo e o tratamento médico otimizado.

Stroke after MitraClip: Systematic Review and Meta-Analysis

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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 (CENTRAL), in December 2018, for both interventional and observational studies comparing TMVR with SMVR and/or OMT for the treatment of severe mitral regurgitation. Random-effects and a cumulative meta-analysis were performed. Ten studies were included: seven of TMVR versus SMVR and three of TMVR versus OMT, providing a total of 1881 patients. There was no significant difference in stroke incidence between TMVR and SMVR (pooled OR 0.49 [0.17, 1.42], P=0.19). However, cumulative meta-analysis showed a significantly lower stroke rate in TMVR, compared to SMVR (OR 0.4 [0.40, 0.67], P< 0.05). 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 (pooled OR 0.20 [0.06-0.7]).

Conclusions: According to our methodology, post-procedure stroke rate was lower for TMVR when compared with SMVR. For the same outcome, rates were similar 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 | AF atrial fibrillation |
| SMVR surgical mitral valve repair | RCTs Randomised Controlled Trials |
| OMT optimal medical treatment | CI confidence intervals |
| MR mitral regurgitation | 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 medicine¹. 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)².

The MitraClip is inspired by the surgical Alfieri technique, which creates a double orifice mitral area³. 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 events⁴⁻⁷. Additionally, atrial fibrillation (AF) complicates the course of MR and is itself a risk factor for stroke and peripheral embolic events⁸. 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 stenosis⁹. Despite this, no strict peri and post-MitraClip procedure antithrombotic therapies have been defined so far and 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-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^{14, 15}. However, none of these reviews specifically analysed stroke incidence. In 2018, the

COAPT trial¹⁶ reinforced the increased safety of the edge-to-edge repair technique compared to optimal medical treatment (OMT) while the MITRA-FR trial¹⁷ 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 5th 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. Appendix 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).

| | 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 | + | + | - | - | + | + | + |

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 risk ratios (RR) to describe effect sizes in a random effects model, using a continuity correction for the individual odds ratios and the overall measure. 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 participants¹⁸⁻²¹. 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). Baseline characteristics of included studies are shown in Table 1.

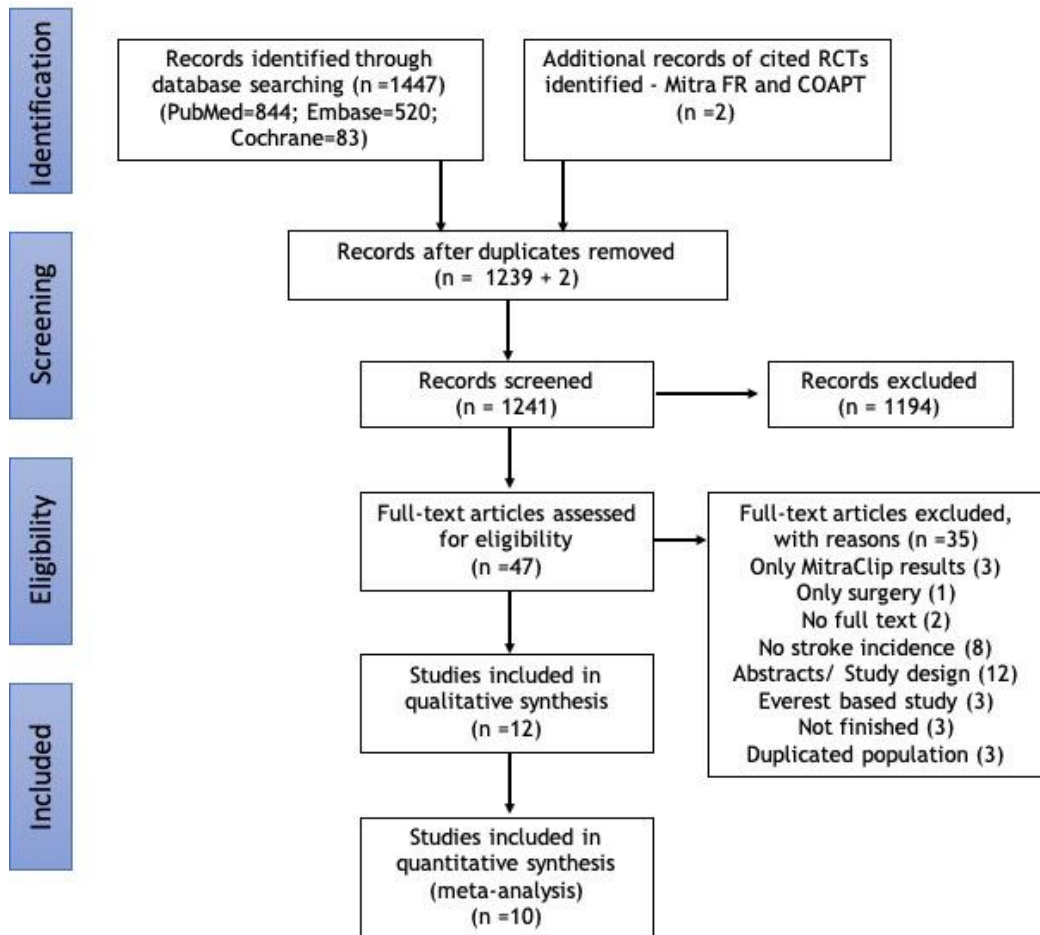


Figure 3- Flow diagram of literature search

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 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, LA ³¹ | 2018 | Retrospective | SMV repair | 56 | 75 | 75.7 (8.6) | 68.6 (13.1) | 11 | 11 | - |
| Conradi, L ²² | 2013 | Retrospective | SMV repair | 95 | 76 | 72.4 (8.1) | 64.5 (11.4) | 5 | 6 | - |
| Feldman, T 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 SAP |
| Geis, N ³³ | 2017 | Retrospective | OMT | 86 | 69 | 68.2 (11) | 53.4 (13) | 24 | 24 | Coumadin for at least 4 weeks post implantation |
| Giannini, C ³⁴ | 2016 | Retrospective | OMT | 60 | 60 | 74 (8) | 76 (8) | 17 | 17 | - |
| Krawczyk-Ozog, A ³⁵ | 2018 | Retrospective | OMT | 10 | 23 | 71.8 (7.8) | 73.0 (11.5) | 4 | 4 | - |
| Obadia, J-F 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, T ³⁶ | 2016 | Retrospective | Minimally invasive MV repair | 24 | 48 | 75 (9) | 76 (4) | 34 | 30 | - |
| Paranskaya, L ³⁷ | 2013 | Retrospective | SMV repair | 24 | 26 | 80 (5) | 63 (12) | 12 | 12 | 3 months DAPT, followed by SAPT indefinitely |
| Stone, GW ¹⁶ | 2018 | RCT-COAPT | OMT | 302 | 312 | 71.7 (11.8) | 72.8 (10.5) | 22.7 | 16.5 | 6 months DAPT |
| Taramasso, M ¹⁸ | 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.

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.

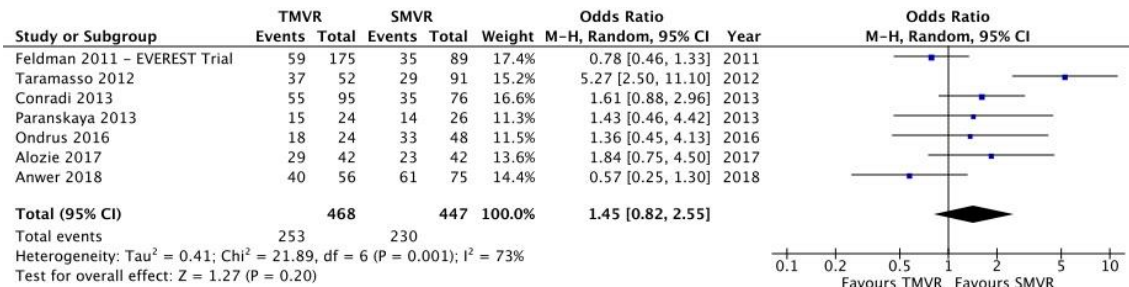


Figure 4- TMVR vs. SMVR - Previous atrial fibrillation

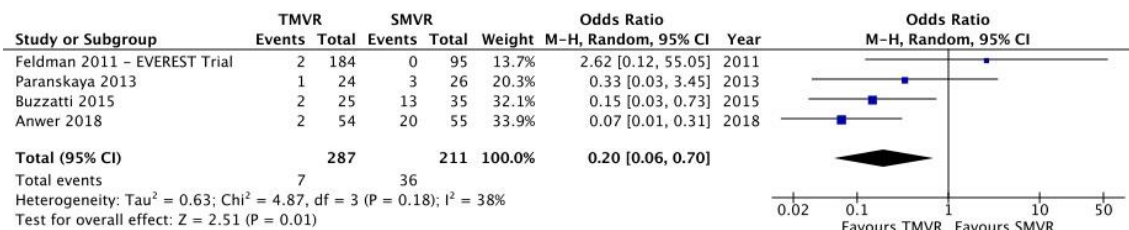


Figure 5- TMVR vs. SMVR - De novo atrial fibrillation

There was no significant difference in stroke incidence between TMVR and SMVR (pooled OR 0.49 [0.17, 1.42], P=0.19, I²= 0%, Figure 6). The cumulative meta-analysis showed a significantly lower stroke rate in TMVR compared with SMVR (OR 0.4 [0.40, 0.67], P< 0.05, Figure 7). This result was evident from 2013, after adding Conradi²² to the previous studies (OR 0.46 [0.17, 1.20], P< 0.05).

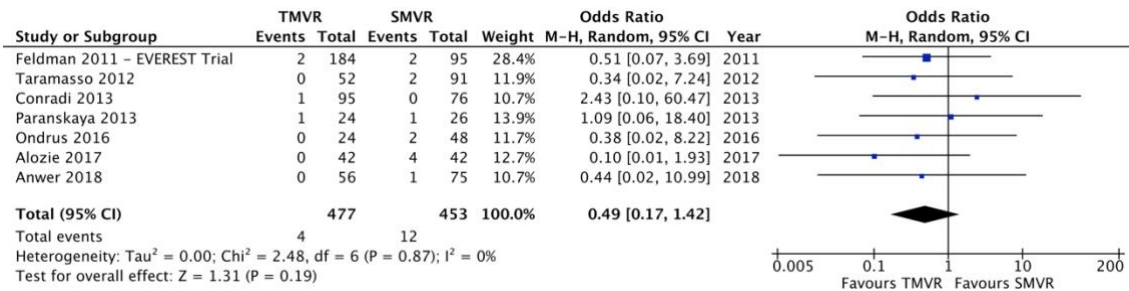


Figure 6- TMVR vs. SMVR - All stroke incidence

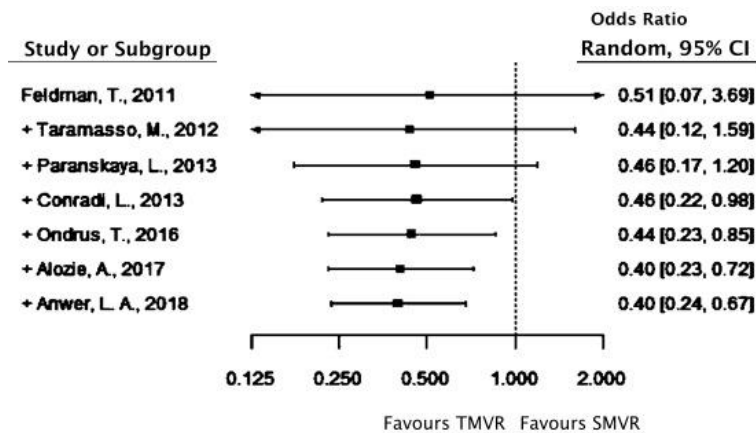


Figure 7- TMVR vs. SMVR - All stroke incidence, Cumulative Meta-analysis

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 (Appendices 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; $R_2 = 0.013$, Appendix 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).

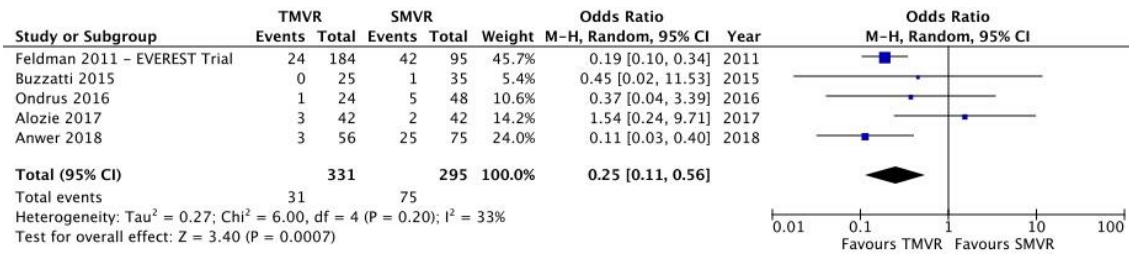


Figure 8- TMVR vs. MV Surgery – Bleeding events

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, I²=0%, Figure 9).

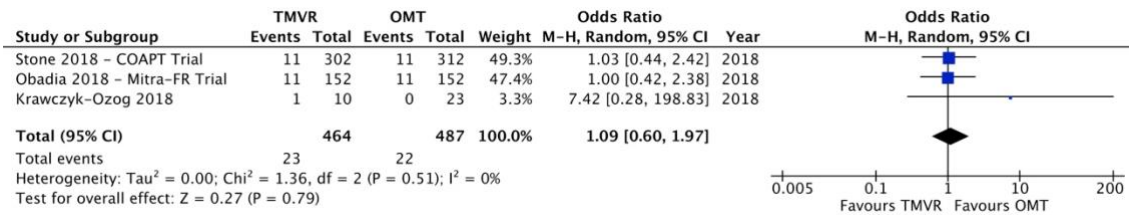


Figure 9- TMVR vs. OMT - All stroke incidence

Discussion and Limitations

According to our meta-analysis in the context of MR treatment: (i) there was a lower stroke rate for patients submitted to TMVR compared to SMVR; (ii) there was a similar stroke rate for patients treated with TMVR when compared to patients allocated to OMT; and (iii) 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 comorbidity¹. 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 group²³. 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 trial¹⁷ showed that both treatments were similar regarding adverse effects, but the COAPT trial¹⁶ 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 arrhythmia²⁴. 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 decision²⁵.

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 direction²⁶. Cumulative meta-analysis is still not a widely used statistical tool, but 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 TMVR 1-year survival rate, but did not address specific post-procedure adverse events or *de novo* AF¹³. 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 ²⁹. 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 prothesis⁹. 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 atrium⁴⁻⁷.

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 is a low number of pooled events. We tried to overcome this limitation by applying a continuity correction and a cumulative meta-analysis²⁸. Regarding pooled stroke, data was not available for fatal versus non-fatal stroke, haemorrhagic stroke and transient ischemic attack.

Conclusion

According to our methodology, post-procedure stroke rate was lower 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.

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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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Appendices

PubMed Search

Date: 5/12/2018

| | |
|---|--------|
| Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND ((English[lang] OR French[lang] OR Portuguese[lang] OR Spanish[lang])))) AND "Stroke"[Mesh]Filters: English; French; Portuguese; Spanish | 9 |
| #30 Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND "Mitral Valve Insufficiency"[Mesh] Filters: English; French; Portuguese; Spanish | 844 |
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| #28 Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND "Mitral Valve Insufficiency"[Mesh] Filters: English; French | 843 |
| #27 Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND "Mitral Valve Insufficiency"[Mesh] Filters: English | 839 |
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| #24 Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND "Mitral Valve Insufficiency"[Mesh] Filters: published in the last 5 years | 714 |
| #23 Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND "Mitral Valve Insufficiency"[Mesh] Filters: Humans | 667 |
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| #20 Search (((((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "last 5 years"[PDat]) OR (((((mitraclip[Title/Abstract] OR "mitral valve clip"[Title/Abstract] OR "mitral clip"[Title/Abstract]) AND "Mitral Valve Insufficiency"[Mesh])) AND "Mitral Valve Insufficiency"[Mesh] | 118083 |
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| #18 Search "Stroke"[Mesh] | 488 |
| #17 Search "mitral clip" | 893 |
| #16 Search "mitral valve clip" | |
| #15 Search mitraclip | |

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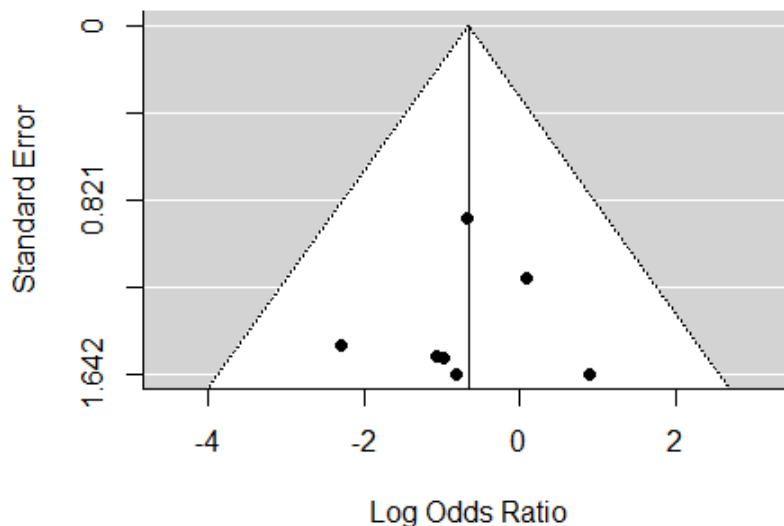
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Embase search

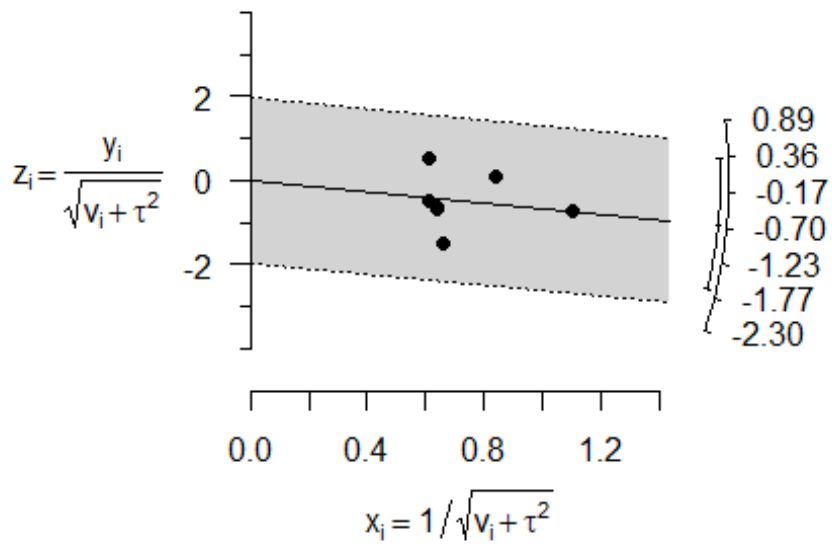
Date: 5/12/2018

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| #7 #5 AND 'article'/it AND ('clip'/de OR 'implantable clip'/de) | 520 |
| #6 | #5 AND 'article'/it 920 |
| #5 | #2 OR #3 OR #4 2,563 |
| #4 | mitral AND clip 2,024 |
| #3 | mitraclip 2,188 |
| #2 | mitral valve clip' 426 |

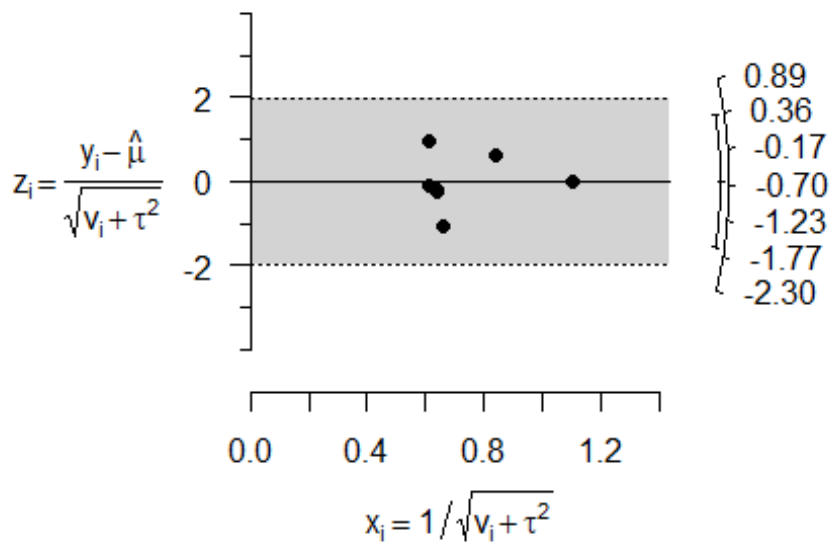
Appendix 1- Search equation



Appendix 2- Funnel plot

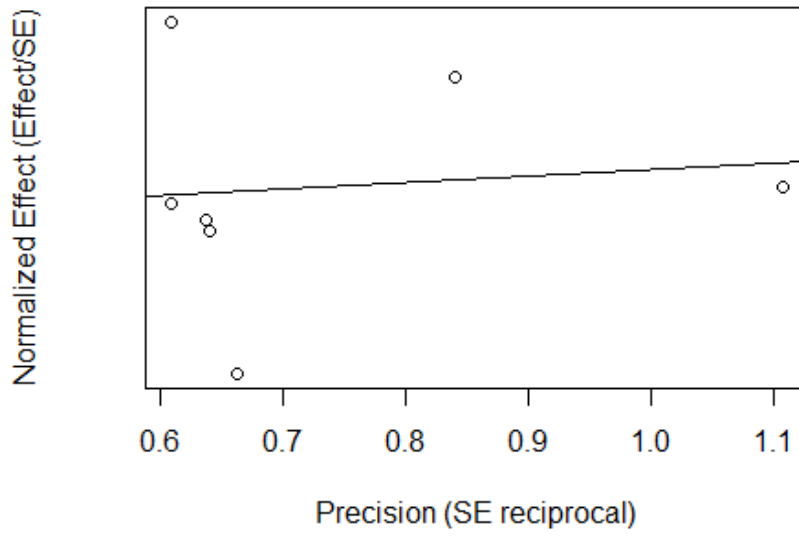


Appendix 3- Galbraith Plot



Appendix 4- Normalized Galbraith Plot

Egger Regression



Appendix 5- Egger regression

Supplements

Supplement 1- European Society of Cardiology Congress - Abstract

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| Miss Patricia Coimbra Barros da Silva (EUD ID : 910002) | |
| 3045-160 - Coimbra Portugal Email : apatriciabarrosdasilva@gmail.com | |
| Title : | Is stroke an issue after transcatheter mitral valve repair? A systematic review and meta-analysis |
| Topic : | 25.3.2 - Mitral Valve Intervention |
| Category : | Bedside |
| Option : | Young Investigator Award (YIA) Clinical |
| P. Barros Da Silva ¹ , J P. Sousa ² , B. Oliveiros ¹ , H. Donato ² , L. Goncalves ¹ , R. Teixeira ¹ - (1) Faculty of Medicine of the University of Coimbra, Coimbra, Portugal (2) University Hospitals of Coimbra, Cardiology, Coimbra, Portugal | |
| <p>Background: Transcatheter mitral valve repair (TMVR) is a minimally invasive therapeutic procedure used as an alternative to surgery for mitral valve regurgitation in high risk patients. This technique creates a double orifice area, which might be comparable to a mitral prosthesis or mitral stenosis. So far, no strict antithrombotic therapy has been recommended and different post-procedure protocols are being currently applied.</p> <p>Objectives: To assess stroke rate after TMVR, comparing it with surgical mitral valve repair (SMVR) and optimal medical treatment (OMT).</p> <p>Methods: We systematically searched PubMed, Embase and Cochrane databases, in December 2018, for both interventional or observational studies comparing TMVR with SMVR and/or OMT in the treatment of severe mitral regurgitation. Only studies including data on post-procedure stroke incidence were selected. Two authors independently screened articles for inclusion, risk of bias and data extraction. Random-effects meta-analysis for TMVR, SMVR and OMT were performed. Due to the low number of pooled events, a cumulative meta-analysis was subsequently implemented. The meta-analysis was registered on the Prospero database.</p> <p>Results: 15 studies were selected for qualitative analysis and, among these, 10 were included in the quantitative analyses (7 of TMVR vs. SMVR and 3 of TMVR vs. OMT), providing a total of 1881 patients. TMVR patients were older and had higher surgical risk scores than SMVR patients. Groups were homogeneous regarding previous atrial fibrillation rate (pooled OR 1.45 [0.82-2.55]), whereas post-procedure de novo atrial fibrillation was more frequent in SMVR when compared with TMVR (pooled OR 0.20 [0.06-0.7]). Although the pooled stroke rate was numerically lower in the TMVR group, there was no statistically difference in the stroke incidence between TMVR and SMVR (pooled OR 0.49 [0.17, 1.42], p=0.19, I²= 0%) - Panel A. On the other hand, cumulative meta-analysis was able to show a significantly lower stroke rate in TMVR, when compared to SMVR (OR 0.4 [0.40, 0.67], p< 0.05). As for TMVR vs. OMT, no difference in stroke rate was identified (pooled OR 1.09 [0.60, 1.97], p=0.79, I²=0%) - Panel B.</p> <p>Conclusions: Post-procedure TMVR stroke rate was similar to that of patients managed with OMT only. For the same outcome, results favored TMVR when compared with SMVR, which might be related to its lower incidence of post-procedure de novo atrial fibrillation. These findings may prove insightful to future recommendations regarding the conundrum of the best antithrombotic strategy, particularly for patients with atrial fibrillation.</p> | |

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- (11) Impact on daily practice
- (12) Acknowledgements, if appropriate
- (13) Funding
- (14) Conflict of interest statement
- (15) References
- (16) Figure legends
- (17) Appendices, if applicable
- (18) Tables in text form
- (19) Figures
- (20) Moving image legends, if applicable.

You may find it useful to use the above list as a checklist.



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Enquiries

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