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1 Mitral transcatheter edge to edge repair versus isolated mitral surgery for severe mitral regurgitation: a
2 French nationwide study

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33 Running title: TEER versus mitral surgery for severe MR.

34 Keys words: MitraClip, surgery, TEER, mitral valve replacement.

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3 **Abstract**

4 **Background and Aims** Mitral valve surgery and more recently mitral transcatheter edge-to-edge
5 repair (TEER) are the two treatments of severe mitral regurgitation in eligible patients. Clinical
6 comparison of both therapies remains limited by the number of patients analysed. The objective
7 of this study was to analyse the outcomes of mitral TEER versus isolated mitral valve surgery at a
8 nationwide level in France.

9 **Methods** Based on the French administrative hospital-discharge database, the study collected
10 information for all consecutive patients treated for mitral regurgitation with isolated TEER or
11 isolated mitral valve surgery between 2012 and 2022. Propensity score matching was used for the
12 analysis of outcomes.

13 **Results** A total of 57,030 patients were found in the database. After matching on baseline
14 characteristics, 2,160 patients were analysed in each arm. At 3-year follow-up, TEER was
15 associated with significantly lower incidence of cardiovascular death (HR 0.685, 95% CI 0.563-
16 0.832; p=0.0001), pacemaker implantation and stroke. Non-cardiovascular death (HR 1.562, 95%
17 CI 1.238-1.971; p=0.0002), recurrent pulmonary edema and cardiac arrest were more frequent
18 after TEER. No significant differences between the two groups were observed regarding all-cause
19 death (HR 0.967, 95% CI 0.835-1.118; p=0.65), endocarditis, major bleeding and atrial
20 fibrillation and myocardial infarction.

21 **Conclusions** Our results suggest that TEER for severe mitral regurgitation was associated with
22 lower cardiovascular mortality than mitral surgery at long-term follow-up. Pacemaker
23 implantation and stroke were less frequently observed after TEER.

24
25 **Key words:** Mitraclip, surgery, TEER, mitral valve replacement.

27 **INTRODUCTION**

28 Mitral regurgitation (MR) is recognized as the most frequent acquired valvular disease
29 worldwide, with a prevalence increasing with age ⁽¹⁾. However, in a large European survey, it
30 was shown that a suboptimal proportion of patients with severe MR were referred for surgical
31 treatment and often at an advanced stage of the disease ⁽²⁾. Developed over the years,

1 transcatheter edge-to-edge repair (TEER) has offered a less invasive therapy for patients
2 suffering of severe MR. Originally designed for the treatment of primary MR, two large
3 randomized trials showed that TEER is safe and effective for secondary MR treatment, compared
4 to optimal medical therapy (3,4). Interestingly, in those two randomized trials TEER appeared
5 superior to medical therapy mostly in more severe MR associated with less left ventricular
6 damage.

7 The MitraClip® system (Abbott Vascular, Santa Clara, CA, USA) received CE mark
8 approval in 2008. This therapy has been introduced in France by the end of the year 2010 and
9 over the last 10 years, indications for TEER and number of patients treated have increased
10 consistently (5,6).

11 While European guidelines recommend consideration of TEER for high surgical risk or
12 inoperable patients only in both primary and secondary MR (class of recommendation IIb),
13 American guidelines tend to favour TEER in patients with primary MR or secondary MR and
14 poor left ventricular function (class of recommendation 2A). (5,6) Although randomized trials are
15 ongoing in high and intermediate surgical risk patients, comparisons of mitral surgery versus
16 TEER are still rare in the literature (7,8).

17 The French Programme de Médicalisation des Systèmes d'Information (PMSI), a
18 mandatory administrative database, offers a unique opportunity to assess exhaustive and
19 comprehensive data on all consecutive TEER and isolated mitral valve surgery performed in
20 France. Therefore, based on this large, nationwide, administrative French database, we aimed to
21 compare long-term outcomes of mitral TEER versus isolated mitral valve surgery in patients with
22 severe MR.

23

24 **METHODS**

25 **Study design**

26 This longitudinal cohort study was based on the national hospitalization database covering
27 hospital care from the entire French population. The data for all patients admitted with severe
28 MR in France from January 2012 to June 2022 were collected from the national administrative
29 PMSI database, which was inspired by the US Medicare system. Through this program, which
30 was implemented in 2004, medical activity is recorded in a database, computed, and rendered
31 anonymous. It includes more than 98% of the French population (67 million people) from birth

1 (or immigration) to death (or emigration), even if a person changes occupation or retires. Each
2 hospitalization is encoded in a standardized dataset, which includes information about the patient
3 (age and sex), hospital, stay (date of admission, date of discharge, and mode of discharge),
4 pathologies, and procedures. Routinely collected medical information includes the principal
5 diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded
6 according to the International Classification of Diseases, Tenth Revision (ICD-10). All medical
7 procedures are recorded according to the national nomenclature, Classification Commune des
8 Actes Medicaux (CCAM). The PMSI contains individual pseudoanonymised information on each
9 hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for
10 each patient. The reliability of PMSI data has already been assessed and this database has
11 previously been used to study patients with cardiovascular conditions such as severe MR,
12 including comparison of transcatheter cardiac intervention versus cardiac surgery (^{9 10}).

13 The study was conducted retrospectively and, as patients were not involved in its conduct,
14 there was no impact on their care. Ethical approval was not required, as all data were
15 anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures
16 for data collection and management were approved by the Commission Nationale de
17 l'Informatique et des Libertés (CNIL), the independent National Ethics Committee protecting
18 human rights in France, which ensures that all information is kept confidential and anonymous, in
19 compliance with the Declaration of Helsinki (authorization number 1897139).

20

21 **Study population**

22 From 1 January 2012 to 30 June 2022, 598,036 adults (age ≥ 18 years) were hospitalized and had
23 a diagnosis of MR (I34.0 using ICD-10 codes) as the principal diagnosis (i.e., the health problem
24 that justified admission to hospital), the related diagnosis (i.e., potential chronic disease or health
25 state during the hospital stay), or a significantly associated diagnosis (i.e., comorbidity or
26 associated complication). For the analysis of mitral TEER procedures, we included all adults with
27 a single percutaneous procedure (CCAM code: DBBF198). For the analysis of isolated mitral
28 valve surgery procedures, we included all adults with a single procedure of valve repair or
29 replacement (CCAM codes: DBKA010, DBKA005, DBMA003, DBMA002, DBMA007,
30 DBMA013, DBMA005). We defined a specific subgroup of patients who underwent isolated
31 surgical mitral valve repair by excluding mitral replacement (DBKA010 DBKA002 DBKA009

1 DBKA005). Patient information (demographics, comorbidities, medical history, and events
2 during hospitalization or follow-up) was described using data collected in the hospital records.
3 For each hospital stay, combined diagnoses at discharge were obtained. Each variable was
4 identified using ICD-10 codes. Exclusion criteria were age <18 years.

5 Distinction between primary and secondary MR is difficult when using nationwide
6 analysis due to the same ICD-10 code being used for both entities. However, a previous analysis
7 of the French nationwide cohort did define criteria to help distinguish primary (patients had to be
8 free from prior history of ischaemic/dilated cardiomyopathy, coronary disease, myocardial
9 infarction and coronary artery bypass graft or other cardiac surgery) and secondary (patients with
10 secondary MR had to have at least one of the above-mentioned associated conditions in their
11 medical history) MR (¹⁰).

12

13 **Outcomes**

14 Patients were followed until 30 June 2022 for the occurrence of outcomes. We aimed to evaluate
15 the incidence of all-cause death, cardiovascular death, ischemic stroke, rehospitalization for
16 pulmonary oedema, myocardial infarction, major or life-threatening bleeding, new onset of atrial
17 fibrillation, endocarditis, cardiac arrest and pacemaker implantation. Definitions of events and
18 statistical analysis were in accordance with the Mitral Valve Academic Research Consortium
19 consensus document (¹). The endpoints were evaluated with follow-up starting from date of either
20 TEER or surgery until date of each specific outcome or date of last news in the absence of the
21 outcome. Information on outcomes during follow-up was obtained by analysing the PMSI codes
22 for each patient. All-cause death, heart failure, ischemic stroke, endocarditis, cardiac arrest,
23 myocardial infarction, major or life-threatening bleeding, new onset of atrial fibrillation and
24 permanent pacemaker implantations were identified using their respective ICD-10 or procedure
25 codes. Mode of death (cardiovascular or non-cardiovascular) was identified based on the main
26 diagnosis during hospitalization resulting in death. Rehospitalization was considered to be due to
27 heart failure when heart failure was recorded as the first diagnosis. A supplemental analysis did
28 compare outcomes between isolated surgical mitral valve repair and TEER. Clinical outcomes
29 during the first 3 months and after the first 3 months were analyzed.

30

31

1 **Statistical analysis**

2 Qualitative variables are described as frequency and percentages and quantitative variable as
3 means (standard deviations [SDs]). Comparisons were made using chi-square tests for categorical
4 variables and the Student *t*-test or non-parametric Kruskal–Wallis test, as appropriate, for
5 continuous variables.

6 Due to the non-randomized nature of the study, and considering for significant differences
7 in baseline characteristics and year of intervention, propensity-score matching was used to
8 control for potential confounders of the treatment outcome relationship. Propensity scores were
9 calculated using logistic regression with treatment (i.e. TEER or surgery) as the dependent
10 variable. The propensity score included all baseline characteristics listed in Table 1. For each
11 patient with TEER, a propensity score-matched patient with surgery was selected (1:1) using the
12 one-to-one nearest neighbour method (with a calliper of 0.05 of the SD of the propensity score on
13 the logit scale) and no replacement. We assessed the distributions of demographic data and
14 comorbidities in the two cohorts with standardized differences, which were calculated as the
15 difference in the means or proportions of a variable divided by a pooled estimate of the SD of
16 that variable. A standardized mean difference of 5% or less indicated a negligible difference
17 between the means of the two cohorts.

18 A Cox-analysis adjusted on all variables selected for the propensity matching was
19 performed.

20 For the analysis in the matched cohort, we report outcomes of interest during the whole
21 follow up. ~~The number of patients with newly diagnosed outcomes in number per person time of~~
22 ~~follow up in each subgroup of patients were compared using Poisson regression to yield an~~
23 ~~incidence rate ratio (IRR).~~ The incidence rates (%/year) for each outcome of interest during
24 follow-up was estimated in both groups and compared using incidence rate ratio. The
25 corresponding asymptotic two-sided 95% confidence interval (CI) of the hazard ratio (HR) was
26 reported. Subgroups analysis has been performed to analyse incidental outcomes in TEER and
27 surgical groups. P-values are reported without and with correction for multiple comparisons using
28 Bonferroni correction (a correction of 4 was defined as appropriate to counteract the multiple
29 comparisons issues). All analyses were performed using Enterprise Guide 7.1 (SAS Institute Inc.,
30 SAS Campus Drive, Cary, NC, USA), and STATA version 12.0 (Stata Corp, College Station,
31 TX, USA).

1 **RESULTS**

2 **Baseline characteristics**

3 Between 1 January 2012 and 30 June 2022, 598,036 patients suffering from severe MR were
4 identified in the database, including 57,030 patients who underwent either isolated mitral valve
5 surgery or isolated mitral TEER (Figure 1 and Table 1). In the unmatched population, patients
6 treated with TEER were older, with higher rates of cardiovascular risk factors, vascular disease,
7 chronic kidney disease and percutaneous coronary intervention history (Table 1). Of note patients
8 with mitral surgery were more often included in the early years of the analysis, while patients
9 with TEER were more often included later.

10 After propensity score matching, there were 2,160 patients in each group. Baseline
11 characteristics in these populations were well matched (Table 1).

12

13 **Clinical outcomes**

14

15 Clinical outcomes during follow-up are reported in supplemental Table 1 (unmatched cohort) and
16 Table 2 (matched cohort). In the matched population, mean (SD) follow-up was 1.0 (1.2) year
17 (median 0.4, interquartile range 0.1-1.7, minimum 0 maximum 6 years).

18 No significant differences was reported between TEER and mitral surgery (HR 0.967, 95% CI
19 0.835-1.118; p=0.65) for all-cause death. Cardiovascular death was reported in 172 patients after
20 TEER (7.96%) versus 247 after surgery (11.44%) (HR 0.685, 95% CI 0.563-0.832; p=0.0001;
21 Figure 2). Non-cardiovascular death was more frequently reported after TEER (HR 1.562, 95%
22 CI 1.238-1.971; p=0.0002).

23 TEER was associated with significantly lower incidence of pacemaker implantation (HR 0.685,
24 95% CI 0.559-0.838; p=0.0002), stroke (HR 0.653, 95% CI 0.442-0.965; p=0.03).

25 TEER was associated with significantly higher incidence of recurrent pulmonary oedema (HR
26 2.089, 95% CI 1.326-3.291; p=0.002) and cardiac arrest (HR 1.572, 95% CI 1.027-2.404;
27 p=0.04).

28 Atrial fibrillation (HR 0.890, 95% CI 0.666-1.189; p=0.43), endocarditis (HR 0.944, 95% CI
29 0.625-1.428; p=0.79), major bleeding (HR 0.896, 95% CI 0.677-1.187; p=0.44), and myocardial
30 infarction (HR 1.125, 95% CI 0.554-2.284; p=0.74) did not differ significantly between the two
31 groups.

1 A Cox-adjusted analysis on all variables selected in the propensity matching is presented
2 in supplementary analysis (supplemental Table 2). Similar results were obtained with lower
3 incidence of cardiovascular mortality after TEER (HR 0.782, 95% CI 0.697-0.878; $p < 0.0001$). A
4 supplementary analysis taking into account endocarditis within the propensity matching
5 parameters is provided in supplemental analysis (supplemental Tables 3 and 4), as well as
6 outcomes analysis within the first 3 months and after the first 3 months following mitral
7 intervention (supplemental Tables 5 and 6).

8 For both all-cause mortality and cardiovascular mortality, we found a significant
9 interaction of EuroSCORE II and age with incidence of those outcomes (Supplemental Tables
10 Tables 7 and 8). EuroSCORE II ≥ 4 was associated with significantly lower incidence of all-
11 cause death (HR for interaction 0.489, 95% CI 0.361-0.663; p -value for interaction < 0.0001) and
12 cardiovascular death (HR for interaction 0.487, 95% CI 0.322-0.736; p -value for interaction
13 =0.0006) after TEER versus surgery in comparison with those with EuroSCORE II < 4 .
14 Similarly, in patient older than 75 years TEER was associated with lower all-cause death (HR for
15 interaction 0.627, 95% CI 0.453-0.870; p -value for interaction =0.005) and cardiovascular death
16 (HR for interaction 0.611, 95% CI 0.391-0.955; p -value for interaction =0.03) compared to those
17 younger than 75 years old.

18 Comparison between isolated surgical mitral valve repair (excluding replacement) and
19 TEER are provided in supplemental analysis (supplemental Tables 9 and 10).

21 DISCUSSION

22
23 We report here the most contemporary data and the largest analysis of mitral TEER versus
24 isolated mitral valve surgery in unselected patients with severe MR seen at a nationwide level. In
25 this propensity score-matched analysis, TEER was associated with lower rates of cardiovascular
26 mortality compared with isolated mitral valve surgery for the treatment of severe MR (Structured
27 Graphical Abstract).

28 In a large European survey, it was shown that a relatively low number of patients with
29 severe MR was referred for surgery, indicating an unmet need for severe MR treatment (²).
30 Patients were often treated at an advanced stage of disease, due to age, high operative risk and
31 late referral (²). Since its introduction, a marked increase in the number of annual TEER has been

1 observed in different European countries, confirming the wide adoption and safety of TEER ⁽¹¹⁾.
2 Indeed, in our database, we observed a significant increase in TEER use in France over the last
3 10 years. In French population, such as in previous reports, patient risk factors differ significantly
4 between those undergoing surgery versus TEER. Patients undergoing TEER remained typically a
5 sicker population at baseline and may, therefore, be at increased risk for adverse events ⁽¹²⁾. In
6 our cohort including all TEER and isolated mitral surgery in France, non-cardiovascular death
7 was significantly more frequent in the TEER group compared to surgery. This may be related to
8 more fragile and comorbid patients undergoing TEER and potentially to factors not taken into
9 account in the matching process. However, over time, the potential improvement in TEER device
10 implantation and physicians' expertise may have led to a shift in patient characteristics for
11 eligibility, procedural success, and ultimately clinical outcomes. Overall, the lower incidence for
12 cardiovascular death following TEER is in favour of the benefit of this treatment in current
13 indications and practices at a nationwide level.

14 MR can be divided into two different subtypes. In primary MR, the pathology of the valve
15 leaflets or chordae represent the origin of the disease and a correction of the MR is curative. In
16 secondary MR, the mitral leaflets are anatomically normal, and distortion of the mitral valve
17 apparatus secondary to left ventricular or left atrial disease results in MR. Therefore, in secondary
18 MR therapeutic intervention to reduce MR might be beneficial but remains debated. Two recent
19 large randomized trials did compare TEER versus optimal medical therapy in secondary MR ^(3,4).
20 Following their results, the last European guidelines recommend considering TEER versus
21 surgery in symptomatic patients who fulfil the echocardiographic criteria of eligibility and
22 judged inoperable or at high surgical risk by the Heart Team ⁽⁵⁾. However, despite a large
23 population of patients treated with medical therapy only, both mitral surgery and TEER remain
24 the two only invasive treatments of severe MR in both subtypes. TEER and surgery have been
25 compared mainly in the setting of primary MR in the EVEREST II trial ⁽¹³⁾ that showed
26 comparable mortality rates in both treatments despite more reintervention after TEER. However,
27 no large comparisons of surgery versus TEER are available in secondary MR, while meta-
28 analysis of data is in favour of lower mortality of TEER in this scenario ⁽¹⁴⁾. Interestingly, we
29 found an interaction between lower all-cause death incidence after mitral TEER versus isolated
30 mitral surgery and secondary MR in our cohort. However, primary and secondary MR may not be
31 easily firmly classified in all patients, and we can only speculate on the benefit of TEER versus

1 surgery in each subset, since we could not precisely distinguish between primary and secondary
2 MR in our sample data from an administrative database. The adoption of TEER technique over
3 time has shown a shift from a vast majority of primary MR cases during the initial experience to
4 a significant proportion of secondary MR treated with TEER ⁽¹¹⁾. This is likely because surgical
5 results are discouraging in those complex patients, while TEER has proved to be an effective
6 treatment compared to medical therapy ^(3,4). Our nationwide analysis represents a real-world
7 sample, which includes all TEER implantations from every high-volume as well as low-volume
8 centre in France during the last 10 years, for both primary and secondary MR. Despite these
9 limitations, the clinical outcomes of TEER in a real-life population of patients with severe MR
10 are encouraging.

11 The two largest meta-analyses comparing surgery to TEER for severe MR included only
12 1,171 patients in total (pooled TEER and surgery). Those meta-analysis showed higher residual
13 MR after TEER but lower bleeding and pacemaker implantation. The Authors concluded that
14 TEER and surgery have similar short- and long-term mortality, despite higher risk in the TEER
15 group, up to 5 years ^(15, 16). Those results were similar in both primary and secondary MR.
16 Previous propensity matched analysis suggested that TEER was associated with higher survival
17 up to 1-year follow-up, and thereafter surgery was more beneficial on death, likely related to
18 higher MR recurrence rates. ⁽¹⁷⁻¹⁹⁾ Our results differ from those conclusions as cardiovascular
19 mortality was lower in TEER up to 2.5 years and thereafter the curves did cross. It should be
20 noted that the mean follow-up was 1.0 year and the mean year of inclusion for TEER was 2020
21 compared to 2017 for surgery before matching, and 2020 for both after matching, indicating that
22 TEER procedures increased over the studied period. This relatively short follow-up may favour
23 the percutaneous strategy. Interestingly, the analysis of outcomes within the first 3 months and
24 after the first 3 months provide the same trends. Percutaneous strategy, being a less invasive
25 approach, is associated with earlier benefit, while surgical intervention is associated with
26 improved long-term outcomes. Physicians will still have to select the patients who will be likely
27 to benefit from long-term effects of surgery. Moreover, our results are particularly interesting in
28 showing interaction between age >75 years and EuroSCORE II $\geq 4\%$ and cardiovascular
29 mortality after TEER versus surgery. This emphasizes the fact that some group of patients may
30 benefit from a less invasive approach. Intermediate risk patients treated with TEER or surgery
31 have been evaluated in a German cohort ⁽¹²⁾ that showed similar in-hospital mortality rates in this

1 cohort. In our analysis, it seems that the older and at intermediate to high risk patient derives
2 most of benefit from percutaneous MR correction, which likely mirror the adoption of TEER in
3 France nowadays.

4 **Limitations**

5 We acknowledge several limitations of our work. A main limitation is inherent to the
6 retrospective, observational nature of the study and its potential residual confounding and biases.
7 Further, the study was based on administrative data, with limitations inherent to such
8 methodology. The PMSI database has limited granularity and contains diagnoses coded using
9 ICD-10, which are obtained at hospital discharge and are the physician's responsibility. Data
10 were not systematically externally checked and this could have caused information bias.
11 However, the large scale of the database is likely to partly compensate this bias and, as coding of
12 complications is linked to reimbursement and is regularly controlled, it is expected to be of good
13 quality.

14 Moreover, we were unable to discern primary and secondary severe MR due to the same
15 ICD-10 code being used for both entities. However, based on previous publication we tried to
16 distinguish both MR aetiologies. However, this limitation should be taken in the context now that
17 TEER is FDA approved for both functional and degenerative MR. Additionally, there is no ICD-
18 10 diagnosis code for right-sided heart failure and therefore could not accounted for. Similarly,
19 specific surgical technique (neo chordae, annulus etc.) could not be properly differentiated, such
20 as failed mitral repair attempts. Moreover, details of the TEER procedure (number of clips, type
21 of clips...) were not available. We included both replacement and repair in surgical arm to allow
22 inclusion of primary and secondary MR as we could not accurately differentiate those origins
23 from the PMSI database. Even if repair should be favoured as surgical therapy, in real-life a
24 significant proportion of patient do not benefit from this technique due anatomical or other
25 factors such as severe left ventricular dysfunction.

26 Our large population of patients admitted for either TEER or surgical mitral valve surgery
27 likely represents a heterogeneous group of patients admitted with various kinds of illnesses and
28 severities, which may have affected prognosis. We were not able to evaluate specific
29 echocardiographic and procedural risk factors such as biological parameters, left ventricular

1 ejection fraction, MR severity, pulmonary hypertension, right ventricular function or extent of
2 coronary disease. Lastly, patients with ischemic MR may have been excluded from the surgical
3 group due to the exclusion of patients undergoing concomitant coronary artery bypass grafting.

4 Further, the non-randomised design of the analysis leaves a risk of residual confounding
5 factors. Definite conclusions for comparisons between groups may not be fully appropriate even
6 though multivariable matching was done, as it cannot fully eradicate the possible confounding
7 variables between these groups. Non-cardiovascular death was found to be more frequent after
8 TEER without clear explanation. This may induce a competing risk bias with potential reduction
9 of the number of cardiovascular deaths. Another limitation is the lack of information on optimal
10 medical therapy used, as drug therapies were not available in the database.

11

12 **CONCLUSIONS**

13 This analysis included the largest propensity matched comparison of mitral TEER versus isolated
14 mitral valve surgery for patients with severe MR. During a median follow-up of 1 year (and
15 maximum of 6 years) we observed that mitral TEER was associated with lower rates of
16 cardiovascular death, pacemaker implantation and stroke. Non-cardiovascular death, recurrent
17 pulmonary oedema and cardiac arrest were more frequent after TEER. No significant differences
18 were observed regarding all-cause death, endocarditis, major bleeding, atrial fibrillation and
19 myocardial infarction. We observed a significant interaction between age >75 years and
20 EuroSCORE II $\geq 4\%$ and reduced cardiovascular and all-cause mortality after TEER versus
21 surgery. These data should be confirmed in ongoing dedicated randomized trials.

22 **References**

- 23 1. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, et al. Clinical Trial
24 Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and
25 Replacement: Part 1: Clinical Trial Design Principles. *J Am Coll Cardiol* 2015;**66**:278–307.
- 26 2. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, et al. Contemporary
27 presentation and management of valvular heart disease: the EURObservational Research
28 Programme Valvular Heart Disease II Survey. *Circulation* 2019;**140**:1156–1169.
- 29 3. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous
30 Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med*
31 2018;**379**:2297–2306.

- 1 4. Stone GW, Abraham WT, Lindenfeld J, Kar S, Grayburn PA, Lim DS, et al. Five-Year
2 Follow-up after Transcatheter Repair of Secondary Mitral Regurgitation. *N Engl J Med*
3 2023.
- 4 5. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al, ESC
5 National Cardiac Societies. 2021 ESC/EACTS Guidelines for the management of valvular
6 heart disease: Developed by the Task Force for the management of valvular heart disease of
7 the European Society of Cardiology (ESC) and the European Association for Cardio-
8 Thoracic Surgery (EACTS). *Eur Heart J* 2022;**43**:561–632.
- 9 6. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020
10 ACC/AHA guideline for the management of patients with valvular heart disease: executive
11 summary: a report of the American College of Cardiology/American Heart Association
12 Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2021;**77**:450–500.
- 13 7. Piriou N, Al Habash O, Donal E, Senage T, Le Tourneau T, Pattier S, et al. The MITRA-HR
14 study: design and rationale of a randomised study of MitraClip transcatheter mitral valve
15 repair in patients with severe primary mitral regurgitation eligible for high-risk surgery.
16 *EuroIntervention* 2019;**15**:e329–e335.
- 17 8. McCarthy PM, Whisenant B, Asgar AW, Ailawadi G, Hermiller J, Williams M, et al.
18 Percutaneous MitraClip Device or Surgical Mitral Valve Repair in Patients With Primary
19 Mitral Regurgitation Who Are Candidates for Surgery: Design and Rationale of the
20 REPAIR MR Trial. *J Am Heart Assoc* 2023;**12**:e027504.
- 21 9. Deharo P, Bisson A, Herbert J, Lacour T, Etienne CS, Porto A, et al. Transcatheter valve-in-
22 valve aortic valve replacement as an alternative to surgical re-replacement. *J Am Coll*
23 *Cardiol* 2020;**76**:489–499.
- 24 10. Messika-Zeitoun D, Candolfi P, Enriquez-Sarano M, Burwash IG, Chan V, Philippon JF, et
25 al. Presentation and outcomes of mitral valve surgery in France in the recent era: a
26 nationwide perspective. *Open Heart* 2020;**7**:e001339.
- 27 11. Bardeleben RS von, Hobohm L, Kreidel F, Ostad MA, Schulz E, Konstantinides S, et al.
28 Incidence and in-hospital safety outcomes of patients undergoing percutaneous mitral valve
29 edge-to-edge repair using MitraClip: five-year German national patient sample including
30 13,575 implants. *EuroIntervention* 2019;**14**:1725–1732.
- 31 12. Frankenstein L, Kaier K, Katus HA, Bode C, Wengenmayer T, von Zur Mühlen C, et al.
32 Impact of the introduction of percutaneous edge-to-edge mitral valve reconstruction on
33 clinical practice in Germany compared to surgical valve repair. *Clin Res Cardiol*
34 2021;**110**:620–627.
- 35 13. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized
36 comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of
37 EVEREST II. *J Am Coll Cardiol* 2015;**66**:2844–2854.

- 1 14. Felbel D, Paukovitsch M, Förg R, Stephan T, Mayer B, Keßler M, et al. Comparison of
2 transcatheter edge-to-edge and surgical repair in patients with functional mitral regurgitation
3 using a meta-analytic approach. *Front Cardiovasc Med* 2022;**9**:1063070.
- 4 15. Wang TKM, Chatfield A, Wang MTM, Ruygrok P. Comparison of percutaneous MitraClip
5 versus mitral valve surgery for severe mitral regurgitation: a meta-analysis: Mitraclip and
6 mitral valve surgery meta-analysis. *AsiaIntervention* 2020;**6**:77–84.
- 7 16. Oh NA, Kampaktsis PN, Gallo M, Guariento A, Weixler V, Staffa SJ, et al. An updated
8 meta-analysis of MitraClip versus surgery for mitral regurgitation. *Ann Cardiothorac Surg*
9 2021;**10**:1-14.
- 10 17. Buzzatti N, Van Hemelrijck M, Denti P, Ruggeri S, Schiavi D, Scarfò IS, et al.
11 Transcatheter or surgical repair for degenerative mitral regurgitation in elderly patients: a
12 propensity-weighted analysis. *J Thorac Cardiovasc Surg* 2019;**158**:86–94.
- 13 18. Gyoten T, Schenk S, Rochor K, Herwig V, Harnath A, Grimmig O, et al. Outcome
14 comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced
15 left ventricular dysfunction. *ESC Heart Fail* 2020;**7**:1781–1790.
- 16 19. Okuno T, Praz F, Kassab M, Biaggi P, Mihalj M, Külling M, et al. Surgical versus
17 transcatheter repair for secondary mitral regurgitation: a propensity score–matched cohorts
18 comparison. *J Thorac Cardiovasc Surg* 2023;**165**:2037–2046.e4.

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20 **Figures legends**

21

22 **Figure 1: Flow chart.**

23

24 **Figure 2: Incidence of cardiovascular mortality in the TEER and mitral surgery groups.**

25 IRR: incident rate ratio; TEER: transcatheter edge-to-edge repair

26

27 **Structured graphical abstract: Outcomes of mitral transcatheter edge-to-edge repair versus**
28 **isolated mitral surgery for the treatment of severe mitral regurgitation.**

29 CV: cardiovascular; FUP: follow-up; TEER: transcatheter edge-to-edge repair

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Table 1. Baseline characteristics of unmatched and matched patients.

| | Before PS matching | | | After PS matching | | | | |
|------------------------------------|---|---|---------|-----------------------------|--|---|------|-----------------------------|
| | Isolated mitral valve surgery (n=52289) | Mitral transcatheter edge-to-edge repair (n=4741) | p | Standardized difference (%) | Isolated mitral valve surgery (n=2160) | Mitral transcatheter edge-to-edge repair (n=2160) | p | Standardized difference (%) |
| Age (years), mean±SD | 65.9±12.3 | 79.7±9.2 | <0.0001 | 113.6 | 76.0±8.5 | 76.0±8.5 | 1.00 | 0.0 |
| Male sex, n (%) | 32153 (61.5) | 2727 (57.5) | <0.0001 | -8.1 | 1253 (58.0) | 1259 (58.3) | 0.85 | 0.6 |
| Hypertension, n (%) | 27954 (53.5) | 3388 (71.5) | <0.0001 | 36.4 | 1451 (67.2) | 1482 (68.6) | 0.31 | 3.1 |
| Diabetes mellitus, n (%) | 7577 (14.5) | 926 (19.5) | <0.0001 | 14.2 | 380 (17.6) | 419 (19.4) | 0.13 | 4.7 |
| Heart failure, n (%) | 33784 (64.6) | 4026 (84.9) | <0.0001 | 43.3 | 1764 (81.7) | 1746 (80.8) | 0.48 | -2.2 |
| History of pulmonary oedema, n (%) | 10887 (20.8) | 617 (13.0) | <0.0001 | -19.5 | 379 (17.6) | 348 (16.1) | 0.21 | -3.8 |
| Aortic stenosis, n (%) | 7911 (15.1) | 742 (15.7) | 0.34 | 1.4 | 349 (16.2) | 345 (16.0) | 0.87 | -0.5 |
| Aortic regurgitation, n (%) | 7205 (13.8) | 626 (13.2) | 0.27 | -1.7 | 317 (14.7) | 310 (14.4) | 0.76 | -0.9 |
| Mitral valve replacement, n (%) | 12842 (24.6) | - | - | - | 549 (25.4) | - | - | - |
| Dilated cardiomyopathy, n (%) | 7132 (13.6) | 1193 (25.2) | <0.0001 | 32.8 | 473 (21.9) | 451 (20.9) | 0.41 | -2.5 |
| Coronary artery disease, n (%) | 19870 (38.0) | 2584 (54.5) | <0.0001 | 33.9 | 1090 (50.5) | 1065 (49.3) | 0.45 | -2.3 |
| Previous MI, n (%) | 3718 (7.1) | 593 (12.5) | <0.0001 | 20.5 | 239 (11.1) | 231 (10.7) | 0.70 | -1.2 |
| Previous PCI, n (%) | 3498 (6.7) | 1120 (23.6) | <0.0001 | 63.0 | 380 (17.6) | 371 (17.2) | 0.72 | -1.1 |
| Previous CABG, n (%) | 7666 (14.7) | 150 (3.2) | <0.0001 | -33.6 | 103 (4.8) | 122 (5.7) | 0.19 | 4.0 |
| Vascular disease, n (%) | 10453 (20.0) | 1615 (34.1) | <0.0001 | 34.6 | 661 (30.6) | 673 (31.2) | 0.69 | 1.2 |
| Atrial fibrillation, n (%) | 34072 (65.2) | 3328 (70.2) | <0.0001 | 10.6 | 1568 (72.6) | 1566 (72.5) | 0.95 | -0.2 |
| Previous pacemaker or ICD, n (%) | 4748 (9.1) | 1069 (22.6) | <0.0001 | 44.9 | 415 (19.2) | 366 (16.9) | 0.05 | -5.9 |
| Ischemic stroke, n (%) | 2677 (5.1) | 207 (4.4) | 0.02 | -3.4 | 115 (5.3) | 113 (5.2) | 0.89 | -0.4 |
| Intracranial bleeding, n (%) | 858 (1.6) | 91 (1.9) | 0.15 | 2.2 | 46 (2.1) | 52 (2.4) | 0.54 | 1.9 |
| Smoker, n (%) | 8073 (15.4) | 754 (15.9) | 0.4 | 1.3 | 359 (16.6) | 335 (15.5) | 0.32 | -3.0 |
| Dyslipidaemia, n (%) | 14908 (28.5) | 1779 (37.5) | <0.0001 | 19.8 | 793 (36.7) | 780 (36.1) | 0.68 | -1.2 |
| Obesity, n (%) | 9156 (17.5) | 965 (20.4) | <0.0001 | 7.4 | 464 (21.5) | 479 (22.2) | 0.58 | 1.7 |
| Alcohol-related diagnoses, n (%) | 2845 (5.4) | 268 (5.7) | 0.54 | 0.9 | 136 (6.3) | 144 (6.7) | 0.62 | 1.5 |
| Chronic kidney disease, n (%) | 4460 (8.5) | 1084 (22.9) | <0.0001 | 48.8 | 335 (15.5) | 380 (17.6) | 0.07 | 5.6 |
| Lung disease, n (%) | 8162 (15.6) | 1083 (22.8) | <0.0001 | 19.6 | 459 (21.3) | 477 (22.1) | 0.51 | 2.0 |
| Sleep apnoea syndrome, n (%) | 3854 (7.4) | 577 (12.2) | <0.0001 | 18.0 | 240 (11.1) | 275 (12.7) | 0.10 | 5.0 |
| COPD, n (%) | 4701 (9.0) | 710 (15.0) | <0.0001 | 20.5 | 285 (13.2) | 303 (14.0) | 0.42 | 2.4 |
| Liver disease, n (%) | 3373 (6.5) | 386 (8.1) | <0.0001 | 6.8 | 198 (9.2) | 183 (8.5) | 0.42 | -2.5 |
| Thyroid diseases, n (%) | 5318 (10.2) | 796 (16.8) | <0.0001 | 21.4 | 340 (15.7) | 325 (15.1) | 0.53 | -1.9 |
| Inflammatory disease, n (%) | 3441 (6.6) | 613 (12.9) | <0.0001 | 24.8 | 246 (11.4) | 254 (11.8) | 0.70 | 1.2 |
| Anaemia, n (%) | 13762 (26.3) | 1545 (32.6) | <0.0001 | 14.2 | 690 (31.9) | 708 (32.8) | 0.56 | 1.8 |

| | | | | | | | | |
|---|------------------|------------------|---------|-------|------------------|------------------|---------|-------|
| Previous cancer, n (%) | 4220 (8.1) | 857 (18.1) | <0.0001 | 35.3 | 358 (16.6) | 353 (16.3) | 0.84 | -0.6 |
| Poor nutrition, n (%) | 6317 (12.1) | 1293 (27.3) | <0.0001 | 45.0 | 490 (22.7) | 522 (24.2) | 0.25 | 3.5 |
| Cognitive impairment, n (%) | 494 (0.9) | 162 (3.4) | <0.0001 | 23.3 | 44 (2.0) | 52 (2.4) | 0.41 | 2.5 |
| Charlson comorbidity index, mean±SD | 3.1±2.8 | 4.2±2.7 | <0.0001 | 37.3 | 3.8±2.8 | 4.0±2.6 | 0.19 | 4.0 |
| Frailty index, mean±SD | 7.0±7.6 | 9.4±8.6 | <0.0001 | 30.6 | 9.1±8.6 | 9.0±8.5 | 0.60 | -1.6 |
| EuroSCORE II, mean±SD | 3.9±1.2 | 3.9±1.2 | 0.29 | 3.2 | 3.9±1.2 | 3.9±1.2 | 0.29 | 3.2 |
| Year of inclusion, median (IQR) | 2017 (2014-2019) | 2020 (2019-2021) | <0.0001 | 108.2 | 2020 (2018-2021) | 2020 (2018-2021) | 1 | 0.0 |
| Previous endocarditis, n (%) | 5977 (11.4) | 119 (2.5) | <0.0001 | -29.0 | 251 (11.6) | 54 (2.5) | <0.0001 | -36.2 |
| PCI in the 2 months pre-procedure, n (%) | 1051 (2.0) | 326 (6.9) | <0.0001 | 31.8 | 94 (4.4) | 112 (5.2) | 0.20 | 3.9 |
| PCI in the 2 months post-procedure, n (%) | 478 (0.9) | 56 (1.2) | 0.07 | 2.8 | 30 (1.4) | 29 (1.3) | 0.90 | -0.4 |

- 1 Values are n (%), mean±SD or median (IQR) for year of inclusion, CABG=coronary artery
- 2 bypass graft; COPD = chronic obstructive pulmonary disease; ICD= Implantable cardiac
- 3 defibrillator; IQR= interquartile range; MI= myocardial infarction; PS= propensity score;
- 4 PCI=percutaneous coronary intervention; SD=standard deviation

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Table 2. Clinical outcomes during follow-up in the matched population.

| | Isolated mitral valve surgery (n=2160) | | | Mitral transcatheter edge-to-edge repair (n=2160) | | | Hazard ratio (95% CI) | P | p (corrected by Bonferroni) |
|------------------------------------|--|------------------|----------------------------|---|------------------|----------------------------|-----------------------|------|-----------------------------|
| | Person-time (patient-year) | Number of events | Incidence, %/year (95% CI) | Person-time (patient-year) | Number of events | Incidence, %/year (95% CI) | | | |
| All-cause death | 2124 | 360 | 16.95 (15.20-18.70) | 2332 | 364 | 15.61 (14.01-17.22) | 0.967 (0.835-1.118) | 0.65 | 1 |
| Cardiovascular death | 2124 | 247 | 11.63 (10.18-13.08) | 2332 | 172 | 7.38 (6.27-8.48) | 0.685 (0.563-0.832) | 0.00 | 0.0004 |
| Non-cardiovascular death | 2124 | 113 | 5.32 (4.34-6.30) | 2332 | 192 | 8.24 (7.07-9.40) | 1.562 (1.238-1.971) | 0.00 | 0.0008 |
| Pulmonary oedema during FU | 2114 | 27 | 1.28 (0.80-1.76) | 2305 | 60 | 2.60 (1.94-3.26) | 2.089 (1.326-3.291) | 0.00 | 0.006 |
| Incident AF | 2039 | 94 | 4.61 (3.68-5.54) | 2253 | 90 | 4.00 (3.17-4.82) | 0.890 (0.666-1.189) | 0.43 | 1 |
| VF / sustained VT / cardiac arrest | 2104 | 34 | 1.62 (1.07-2.16) | 2298 | 57 | 2.48 (1.84-3.12) | 1.572 (1.027-2.404) | 0.04 | 0.15 |
| Pacemaker or ICD | 1928 | 227 | 11.77 (10.24-13.30) | 2188 | 162 | 7.40 (6.26-8.54) | 0.685 (0.559-0.838) | 0.00 | 0.0008 |
| Ischemic stroke | 2092 | 61 | 2.92 (2.19-3.65) | 2302 | 43 | 1.87 (1.31-2.43) | 0.653 (0.442-0.965) | 0.03 | 0.13 |
| Incident MI | 2117 | 14 | 0.66 (0.32-1.01) | 2314 | 17 | 0.74 (0.39-1.08) | 1.125 (0.554-2.284) | 0.74 | 1 |
| Endocarditis | 2094 | 44 | 2.10 (1.48-2.72) | 2301 | 46 | 2.00 (1.42-2.58) | 0.944 (0.625-1.428) | 0.79 | 1 |
| Major bleeding | 2024 | 99 | 4.89 (3.93-5.86) | 2259 | 96 | 4.25 (3.40-5.10) | 0.896 (0.677-1.187) | 0.44 | 1 |
| Cardiovascular death / | 2112 | 266 | 12.59 (11.08- | 2303 | 211 | 9.16 (7.93- | 0.779 (0.650- | 0.00 | 0.03 |

| | | | | | | | | | |
|---|------|-----|---------------------|------|-----|---------------------|---------------------|------|------|
| Pulmonary edema during FU | | | 14.11) | | | 10.40) | 0.934) | 7 | |
| All-cause death / hospitalisation for HF / AF or ischemic stroke during FU | 1998 | 483 | 24.17 (22.02-26.33) | 2200 | 470 | 21.36 (19.43-23.29) | 0.923 (0.813-1.049) | 0.22 | 0.88 |

- 1 FU follow up; AF atrial fibrillation; VF ventricular fibrillation; VT ventricular tachycardia; ICD
- 2 Implantable cardiac defibrillator; MI myocardial infarction; CI confidence interval.
- 3

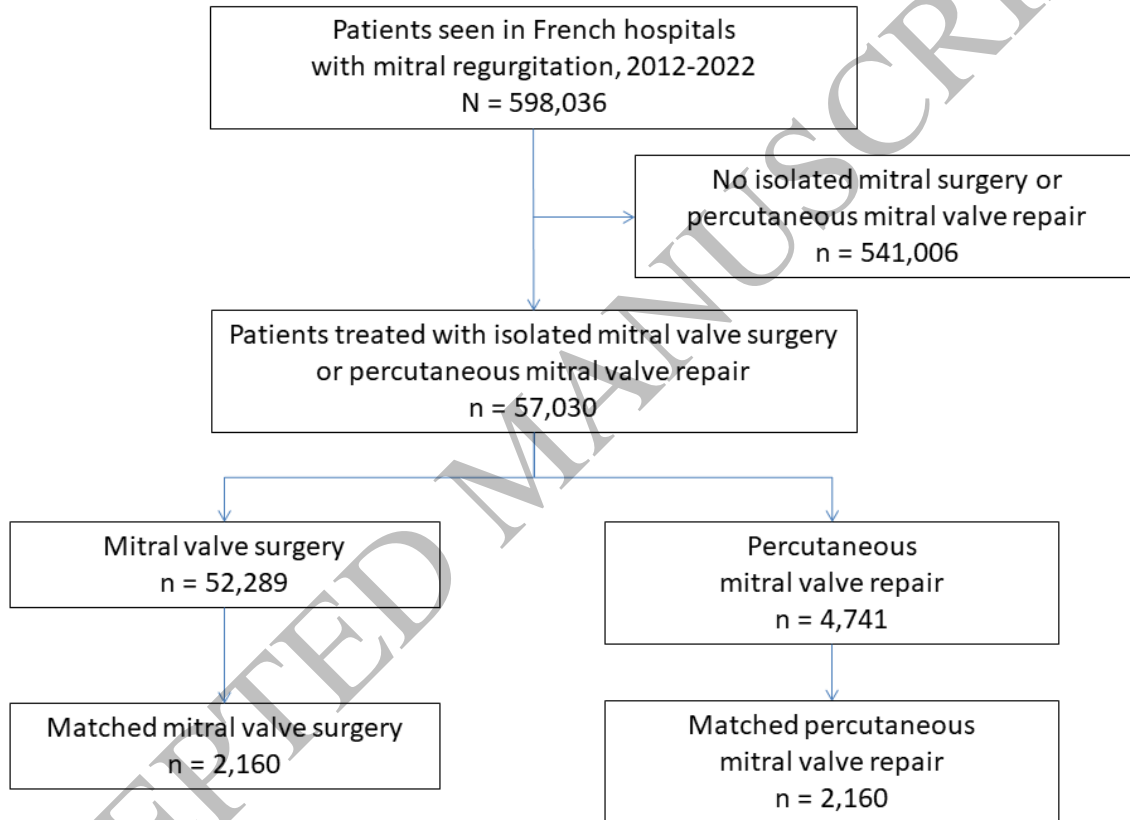
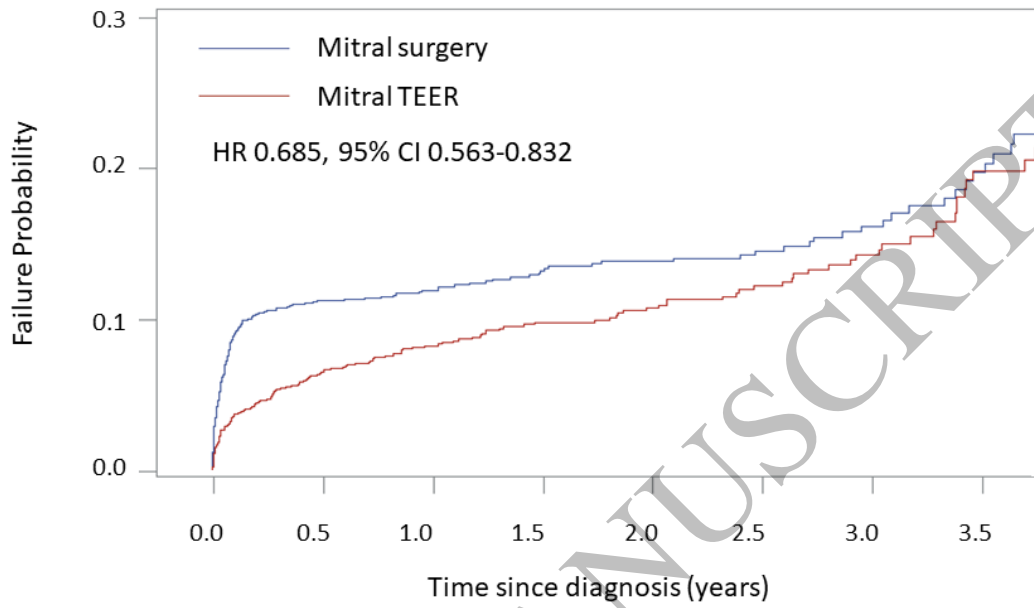


Figure 1
160x120 mm (x DPI)

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Cardiovascular death



| | No at Risk | | | | | | | |
|----------------|------------|------|-----|-----|-----|-----|-----|-----|
| Mitral surgery | 2160 | 988 | 766 | 578 | 446 | 317 | 202 | 130 |
| Mitral TEER | 2160 | 1116 | 845 | 659 | 498 | 345 | 231 | 129 |

Figure 2
160x120 mm (x DPI)

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Key Question

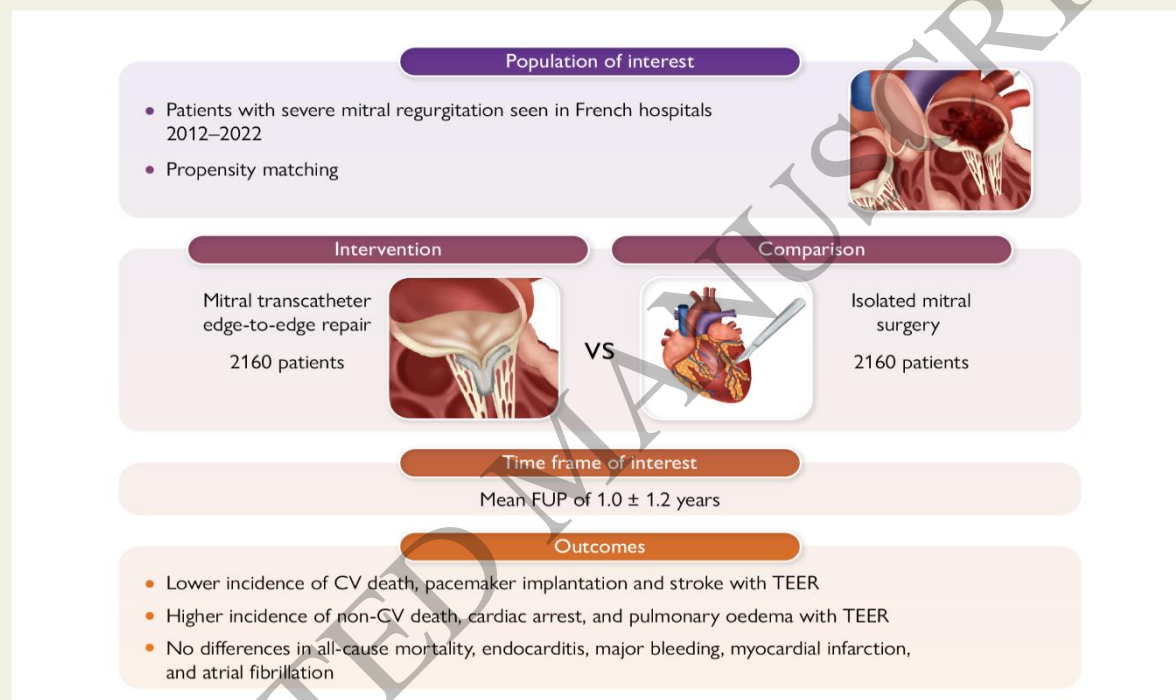
Surgery and more recently transcatheter edge-to-edge repair (TEER) represent the two leading interventions to correct severe mitral regurgitation (MR). However, large and real-life comparisons of both techniques are lacking.

Key Finding

Results from a propensity matched analysis of all patients treated in France between 2012 and 2022 were in favour of lower rates of long-term cardiovascular death, pacemaker implantation and stroke after TEER versus surgery for severe MR. Non-cardiovascular death, recurrent pulmonary oedema and cardiac arrest were more frequent after TEER. No significant differences between the two groups were observed regarding all-cause death, endocarditis, major bleeding, atrial fibrillation and myocardial infarction.

Take Home Message

TEER could be considered as an alternative to mitral surgery, particularly in older patients and patients with EuroSCORE II \geq 4%.



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Graphical Abstract
160x228 mm (x DPI)