Archives of Cardiovascular Disease (2019) 112, 370—373

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

SCIENTIFIC EDITORIAL

Lessons from MITRA-FR and COAPT studies: Can we hope for an indication for severe functional mitral regurgitation in systolic heart failure?

Leçons après MITRA-FR et COAPT : peut-on espérer une indication pour l'insuffisance mitrale fonctionnelle sévère dans l'insuffisance cardiaque systolique ?

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Received 23 October 2018; accepted 5 November 2018
Available online 31 December 2018

KEYWORDS
Mitral regurgitation;
Clip;
Heart failure

MOTS CLÉS
Insuffisance mitrale ;
Clip ;
Insuffisance cardiaque

Background

Functional (or secondary) mitral regurgitation (FMR) is frequent in patients with left ventricular dysfunction, especially those with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) [1]. FMR occurs in the absence of organic mitral valve disease; it is more common than primary mitral regurgitation [2], and is associated with a worse prognosis. Strong associations between FMR severity and both all-cause mortality and HF hospitalisation have been reported [1]. Severe FMR, characterized by the presence of a regurgitant volume > 30 mL, an effective regurgitant orifice area (EROA) > 20 mm^2 or a vena contracta width > 40 mm, is responsible for severe clinical symptoms and a very important prognostic effect, with increased mortality and morbidity, in ischaemic or non-ischaemic cardiomyopathies [3]. In this context, the most effective therapies are those that treat left ventricular dysfunction, including recommended HF medical therapy and biventricular pacing. However, in patients with FMR who cannot be treated surgically because their LVEF is too low,

Abbreviations: CI, confidence interval; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; HF, heart failure; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system.

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https://doi.org/10.1016/j.acvd.2018.11.004

the use of transcatheter mitral valve repair (Mitraclip™; Abbott Vascular, Santa Clara, CA, USA) has been suggested to improve clinical symptoms, although superiority to surgery has not been established as yet in terms of morbimortality [4].

What were the main results from the recent MITRA-FR and COAPT trials?

Recently, two large, randomised, controlled studies were published on the role of Mitraclip™ in reducing morbimortality in HF with reduced LVEF and severe FMR. The first published study (MITRA-FR) was a French, multicentre, randomised, open-controlled (medically treated control group) institutional study, including 304 symptomatic patients with HF with severe FMR, and LVEF between 15% and 40% (152 patients in each group). The study assessed a primary composite criterion of all-cause mortality or unplanned hospitalisation for HF at 12-month follow-up [5]. MITRA-FR appeared to be neutral in terms of the primary criterion (54.6% in the device group vs. 51.3% in the control group: odds ratio 1.16, 95% confidence interval [CI] 0.73—1.84; $P = 0.53$). Neutral results were also observed for each individual criterion constituting the primary criterion.

The second study (COAPT) was a North American, multicentre, randomised, open-controlled (medically treated control group) industry-sponsored study, including 614 symptomatic HF patients with moderate-to-severe or severe FMR, and LVEF between 20% and 50% (302 patients in the device group and 312 in the control group). The study assessed a primary efficacy criterion of hospitalisation for HF at 24-month follow-up, and a primary safety criterion of freedom from device-related complications at 12-month follow-up, the rate for this endpoint being compared with a prespecified objective performance goal of 88% [6]. The study was very positive, with a significant reduction in the HF hospitalisation rate of 35.8% per patient-year in the device group versus 67.9% in the control group (hazard ratio 0.53, 95% CI 0.40—0.70; $P < 0.001$). The rate of freedom from device-related complications at 12-month follow-up was 96.6%. All-cause mortality at 24-month follow-up—a secondary endpoint—was also significantly reduced (29.1% in the device group vs. 46.1% in the control group: hazard ratio 0.62, 95% CI 0.46—0.82; $P < 0.001$).

Why were there differences in mortality and procedural complications between the two studies?

The MITRA-FR and COAPT studies reported different results in terms of morbimortality, although all-cause mortality at 1-year follow-up in the control group was similar in both studies (24.3% in MITRA-FR and 23.2% in COAPT). Two main points warrant discussion.

First, in terms of device-related complications, the MITRA-FR study reported fewer implanted clips (90.8% vs. 95% in COAPT), with more procedural complications (14.6% vs. 8.5%) and more residual severe FMR immediately after the implantation (9% vs. 5%) as well as at 12-month follow-up (17% vs. 5%). A trivial first explanation might be that French cardiologists are less competent than North Americans in terms of their ability to implant mitral clips, but a more realistic explanation is the selection of more severe patients in the MITRA-FR study, with anatomical characteristics (namely, left ventricular dilatation, as discussed below) leading to more complicated clip implantations.

Second, differences existed in terms of the medical therapy administered. Whereas the MITRA-FR study included patients receiving well-prescribed recommended HF classes of drugs at baseline, with no statistical differences between the compared groups (renin-angiotensin system [RAS] blockers, 83% in the device group vs. 86.4% in the control group; beta-blockers, 88.2% in the device group vs. 90.8% in the control group), this was not the case in the COAPT study. Significantly fewer patients in the control group received RAS blockers at baseline (62.8% vs. 71.5%; $P = 0.02$), and this unfavourable difference increased at 1-year follow-up (63.1% vs. 76.5%; $P = 0.002$); there was also a significant difference in treatment with beta-blockers at 1-year follow-up, which again was unfavourable for the control group (86.7% in the control group vs. 93.3% in the device group; $P = 0.02$), whereas no significant difference existed at baseline (89.7% in the control group vs. 91.1% in the device group). The COAPT authors also reported major changes in HF medications (i.e. dose decreased by > 50% or was discontinued, or dose increased by > 100% or a new drug class started) during the first 12-month follow-up, showing that a low number of patients were involved in these changes, with no statistical differences between groups except for an unfavourable change in beta-blocker treatment (dose increased or new drug class started) in the control group compared with the device group (3.8% vs. 8.6%; $P = 0.01$). International guidelines on HF strongly recommend the combination of both classes of drugs (RAS blockers and beta-blockers) to reduce mortality in HF (between 20% and 30% of mortality reduction attributable to RAS blockers, with an additional 35% of mortality reduction attributable to beta-blockers, in New York Heart Association class III—IV HF). Moreover, almost 40% of patients with HF and severe FMR who are managed well medically can have successful regression of FMR [7]. Finally, the treatment difference seen in the COAPT study might have increased mortality in the control group, thereby contributing to the significant difference in mortality between groups. Indeed, 1-year mortality was similar in both studies, but an increase in mortality related to worse medical treatment in the COAPT control group might give the artificial impression that both study populations were similar, when, in fact, the COAPT study population was less severe than the MITRA-FR study population.

What are the potential functional benefits for implanted patients?

Questioning mortality in patients with HF with severe FMR might not be as essential in this indication as it would be for medical therapies. The patients involved are inoperable and often elderly. When medical treatment is optimised, and if severe FMR persists, only correction of regurgitation can improve a patient's clinical status. Both studies showed

improvement in FMR grade as a result of clips, in addition to improvement in functional New York Heart Association class, quality of life (Kansas City Cardiomyopathy Questionnaire), exercise functional capacity and left ventricular size in the COAPT study. Decrease in left ventricular end-diastolic volume reflected the anti-remodelling effect related to the reduction in mitral regurgitation. Furthermore, in both studies, there appeared to be less need for left ventricular assist devices or heart transplantation in the group treated with the Mitraclip™, which is a non-negligible benefit in terms of patient quality of life, and results in a reduction in disease costs.

Were there baseline anatomical differences between the two study populations?

Why were the morbimortality results so different in the MITRA-FR and COAPT studies? The MITRA-FR study population was probably more severe, although the patients in both studies had similar mean ages and clinical characteristics. Major differences concerned the echocardiographic profiles of the two populations.

Despite a similar LVEF ($33 \pm 7\%$ in MITRA-FR and $31 \pm 10\%$ in COAPT), COAPT patients had a left ventricle that was less dilated compared with MITRA-FR patients (indexed left ventricular end-diastolic volume: $101 \pm 34\,mL/m^2$ vs. $135 \pm 35\,mL/m^2$, respectively), while mitral regurgitation was more severe (EROA: 41 ± 15 mm^2 vs. 31 ± 11 mm^2, respectively), with only 14% of the COAPT patients having an EROA < 30 mm^2 compared with more than half (52%) of the MITRA-FR patients. Stratifying the COAPT study population according to the level of EROA, there was no statistical difference in the combined criterion of all-cause mortality or HF hospitalisation in the subgroup of patients with values ≤ 30 mm^2, reduction of the criterion only becoming significant for values > 30 mm^2 (G.W. Stone, unpublished data). This sub analysis agreed with the MITRA-FR results, which were largely influenced by the 52% of patients with EROA < 30 mm^2. Moreover, left ventricular dilatation in patients from the MITRA-FR study appeared to be enormous, according to recommendations for chamber quantification (indexed left ventricular end-diastolic volume considered to be severely abnormal when $\geq 97\,mL/m^2$) [8]. In the literature, a strong relationship between left ventricular volume and hospitalisation rate after Mitraclip™ implantation has already been shown [9]. Therefore, the COAPT study probably included patients with more severe FMR, but at an earlier stage, before the left ventricular impact was too significant, while the MITRA-FR study included patients at a more advanced stage, thereby causing a non-negligible risk of procedural complications.

It will be interesting to see future publications using the data from these two studies. As the patients in both studies were very clinically comparable, a pooling of data would be best to get precise subgroup analyses, integrating both EROA and indexed left ventricular end-diastolic volume, and thereby defining the ideal population for clip implantation.

What is the proposed indication for mitral clip use in FMR in systolic HF?

In light of the results of the two large, randomised, open-controlled (by necessity) trials (both with favourable functional results and one with encouragingly positive morbimortality results, despite preceding remarks and the neutral results of the other), optimisation of patient selection could lead to an indication for the use of the mitral clip in patients with HF with severe FMR when:

- symptoms persist or HF worsens, despite well-driven optimal medical therapy;
- in the presence of LVEF < 50% and a contraindication for cardiac surgery;
- when there is existing severe FMR (characterized by an EROA > 30 mm^2), accompanied by an as yet limited left ventricular impact (characterized by an indexed left ventricular end-diastolic volume between $75\,mL/m^2$ and $100–110\,mL/m^2$, the upper value to be determined by secondary analyses of MITRA-FR and COAPT study populations).

After the benefit of the mitral clip in non-operable organic mitral regurgitation, it might soon be possible to witness the extension of the mitral clip indication to severe FMR in patients with systolic HF.

Disclosure of interest

Y.J. Participation on boards for the following companies: Abbott Vascular, Bayer, Boston Scientific, St. Jude Medical and Novartis. Participation in sponsored investigational trials and/or meetings as speaker or chairperson for the companies Abbott Vascular, Amgen, Bayer, Bristol-Myers Squibb, Boston Scientific, GSK, The Medicines Company, MSD/Schering-Plough, Novartis, Roche Diagnostics, Sanofi-Aventis, Servier and St. Jude Medical.

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