EDITORIAL
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A study that fails to move the needle: MATTERHORN and the confirmation of the obvious in a highly selective population

Un estudio que no cambia el juego: el MATTERHORN y la confirmación de lo obvio en una población altamente selectiva

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Recently, the Matterhorn (A Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN) trial (NCT02371512) results have been released through the article by Baldus S et al.[1] In this non-inferiority randomized-controlled trial (RCT) the authors studied the efficacy of transcatheter edge-to-edge repair (TEER) compared to mitral valve (MV) surgery by the composite primary endpoint encompassing death for any-cause, rehospitalization for heart failure, stroke, reintervention, implantation of left ventricular assistant device (LVAD) at one year of follow-up in patients with functional mitral regurgitation (FMR) who are at high surgical risk. The authors concluded that TEER was non-inferior to MV surgery with respect to the primary composite endpoint efficacy at one year of follow-up.

As previously mentioned, TEER proved to be non-inferior to MV surgery in FMR, but did this study truly break new ground? Does it offer any paradigm-shifting insights?

Let us premise that it is a well-established fact that MV surgery in FMR assumes particular importance solely in the context of concomitant coronary artery bypass grafting (CABG). The recommendation is class I or IIa in the current guidelines for valvular heart disease (VHD), whereas isolated MV surgery is relegated to class IIb when CABG is not part of the therapeutic strategy.[2,3] Notably, this critical aspect was conspicuously absent from the Matterhorn trial, as reflected in the reported data from this RCT. Indeed, as detailed in *Table S2*: surgical technique provided in the supplementary material by Baldus et al,[1] no cases of concomitant CABG were reported in the surgical group. In addition, patients who had undergone CABG within the preceding month were excluded from participation.

Moreover, the study enrolled 208 patients, with 104 patients allocated to the intervention group and 104 patients assigned to the surgical group. In the surgical group, 72% of patients underwent MV repair, while 28.0% underwent MV

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replacement, at the surgeon's discretion. However, the concern arises because the absence of a clear algorithm for selecting the type of MV surgery is a significant omission, especially in a multicenter trial, such as the Matterhorn. As a point of reference, the efficacy of MV repair in FMR is contingent upon the fulfillment of rigorous echocardiographic criteria, as described by Lancellotti, et al. These criteria provide a framework for predicting MV repair success and guiding clinical decision-making.[4] The absence of standardized selection criteria for MV repair or replacement may substantially influence the constituent elements of the primary composite endpoint for efficacy, including reoperation, HFH, and stroke, as well as the components of the composite endpoint for safety (stroke, bleeding, reoperation, MR recurrence, and others), with a distinctly different impact depending on whether the procedure involves MR repair or replacement.

This trial exemplifies a flawed approach, where the lack of specific subsets (MV repair or replacement) with corresponding results, precludes the possibility of drawing meaningful conclusions under the misleading term of "mitral valve reconstruction". This term, in fact, represents a fictional construction, rather than a legitimate clinical entity which rules out MV replacement.

Although it has been consistently and concisely stated that MV replacement is superior to MV repair in FMR, with regards to the absence of MR recurrence at 1 and 2 years of follow-up, it is essential to highlight that these findings were derived from studies conducted in cohorts that incorporated CABG as a component of the therapeutic approach; that means to say, corresponding to a class I or IIa recommendation for MV surgery in FMR. Importantly, in both Cardiothoracic Surgery Network Trials, this reduced recurrence of MR did not result in improved patient survival.[5,6] In addition to this, it has been emphasized that no benefit on survival is obtained by adding MV surgery to CABG in cases with FMR ≥ 3+.[7] Survival and symptom relief are primarily determined by CABG, whereas MV surgery is centered on enhancing quality of life and alleviating symptoms.[7-9]

However, it is crucial to acknowledge that, in the context of isolated MV surgery without CABG, the indication is downgraded to class IIb. This has significant implications, as the indication for isolated MV surgery without CABG *per se* in this trial is rendered increasingly contentious, particularly when employed as a point of comparison for the concept of "non-inferiority".

Furthermore, this RCT does not provide a compelling information for upgrading TEER recommendation to a class I indication, given that the subset of FMR patients eligible for TEER or isolated MV surgery typically present with disproportionate FMR,[10] which is often a consequence of underlying coronary artery disease (CAD) necessitating concomitant CABG,[11] a scenario explicitly excluded from the Matterhorn trial. As mentioned above, no cases including CABG are reported in this RCT. At the same time, it is unknown in this RCT the proportion of patients having proportionate or disproportionate FMR, as well as the specific type of tethering, viz, symmetrical or asymmetrical tethering. This fact is commonly associated to proportionate and disproportionate FMR, respectively.[12]

Within the total population, the overall prevalence of CAD was 43.7%, yet no cases of CABG were reported. Theoretically, this implies that 43.7% of the population had ischemic dilated cardiomyopathy (IDCM). However, it is impossible to determine the exact number of cases attributable to non-ischemic dilated cardiomyopathy (NIDCM). Notably, only 46.9% of the population exhibited left ventricular tethering (Carpentier's type IIIb), whereas the remaining 53.1% had annular dilation (Carpentier's type I). Furthermore, 51% of the population had a prior history of atrial fibrillation. It can be inferred that this 51% is directly correlated with the 53.1% displaying solely annular dilation, characteristic of atrial-type FMR. In general, atrial-type FMR tends to have a more favorable prognosis compared to ventricular-type FMR, particularly following successful intervention.[13] To make matters worse, no special separate subsets of patients with these aforementioned characteristics are shown in this RCT. In other words, the Matterhorn trial's results may not be broadly applicable to everyday clinical practice, as the trial focus on dilated cardiomyopathy (not needing CABG) and atrial FMR represents a relatively narrow subset of the FMR population, which is often characterized by a more diverse range of underlying causes in real-world, spearheading the list by ventricular-type FMR mainly due to IDCM cases.[14,15]

It is widely acknowledged that the adjunctive use of MV surgery in the management of FMR, with or without concomitant CABG, primarily yields palliative benefits, improving symptoms and quality of life, whereas the survival advantage is predominantly driven by CABG.[7-9] Therefore, adding death and rehospitalization for heart failure as part of the composite primary efficacy endpoint in this RCT excluding CABG appears spurious, arbitrary and unjustified.

Since intention-to-treat (ITT) analytical approach involves assessing the outcomes of all patients who underwent randomization and were allocated to a specific treatment group, without regard to their treatment adherence, completion, or withdrawal, the results reported in the article need to be deeply analyzed. A closer examination of the Matterhorn trial's supplementary material reveals that, upon applying basic statistical by Intention-to-Treat ITT analytical approach, the only parameters that demonstrated statistically highly significant benefits favoring TEER (with p-values ranging from 0.01 to 0.001) were new-onset atrial fibrillation and bleeding complications, both of which are predictable consequences of surgical procedures *(Table 1)*.

Table 1: Statistical by intention-to-treat analytical approach regarding the primary composite endpoint for safety.

Parameter	TEER (1-year, %)	MV Surgery (1-year, %)	Difference (%)	p*
Death for any cause	8.3	10.3	2.0	0.620
Rehospitalization for any cause	24.7	39.0	14.3	0.027
Rehospitalization for HF	3.4	8.5	5.1	0.120
CV Rehospitalization	8.0	14.6	6.6	0.133
Reintervention	7.6	18.5	10.9	0.019
Stroke	1.1	4.8	3.7	0.115
VARC major bleeding	3.3	29.8	26.5	< 0.0001
Deep wound infection	1.1	4.9	3.8	0.109
AKF	4.3	10.7	6.4	0.080
New onset AF	8.7	33.3	24.6	< 0.0001
Intubation > 48 hours	4.3	11.8	7.5	0.047
Sepsis	1.1	4.8	3.7	0.115
Endocarditis	0.0	1.2	1.2	0.263

AF = atrial fibrillation. AKF = acute kidney failure. CV = cardiovascular. HF = heart failure. MV = mitral valve. TEER = transcatheter edge-to-edge repair. VARC = valvular academic research consortium.
* p values are considered as statistically highly significant as < 0.001.

It is alarming to note that the "high surgical risk" criterion was employed as a determining factor for inclusion in this trial, in direct contravention of clinical guidelines which do not recognize this parameter as a valid criterion for FMR decision-making.[2,3] Moreover, the mean STS-PROM and EuroSCORE II scores in this trial were 2.0 and 3.0, respectively, which translates to low surgical risk (≤ 3%).

In conclusion, the Matterhorn trial has succinctly illustrated that, in the realm of medical science, reality is ostensibly whatever we deem it to be. Thus, if reality does not conform to our expectations, we can simply create a new one through misleading and confusing selection criteria.

Unfortunately, the needle seems to remain largely unchanged after this trial. We would expect the authors' sound judgment to prevail, and that the utilization of this type of RCT does not unduly influence the development of forthcoming clinical guidelines.

One would hope that the authors' prudent discernment prevailed, and that the utilization of this type of RCT does not unduly influence the development of forthcoming clinical guidelines.

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