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Lessons from the trials

The RIME trial: Are we closer to the answer of when to repair ischemic mitral regurgitation?

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BACKGROUND

The development of mitral valve regurgitation as a result of left ventricular remodelling following myocardial infarction carries adverse implications on survival and quality of life (QOL). There is uncertainty whether mitral valve repair at the time of surgical revascularization improves survival and quality of life and enhances left ventricular reverse remodelling in patients with moderate ischemic mitral regurgitation (IMR). The Randomized Ischemic Mitral Evaluation (RIME) trial investigators tried to address this issue by studying whether repairing moderate IMR at the time of surgical revascularization can lead to more favourable outcomes compared with surgical revascularization only. Results of this multicentre, randomized, controlled trial were recently published in Circulation.[1]

RIME was conducted in 6 centres in the UK and one in Poland. Out of 172 patients referred for CABG with moderate IMR, the RIME investigators randomized 73 eligible patients to receive either CABG alone (CABG group; $n = 39$ patients) or CABG with mitral valve repair (Repair group; $n = 34$ patients) The primary end-point was oxygen consumption at maximal exercise (VO_2Max) measured by cardiopulmonary exercise testing, as an objective measure of functional capacity, at one year. The secondary end-points were left ventricular end-systolic volume indexed to body surface area (LVESVI) and mitral regurgitation volume as well as plasma B-type natriuretic peptide (BNP). All measurement were performed before enrollment and at one year postoperatively.

Moderate IMR was defined by echocardiographically derived quantitative measures – namely regurgitant orifice area, regurgitant volume and vena contracta width – as per the ACC/AHA/ASE Valvular Heart Disease Guidelines. Patients were considered eligible if they met any of the above criteria whether at rest or during exercise.[2] Patients were excluded if they had ejection fraction $<30\%$, structural mitral valve disease (including papillary muscle rupture), significant aortic valve disease, previous or active endocarditis, previous cardiac surgery, unstable angina, symptoms of advanced heart failure or cardiogenic shock or significant comorbidities like liver or renal impairment and chronic obstructive airway disease. All CABG procedures utilized the left internal mammary artery to graft the left anterior descending coronary artery All technically graftable, significantly narrowed coronary arteries were addressed. Mitral repair was performed using a complete annuloplasty ring with the aim of achieving a leaflet coaptation length of at least 8 mm and no or trace mitral regurgitation at the end of the operation. Both groups received similar number of grafts but the repair group expectedly had longer bypass and cross clamp times compared to the CABG group.

The trial met all its end points with high statistical significance at the proposed follow up period of one year. The primary end point of change in peak oxygen consumption (Peak VO2) showed significant improvement at 1 year. The Peak VO2 in the repair group increased by 22% (*from* 14.8 ± 3.2 *to* 18.1 ± 2.9 mL/kg/min) while the CABG group only increased by 5% (*from* 15.1 ± 3.3 *to*

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15.9 ± 2.5 mL/kg/min) $p = 0.001$. All the secondary end points demonstrated significantly greater improvements in the repair group compared with the CABG group. The LVESVI decreased by 28% [22.2 (± 25.6) mL/m^2] in the repair group compared with a decrease of 6% [4.4 (± 17.4) mL/m^2] in the CABG group ($p = 0.002$). The MR volume decreased by 80% [28.2 (± 24.6) mL/beat] in the repair group compared with a decrease of 29% [9.2 (± 19.1) mL/beat] in the CABG group ($p = 0.001$). BNP levels decreased by 557.4 pg/mL (75%) in the repair group while BNP in the CABG group decreased by 394.7 pg/mL (58%) ($p = 0.003$). In the repair group, 96% (26 patients) had no or mild MR versus 50% (16 patients) in the CABG group.

In the early postoperative period the repair group required more blood transfusion [900 (225–1439) mL versus 153 (0–818) mL, $p = 0.016$]. They also required longer mechanical ventilation and stayed more days in the hospital than the CABG group [a median of 28 (17–102) hours versus 17 (12–20) hours, $p = 0.004$; and 15 days versus 9 days, $p = 0.05$ respectively].The perioperative use of intra-aortic balloon pump (IABP) was generally high in both arms – with no significant difference between both groups. which was noticeably high even in view of the overall risk profile of the patients. That was in part due to some participants inserting IABP routinely in high risk patients.

At one year the survival, rate of hospital readmission and incidence of AF were similar. The repair group reported better symptomatic benefit than the CABG group at one year (NYHA I: 76% vs. 21%; NYHA II: 20% vs. 64%; NYHA III: 4% vs. 15%) as the median NYHA functional class was I for the repair group and II for the CABG group ($p = 0.03$).

DISCUSSION

The importance of this trial lies in the clinical value of the question at hand. The investigators are to be commended for successfully conducting a trial in this difficult patient population where recruitment and follow-up have always been challenging.[3] The contemporary study end points used serve as good surrogates for the clinical question and are powerful predictors of worsening heart failure and survival.[4–6] In addition the use of Cardiac Magnetic Resonance (CMR) to quantify volumes (both LVESVI and MR volume) ensures accuracy and excellent reproducibility. In the interpretation of the clinical significance of these results, several important points warrant consideration:

During inclusion, the authors did not adopt the new paradigm of using lower cut-off values for estimating IMR severity that is gaining wide acceptance.[7,8] By following the AHA/ACC/ASE guidelines –which do not differentiate between the grading of functional and organic mitral regurgitation- the RIME investigators inadvertently recruited a significant number would then indicate severe rather than moderate ischemic MR.

The trial was stopped early after interim analysis due to difficulties in recruitment together with prominent benefit demonstrated in the repair group. The investigators initially intended to randomly assign 100 patients but the data available for analysis was that for only 59 patients. 73 patients were enrolled with 2 deaths before surgery, 2 postoperative deaths, 3 deaths before one year and 7 withdrawals from the study. This raises the possibility of a falsely exaggerated benefit in the repair group. One year is a short follow up period. LV reverse remodelling is reported to continue for up to 2 years after coronary artery revascularization, and it is possible that patients in the CABG-only group may demonstrate greater reverse remodelling with time. On the other hand, significant recurrence of MR after complete ring annuloplasty is also reported to only become apparent after 3 years.[9,10] It is possible that these two observations might attenuate the relative benefit observed in the repair group on long-term follow-up.

WHAT HAVE WE LEARNED?

The considerable effort that was put in this well executed manuscript makes it a welcome addition to the literature. We do not, however, expect it to result in a consequent change in the clinical practice. Further studies are needed to identify the moderate IMR patients who will in fact improve with revascularization alone rather than generalize a surgical strategy for the population as a whole. Until that happens we believe that individualizing surgical approach can lead to the best collective results. Patients who present with significant heart failure symptoms, a clearly audible pan-systolic murmur on auscultation with echocardiograms showing enlargement of the left atrium and consistent moderate IMR, as opposed to mild MR that increases on exercise, are more likely to benefit from an additional surgical maneuver to the mitral valve at the time of coronary revascularization.[11]

Surgical treatment for IMR has advanced greatly, perhaps too fast to validate its results by clinical research. This has left several areas of uncertainty. RIME is the only randomized controlled trial next to the one published from a single Italian centre in 2009, Fattouch et al. randomized 102 patients with the primary outcome of change in postoperative LV end-systolic dimension.[12] Follow up time was more prolonged (1, 3, and 5 years). Similarly they found a significant decrease in LV end-systolic dimension at follow-up along with favourable changes in LV end-diastolic dimension, LV ejection fraction, pulmonary artery systolic pressure and NYHA class. There were no differences in 5-year survival as would be expected from a small trial. Like the RIME trial firm conclusions regarding the efficacy and safety of mitral repair with CABG in patients with moderate ischemic MR cannot be extrapolated.

To find more definitive answers larger RCTs are required. A trial sponsored by the National Heart, Lung, and Blood Institute will shortly complete enrolment of 300 patients in a study of CABG plus repair versus CABG alone in patients with moderate ischemic MR. The primary end point is similarly the change in LVESVI at 1 year with several secondary end points including survival, exercise capacity, quality of life, and neurocognitive performance and other indices of LV function and MR severity.[13] Perhaps these collective efforts, and others to come, will lead to a future meta-analysis using the outcome data. Until the many conflicts resolve it is sensible to aim for balance between aggressive surgical therapy and conservative management. This is only possible by taking into account the patient characteristics and needs in order to achieve the difficult poise between early safety and long term attainment.

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