

The MITRA-FR study: design and rationale of a randomised study of percutaneous mitral valve repair compared with optimal medical management alone for severe secondary mitral regurgitation

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KEYWORDS

- edge-to-edge repair
- mitral valve disease
- valvular heart disease

Abstract

Aims: Percutaneous mitral valve repair (pMVR) is a new therapeutic option for mitral valve regurgitation. Positive preliminary results in non-randomised studies have been published supporting the use of the MitraClip system in patients with secondary mitral regurgitation (MR) and poor left ventricular (LV) function contraindicated to surgery. The aim of the MITRA-FR study is to provide a higher level of evidence for the efficacy of the MitraClip device in this setting.

Methods and results: The MITRA-FR study is a national, multicentre, investigator-initiated, open-label, randomised trial to evaluate the benefits and safety of pMVR using the MitraClip system plus optimal medical therapy (OMT) compared with OMT alone (control) in patients with severe symptomatic secondary MR contraindicated to surgical repair. The trial aims to enrol 144 MitraClip-treated subjects and 144 control (OMT alone) patients. The primary endpoint is a composite of all-cause mortality and unplanned hospitalisations for heart failure at 12 months after randomisation.

Conclusions: MITRA-FR is a randomised controlled national trial designed to evaluate the performance of pMVR in comparison to OMT in patients with severe symptomatic secondary MR contraindicated to cardiac surgery.

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Abbreviations

ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor
AHA	American Heart Association
BNP	brain natriuretic peptide
CABG	coronary artery bypass grafting
CE	Conformité Européenne
CRT	cardiac resynchronisation therapy
DSMB	data safety monitoring board
EACTS	European Association of Cardio-Thoracic Surgery
eCRF	electronic case report form
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HF	heart failure
LV	left ventricular
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
MV	mitral valve
MVR	mitral valve repair
NYHA	New York Heart Association
OMT	optimal medical therapy
pMVR	percutaneous mitral valve repair
TAVI	transcatheter aortic valve implantation
TOE	transoesophageal echocardiographic
TTE	transthoracic echocardiographic

Introduction

Mitral regurgitation (MR) is the second most frequent valve disease requiring surgery in European countries¹. MR is separated into primary MR (organic lesion of the valve) and secondary MR (functional MR with dilated ventricles mainly in ischaemic or idiopathic cardiomyopathy). Primary MR remains an indication for surgical mitral valve (MV) repair as confirmed by the European Society of Cardiology (ESC)/European Association of Cardio-Thoracic Surgery (EACTS) and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines^{2,3}.

Conversely, and despite a worse prognosis, surgical indications for secondary MR are still debated due to controversial results and no demonstrated benefit on clinical outcomes. The potential benefit of secondary MR surgical correction is counterbalanced by an increased postoperative mortality and a lower five-year survival rate⁴. These results may be explained by risk factors such as left ventricular dysfunction, advanced age or the presence of comorbidities⁵. Moreover, the recurrence of MR after MV repair is high. The only recommendation class I or IIa surgical indications for severe secondary MR correspond to the association with coronary artery bypass grafting (CABG), while it is only a recommendation class IIb in patients remaining symptomatic despite optimal medical therapy (OMT), including cardiac resynchronisation therapy (CRT) when there is no option for CABG or in patients remaining symptomatic despite OMT^{2,3}. On the other hand, the clinical outcome of unoperated, medically managed patients with secondary MR is poor with 12-month and five-year mortality rates of 20%

and 50%, respectively⁶. This emphasises the need for low-risk procedures to improve this population's survival.

As for aortic valve disease and the emergence over the last decade of transcatheter aortic valve implantation (TAVI), innovative percutaneous approaches have been developed to enable MV repair (MVR) in patients with severe MR^{7,8}. Percutaneous MVR (pMVR) using the MitraClip® system (Abbott Vascular, Santa Clara, CA, USA) is the most advanced of all with more than 15,000 procedures performed worldwide. To date, there are no data from head-to-head comparisons to demonstrate the effectiveness of pMVR in addition to OMT. We describe the design of a randomised controlled trial to assess the clinical efficacy of pMVR plus OMT in comparison to OMT alone in patients with severe secondary MR contraindicated to surgery.

Methods

STUDY DESIGN AND OBJECTIVES

MITRA-FR is a prospective, multicentre, randomised, open-label, controlled study of the MitraClip system for the treatment of severe secondary MR.

The study is being performed according to the principles of the Declaration of Helsinki, and approval has been obtained from ethics committees in France. The study has also received authorisation from the French National Agency for Medicines and Health Products Safety on 23 May 2013 (registration number: 2013-A00464-41). The trial is registered at www.clinicaltrials.gov (identifier: NCT01920698).

All participants give written informed consent prior to enrolment in the study.

The primary objective is to demonstrate that pMVR reduces the occurrence of all-cause mortality or unplanned hospitalisations for heart failure (HF) at 12 months in comparison to OMT alone.

The secondary objectives are to compare the two strategies in terms of morbidity, mortality, safety, quality of life, echocardiographic evaluation, biomarkers, functional evaluation, and cost-effectiveness.

DEVICE AND PROCEDURES

The investigational device is the MitraClip system (Abbott Vascular) designed to perform pMVR of the regurgitant MV. This medical device obtained the Conformité Européenne (CE) certificate in March 2008 and Food and Drug Administration (FDA) approval in October 2013 (with limitation to severe primary MR).

The MitraClip system consists of a clip delivery system and a steerable guide catheter. The implantation procedure starts with a venous femoral access and a transeptal puncture under fluoroscopy, plus two- and three-dimensional transoesophageal echocardiography. The clip delivery system is introduced into the left atrium. The steerable guide is then introduced and the clip is positioned in the middle of the regurgitant jet where the two leaflets are grasped and clipped. After assessment of the decrease in the degree of regurgitation, the decision to deliver or reposition the clip is taken. Additional clip implantation is possible in case of unsatisfactory control of regurgitation.

STUDY POPULATION

Eligible patients include those with severe secondary MR who are contraindicated for heart surgery by a multidisciplinary Heart Team. All inclusion and exclusion criteria are presented in **Table 1** and **Table 2**.

Table 1. Inclusion criteria of the MITRA-FR trial.

- Age >18 years old.
- Severe secondary MR characterised, according to the European guidelines and recommendations^{2,9}, by a regurgitation volume >30 mL/beat or a regurgitant orifice area >20 mm².
- New York Heart Association Class ≥II.
- Left ventricular ejection fraction between 15% and 40%.
- Minimum of one hospitalisation for heart failure within 12 months preceding randomisation.
- Optimal standard of care therapy for heart failure according to investigator.
- Not eligible for a mitral surgery intervention according to the Heart Team.

Table 2. Exclusion criteria of the MITRA-FR trial.

- Primary mitral regurgitation.
- Myocardial infarction or coronary bypass grafting surgery within three months prior to randomisation.
- Cardiac resynchronisation therapy within three months prior to randomisation.
- Need for any cardiovascular surgery (including registration on cardiac transplant list).
- Coronary angioplasty within one month prior to randomisation.
- Previous surgical mitral valve repair.
- Active infection requiring current antibiotic therapy.
- Terminal renal insufficiency (renal replacement therapy).
- Severe hepatic insufficiency.
- Stroke within three months prior to randomisation.
- Concurrent medical condition with a life expectancy of less than 12 months.
- Uncontrolled systemic hypertension.
- Hypersensitivity to nitinol.
- Participation in another trial.
- Pregnancy.
- Non-fulfilment of echocardiographic inclusion criteria as assessed by the Echocardiography Core Laboratory.

SUBJECT SCREENING, ENROLMENT, AND RANDOMISATION

All patients are screened for study eligibility by the principal investigator at each site. Each patient's case is presented at a multidisciplinary meeting of a Heart Team according to the recent guidelines². The Heart Team includes at least a surgeon, an interventional cardiologist, and a general cardiologist. They confirm the contraindication to valve surgery and the persistence of HF symptoms despite optimal medical management. This contraindication takes into account the risks and benefits of an MV surgical intervention according to the patient's status and comorbidities, as well as the current recommendations in this type of clinical situation. This contraindication decision is based upon a consensus among all members of the Heart Team. According to the latest ESC guidelines¹⁰, optimal therapy combines pharmacological and non-pharmacological options. The first consists of the use

of an angiotensin-converting enzyme inhibitor (ACEI) (or angiotensin receptor blocker in patients intolerant of an ACEI), a beta-blocker, and aldosterone receptor antagonist. CRT with or without implantable cardiac defibrillator is considered as part of the optimal therapeutic management in patients presenting with eligible indications according to updated guidelines. In all centres, each case is discussed within the Heart Team and the indication for CRT as well as atrial fibrillation ablation or cardioversion and coronary revascularisation is assessed thoroughly. The opinion of other specialists can be required, at the discretion of each centre's Heart Team.

Based on both transthoracic echocardiographic (TTE) and transoesophageal echocardiographic (TOE) examinations, the vascular access and favourable anatomical conditions are checked locally. Then, the patient is considered eligible for pMVR.

The echocardiographic data are sent by centres to a centralised echocardiography core laboratory for review by independent experts. The core laboratory validates the MR echocardiographic selection criteria for each patient before final inclusion.

The patient's characteristics and the clinical and echocardiographic data at the inclusion are collected using an electronic case report form (eCRF).

The randomisation is performed after the inclusion of the patient using a secure and dedicated web server. Randomisation is centralised and stratified by participating centre. Patients are randomised in a 1:1 ratio between the two arms.

If the patient is randomised to the MitraClip system arm, the procedure is scheduled within 21 days after randomisation. All procedures are performed with proctoring from Abbott Vascular (i.e., the presence of technician specialists during the procedures). One or two additional MitraClips can be used during the procedure when needed. In case of an unsatisfactory result after the procedure has been completed, no additional MitraClip procedure is allowed at any time during the two years of follow-up.

Post-implantation thromboprophylaxis includes acetylsalicylic acid (75 mg per day) indefinitely and clopidogrel (75 mg per day) for three months. In case of concomitant atrial fibrillation or another condition necessitating anticoagulant therapy, the anticoagulation regimen includes a vitamin K antagonist indefinitely plus acetylsalicylic acid (75 mg per day) for three months.

No crossover is allowed between the two arms during the two years of follow-up.

PATIENT FOLLOW-UP, DATA COLLECTION

The investigation schedule is depicted in **Figure 1**. The 30-day, six-month, 12-month and 24-month post-randomisation, follow-up data are collected during clinical visits, or by telephone interview for the 30-day data in the control non-interventional trial arm.

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint is a composite outcome of all-cause death and unplanned hospitalisations for HF, 12 months after randomisation.

The secondary endpoints are all-cause death, cardiovascular death, major cardiovascular event-free survival, and frequency

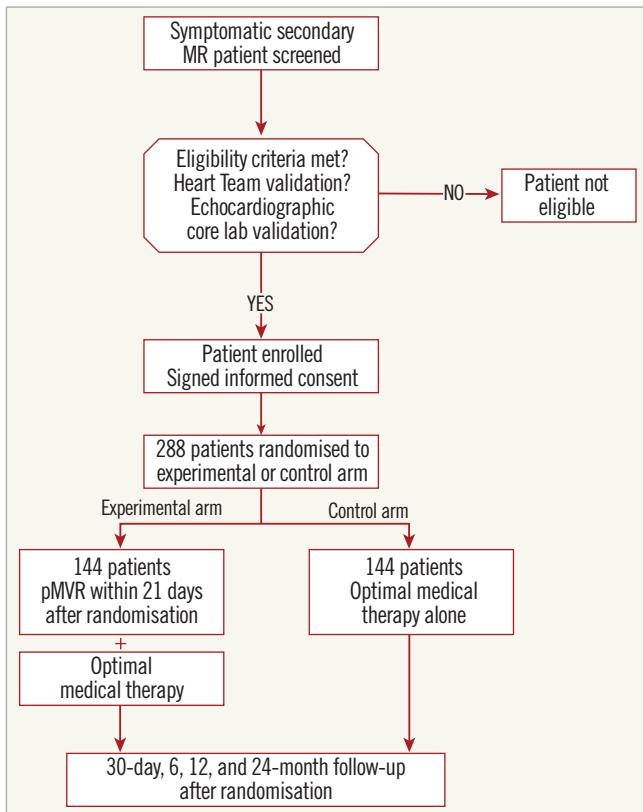


Figure 1. MITRA-FR investigation schedule.

of serious adverse events at 30 days, six months, 12 months, and 24 months after randomisation.

The other secondary outcome measures are the change in quality of life score (European Quality of Life-5 Dimensions instrument), the change in echocardiographic evaluation (pulmonary pressure, left ventricular diameter, grade of MR, left ventricular ejection fraction [LVEF]), measures being performed by the echocardiography core laboratory, the change in biomarkers (brain natriuretic peptide [BNP] levels, creatinine), the change in functional evaluation (New York Heart Association [NYHA] class, six-minute walk test), and the estimation of the incremental cost-effectiveness ratio expressed as a cost per major cardiac event avoided (perspective: French sickness fund, time horizon: 12 months)

ADJUDICATION OF ENDPOINTS

All endpoints are adjudicated by an independent endpoint validation committee.

It will be constituted by at least three physicians experienced in clinical research, including a cardiac surgeon, an interventional cardiologist, and a medical cardiologist. Only the adjudicated endpoints will be used for all statistical analyses.

DATA SAFETY MONITORING BOARD

An independent data safety monitoring board (DSMB) is set up specifically to monitor safety data throughout the study duration, and to determine if it is appropriate, from both the scientific and

the ethical standpoint, to continue the study as planned. The DSMB consists of three members: a cardiac surgeon, a cardiologist, and a statistician. It will evaluate the types and proportions of serious adverse events reported at 30 days post randomisation, after inclusion of 33% and 66% of the study population.

Statistical considerations

SAMPLE SIZE CALCULATION

The percentage of all-cause mortality or unplanned hospitalisations for HF at 12 months was assumed to be 50% in patients with severe secondary MR benefiting from OMT alone. This is consistent with the results describing the clinical outcomes of a US cohort of unoperated patients with severe MR⁶ (all-cause mortality at 12 months: 20%; proportion of patients with congestive HF: 41%). For patients in the interventional arm, the proportion of composite events was estimated to be 33% based on the preliminary results of the EVEREST II High Risk Study¹¹ (all-cause mortality at 12 months: 22.8%; proportion of patients with congestive HF: 19.8%). Based on these assumptions, 131 patients are needed per group to demonstrate a difference between groups using a chi-squared test (power of 80%, alpha risk of 5%), representing 262 patients overall¹². To take into account lost to follow-up patients (10%), a total of 288 patients are being recruited.

STATISTICAL ANALYSIS

The statistical analysis will be performed by an independent statistical department. The primary analysis will be carried out on the intention-to-treat population, defined as all randomised patients, whether they received the study treatment or not. A per-protocol analysis will also be performed to evaluate pMVR under optimal conditions. It is planned to account for missing outcome data by multiple imputation and/or sensitivity analyses.

A descriptive analysis of included patients will be performed on all recorded parameters. The hypothesis of normal distribution of quantitative variables will be tested using the Kolmogorov-Smirnov test and graphically confirmed with a histogram. If necessary, the variable will be converted to log and/or specifically analysed after exclusion of outliers. Patients' characteristics at the time of randomisation in the two arms will be compared using the chi-squared test or Fisher's exact test when the conditions of application of the chi-squared test are not met for categorical variables. Quantitative variables will be compared between groups using the Student's t-test after verification of equality of variances when data are normally distributed, and with Wilcoxon's non-parametric test when the hypothesis of normality of distribution is not verified.

The proportion of all-cause deaths or unplanned hospitalisations for HF 12 months after randomisation will be estimated with its 95% confidence interval. The proportions will be compared between the two arms using the chi-squared test. For secondary outcome measures, categorical variables will be compared using the chi-squared test or Fisher's exact test, as detailed above. Quantitative variables will be compared using the Student's t-test or the Mann-Whitney U test, as appropriate.

Survival will be described and estimated with the Kaplan-Meier method, and compared using the log-rank test. A Cox proportional hazard model will be fitted, and the proportional hazard hypothesis will be checked with Schoenfeld residuals. The statistical tests are bilateral and the level of significance has been set at 5%. The information presented above forms the basis for the statistical analysis plan. Any other analysis will be pre-specified in the statistical analysis plan before database lock. No subgroup analysis is planned. Two interim safety analyses are planned after inclusion of 1/3 and 2/3 of the total number of patients. No interim analysis for efficacy based on the primary endpoint is planned. Analyses will be performed using SAS 9.3 or a later version (SAS Institute, Cary, NC, USA).

Trial organisation

The MITRA-FR study is promoted by the Clinical and Innovation Research Department of Lyon University Hospitals (France), which is responsible for study monitoring. Trial coordination is performed by the Centre of Clinical Investigation of Lyon University Hospitals, and statistical analyses are under the responsibility of Lyon University Hospitals Biostatistics Department. The trial structure also includes the following groups: the Steering Committee, the Echocardiography Core Laboratory (located in the Xavier Bichat Hospital, Paris, France), the Adjudication Committee, and the DSMB.

The participating centres of the MITRA.FR trial have been selected based on the following criteria: 1) expertise in valvular heart disease and its management through a TAVI programme; 2) presence of a structured Heart Team already used to performing accurate and multidisciplinary patient selection. Furthermore, centres have to justify having experience of at least five MitraClip procedures before entering the study.

Current status of the trial

The first patient was enrolled in December 2013. To date, the MITRA-FR trial has randomised 80 patients from 19 participating centres. Patients' mean age was 71 ± 12 years, 70% were male, 54% had a history of ischaemic heart disease and mean left ventricular ejection fraction was 29.9%.

Discussion

Mitral regurgitation is associated with an increased risk of mortality and morbidity, and an altered quality of life; however, prospective clinical trial data regarding management of patients with severe symptomatic secondary MR are lacking. Many patients are not considered appropriate candidates for surgery because of altered LVEF, age and/or presence of multiple comorbidities. Medical therapy improves HF symptoms, morbidity, mortality, and left ventricular (LV) remodelling in systolic dysfunction, but its impact on MR is poor. The presence of moderate to severe MR is a strong independent predictor of death in systolic HF patients¹³. Moreover, a relationship between increasing MR severity and greater mortality has been observed in HF patients with systolic dysfunction¹⁴. Hence, alternative strategies and therapies are needed in these patients when surgery is contraindicated.

pMVR using the MitraClip system is a new option for patients with severe secondary MR. The MitraClip system was initially developed through the EVEREST programme, mainly represented by a randomised trial comparing pMVR to surgery in patients with severe MR (73% primary/27% secondary)^{15,16}. Several registries have confirmed the procedure's feasibility as well as its low procedural risk, and have shown promising results in terms of improvement of MR grade, functional outcome, and quality of life¹⁷⁻²². These results are based on a limited number of patients with severe secondary MR and at high surgical risk, followed up for a short- to mid-term duration, and are hampered by the influence of potential confounding factors. Within the commercial practice of the MitraClip system, there has been a shift in the indications for pMVR, secondary MR representing up to 65% of aetiologies in the most recent updates²³. With regard to its potential benefit, the ESC guidelines have considered pMVR as a potential option in "patients with symptomatic severe secondary MR despite optimal medical therapy who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a Heart Team"²². Furthermore, the FDA has approved pMVR with the MitraClip system as an option for patients with severe primary MR and at high surgical risk due to existing comorbidities. The indication of pMVR in this population is the only one considered in the latest AHA/ACC guidelines³.

While the MitraClip system is increasingly used in Europe, the level of evidence supporting pMVR in secondary MR patients contraindicated to surgery is low (recommendation class IIb, level of evidence C). The impact of pMVR on mortality and morbidity in patients with optimal medical therapy has to be assessed with prospective, comparative, randomised studies such as the MITRA-FR and the COAPT trials. These studies, as well as the RESHAPE-HF trial which has just been terminated, have large similarities in terms of inclusion criteria and primary outcome measures (**Table 3**). However, they differ in several respects. First, the upper value of the LVEF range of the COAPT trial's inclusion criteria is substantially higher than in the other two studies. Second, the sample sizes vary from a factor of almost one to three between studies which can be explained by different assumptions on primary effectiveness endpoints. Finally, the studies were designed under different circumstances. Despite the MitraClip system being commercially available (CE mark in 2008), access to it varies greatly between European countries.

In France, the MitraClip device has not been evaluated in the public health insurance system for reimbursement. The MITRA-FR trial was therefore designed in order to provide a higher level of evidence of the device efficacy with funding from the French Health Ministry.

In contrast, the RESHAPE-HF trial had been initiated within European countries, such as Germany, where the MitraClip system is already reimbursed and used in routine practice. In the United States, the COAPT trial is aimed at showing the device efficacy to support the FDA approval in patients with secondary MR. Both trials are fully sponsored by the MitraClip manufacturing company whereas the MITRA-FR trial has an academic sponsor.

Table 3. Summary of randomised clinical trials on the MitraClip system for severe secondary mitral regurgitation (source: ClinicalTrials.gov).

	MITRA-FR	RESHAPE-HF*	COAPT
Study sponsor	Hospices Civils de Lyon	Evalve (Abbott Vascular)	Evalve (Abbott Vascular)
ClinicalTrials.gov identifier	NCT01920698	NCT01772108	NCT01626079
Design	Prospective, randomised	Prospective, randomised	Prospective, randomised
Control arm	Optimal medical therapy	Optimal standard of care	Standard hospital clinical practice
MR aetiology	Secondary	Secondary	Secondary
Left ventricular ejection fraction (LVEF)	≥15% and ≤40%	≥15% and ≤40%	≥20% and ≤50%
NYHA class	II to IV	III to IV	II to IV
Hospitalisation for heart failure within 12 months preceding randomisation?	Yes	Yes	Yes
Contraindication to surgery?	Yes (local site Heart Team)	Yes	Yes (local site Heart Team)
Primary effectiveness endpoint	All-cause mortality and unplanned hospitalisations for heart failure at 12 months	All-cause mortality and recurrent heart failure hospitalisations at 12 months	Recurrent heart failure hospitalisations at 12 months
Estimated enrolment	288 (144×2)	800 (400×2)	430 (215×2)
Locations	22 centres (France)	75 centres (Europe)	67 centres (USA)

* this study was terminated in January 2015.

Impact on daily practice

pMVR with the MitraClip system is a promising option in patients with symptomatic severe secondary MR despite optimal medical therapy who are judged inoperable or at high surgical risk. The impact of pMVR on mortality and morbidity in this population has to be assessed with prospective, comparative, randomised studies such as the MITRA-FR. This study, and the COAPT trials, will provide the highest level of evidence of the device efficacy.

Funding

This study is being supported mainly by a grant from the French Ministry of Health (PHRC 2012, ref: 12-027-0355). The study sponsor also received research support from Abbott Vascular France. The study protocol was designed and written by the Steering Committee independently from Abbott Vascular France.

Conflict of interest statement

J-F. Obadia is on the advisory boards of and received consultant fees from Landager and St. Jude Medical. X. Armoiry has been invited as a congress delegate by Daiichi Sankyo. B. Iung has received consultant fees from Abbott, Boehringer Ingelheim and Valtech, and speaker's fees from Edwards Lifesciences. T. Lefèvre has received minor fees from Abbott Vascular. N. Mewton has received consulting fees from Servier, and travel support from Novartis, Servier, and BMS. D. Messika-Zeitoun has received consulting and lectures fees from Abbott, Valtech and Edwards. J-N. Trochu has received consulting and lecture fees from Abbott. A. Vahanian is on the advisory board of Abbott Vascular and Valtech. The other authors have no conflicts of interest to declare.

References

1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F,

Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.* 2003;24:1231-43.

2. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* 2012;33:2451-96.

3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:e521-643.

4. Glower DD, Tuttle RH, Shaw LK, Orozco RE, Rankin JS. Patient survival characteristics after routine mitral valve repair for ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2005;129:860-8.

5. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, Blackstone EH, Lytle BW. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol.* 2007;49:2191-201.

6. Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, Bdair H, Anabtawi A, Rahim S, Whitlow PL, Tuzcu EM, Griffin BP, Stewart WJ, Gillinov M, Blackstone EH, Smedira NG, Oliveira GH, Barzilai B, Menon V, Kapadia SR. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to deter-

mine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol.* 2014;63:185-6.

7. Obadia JF, Jung B, Maisano F. Treatment of mitral regurgitation: from sternotomy to percutaneous approach--a paradigm shift? *Arch Cardiovasc Dis.* 2012;105:401-3.

8. Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation. *J Am Coll Cardiol.* 2014;63:2057-68.

9. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, Hagendorff A, Monin JL, Badano L, Zamorano JL; European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr.* 2010;11:307-32.

10. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33:1787-847.

11. Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, Whitlow PL, Rinaldi MJ, Grayburn P, Mack MJ, Mauri L, McCarthy PM, Feldman T. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol.* 2014;64:172-81.

12. Machin D, Campbell MJ, Tan SB, Tan SH. *Sample Size Tables for Clinical Studies.* 3rd edition. Chichester: Wiley-Blackwell; 2009.

13. Cioffi G, Tarantini L, De Feo S, Pulignano G, Del Sindaco D, Stefenelli C, Di Lenarda A, Opasich C. Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure. *Eur J Heart Fail.* 2005;7:1112-7.

14. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol.* 2003;91:538-43.

15. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med.* 2011;364:1395-406.

16. Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, Hermiller J, Gray W, Wang A, Pedersen WR, Bajwa T, Lasala J, Low R, Grayburn P, Feldman T; EVEREST II Investigators. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol.* 2013;62:317-28.

17. Franzen O, Baldus S, Rudolph V, Meyer S, Knap M, Koschyk D, Treede H, Barmeyer A, Schofer J, Costard-Jäckle A, Schlüter M, Reichenspurner H, Meinertz T. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J.* 2010;31:1373-81.

18. Tamburino C, Ussia GP, Maisano F, Capodanno D, La Canna G, Scandura S, Colombo A, Giacomini A, Michev I, Mangiafico S, Cammalleri V, Barbanti M, Alfieri O. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J.* 2010;31:1382-9.

19. Baldus S, Schillinger W, Franzen O, Bekerredjian R, Sievert H, Schofer J, Kuck KH, Konorza T, Möllmann H, Hehrlein C, Ouarrak T, Senges J, Meinertz T; German Transcatheter Mitral Valve Interventions (TRAMI) investigators. MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail.* 2012;14:1050-5.

20. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol.* 2013;62:1052-61.

21. Armoiry X, Brochet E, Lefevre T, Guerin P, Dumonteil N, Himbert D, Cormier B, Piriou N, Gautier M, Messika-Zeitoun D, Romano M, Rioufol G, Warin Fresse K, Boudou N, Leclercq F, Bedossa M, Obadia JF. Initial French experience of percutaneous mitral valve repair with the MitraClip: a multicentre national registry. *Arch Cardiovasc Dis.* 2013;106:287-94.

22. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, Moat N, Price S, Dall'Ara G, Winter R, Corti R, Grasso C, Snow TM, Jeger R, Blankenberg S, Settergren M, Tiroch K, Balzer J, Petronio AS, Büttner HJ, Etti F, Sievert H, Fiorino MG, Claeys M, Ussia GP, Baumgartner H, Scandura S, Alamgir F, Keshavarzi F, Colombo A, Maisano F, Ebelt H, Aruta P, Lubos E, Plicht B, Schueler R, Pighi M, Di Mario C; Transcatheter Valve Treatment Sentinel Registry Investigators of the EURObservational Research Programme of the European Society of Cardiology. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol.* 2014;64:875-84.

23. Vakil K, Roukoz H, Sarraf M, Krishnan B, Reisman M, Levy WC, Adabag S. Safety and efficacy of the MitraClip® system for severe mitral regurgitation: a systematic review. *Catheter Cardiovasc Interv.* 2014;84:129-36.

Online data supplement

Online Appendix 1. Primary outcome definition.

Online Appendix 2. List of committees and members, participating centres and investigators (as of December 2014).

Online data supplement

Online Appendix 1. Primary outcome definition

Outcome: All-cause mortality

Definition: Defined as the occurrence of all-cause death

Outcome: Unplanned hospitalisations for heart failure

Definition: Any presentation at a hospital or urgent treatment centre requiring completion of the hospital admission procedures or equivalent and/or at least a 24-hour stay or until death of the patient

OR

An unplanned treatment given in an outpatient setting in which an IV diuretic and/or IV vasodilator and/or IV inotrope is administered AND presence of all the following criteria:

- a) New or increased symptoms of heart failure (e.g., shortness of breath/dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, fatigue/reduced exercise tolerance, pulmonary oedema, jugular venous distension, hepatojugular reflux, altered haemodynamics, peripheral oedema, cardiomegaly)
- b) New or increasing signs of heart failure including signs of fluid retention

Online Appendix 2. List of committees and members, participating centres and investigators (as of December 2014)

1. STEERING COMMITTEE

Pr Jean-François Obadia; Dr Xavier Armoiry; Pr Frédéric Collart; Pr Jean-Philippe Collet; Dr Bertrand Cormier; Pr Bernard Iung; Dr Thierry Lefèvre; Pr Jean-Noël Trochu; Pr Alec Vahanian

2. DATA SAFETY AND MONITORING BOARD

Dr Jean-Christophe Eicher; Dr Silvy Laporte; Pr Marc Laskar

3. CLINICAL EVENTS COMMITTEE

Pr Eric Bonnefoy-Cudraz; Dr Raphaël Dauphin; Dr Guy Durand de Gevigney; Dr Laurent Francois; Dr Nathan Mewton; Dr Jacques Robin; Dr Hélène Thibault

4. ECHOCARDIOGRAPHY CORE LABORATORY

Dr Eric Brochet; Dr Bernard Cormier; Pr David Messika-Zeitoun

5. MITRA-FR INVESTIGATORS

Lyon, Hôpital Louis Pradel: Jean-François Obadia, Gilles Rioufol, Hélène Thibault, Martine Barthelet, Sophie Thivolet

Paris, Hôpital Bichat: Alec Vahanian, Dominique Himbert, Patrick Nataf, Bernard Iung, Eric Brochet

Massy, Institut Hospitalier Jacques Cartier - Institut Cardiovasculaire Paris Sud: Thierry Lefèvre, Mauro Romano, Bertrand Cormier

Nantes, CHU de Nantes: Patrice Guérin, Vincent Letocart, Jean-Noël Trochu, Olivier Baron, Nicolas Piriou, Thierry Letourneau

Rennes, Hôpital Pontchaillou: Marc Bedossa, Guillaume Leurent, Erwan Donal, Hervé Corbineau

Besançon, CHU de Besançon: Sidney Chocron, François Schiele, Nicolas Meneveau, Romain Chopard

Créteil, Hôpital Henri Mondor: Emmanuel Teiger, Jean-Luc Dubois-Rande, Clémence Antoine, Jean-Paul Couetil, Pascal Lim, Jean-Luc Monin, Thibault Damy, Soulef Guendouz, Stéphane Champagne, Laura Ernande

Le Plessis Robinson, Centre Chirurgical Marie Lannelongue: Alexandre Azmoun, Jean-Yves Angel, Philippe Brenot, Alban Baruteau, Michel Slama, Philippe Deleuze, François Raoux, Philippe Garcon

Lille, CHRU de Lille: Alain Prat, André Vincentelli, Thomas Modine, Francis Juthier, Eric Van Belle, Arnaud Sudre, Anne-Sophie Polge, Marjorie Richardson

Marseille, CHU de La Timone: Jean-Louis Bonnet, Mathieu Pankert, Nicolas Michel, Gilbert Habib, Erwan Salaun

Montpellier, CHU de Montpellier: Florence Leclercq, Jean-Christophe Macia, Bernard Albat, Stéphane Cade, Frédéric Cransac

Montpellier, Clinique Le Millénaire: Christophe Piot, Frank Raczka, Catherine Sportouch, Maxime Pons, Fabrice Francois

Nancy, CHU de Nancy-Brabois: Yves Juilliere, Christine Selton-Suty, Olivier Huttin, Thierry Folliguet

Pessac, CHU de Bordeaux: Lionel Leroux, Pierre Coste, Louis Labrousse, Stéphane Lafitte, François Picard, Marina Dijos

Strasbourg, CHU de Strasbourg: Patrick Ohlmann, Jean-Georges Kretz, Arnaud Mommerot, Olivier Morel, Annie Trinh, Hélène Petit-Eisenmann, Paola Goette-Dimarco, Annie Samet

Toulouse, CHU de Toulouse: Nicolas Dumonteil, Mathieu Gautier, Bernard Marcheix

Marseille, Hôpital Saint-Joseph: Rémi Houel, Patrick Joly, Jacques Bille, Philippe Commeau, Emmanuel Philip, Nicolas Michel

Clermont-Ferrand, CHU Gabriel-Montpied: Pascal Motreff, Azamouh Kasra, Charles Vorilhon, Guillaume Clerfond

Grenoble, CHU La Tronche: Bernard Bertrand, Hélène Bouvaist, Carole Saunier

Angers, CHU d'Angers: Frédéric Pinaud, Frédéric Rouleau, Thomas Benard, Alain Furber, Jean-Louis Debrux

Le Chesnay, Hôpital Privé de Parly 2: Claude Vaislic, Xavier Favereau, Philippe Maribas

Toulouse, Clinique Pasteur: Didier Tchetché, Bruno Farah, Olivier Fondard, Atul Pathak, Laurent Bonfils, Issam Abouliatim