Incidental Moderate Mitral Regurgitation in Patients Undergoing Coronary Artery Bypass Grafting: Update on Guidelines and Key Randomized Trials

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Incidental moderate mitral regurgitation (MR) in patients presenting for coronary artery bypass grafting (CABG) is not only common but also probably adversely affects clinical outcome. The echocardiographic evaluation of incidental MR must be comprehensive and integrated, as it remains a cornerstone in management decisions. Current guidelines support surgical mitral intervention in this setting as a reasonable option, reflecting clinical equipoise towards moderate MR in the setting of planned CABG. There are currently 2 major randomized trials in progress that will test whether surgical correction of moderate MR combined with CABG improves major clinical outcomes as compared to CABG alone. These landmark trials will be completed in the near future. In the interim, significant progress in the fields of cardiac resynchronization therapy, transcatheter mitral valve intervention, and minimally invasive mitral valve surgery promise to affect the management alternatives for moderate MR in patients undergoing CABG regardless of operative risk. It is likely that in the coming decade there will be less tolerance for incidental moderate MR given its already known outcome effects and the multimodal interventions that continue to mature with better safety profiles.

KEY WORDS: *moderate mitral regurgitation, clinical outcomes, coronary artery bypass grafting, echocardiography, vena contracta, effective orifice area, regurgitant fraction, regurgitant volume, guidelines, randomized trials, mitral valve repair, mitral valve replacement, clinical equipoise, cardiac resynchronization therapy, transcatheter mitral valve intervention, minimally invasive mitral valve surgery*

PATIENTS PRESENTING for coronary artery bypass grafting (CABG) often will exhibit varying degrees of valvular disease, including mitral regurgitation (MR).[1,2] The prevalence of concomitant MR in this setting has been reported to be up to 50%, with even moderate MR demonstrated to reduce late survival.[3–5] Although moderate MR in this setting may adversely affect patient outcome, its surgical correction at times may be technically challenging and at times may even significantly increase perioperative risk. The perioperative echocardiographer will, thus, not only encounter this scenario commonly but also will be asked to participate in the decision to surgically correct the MR at the time of CABG.[6,7] This expert review will approach this clinical controversy from the following 4 perspectives: Defining the severity of the incidental MR, understanding the current evidence base for the outcome effects of moderate MR in this setting, reviewing the relevant key randomized trials currently in progress to answer this question, and outlining possible future confounders, given the dynamic nature of the authors' understanding of and possible interventions for MR. These perspectives all play a role in the final perioperative decision whether to intervene and correct the moderate MR at the time of CABG.

WHAT IS THE SEVERITY OF THE INCIDENTAL MITRAL REGURGITATION?

The first task is to demonstrate that the observed MR is indeed at least moderate in severity, utilizing a comprehensive integrated echocardiographic examination.[8] This assessment of MR must take into account the preoperative presentation, echocardiographic findings, loading conditions of the mitral valve under general anesthesia, and the dynamic nature of MR in this setting.[9–11] Furthermore, the recent advent of 3D echocardiography also may have a role in the overall grading of MR in selected cases.[12,13] Since these aspects have been reviewed thoroughly already, they will not be handled in depth in this section; the details are covered clearly and comprehensively in the provided references.

If the incidental MR is graded as severe, the current consensus is that it should be corrected at the time of CABG, based on recent guidelines from North America and Europe, which will be reviewed later in this paper. If the incidental MR is graded as mild, then the current consensus is that it should be medically managed. There remains, however, significant clinical equipoise for the management of moderate MR in the setting of CABG. The evidence base supporting this equipoise is discussed in the following section.

WHAT IS THE OUTCOME SIGNIFICANCE OF THE MODERATE MITRAL REGURGITATION?

The second task is to understand the clinical significance of the moderate MR in this operative setting. The outcome effects of moderate MR in patients undergoing CABG have been

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1053-0770/2601-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2013.10.002

examined systematically in a series of single-center studies for the past 25 years.[4–6,14–21] Although a detailed discussion of this extensive dataset is beyond the scope of this expert review, this group of clinical studies, in summary, has suggested no definitive answer but has indicated that surgical correction may be a reasonable option in selected patients with moderate MR presenting for CABG. The gradual focus on this clinical question likely has been augmented significantly by the maturation and integration of transesophageal echocardiography as a standard of care in this setting.[14–21] In the contemporary era, most patients undergoing CABG with a degree of MR likely will undergo intraoperative echocardiography as a routine given the focus on mitral valve intervention.[2,8] This gradual shift in perioperative practice likely has increased the detection of moderate MR in the setting of planned CABG.

The recent 2012 CABG guidelines strongly have recommended mitral valve repair or replacement in the setting of severe MR (Class I recommendation; Level of Evidence B).[22] In the case of moderate MR, the experts have recommended that mitral repair or replacement at the time of CABG is a reasonable option (Class IIa recommendation; Level of Evidence B).[22] Therefore, despite multiple studies over 25 years, the evidence base for surgical correction of incidental moderate MR remains moderate in quality, resulting in an equivocal recommendation, prompting pro and con discussions in the literature.[6,7]

WHAT ARE THE KEY RANDOMIZED TRIALS RELEVANT TO THIS CLINICAL QUESTION?

The present evidence base has prompted the launch of multicenter randomized trials around the world in an effort to resolve the clinical equipoise evident for the management of moderate MR at the time of CABG. The first of these clinical investigations, the RIME (Randomized Ischemic Mitral Evaluation) trial, was published late in 2012.[23] The RIME trial was conducted at 7 European centers (6 in the United Kingdom, 1 in Poland). Moderate MR was defined according to established criteria as an effective orifice area of 0.20 to 0.39 cm^2, a regurgitant volume of 30 to 59 mL per beat, a regurgitant fraction of 30% to 40%, and/or a vena contracta width of 0.30 to 0.69 cm.[23] The trial exclusion criteria included structural mitral valve abnormalities, cardiogenic shock, severe comorbidity, previous cardiac surgery, and any associated conditions that significantly increased perioperative risk. The selected primary trial endpoint was peak oxygen consumption at 1 year. Selected secondary trial endpoints included left ventricular end-systolic volume index, MR volume, and plasma brain natriuretic peptide levels at 1 year. The power calculation estimated that a sample size of 100 patients would yield a 90% power for detection of a 2.5 mL/kg/min difference in peak oxygen consumption, assuming a 3% operative mortality and a 10% dropout rate.[23]

The RIME trial was terminated after interim analysis ($N = 73$).[23] Mitral valve repair significantly improved the primary trial endpoint of peak oxygen consumption at 1 year (3.3 mL/kg/min versus 0.8 mL/kg/min; $p < 0.0001$). Furthermore, mitral valve repair significantly improved all 3 selected trial secondary endpoints ($p < 0.005$). The investigators concluded that repair of moderate MR at the time of CABG significantly improves functional capacity at 1 year but that the impact of this benefit on major clinical outcomes remains to be defined. Although this trial supports surgical management of moderate MR in this setting, it leaves many important questions unanswered.[24]

Fortunately, there are 2 large multicenter randomized trials currently in progress that address whether or not surgical correction of moderate MR at the time of CABG improves patient outcomes beyond functional capacity. The first of these trials is currently in progress primarily in Scandinavia and the second primarily in North America. The details of each of these landmark trials are outlined below based on the latest information available.

The MoMIC (Moderate Mitral Regurgitation in Patients Undergoing CABG) trial was launched in 2008 and currently is still enrolling patients.[25] The MoMIC investigators are randomizing 550 patients with moderate ischemic MR to undergo CABG alone or CABG with surgical correction of the concomitant MR. This landmark trial is registered at www.clincaltrials.gov (trial number 20040224; last accessed September 26, 2013). The hypothesis to be tested is that repair of moderate MR in patients undergoing CABG will significantly improve late survival and freedom from hospitalization. The defined trial primary endpoint is a composite of mortality and re-hospitalization for heart failure at 5 years.[25] The chosen secondary trial endpoints include disabling neurologic deficit, new-onset atrial fibrillation, need for permanent pacemaker, and endocarditis. The power calculation yielded a sample size of 550 patients, assuming a 10% improvement in the primary trial endpoint at 5 years. The MoMIC trial is a multicenter international trial with 19 listed participating centers (Denmark 6, Sweden 4, Finland 1, Norway 6, USA 1, Canada 1).[25]

In the MoMIC trial, ischemic MR was defined as MR associated with coronary artery disease caused by mitral annular dilation (Carpentier type I) and/or restriction of the posterior mitral leaflet (Carpentier type IIIb).[2,8] Furthermore, the investigators specified that the mitral leaflets should be free of organic disease and the mitral valve annulus should have no significant calcification responsible for MR.[25] The study protocol has defined moderate ischemic MR as a calculated effective orifice area of 15 to 30 mm^2 at rest, utilizing the proximal isovelocity surface area method.[2,8,25] Although study inclusion was independent of left atrial size and left ventricular function, the following exclusion criteria have been outlined: Previous cardiac surgery, emergency surgery, ST-elevation myocardial infarction within 16 days, aortic valve disease requiring valve replacement, and calcification of the ascending aorta.[25]

The second major randomized trial, Surgical Interventions for Moderate Ischemic Mitral Regurgitation, was launched in 2008 by the Cardiothoracic Surgical Trials Network (full details at www.ctsurgerynet.org; last accessed September 27, 2013). Although this study is ongoing, patient recruitment has been completed (full details available at www.clincaltrials.gov: trial number 00806988; last accessed September 27, 2013). The target enrollment for this trial was 301 at 27 participating centers throughout the United States and Canada. Moderate ischemic MR was defined as effective regurgitant orifice area between 20 and 39 mm^2. The listed trial exclusion criteria included the following: Structural mitral valve disease; planned concomitant surgical procedures other than CABG, mitral