32nd EACTS Annual Meeting Clinical Trials Update

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Introduction

Decision making for treatment strategies is based on clinical evidence often summarised in clinical guidelines. Clinical evidence results often from randomised trials which are published in high impact medical journals and presented at scientific meetings. These presentations and publications present a challenge for the correct interpretation of the design and the analyses. Appropriate interpretation is a necessary step for the clinical teams when attempting to apply this evidence to everyday clinical practice. Even high impact journals have identified areas for improvement in the way they publish research (REF WONG NEJM), and the EACTs Annual Meeting provides an excellent opportunity to interpret and debate important evidence from different perspectives.

The European Association for Cardio-thoracic Surgery (EACTS) has established an Analytical Support Unit, in collaboration with the Institute of Clinical Trials and Methodology, University College London, UK. The EACTS Analytical Support Unit's scope is to bolster appropriate methodological interpretation of clinical evidence, and as part of this at the 32nd Annual Meeting in Milan a trial update session was held during which the following trails were presented and critically appraised: ART- 10 year (primary) results[1]; IMPAG; and the MITRA-FR [2] and COAPT [3].

In conjunction with the Trials Update Sessions at the Annual Meetings, the European Journal of Cardio-thoracic Surgery aims to publish trial update paper with an in-depth critical appraisal and explanation of the methodology and an independent interpretation of the results of emerging clinical trials.

ART (Arterial Revascularisation Trial) – 10 Year Results

Study Design

ART randomly assigned 3102 patients scheduled for Coronary Artery Bypass Grafting (CABG) to undergo single or bilateral internal-thoracic-artery grafting in 28 cardiac surgical centres in UK, Poland, Australia, Brazil, India, Italy and Austria. The primary outcome was death from any cause at 10 years, with results at 5 years shared in an interim analysis.[1] Like the 5 year results,[1] the primary analysis at 10 years based upon the intention to treat analysis showed very similar outcomes for Bilateral versus Single Internal-Thoracic-Artery Grafts, with no evidence of a difference between the groups (hazard ratio 0.96 (95% CI 0.82 to 1.12; p = 0.62). Intention to treat analysis preserves randomisation, as patients are analysed according to their randomised treatment group and not the treatment that they actually receive.[I4] Although this may seem counterintuitive, particularly where there is a mismatch between allocated treatment and that actually received, it is the only unbiased approach and the commonly used alternative of analysis by protocol (eg according to the treatment actually received) is open to severe bias.[4] In ART 14% of patients allocated to bilateral internal-thoracic-artery grafting actually received single internal-thoracic-artery grafting, and the reverse cross over was experienced by 4% of patients. In addition radial artery grafting was used in 22% of subjects in the single internal-thoracic-artery grafting group. The potential for bias was observed in the apparent benefit for bilateral internal-thoracic-artery grafting observed at 10 years, with a statistically significant 19% reduction in

the hazard of death observed in the as treated analysis, highlighting the importance of randomisation to avoid bias.

Results
ART was a very well designed and conducted trial. The planned 10 year follow up is at stark contrast with that available for other important questions such as the choice of intervention for Left Main disease where trials are too short to describe the entire experience of patients required to make informed decisions on treatment options. The primary outcome is an objective measure (all cause mortality) which is important in open studies, and vital status was available for more than 98% of patients randomised at 10 years, an amazing achievement which demonstrates what is possible. The long wait for the final results is mitigated by the release of 5 year outcomes, an interim analysis, but one released after the intervention has been delivered and when there can be no anticipated bias from knowledge of patient outcome. ART was funded by the British Heart Foundation and others; ART Current Controlled Trials number, ISRCTN46552265.

The result of the ART trial do not suggest that a change in the recommendation (Class IIa, Level B) in the recently published EACTS/ESC myocardial revascularisation guidelines [5] is necessary.

Prof Doug Altman was the statistician on ART until his death in June 2018.[6] ART has set the standard for trials in cardiac surgery, and leaves a lasting legacy for a statistician who has contributed more than any other to the excellence of statistics in medicine.

IMPAG (Impact of Preoperative FFR on Arterial Bypass Graft Functionality)

Study Design
IMPAG (NCT02527044), is a 2 centre, single arm study to assess the association of preoperative fractional flow reserve (FFR) on coronary graft functionality 6 months postoperatively in patients with triple vessel disease undergoing isolated total arterial CABG. In the study, all patients had preoperative FFR assessment of all target vessels. The findings of the FFR assessment were not revealed to the surgeon or the patient. Patients then underwent total arterial CABG either on or off-pump. Other details of the operative procedure such as graft selection, graft configuration, use of sequential anastomoses or on- vs. off-pump were at the discretion of the operating surgeon. Patients underwent protocol angiography 6 months postoperatively. Grafts were reported as either patent or occluded. Grafts were reported as functional if the target vessel was completely opacified by the graft. The association of graft patency and functional occlusion with preoperative FFR was determined by area-under-the-curve analysis. Funding was obtained by the Ottawa Heart Institute Research Corporation.

Results
The interim results of 63 of the planned 120 patients were presented. The median age was 67 years (interquartile range 57-74), 20% of the patients were female, and 38% were diabetic. There were data relating to 199 coronary anastomoses, of which 135 were sequential anastomoses. Altogether, 54 of the 63 patients had bilateral internal thoracic

arteries constructed with a y graft configuration. Overall, 151 of the arterial anastomoses were patent and fully functional (76%) – 85% of the left internal thoracic artery vs. 69% of the right internal thoracic artery (p=0.01). Visual assessment of the severity of the target vessel stenosis did not correlate with graft patency or functionality, where as graft patency and functionality were strongly associated with the preoperative FFR measurements (p<0.001). A FFR cutoff of 0.78 was identified as the single best threshold value overall. Furthermore, sequential anastomosis seemed protective for FFR values >0.78. A FFR of 0.71 was identified as the most appropriate cutoff value for the right coronary territory. The interim results of the study are certainly interesting. The authors are using a definition of arterial graft patency which is not commonly used. The interim results are consistent with the concept that arterial grafts are sensitive to competitive flow, and that the right coronary territory is more sensitive to competitive flow than the left coronary. Further results will be forthcoming including angina and adverse cardiac events, although the size of the study is unlikely large enough to be able to identify moderate differences in clinical events.

MITRA-FR [2] and COAPT [3].

Chronic heart failure (HF) with reduced left ventricular ejection fraction (LVEF) and severe secondary mitral regurgitation (MR) is associated with increased morbidity, disability, hospital admission, and death.[7] Overall, there is emerging evidence for a relationship between use and up-titration of multiple neuro-hormonal antagonists to target the dose according to the tolerance and clinical outcomes of HF. Thus, the combined use of the renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARB] or angiotensin receptor neprilysin inhibitor [ARNI] with mineralocorticoid receptor antagonist [MRA]) in addition to a beta-blocker and loop diuretics holds a Class I Level of Evidence (LOE) A recommendation in the 2016 European Guideline for the diagnosis and treatment of acute and chronic heart failure[8] to improve symptoms, slow or even reverse cardiac remodeling, and reduce mortality. Based on limited evidence and high operative risk profile of these patients, the 2017 ESC/EACTS Guideline for the management of valvular heart disease recommends mitral valve surgery only in patients who require myocardial revascularization (Class I LOE C), while a highly selected group of patients who remained symptomatic despite maximally-tolerated doses may derive benefit from either surgical or transcatheter valves intervention when myocardial revascularization is not indicated (Class IIb LOE C).[9] Over the recent decade, several clinical trials have been designed to evaluate the safety and efficacy of mitral valve repair therapy as compared to the guideline-directed medical treatment alone in patients with HF and severe secondary MR. Recently, the results of two clinical trials, MITRA-FR and COAPT, comparing the MitraClip™ with conservative approach have been published.[2,3] However, the results of those trials have reported conflicting results. While the MITRA-FR trial showed no difference between mitral valve repair therapy and the optimal medication treatment, the COAPT trial appears to support mitral valve repair therapy as a superior alternative.

MITRA-FR
Study design
The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) randomized 304 patients at 37 centres in France to assess clinical

outcomes after percutaneous mitral valve repair in addition to optimal medical therapy (device group) compared with results of optimal medical treatment alone (control group), for the treatment of patients with severe secondary MR. European echocardiographic objective thresholds were used to establish severe secondary MR: proximal isovelocity surface area-derived (PISA) effective regurgitation orifice area (EROA) > 200 mm2 and regurgitation volume < 30 ml.[8] Eligible patients for the study inclusion were symptomatic despite maximal medical treatment (NYHA ≥2); they were not suitable for conventional surgery by Heart Team assessment and had left ventricular ejection fraction between 15% and 40%. The primary efficacy endpoint was the composite of all-cause death or unplanned hospitalization for HF at 1 year. Secondary endpoints in this study have included individual components of the primary composite, freedom from major adverse cardiovascular events (the composite of death, stroke, myocardial infarction [MI] or unplanned hospitalization for HF) and cardiovascular mortality. The study is funded by the French Ministry of Health and Research National Program and Abbott Vascular and is registered at ClinicalTrials.gov, identifier NCT01920698.

Results

A total of 152 patients were included in each group. In the device group, eight patients crossed over to the control group and six patients had device procedure failure, while in the control group two patients crossed over to the device group. Follow-up at 12 months was completed for 99% of patients. Compared with control patients, those who underwent device therapy had similar baseline characteristics including age, the stages of heart failure, the severity of mitral regurgitation, left ventricular ejection function, and comparable medical treatments.

Periprocedural complications following Mitraclip implantation had occurred in 21 patients (14.6%), none needed surgical conversion. Technical success of mitral repair procedure was achieved in 138 patients (95.2%) with one implanted device in 63 patients (45.7%), two implanted devices in 62 patients (44.9%) and three implanted devices were required in 13 patients (9.4%), thereby reducing the MR to 2+ or lower in 91.9% of patients at discharge. At 1 year, the regulatory standard composite endpoint of all-cause death or unplanned hospitalization for HF in the device group was similar to the control group (54.6% vs. 51.3%, odds ratio = 1.16; 95% confidence interval [CI] 0.73-1.84; P = 0.53). There was no difference between the device and the control group in the rate of all-cause death (24.3% vs. 22.4%, HR=1.11; 95% CI 0.69-1.77), unplanned hospitalization for HF (48.7% vs. 47.4%; HR=1.13, 95% CI 0.81-1.56), or major adverse CV events (56.6% vs. 51.3%; HR=1.22, 95% CI 0.89-1.66). Longer follow-up of this methodologically high quality trial, which is underway, will cast further light on the potential effects of the MitraClip on important outcomes such as all cause mortality. MitraFR was funded by the French Ministry of Health and Research National Program and Abbott Vascular, and is registered at ClinicalTrials.gov number, NCT01920698.

COAPT

Study design

The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial randomized 614 patients at 78 centres across the United States and Canada. Patients with HF and moderate-to-

severe secondary mitral regurgitation were randomly assigned to percutaneous mitral valve repair in addition to optimal medical therapy (device group) or optimal medical treatment alone (control group). An independent echocardiographic core laboratory-confirmed moderate-severe secondary MR for all enrolled patients, but the criteria used to define severe MR differed from the MITRA-FR study. The COAPT study used a combination of qualitative and quantitative assessments including colour flow Doppler to assess MR jet area and pulmonary venous flow Doppler. The PISA-derived regurgitant volume and fraction criteria were also different from the MITRA-FR at 45ml and 40% respectively.

In addition, patients were eligible for the study if they fulfilled all the following criteria: symptomatic disease despite optimal medical treatment (NYHA ≥2), the site Heart Team decision that patient is not candidate for conventional surgical procedure, LVEF between 20 and 50% with end-systolic dimension ≤70 mm, and the high probability of successful percutaneous mitral valve intervention. The primary effectiveness endpoint was all-cause hospitalizations for HF at 2 years that has been analyzed when the last enrolled patient complete 1-year follow-up. The primary safety endpoint was freedom from device-related complications at 1 year. Secondary endpoints include all-cause death at 1- and 2-year, MR grade ≤2+ and NYHA<2 at 1-year, change in quality of life and six-minute walk test distance from baseline to 1-year, all-cause hospitalization at 2-year, and the composite safety of all-cause death, stroke, MI, or surgery for device-related complications at 30-day. The study is registered at ClinicalTrials.gov, identifier NCT01626079 and was funded by Abbott Vascular.

Results

In the COAPT trial, 302 patients were assigned to the device group, and 312 patients to the control group. The device implantation was attempted in 293 patients, and one patient underwent early surgical revision. During the study period, the crossover was not permitted. Follow-up at 1-year was completed in 97.7% of patients in the device group and 94.2% in the control group, while the median follow-up was 22.7 months (interquartile range [IQR], 12.4-24.0) and 16.5 months (IQR, 10.1-24.0), respectively. The age, gender, the severity of mitral regurgitation, and LVEF were evenly distributed between the two groups. However, a close analysis of the data shows that the patients in the control group had worse heart failure symptoms as described by NYHA class (Proportional Odds ratio 1.44, 95% CI 1.06 1.97 p=0.02), and a lower rate of patients were on ACEI/ARB or ARNI therapy at baseline(62.8% vs. 71.5%, P=0.02; respectively).

Of 293 patients who underwent device therapy, mitral valve repair was accomplished in 287 patients (98.0%). One device was implanted in 106 patients (36.2%), two devices were implanted in 157 patients (53.6%), and three or four devices were implanted for 24 patients (8.2%), reducing the MR to 2+ or lower in 95% patients at discharge. At 30 days, the composite of all-cause death, stroke, MI, or surgery for device-related complications was 5.3%.

At 2 years, the primary endpoint of all hospitalization for HF was significantly lower in the device group as compared to the control group (35.8% per patient-year vs. 67.9% per patient-year, P<0.001). There was no difference between the device and the control group in the rate of all-cause death at 1-year (19.1% vs. 23.2%, HR=0.81, 95% CI 0.57-1.15), but a nominally significantly lower number of patients in the device group experienced all-cause death at 2-year (29.1 vs. 46.1; HR=0.62, 95% CI 0.46-0.82), with 6.4% of subjects withdrawn or lost to follow up at this time.

COAPT aim to exclude a 12% incidence of safety events defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to non elective cardiovascular surgery. The occurrence of these safety events in the COAPT can be calculated from the supplied data to be 3.2% and highly significant (95% CI 1.5% to 5.9%; P<.0001).

In summary, the results of the COAPT trial suggest that percutaneous mitral valve repair is the preferred treatment strategy over optimal medical therapy in selected patients with HF reduced LVEF and severe secondary MR. The study showed a nominally significant decrease in mortality after 1-year of percutaneous mitral intervention.

Why do we see a difference between the trials?

COAPT and MITRA-FR provide very different results, and may relate to a number of differences between the studies. Firstly, the use of all cause heart failure hospitalisation in COAPT as the primary outcome is unorthodox, and open to bias as it is clinician (unblinded to the treatment arm) driven [ICH E9]. The composite of unplanned hospitalisation for heart failure or all cause mortality used as the primary outcome in MITRA-FR may be considered the more robust in this setting. The 12% threshold for serious safety events considered in COAPT may also be seen to be excessively high by many and it is not surprising that the trial overcame such an easy challenge. With the upper confidence interval of 5.9%, a more realistic threshold relevant to patients may not have been excluded.

Secondly, the inclusion criteria differed between studies, including the assessment and grading of the severity of secondary MR. The differences in the assessment of secondary MR reflect the ongoing debate in this field, and the challenges and limitations of PISA-derived assessment of secondary MR [10]. The different qualitative or quantitative criteria and grading systems used in COAPT and MITRA-FR may not be comparable. The corollary is that the prognostic significance of the criteria used to define or grade secondary MR may also differ significantly.

Thirdly, there were significant differences in the use of neurohormonal antagonists between treatment arms in the COAPT trial at baseline, which persisted throughout the study. Such differences were not evident in the MITRA-FR trial. The difference in medical therapy may have influenced the secondary endpoint of mortality in favour of the device group, especially with the small number of events.

However, there are also notable similarities between MITRA-FR and COAPT. Firstly, both trials demonstrated significant reduction in the severity of MR. In the case of COAPT, the reduction in MR was maintained at 2 years, which is remarkable in light of the high MR recurrence rates reported in surgical studies [11]. However, neither study showed

significant reduction in left ventricular volume to suggest reverse remodelling, which casts doubts on the putative mechanism of benefit with Mitraclip.

Secondly, both studies have shown some of the highest mortality rates compared to other contemporary heart failure trials, confirming the poor prognosis associated with secondary MR and severe left ventricular dysfunction. In particular, the 2-year mortality in the COAPT trial of 29% and 46% in the device and control groups respectively. As a (indirect) comparison, the 2-year mortality rate with contemporary left ventricular assist device therapy in patients with predominantly inotrope-dependent advanced heart failure reported in MOMENTUM 3 was 17% [12].

At one year there is no difference in the mortality for the pooled populations of both trials (Figure 1). We eagerly await the results of the MITRA-FR trial at 2 years to address the residual uncertainty. If MitraClip was a pharmaceutical and thus subject to more rigorous regulatory procedures than those used for Class 3 devices, it is uncertain that a marketing authorisation would be granted for its use on the basis of the conflicting results and the limitations of the COAPT study. The balance of risks and benefits is quite unclear currently. The spectacular and unexpected benefits seen on all cause mortality in the COAPT trial at two years show considerable promise if these can be replicated in a second well designed study.

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Figure 1. All Cause Mortality at 12 Months (95% CI)