

# Deconstructing the interplay: CABG and concomitant mitral valve surgery in ischemic functional mitral regurgitation. Which one drives long-term survival?

*Descifrando la interacción: revascularización coronaria y cirugía valvular mitral concomitante en la insuficiencia mitral funcional isquémica. ¿Cuál de ellos determina la sobrevida a largo plazo?*

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## ABSTRACT

The intricate management of ischemic functional mitral regurgitation (FMR) in patients undergoing coronary artery bypass grafting (CABG) remains a formidable challenge and a subject of continuous scientific discourse. While the profound impact of CABG on survival in patients with significant coronary artery disease (CAD) and left ventricular (LV) dysfunction is well-established, the precise, independent benefit derived from adding concomitant mitral valve (MV) surgery for FMR warrants a comprehensive and nuanced discussion, especially given the inherent increase in surgical complexity. It is crucial to note that in FMR, the valvular incompetence is a consequence, rather than the cause, of an underlying pathology that distinctly differs from primary mitral regurgitation. Specifically, FMR in these patients predominantly stems from ischemic LV dysfunction, which precipitates MV annular deformation and papillary muscle displacement, thereby hindering effective MV leaflet coaptation.

**Keywords:** coronary artery bypass grafting, functional mitral regurgitation, mitral regurgitation, mitral valve, mitral valve repair, mitral valve replacement.

## RESUMEN

*El complejo manejo de la insuficiencia mitral funcional (FMR, por sus siglas en inglés) isquémica en pacientes sometidos a cirugía de revascularización coronaria (CABG, por sus siglas en inglés) sigue siendo un desafío formidable y un tema de continuo debate científico. Si bien, el profundo impacto de la CABG en la supervivencia de pacientes con enfermedad arterial coronaria significativa y disfunción del ventrículo izquierdo está bien establecido, el beneficio preciso e independiente derivado de agregar cirugía valvular mitral concomitante para la FMR justifica un análisis exhaustivo y matizado, especialmente dado el aumento inherente en la complejidad quirúrgica. Es crucial señalar que, en la FMR, la incompetencia valvular es una consecuencia, más que la causa, de una patología subyacente que difiere claramente de la insuficiencia mitral primaria. Específicamente, la FMR en estos pacientes se deriva predominantemente de la disfunción isquémica del ventrículo izquierdo, que precipita la deformación anular mitral y el desplazamiento de los músculos papilares, dificultando así la coaptación efectiva de las valvas de la mitral.*

**Palabras clave:** revascularización coronaria, insuficiencia mitral funcional, insuficiencia mitral, válvula mitral, reparación valvular mitral, reemplazo valvular mitral.

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**Abbreviations:**

CABG = coronary artery bypass grafting

CAD = coronary artery disease

FMR = functional mitral regurgitation

LV = left ventricular

LVEF = left ventricular ejection fraction

According to the 2021 American College of Cardiology, American Heart Association and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) Guideline for Coronary Artery Revascularization,<sup>1</sup> coronary artery bypass grafting (CABG) is recommended to improve survival rates for certain patients with stable ischemic heart disease. CABG is notably indicated as a class I recommendation for patients with multivessel coronary artery disease (CAD) and severe left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] < 35%) or significant left main stenosis. For patients with a LVEF between 35-50%, the recommendation shifts to class IIa. For patients with normal LVEF and significant stenosis in three major coronary arteries, CABG may be considered reasonable to improve survival, albeit with a weaker class IIb recommendation.

The present analysis focuses specifically on cases where CAD is the primary pathological disease. In contrast, scenarios where valvular disease (aortic, mitral, or tricuspid) is the primary indication for surgery, and there is concomitant CAD with significant (> 70%) proximal stenosis, concomitant CABG may be warranted in such cases.<sup>2</sup> However, since the underlying pathophysiology differs from that of functional causes, these cases are beyond the scope of this analysis. Similarly, patients with atrial-type functional mitral regurgitation (FMR) were excluded because their pathophysiology and clinical implications are fundamentally different.

**CABG as a paramount driver of survival**

It is unequivocally evident that CABG stands as a paramount driver of survival in patients with multivessel CAD and severely compromised left ventricular ejection fraction (LVEF ≤ 35%). Based on the groundbreaking findings of the STICH trial (NCT00023595), a landmark randomized controlled study with a 10-year follow-up period, Velazquez et al.<sup>3</sup> compellingly demonstrated that the combined approach of CABG and optimal medical therapy significantly reduces long-term mortality and hospitalization rates for cardiovascular issues compared to medical therapy alone. Specifically, the hazard ratios of 0.84 ( $p = 0.02$ ) for primary events, 0.79 ( $p = 0.006$ ) for cardiovascular mortality, and 0.72 ( $p < 0.001$ ) for death or cardiovascular hospitalization underscore the unequivocal benefits of CABG in this high-risk population. These findings furnish robust evidence that

revascularization confers a dramatic improvement in long-term survival by mitigating underlying myocardial ischemia and facilitating crucial LV reverse remodeling, thereby defining the therapeutic paradigm for patients with ischemic cardiomyopathy.

**The prognostic burden of FMR in heart failure: a critical determinant of mortality and morbidity**

However, the presence of severe FMR itself introduces a significant independent prognostic burden, correlating directly with increased morbidity and mortality in patients with ischemic cardiomyopathy. Uncorrected severe FMR imposes chronic volume overload on an already compromised left ventricular (LV), accelerating ventricular dilatation, perpetuating dysfunction, and exacerbating symptoms of heart failure (HF). Therefore, can we affirm that FMR serves as a marker of poor prognosis and mortality in patients with HF? The study by Nasser et al. provides compelling evidence that FMR serves as a robust marker of poor prognosis and mortality in patients with HF. A strong graded association was observed between the severity of FMR and the risk of mortality or hospitalization, with progressively higher grades of FMR corresponding to a significantly increased risk. Specifically, compared to grade I FMR, patients with grade II FMR had a 47% increased risk (Hazard Ratio [HR]: 1.47,  $p = 0.107$ ). Those with grade III FMR demonstrated a nearly three-fold increased risk (HR: 2.72,  $p < 0.001$ ), and those with grade IV FMR exhibited a more than three-fold increased risk (HR: 3.48,  $p < 0.0001$ ). The 4-year death or admission-free survival rates demonstrated a discernible inverse correlation with FMR severity, ranging from 83.5% in grade I to 44.7% in grade IV ( $p < 0.0001$ ).<sup>4</sup> These findings unequivocally support the notion that FMR is a potent predictor of adverse outcomes in HF patients. Then, the critical question then arises: does addressing this severe valvular pathology with concomitant mitral valve (MV) surgery, beyond the benefits of revascularization alone, further enhance survival?

**Guideline recommendations for concomitant mitral valve surgery in patients with severe functional mitral regurgitation undergoing CABG**

Current guidelines, including the 2020 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Valvular Heart Disease<sup>5</sup> confer a class IIa recommendation for concomitant MV surgery in patients with severe FMR undergoing CABG, while the 2021 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines for Valvular Heart Disease<sup>6</sup> provide a class I recommendation for MV repair or replacement in similar scenarios. This strong

endorsement reflects the clinical consensus about the detrimental impact of untreated severe FMR on prognosis, underscoring the necessity for intervention in cases where CABG is being considered. MV surgery in severe FMR does not translate into improved long-term survival.

While CABG definitively tackles the etiological ischemic substrate, the concomitant MV surgery serves to manage the profound pathological consequence of severe regurgitation. The primary aims of MV surgery in this setting are to achieve a durable reduction in MR, facilitate favorable LV reverse remodeling by alleviating chronic volume overload. This translates as better quality of life and symptoms improvement, but not better survival. Although establishing an independent, additional survival benefit over and above the CABG for severe FMR remains challenging through randomized trials—given the ethical implications of withholding MV surgery for severe cases during a planned cardiac surgery—the aggregate body of evidence, including observational studies and expert consensus, supports the belief that optimal management of severe FMR is integral to maximizing overall long-term outcomes. By eliminating a major source of myocardial inefficiency and progressive ventricular dysfunction, MV surgery contributes synergistically with revascularization (but not alone per se) to enhance the cardiac overall performance. Nevertheless, it is imperative to emphasize that, hitherto, *no impact on survival* has been observed after adding MV surgery to CABG in FMR.

A seminal study conducted by Mihaljevic et al.<sup>7</sup> provides compelling evidence that the addition of MV surgery to CABG does not confer a long-term survival benefit in patients with moderate-to-severe FMR. In a retrospective analysis of 390 patients with severe ischemic mitral regurgitation (3+/4+) who underwent CABG with (n = 290) or without (n = 100) MV annuloplasty, the investigators observed comparable survival rates at 1, 5, and 10 years postoperatively, with actuarial survival rates of 88%, 75%, and 47% in the CABG-alone group, and 92%, 74%, and 39% in the CABG plus MV annuloplasty group (p = 0.6). Notably, while the combined procedure resulted in a significant reduction in postoperative mitral regurgitation (48% vs 12% at 1 year, p < 0.0001) and provided early symptomatic relief, it did not translate into improved long-term functional status or survival, with 23% and 25% of patients in NYHA functional class III/IV at 5-year follow-up, respectively.

### **No evidence for MV surgery benefit in non-severe FMR**

Yet, this recommendation is viewed through the lens of a crucial trade-off. Adding MV surgery to CABG invariably prolongs cardiopulmonary bypass and aortic cross-clamp times, thereby increasing the immediate perioperative risks, including

higher rates of mortality and morbidity. This increased risk profile must be carefully taken into account, particularly when considering patients with less than severe FMR.

In this regard, a meta-analysis of patients with ischemic *moderate FMR* undergoing CABG with or without MV repair or replacement was performed. It was composed by 13 articles, out of them, 4 were randomized control trials and nine were retrospective cohort studies, and revealed that, although long-term mortality was lower in the CABG-only group compared to the CABG plus MV surgery group, the difference was statistically insignificant (RR: 0.88, 95% confidence interval [CI]: 0.77, 1.02); conversely, NYHA scores were significantly lower in the CABG plus MV repair group compared to the CABG-alone group (mean difference: 0.39, 95% CI: 0.06, 0.72), ultimately suggesting that concomitant MV surgery during CABG may *not yield significant benefits in terms of clinical outcomes or survival*.<sup>8</sup>

A comprehensive meta-analysis of 1038 patients with *less than severe FMR* yielded intriguing insights into the comparative efficacy of CABG alone (n = 423) versus combined CABG and MV repair/replacement (n = 615). Although the combined CABG plus MV surgery approach demonstrated a notable reduction in postoperative mitral regurgitation grade (weighted mean difference [WMD]: 1.34, 95% CI: 0.47 to 2.21, p = 0.003), this improvement did not translate into significant differences in in-hospital mortality (odds ratio [OR]: 0.84, 95% CI: 0.44 to 1.61, p = 0.60), NYHA functional class (WMD: 0.33, 95% CI: -0.29 to 0.94, p = 0.30), or long-term survival (OR: 0.77, 95% CI: 0.34 to 1.73, p = 0.53), thereby raising questions about the incremental benefits of adding MV surgery to CABG in patients with non-severe FMR. While MV surgery with concomitant CABG improves postoperative MR grade, *there is no evidence for superiority in mortality, functional class, and long-term survival*.<sup>9</sup>

Another meta-analysis of 14 studies (n = 2,836) found that adding MV surgery to CABG did not significantly impact in-hospital mortality or 1-, 3-, or 5-year survival compared to CABG alone [in-hospital mortality (OR = 1.45, 95% CI: 0.93-2.28, p = 0.10) and one- (OR = 0.89, 95% CI: 0.68-1.15, p = 0.37), three- (OR = 1.10, 95% CI: 0.79-1.55, p = 0.56) and five- (OR = 0.93, 95% CI: 0.73-1.18, p = 0.55)], respectively. Therefore, while concomitant MV surgery during CABG yields superior postoperative mitral regurgitation outcomes, *the current evidence fails to demonstrate significant benefits of combined surgery over CABG alone in terms of in-hospital mortality and long-term survival*.<sup>10</sup>

A comprehensive meta-analysis of nine observational studies encompassing 2,479 patients with *ischemic moderate or severe FMR* revealed that concomitant MV surgery during CABG yielded *no discernible benefits in terms of late mortality* compared to CABG alone (relative risk [RR]: 1.02, 95% CI: 0.90-1.14, p = 0.73).<sup>11</sup>

Similarly, in patients with moderate ischemic FMR undergoing CABG, the addition of MV repair provided more durable correction of mitral regurgitation (32.3% vs 11.2% moderate or severe residual mitral regurgitation at two years,  $p < 0.001$ ), *but did not significantly improve survival* (mortality rate: 10.6% vs 10.0%; hazard ratio, 0.90;  $p = 0.78$ ) or reduce overall adverse events or readmissions.<sup>12</sup>

## CONCLUSIONS

In conclusion, while MV surgery alone effectively reduces postoperative mitral regurgitation and alleviates symptoms—thereby enhancing short-term quality of life—it is CABG that remains the cornerstone of long-term survival, as it directly targets the underlying ischemic substrate in patients with severe LV dysfunction and FMR. Accordingly, given that CABG serves as the principal determinant of survival in the surgical management of ventricular-type FMR, isolated MV surgery—performed in the absence of concomitant CABG—has been downgraded to a class IIb recommendation. In contrast, transcatheter edge-to-edge repair, which likewise excludes surgical revascularization, retains a class IIa indication due to its less invasive nature and procedural advantages. The overarching conclusion supported by current evidence is thus unequivocal: isolated MV surgery without CABG occupies a markedly limited therapeutic role in ventricular-type FMR, a perspective previously articulated by García-Villarreal.<sup>13</sup> Therefore, a balanced strategy that simultaneously prioritizes improved survival and quality of life enhancement is justified, to the extent possible—and such an approach warrants careful reconsideration before being pursued in clinical practice.

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