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Lessons from the trials

CTS Trials Network: A paradigm shift in the surgical treatment of moderate ischemic mitral regurgitation?

Ahmed Afifi*

Aswan Heart Center, Aswan, Egypt
*Email: ahmedafifi@doctors.org.uk

ABSTRACT

The Cardiothoracic Surgery Trials Network has reported results of the one-year follow up of their randomized trial "Surgical Treatment of Moderate Ischemic Mitral Regurgitation". They studied 301 patients with moderate ischemic mitral regurgitation (IMR) undergoing coronary artery bypass grafting (CABG) with or without mitral repair with the primary end-point of change in left ventricular end-diastolic volume index (LVEDVI) at one year and multiple clinical and echocardiographic secondary endpoints. Although their results were against repairing the mitral valve, the debate on surgical management of moderate IMR remains unsettled.

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BACKGROUND

Myocardial infarction (MI) is a major cause of morbidity and mortality worldwide. More than 10% of patients presenting with MI develop moderate ischemic mitral regurgitation (IMR), which further increases the morbidity and mortality.[1] Many patients with ischemic heart disease are indicated for surgical revascularization but repairing the mitral valve, by restrictive annuloplasty, is still a matter of controversy.[2,3] The Cardiothoracic Surgical Trials Network has attempted to address this problem by conducting a randomized trial, involving 26 centers in Europe and North America, overseen by the National Institute of Health. The one year results of the trial were recently published in *The New England Journal of Medicine*.[4]

The investigators randomized 301 patients with moderate ischemic mitral regurgitation (IMR) into two groups with similar baseline characteristics. The first; CABG group, 151 patients, to receive coronary artery bypass grafting (CABG) alone and the second; combined group, 150 patients, to receive CABG with mitral valve repair (Table 1). The trial had a single primary end-point of the change in left ventricular end-diastolic volume index (LVEDVI) as measured by transthoracic echocardiography at 12 months. There were multiple secondary end-points which included major adverse cardiac or cerebrovascular events (MACCEs), mortality, residual mitral incompetence, NYHA dyspnea class, quality of life and rehospitalization.

Table 1. CABG versus CABG and mitral repair

	CABG only	CABG and mitral repair
Preoperative LVEDVI	54.8(+/−24.9)ml/m^2	59.6(+/−25.7)ml/m^2
LVEDVI (at 1 year)	46.1(+/−22.4) ml/m^2	49.6(+/−31.5)ml/m^2
Mean change in LVEDVI	−9.4ml/ml^2	−9.3ml/ml^2
30-day mortality	2 (2.7%)	1 (1.3%)
1 year mortality	11 (7.3%)	10 (6.7%)
MACCEs	38 (25.2%)	38 (25.3%)
Residual moderate MR (at 1 year)	17 (25.9%)	7 (10.4%)
Residual severe MR (at 1 year)	3 (5.2%)	1 (0.8%)
Increased NYHA Class (at 1 year)	9 (6%)	12 (8%)
Rehospitalization (at 1 year)	20 (13.2%)	22 (14.7%)

All patients having mitral repair received complete, rigid, downsized annuloplasty rings. 19% of patients had concomitant surgical procedures (e.g. left atrial appendage ligation or maze procedure). As it was an intention to treat analysis, 8 patients from the CABG group had mitral valve repair as well, due to increase in the severity of IMR, and 3 patients from combined group had CABG only, due to concerns about the safety of performing a repair. Understandably patients with combined procedure had longer bypass and cross clamp times.

At one year there was no significant difference in the primary end-point as the LVEDVI changed from 54.8(+/−24.9) ml/m^2 to 46.1(+/−22.4) ml/m^2 in the CABG group and from 59.6(+/−25.7) ml/m^2 to 49.6(+/−31.5) ml/m^2 in the combined group (mean change from baseline, −9.4 and −9.3 ml/m^2 respectively). The difference in one year mortality rate was not statistically significant, 7.3% in the CABG group and 6.7% in the combined group, neither was the 30 day mortality (2.7% in the CABG group and 1.3% in the combined group, $P = 0.68$) the rate of MACCEs also did not show a statistically significant difference (hazard ratio, 0.99; 95% CI, 0.62 to 1.59; $P = 0.97$). There were also no differences in the rates of hospital readmission, need for reoperation or quality of life measures.

The combined group showed significantly lower rates of residual mitral regurgitation (11.2% [moderate, 10.4%; severe, 0.8%] vs. 31.0% [moderate, 25.9%; severe, 5.2%] $P < 0.001$) which came at the expense of longer mean length of hospital and ICU stay and higher incidence of serious neurologic adverse events and supra-ventricular arrhythmias.

DISCUSSION

The substantial effort put into this study together with the interesting findings make it a welcome addition to the literature. This would be the second trial by the same group to raise eyebrows within the cardiac surgery community after their study of surgical treatment of severe IMR concluded that together

with CABG replacement is superior to repair.[5] Studies like these may, in the future, help to shape how surgeons approach IMR.

The CTS Trials Network have presented a well-designed clinical trial. The study was not able to demonstrate a significant benefit from adding mitral valve repair to CABG in the treatment of moderate IMR as the CABG group showed slightly higher post-operative grade of MR which did not translate into worse functional or left ventricular echocardiographic outcomes in the first year. Instead the combined group has shown increased incidence of supraventricular arrhythmias, ICU and hospital stay and, more importantly, serious neurologic events occurred significantly more often in the combined group, (4% vs. 13%, $p = 0.03$).

Patient recruitment is a difficult task due to the fragility of this cohort, the complexity of the disease and the high risk of complications with both approaches. The number of patients recruited, albeit increased from any study of IMR to date, could not support the use of a clinical primary end-point, instead an echocardiographic endpoint was used. The definition of ischemic mitral regurgitation was slightly vague and the more emphasis was applied on defining the severity, as per the guidelines of the American College of Cardiology and American Heart Association[6] than the type of ischemic mitral regurgitation, whether global functional regurgitation or regional with motion abnormalities.

Two other groups have recently conducted randomized trials studying outcomes in patients with moderate IMR. Their results have been supportive of restrictive annuloplasty. The first was by Fattouch *et al.*[7] who studied 102 patients for an average of 32 months and found a significant difference in left ventricular reverse remodeling, the degree of mitral regurgitation and the NYHA functional class of dyspnea. The second by Chan *et al.*,[8] the RIME trial, randomized 73 patients and showed a significant improvement in peak oxygen consumption in their combined group as well as lower plasma B natriuretic peptide levels and left ventricular end systolic volume index. The results of the CTS Trials Network study, so far, represent a shift from the general paradigm of performing restrictive annuloplasty for moderate IMR and the recent studies supporting it.

WHAT HAVE WE LEARNED?

Despite the substantial effort by the CTS Trials Network and other groups treatment of moderate IMR continues to be a matter of debate. Clear distinction between ischemic cardiomyopathy with secondary moderate IMR and moderate IMR with regional wall motion abnormalities may show that they are two distinct diseases which need to be treated, and studied, individually. The follow-up period of one year may not allow for the outcomes to become significantly apparent which makes the data, despite statistically sound, somewhat immature. We await, with interest the results of the second year follow-up, which may show more compelling differences that would have greater impact on clinical practice. Currently we continue to believe that severity of left sided heart failure, left atrial size, the degree of annular dilatation and increase of the regurgitation with exercise will guide the surgical management in many cases. Until the evidence becomes more persuasive it might be safe to practice a tailored approach to the treatment of moderate IMR.

REFERENCES

[1] Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, Meverden RA, Roger VL. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. *Circulation*. 2005;111:295–301.
[2] Duarte IG, Shen Y, MacDonald MJ, Jones EL, Craver JM, Guyton RA. Treatment of moderate mitral regurgitation and coronary disease by coronary bypass alone: late results. *Ann Thorac Surg*. 1999;68:426–430.
[3] Harris KM, Sundt TMIII, Aeppli D, Sharma R, Barzilai B. Can late survival of patients with moderate ischemic mitral regurgitation be impacted by intervention on the valve? *Ann Thorac Surg*. 2002;74:1468–1475.
[4] Smith PK, Puskas JD, Ascheim DD, Voisine P, Gelijns AC, Moskowitz AJ, Hung JW, Parides MK, Ailawadi G, Perrault LP, Acker MA, Argenziano M, Thourani V, Gammie JS, Miller MA, Pagé P, Overbey JR, Bagiella E, Dagenais F, Blackstone EH, Kron IL, Goldstein DJ, Rose EA, Moquete EG, Jeffries N, Gardner TJ, O'Gara PT, Alexander JH, Michler RE, Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178–2188.
[5] Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo YJ, D'Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O'Gara PT, Michler RE, Kron IL, CTSN. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23–32.
[6] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 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. *J Am Coll Cardiol*. 2014;63:e57–e185.

[7] Fattouch K, Guccione F, Ruvolo G. POINT: efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. *J Thorac Cardiovasc Surg.* 2009;138(2):278–285.
[8] Chan KMJ, Punjabi PP, Flather MD, Pepper JR, for the RIME Investigators. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation Trial. *Circulation*. 2012;126(21):2502–2510.