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# Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years

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## Aims

The MITRA-FR trial showed that among symptomatic patients with severe secondary mitral regurgitation, percutaneous repair did not reduce the risk of death or hospitalization for heart failure at 12 months compared with guideline-directed medical treatment alone. We report the 24-month outcome from this trial.

## Methods and results

At 37 centres, we randomly assigned 304 symptomatic heart failure patients with severe secondary mitral regurgitation (effective regurgitant orifice area >20 mm<sup>2</sup> or regurgitant volume >30 mL), and left ventricular ejection fraction between 15% and 40% to undergo percutaneous valve repair plus medical treatment (intervention group,  $n = 152$ ) or medical treatment alone (control group,  $n = 152$ ). The primary efficacy outcome was the composite of all-cause death and unplanned hospitalization for heart failure at 12 months. At 24 months, all-cause death and unplanned hospitalization for heart failure occurred in 63.8% of patients (97/152) in the intervention group and 67.1% (102/152) in the control group [hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.77–1.34]. All-cause

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mortality occurred in 34.9% of patients (53/152) in the intervention group and 34.2% (52/152) in the control group (HR 1.02, 95% CI 0.70–1.50). Unplanned hospitalization for heart failure occurred in 55.9% of patients (85/152) in the intervention group and 61.8% (94/152) in the control group (HR 0.97, 95% CI 0.72–1.30).

## Conclusions

In patients with severe secondary mitral regurgitation, percutaneous repair added to medical treatment did not significantly reduce the risk of death or hospitalization for heart failure at 2 years compared with medical treatment alone.

## Keywords

Secondary mitral regurgitation • Heart failure • Percutaneous mitral valve repair

## Introduction

Secondary mitral regurgitation is the consequence of left ventricular and mitral annulus remodelling, which leads to incomplete mitral valve closure through tethering on a structurally normal valvular and subvalvular apparatus. The treatment of the causal disease, i.e. left ventricular dysfunction, relies on medical treatment according to guidelines on heart failure with reduced ejection fraction.<sup>1,2</sup> The rationale for correcting secondary mitral regurgitation is to avoid further volume overload superimposed to the underlying left ventricular disease. This volume overload has been associated with adverse left ventricular remodelling, worse functional status and adverse clinical outcomes.<sup>3</sup> Concerns on risk–benefit analysis, contradictory findings from observational series and the negative findings of a randomized trial account for more restricted indications for the surgical correction of secondary than for primary mitral regurgitation.<sup>4,5</sup> Reduction of the severity of mitral regurgitation may be accomplished safely and efficiently by percutaneous mitral valve repair with the MitraClip device (Abbott Vascular, Abbott Park, IL, USA). Positive results for the correction of secondary mitral regurgitation were first reported in observational studies.<sup>6–8</sup>

The first two randomized trials assessing the efficacy of percutaneous repair exclusively in symptomatic patients with severe secondary mitral regurgitation treated using guideline-directed medical treatment were recently reported and led to contradictory conclusions. The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial did not report any difference in a composite primary outcome of death from any cause or unplanned hospitalization for heart failure at 12 months.<sup>9</sup> Conversely, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial showed a decrease on all hospitalizations for heart failure, all-cause mortality and a composite of all-cause mortality and heart failure hospitalizations within 24 months of follow-up in the percutaneous repair group.<sup>10</sup> Many hypotheses have been suggested to account for these differences in outcomes between both trials.<sup>11–14</sup> One of these hypotheses is a longer follow-up period of 24 months in COAPT.

We therefore conducted a 24-month clinical follow-up of the MITRA-FR trial since longer-term results are of particular interest to determine if there may be a deferred outcome difference.<sup>14</sup>

## Methods

### Study design and oversight

The study design and data management practice have been previously described.<sup>9,15</sup> A total of 304 patients recruited among 37 centres were randomized to percutaneous repair or medical treatment from December 2013 to March 2017. The trial was approved by the French centralized ethics committee and the French National Agency for the Safety of Medicines and Health Products. Written informed consent was obtained from all patients. The study is registered on the Clinicaltrials.gov website under the identifier NCT01920698.

Hospices Civils de Lyon, a French public academic institution, assumed overall responsibility for the trial. The steering committee designed the study protocol. An independent data and safety monitoring board oversaw the safety of the trial. The study was conducted and coordinated by the Clinical Investigation Center of Lyon, which is an academic research organization based at Hospices Civils de Lyon (INSERM 1407). All statistical analyses were performed by the Statistical Department of the Hospices Civils de Lyon.

We obtained the primary funding from the French Ministry of Health and Research National Program. Abbott Vascular provided devices and support for investigators' meetings. Neither Abbott Vascular nor any other commercial entity had a role in trial design, participating centre selection, centre monitoring and oversight, data collection, patient enrolment, patient management, data storage, data analysis, data interpretation, the writing of the manuscript, or the decision to submit the manuscript.

### Patients and randomization

Patient selection has been previously described.<sup>9,15</sup> Briefly, inclusion criteria were patients who had severe secondary mitral regurgitation with a regurgitant volume >30 mL/beat or an effective regurgitant orifice area >20 mm<sup>2</sup> by echocardiography according to the 2012 guidelines of the European Society of Cardiology and European Association for Cardio-Thoracic Surgery.<sup>16</sup> Patients were also required to have a left ventricular ejection fraction between 15% and 40% and chronic heart failure symptoms [New York Heart Association (NYHA) functional class II–IV] with at least one hospitalization for heart failure decompensation in the preceding 12 months.

Prior to randomization, all patients had to undergo a prospective screening protocol including one transthoracic echocardiogram and one transoesophageal echocardiogram, with all echocardiograms being reviewed by an independent centralized core laboratory (Hôpital Bichat, University of Paris Diderot VII, Paris, France) according to the European Association of Echocardiography guidelines.<sup>17</sup>

Patients were then randomly assigned in a 1:1 ratio in permuted blocks, with stratification by study centre, to either percutaneous mitral valve repair plus medical treatment or to guideline-directed medical therapy alone. Each investigator was instructed to up-titrate all guideline driven medical therapies to maximally tolerated doses according to updated European guidelines for medical management of heart failure with reduced left ventricular ejection fraction at the time of inclusion.<sup>1,18</sup> Each eligible patient was included after local discussion within a local Heart Team that comprised at least a heart failure specialist, an interventional cardiologist and a cardiac ultrasound imaging specialist.

## Study device and procedure

The MitraClip device (Abbott Vascular) and percutaneous procedure have been previously described.<sup>9,15</sup> After randomization to the study device intervention group, the procedure was performed within a median of 14 days [interquartile range (IQR) 9–18]. All procedures were performed with technical proctoring from Abbott Vascular.

## Outcomes

The original primary efficacy outcome was the composite of all-cause death or unplanned hospitalization for heart failure at 12 months. The prespecified secondary outcomes were individual components of the primary outcome at 12 months, cardiovascular death, and survival free from major cardiovascular events (the composite of death, stroke, myocardial infarction, or unplanned hospitalization for heart failure). Prespecified serious adverse events included ischaemic stroke, myocardial infarction, renal replacement therapy, peri-procedural complications, and bleeding events at 1 year after randomization. Clinical follow-up was planned at 24 months to evaluate the same prespecified secondary outcomes as at 12 months. Additional prespecified secondary outcome at 24 months were NYHA heart failure class, 6-min walk test distance and brain natriuretic peptide levels. In order to compare with the COAPT trial, all hospitalizations for heart failure within 24 months were added as exploratory endpoint.

Patients were followed for 24 months and had annual clinical visits.

An independent events validation committee adjudicated all serious adverse events to classify them in the corresponding clinical outcomes according to prespecified definition of events. The members of this committee were blinded to treatment assignment.

## Statistical analysis

All the efficacy analyses were carried out according to the intention-to-treat principle.<sup>9</sup> As previously prespecified, all efficacy endpoints were analysed with the Cox's proportional hazard regression model stratified on centre to estimate the treatment effect [hazard ratio (HR) and 95% confidence interval (CI)] on time-to-event data.<sup>19</sup> There was no control for multiplicity when analysing secondary endpoints and subgroups. Kaplan–Meier survival curves were drawn.

The distribution of the number of hospitalizations for heart failure per patient was compared between the two treatment groups with a Wilcoxon rank sum test. The rate of hospitalizations for heart failure per patient-years was calculated and compared between the two treatment groups with a negative binomial generalized linear regression model accounting for overdispersed data and correlated events, using the log of follow-up time as an offset. In addition, the competitive risk of death with the recurrent events process was explored using a joint

frailty model with a Weibull distribution for modelling the baseline hazard.<sup>20</sup>

Changes from baseline were compared between the two groups with the Student's *t*-test, or the Wilcoxon rank-sum test in case of non-normality of the distributions.

A per-protocol analysis was also performed on the primary outcome. This analysis excluded all patients with any protocol deviation and all patients with failure of device implantation; it also excluded all events occurring in the first 21 days after randomization.

A two-sided *P*-value of <0.05 indicates statistical significance. *P*-values for secondary outcomes are not reported because there was no control for multiplicity. All statistical analyses were performed using SAS software version 9.4 in a Windows environment (SAS Institute Inc., Cary, NC, USA).

## Results

### Patients and procedures

Baseline characteristics and clinical outcomes at 1 year have already been reported.<sup>9</sup> A total of 307 patients with secondary mitral regurgitation underwent randomization, 152 to percutaneous repair in addition to medical treatment (intervention group) and 155 to medical treatment alone (control group). Since three patients were excluded from the control group after randomization owing to issues with informed consent, the final control group comprised 152 patients. (online supplementary *Figure S1*). The two study groups had similar characteristics at baseline, with the exception of history of myocardial infarction, which was more common in the intervention group. There were no differences in guideline-directed medical treatment at baseline (online supplementary *Table S1*).

Among the 152 patients in the intervention group, implantation was not attempted in eight patients.<sup>9</sup> Of the 144 patients in whom implantation was attempted, technical device success was achieved in 138 (95.8%) according to the consensus document from the Mitral Valve Academic Research Consortium.<sup>21</sup>

### Efficacy outcomes

All endpoints at 12 months have been reported previously.<sup>9</sup> At 24 months of follow-up, data were available in 149 patients (98.0%) in the intervention group and 140 patients (92.1%) in the control group; the median follow-up was 23.9 months (IQR 11.4–24.6) and 23.5 months (IQR 12.0–24.6), respectively.

In the intention-to-treat analysis, death from any cause or unplanned hospitalization for heart failure at 24 months occurred in 97 patients (63.8%) in the intervention group and 102 patients (67.1%) in the control group (HR 1.01, 95% CI 0.77–1.34) (*Table 1* and *Figure 1*). At 24 months, a total of 53 deaths (34.9%) occurred in the intervention group and 52 (34.2%) in the control group (HR 1.02, 95% CI 0.70–1.50) (*Figure 2A*). Of the patients randomized to the intervention group, 85 (55.9%) had at least one unplanned hospitalization for heart failure as compared with 94 (61.8%) in the control group (HR 0.97, 95% CI 0.72–1.30) (*Table 1* and *Figure 2B*). All other major cardiovascular events are summarized in *Table 1*.

**Table 1** Clinical efficacy outcomes and prespecified serious adverse events at 24 months (intention-to-treat population)

	From baseline to 24 months			From baseline to 12 months			From 12 to 24 months		
	Intervention group	Control group	HR (95% CI)	Intervention group	Control group	HR (95% CI)	Intervention group	Control group	HR (95% CI)
<b>Primary outcome<sup>a</sup></b>									
Time at risk (patient-years)	152	156		93	100		59	56	
No. (rate per 100 patient-year)	97 (63.8)	102 (65.4)	1.01 (0.77–1.34)	83 (89.2)	78 (78.0)	1.17 (0.86–1.59)	14 (23.7)	24 (42.9)	0.54 (0.28–1.06)
<b>Secondary outcomes<sup>b</sup></b>									
Death from any cause									
Time at risk (patient-years)	230	229		127	130		103	99	
No. (rate per 100 patient-year)	53 (23.1)	52 (22.8)	1.02 (0.70–1.50)	37 (29.1)	34 (26.2)	1.12 (0.70–1.78)	16 (15.5)	18 (18.2)	0.86 (0.44–1.69)
Cardiovascular death									
Time at risk (patient-years)	230	229		127	130		103	99	
No. (rate per 100 patient-year)	47 (20.5)	48 (21.1)	0.99 (0.66–1.48)	33 (26.0)	31 (23.8)	1.10 (0.67–1.79)	14 (13.6)	17 (17.2)	0.80 (0.39–1.63)
Unplanned hospitalization for heart failure									
Time at risk (patient-years)	152	156		93	100		59	56	
No. (rate per 100 patient-year)	85 (55.9)	94 (62.3)	0.97 (0.72–1.30)	74 (79.6)	72 (72.0)	1.13 (0.81–1.56)	11 (18.6)	22 (39.3)	0.47 (0.22–0.98)
Major adverse cardiovascular events <sup>c</sup>									
Time at risk (patient-years)	149	156		92	100		57	56	
No. (rate per 100 patient-year)	99 (66.4)	102 (65.4)	1.05 (0.79–1.39)	86 (93.5)	78 (78.0)	1.22 (0.89–1.66)	13 (22.8)	24 (42.9)	0.52 (0.26–1.04)
<b>Prespecified serious adverse events – no. (rate per 100 patient-year)</b>									
All serious adverse events	129 (84.9)	128 (82.1)	NA	125 (134.4)	121 (121.0)	NA	4 (6.8)	7 (12.5)	NA
Heart transplantation or mechanical cardiac assistance	7 (4.6)	9 (5.8)	NA	6 (6.4)	9 (9.0)	NA	1 (1.7)	0 (0.0)	NA
Ischemic or haemorrhagic Stroke	7 (4.6)	3 (1.9)	NA	7 (7.5)	1 (1.0)	NA	0 (0)	2 (3.6)	NA
Myocardial infarction	0 (0)	3 (1.9)	NA	0 (0)	2 (2.0)	NA	0 (0)	1 (1.8)	NA
Need for renal-replacement therapy	6 (3.9)	2 (1.3)	NA	5 (5.4)	1 (1.0)	NA	1 (1.7)	1 (1.8)	NA
Severe haemorrhage <sup>d</sup>	13 (8.6)	6 (3.8)	NA	11 (11.8)	6 (6.0)	NA	2 (3.4)	0 (0.0)	NA
Infections	32 (21.1)	30 (19.2)	NA	28 (30.1)	27 (27.0)	NA	4 (6.8)	3 (5.4)	NA

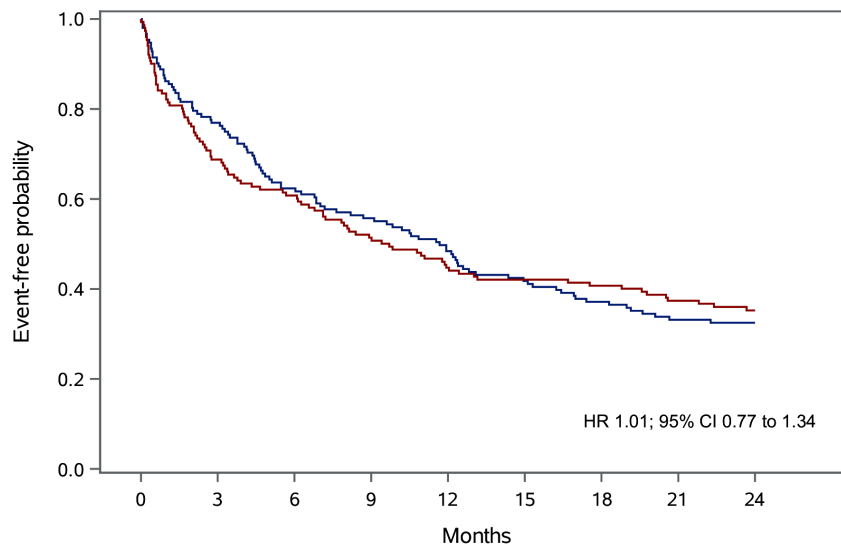
CI, confidence interval; HR, hazard ratio; NA, not applicable.

<sup>a</sup>Death from any cause or unplanned hospitalization for heart failure.

<sup>b</sup>The number of the components of the composite primary outcome does not total the rates of the composite because patients could have more than one event.

<sup>c</sup>This category is a composite of death, stroke, myocardial infarction, or unplanned hospitalization for heart failure.

<sup>d</sup>Severe haemorrhage was defined as bleeding that was categorized as type 2 or higher, according to the modified Bleeding Academic Research Consortium (BARC) bleeding scale,<sup>21</sup> which ranges from type 0 (no bleeding) to type 5b (definite fatal bleeding), with type 2 indicating any overt, actionable sign of bleeding.



	Intervention	Control group	Intervention group
Control group	152	116	94
Intervention group	151	103	91

**Figure 1** Kaplan–Meier estimates of survival without a primary outcome event. Probability of survival without a primary outcome event (death from any cause or unplanned hospitalization for heart failure) in the two trial groups (Kaplan–Meier curves according to individual study outcomes are reported in Figure 2). CI, confidence interval; HR, hazard ratio.

Results from the per-protocol analysis were consistent for all endpoints with the intention-to-treat analysis (Table 2).

## Adverse events

Prespecified serious adverse events are reported in Table 1. Most events occurred during the first 12 months.

## Recurrent hospitalizations for heart failure

The total number of hospitalizations for heart failure within 24 months was 159 in the intervention group and 186 in the control group (Figure 3). The rate of all hospitalizations for heart failure was 88.3 per 100 patient-years in the intervention group and 106.9 per 100 patient-years in the control group (HR derived from the joint frailty model, 0.87; 95% CI 0.56–1.35).

## Other outcomes

Functional status and natriuretic peptides are reported in the online supplementary Table S2. An analysis of NYHA class with imputed results for missing data was performed; these results are shown in the online supplementary Figure S2.

## Prespecified subgroup analysis

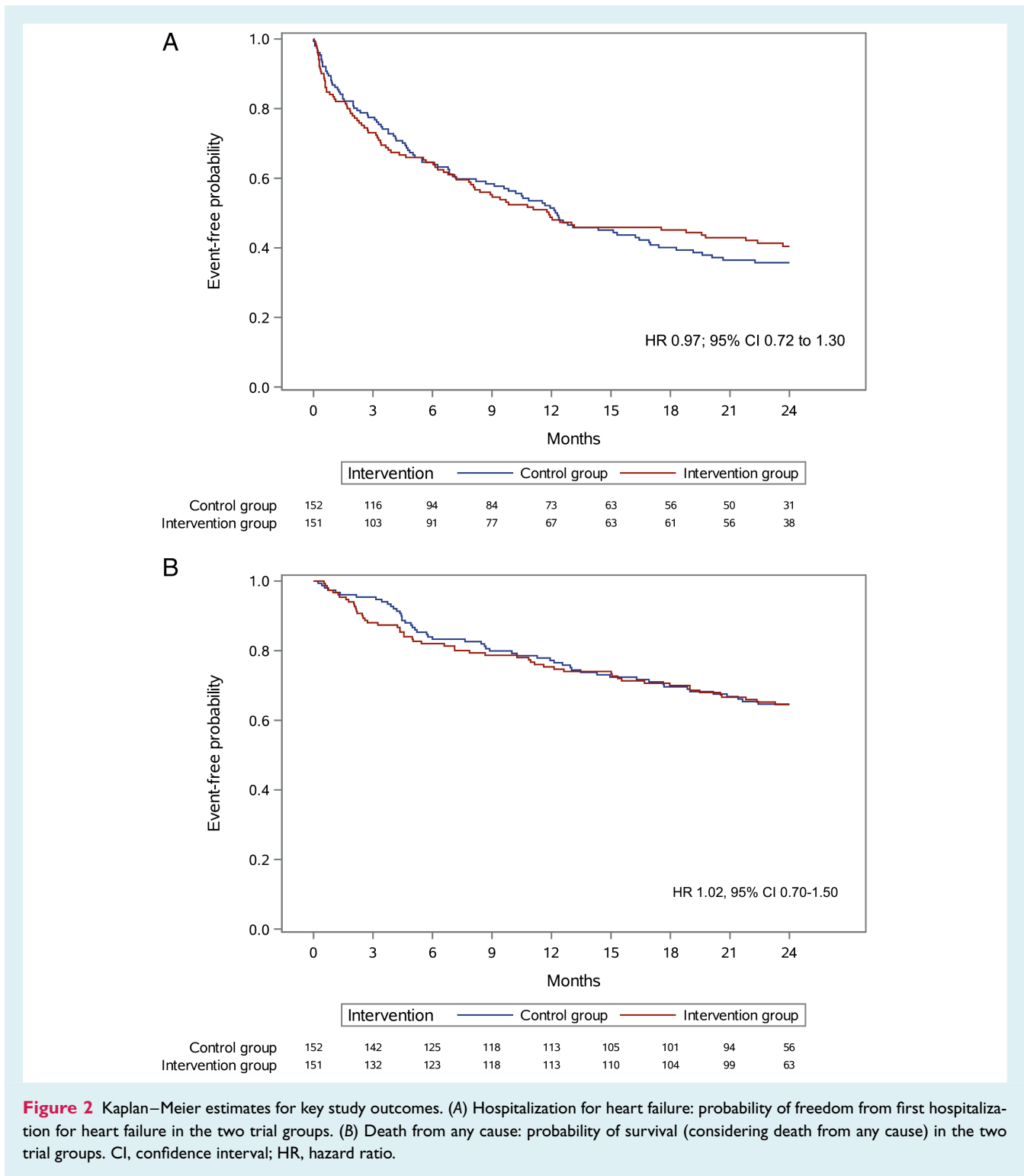
All prespecified subgroups for death from any cause or unplanned hospitalization for heart failure at 24 months with their confidence

intervals are presented in the online supplementary Figure S3. The only variable with a significant interaction with the treatment effect at 24 months was baseline creatinine level. All other interaction terms with subgroup characteristics were not significant.

## Discussion

This analysis of the 24-month outcome of the patients enrolled in the MITRA-FR trial confirms the absence of significant difference in the rate of the composite outcome of death from any cause or unplanned hospitalization for heart failure in symptomatic patients with severe secondary mitral regurgitation treated by percutaneous mitral valve repair plus medical treatment as compared with those receiving medical treatment alone. The safety of percutaneous repair is further confirmed by the very small number of prespecified serious adverse events.

As in any trial showing an absence of difference, concerns were raised on a possible lack of statistical power of the analysis of 12-month outcome.<sup>13</sup> One-year results are confirmed and strengthened by the persistent absence of any difference in the analysis of 24-month outcome of the study population, which takes into account a higher number of events. It should be stressed that all patients alive were followed 24 months after inclusion. As in the analysis of 12-month outcome, the absence of significant difference at 24 months was consistent for death, hospitalization for heart failure and cumulated rates of hospitalizations for heart failure. The consistency between the different endpoints at 24 months and with the results of the per-protocol analysis attests of the robustness of



**Figure 2** Kaplan–Meier estimates for key study outcomes. (A) Hospitalization for heart failure: probability of freedom from first hospitalization for heart failure in the two trial groups. (B) Death from any cause: probability of survival (considering death from any cause) in the two trial groups. CI, confidence interval; HR, hazard ratio.

the findings of MITRA-FR. The mortality rate in the control group was consistent with previous studies in patients with moderate or severe secondary mitral regurgitation.<sup>3</sup>

A deferred benefit of percutaneous repair may have been possible since the decrease in mortality was more marked during the second year following percutaneous repair in the COAPT trial.<sup>10</sup>

The analysis of events occurring between 12 and 24 months in MITRA-FR shows a decreased rate of first hospitalization for heart failure in the intervention group. This is consistent with the visually observed divergence of the curves of recurrent hospitalizations for heart failure, although the difference was not statistically significant at 24 months (as shown by the width of the CI). This repeat-event

**Table 2 Primary efficacy endpoint and secondary efficacy endpoints at 24 months in the per-protocol population<sup>a</sup>**

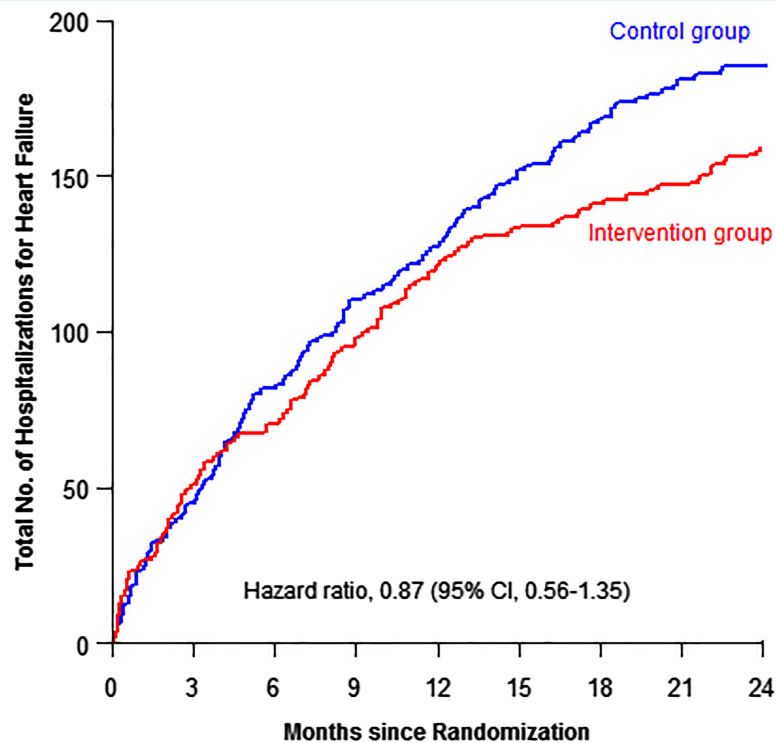
	Percutaneous repair group (n = 109)	Medical treatment group (n = 137)	HR <sup>b</sup> (95% CI)
Composite primary outcome: death from any cause or unplanned hospitalization for heart failure, n (%)	70 (64.2)	94 (68.6)	1.04 (0.76–1.42)
Secondary outcomes, n (%)			
Death from any cause	37 (33.9)	48 (35.0)	0.99 (0.64–1.52)
Cardiovascular death	34 (31.2)	44 (32.1)	0.99 (0.63–1.55)
Unplanned hospitalization for heart failure	64 (58.7)	87 (63.5)	1.03 (0.74–1.43)
Major adverse cardiovascular events <sup>c</sup>	72 (66.1)	94 (68.6)	1.09 (0.80–1.48)

CI, confidence interval; HR, hazard ratio.

<sup>a</sup>The 24-month efficacy analysis and major adverse event analyses included 109 patients in the intervention group and 137 patients in the control group. In this per-protocol analysis, we excluded patients in the percutaneous repair who did not undergo a successful device implantation, who did not fulfil one of the selection criteria (hospitalization for heart failure within 24 months; cardiac resynchronization therapy within 3 months), or who had a device implantation after 21 days following randomization. In this per-protocol analysis, heart failure hospitalization events that occurred before device implantation within the 21 days following randomization were not counted for both study groups.

<sup>b</sup>HRs were calculated with the use of stratified Cox proportional models. The 95% CIs were not corrected for multiple testing; therefore, these intervals should not be used to infer definitive treatment effects.

<sup>c</sup>This category is a composite of death, stroke, myocardial infarction, or unplanned hospitalization for heart failure.



**Figure 3** Cumulated rates of recurrent hospitalizations for heart failure. Cumulative incidence of all hospitalizations for heart failure within 24 months of follow-up among patients who underwent percutaneous mitral valve repair and guideline-directed medical therapy (intervention group) and among those who received guideline-directed medical therapy alone (control group). The data shown here do not account for the competing risk of death, which was considered in the joint frailty model. CI, confidence interval.



analysis was used as main endpoint in the COAPT trial and tends to amplify the difference as compared with the analysis of the time to first event.<sup>22</sup> As any exploratory analysis of secondary endpoints, the interpretation of such an isolated finding should be viewed cautiously, in particular due to the width of the CI and requires confirmation. Overall, in MITRA-FR at 24 months, there were no significant differences in the rates of hospitalizations for heart failure, whatever the endpoint considered.

In our view, one of the main reasons for the different results between COAPT and MITRA-FR trials is patient selection. Differences in inclusion criteria led to more severe mitral regurgitation, less pronounced left ventricular remodelling, lower pulmonary pressure and better right ventricular function in the COAPT than in the MITRA-FR trial.<sup>10</sup> In addition, the run-in period assessed by a central eligibility committee was likely to result in more optimized guideline-directed medical therapy at inclusion in COAPT than in MITRA-FR. However, this scheme may be difficult to translate in everyday practice, which is characterized by a rare, despite desirable, optimization of guideline-directed therapy.<sup>23</sup> Of note, there was a marked functional improvement in the control groups of both COAPT and MITRA-FR trials. In the COAPT trial, the percentage of patients in NYHA class I or II increased from 35.4% before randomization to 55.7% at 12 months. These findings may be partly related to a better patient follow-up and management in randomized trials than in real life. Finally, regurgitation grades are not standardized and grading is likely to differ between the two core laboratories, in particular due to difficulties of regurgitation quantitation in a double mitral orifice.<sup>24,25</sup> This limits the relevance of a head-to-head comparison of the degree of post-procedural severity of mitral regurgitation between the two trials.

The challenge is now to identify more accurately patients who will derive a clinical benefit from percutaneous repair. This is unlikely to be derived from the sole findings of MITRA-FR, in particular due to the lack of significant difference in endpoints between the two groups and the expected low statistical power of subgroup analyses. An individual participant data meta-analysis from the COAPT and MITRA-FR trials is now planned to help identify those patients with secondary mitral regurgitation who are the most likely to respond or not respond to percutaneous repair. At the present time, pooling the population of COAPT and MITRA-FR represent the best opportunity to refine indications of percutaneous repair in secondary mitral regurgitation in a large population of patients with a wide range of characteristics at inclusion. The ongoing RESHAPE II trial may be taken into account in future meta-analyses to further increase the statistical power. This will provide the opportunity to study combined criteria of regurgitation severity, which improve risk stratification in patients with secondary mitral regurgitation.<sup>26</sup> Several expert-reviews have suggested to take into account the respective severity of mitral regurgitation and left ventricular remodelling, but this has not been specifically studied in patients undergoing interventions on the mitral valve.<sup>11,27,28</sup> The usefulness of such a multifactorial approach to refine the selection of patients with secondary mitral regurgitation should be the subject of further analyses.

## Limitations

Cross-overs and procedure failure after randomization resulted in percutaneous repair not performed in 14 patients (9.2%) in the intervention group. However, the consistent findings in primary and secondary endpoints with the per-protocol analysis make unlikely that cross-overs and procedure failure would have been the source of significant bias. We did not present echocardiographic results since some data were missing at 1 year and a core lab analysis was not planned at 24-month follow-up. Missing data limit the relevance of the assessment of functional capacity and natriuretic peptides. The assessment of prespecified primary and secondary endpoints was, however, reliable due to the quality of 24-month clinical follow-up.

## Conclusion

As in the 12-month results of the MITRA-FR trial, the addition of percutaneous mitral valve repair to guideline-directed medical therapy did not significantly decrease the rate of death or unplanned hospitalization for heart failure at 24 months. Further research involving a meta-analysis on individual participant data of the COAPT and MITRA-FR trials, prolonged follow-up and assessment of new indices combining the severity of mitral regurgitation and left ventricular remodelling as predictors of outcome is needed to individualize decision-making in symptomatic patients with secondary mitral regurgitation with a high level of evidence.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1.** MITRA-FR Investigators and Committees.

**Methods S1.** Supplementary methods.

**Figure S1.** Consort diagram.

**Figure S2.** Evolution of the NYHA class at 12 months and 24 months compared to inclusion. Worst-case scenario.

**Figure S3.** Subgroup analyses for death from any cause or hospitalization for heart failure at 24 months.

**Table S1.** Baseline characteristics and medical therapy of the patients in the intention-to-treat population.

**Table S2.** Six-minute walk test and natriuretic peptides end points at 24 months in the intention-to-treat population.

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