OPINION ARTICLE

RE-EVALUATING THE MATTERHORN TRIAL: A CRITICAL ANALYSIS OF ITS METHODOLOGICAL AND CLINICAL IMPLICATIONS

ABSTRACT

The MATTERHORN trial, the sole randomized controlled trial to date comparing mitral valve surgery with transcatheter edge-to-edge repair for functional mitral regurgitation in symptomatic patients ineligible for coronary artery bypass grafting, presents significant limitations. The exclusion of coronary artery bypass grafting is a critical omission, as it is the primary intervention for improving survival in these patients, with isolated mitral valve surgery predominantly addressing symptoms and quality of life. Moreover, numerous methodological deficiencies and inherent flaws compromise the trial's internal validity and its broader applicability in clinical practice. Therefore, a comprehensive re-evaluation, highlighting these biases, methodological shortcomings, and constraints, is essential, particularly as new clinical guidelines are anticipated.

Keywords: *mitral valve; mitral valve surgery; functional mitral regurgitation; randomized controlled trial; secondary mitral regurgitation; transcatheter edge-to-edge repair.*

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Introduction

The majestic Matterhorn, a towering peak of unparalleled prominence in the Alps, lends its name to a recent clinical trial, the MATTERHORN study, whose findings warrant meticulous examination within the cardiology community. This perspective piece undertakes a critical appraisal of the data presented by Baldus et al.,[1] emanating from the MATTERHORN trial (NCT02371512), a randomized controlled trial (RCT) sponsored by Abbott Vascular.[2]

The MATTERHORN trial set out to assess the comparative efficacy and safety between transcatheter edge-to-edge repair (TEER) and surgical mitral valve (MV) repair or replacement in patients suffering from heart failure (HF) and functional mitral regurgitation (FMR) who remained symptomatic despite receiving guideline-directed medical therapy (GDMT). The primary efficacy endpoint was a composite of clinical events at one year, while the primary safety endpoint tracked major adverse events within 30 days. Specifically, the one-year efficacy composite included death, HF rehospitalization, MV reintervention, left ventricular (LV) assist device implantation, or stroke. The trial's key finding asserted the non-inferiority of TEER to MV surgery regarding this composite endpoint at one year.[1]

Considering that the MATTERHORN is the only RCT directly comparing these two treatment modalities for FMR, a detailed critical appraisal of its reported outcomes is imperative. This analysis will highlight the methodological caveats and clinical implications that may impact the study's reliability and generalizability, thereby influencing future clinical practice.

Inconsistencies in the reporting: discordance between registry data and published results

To begin with, the official registry for the MATTERHORN trial reveals a discordance between the anticipated study timeline and the actual reporting of results. Initiated in 2015, the trial was slated for completion by 2019; however, the last reported data update occurred in 2017, with a conspicuous absence of subsequent registry updates. According to established protocols, a registry that remains inactive for an extended period (>2 years) without reported updates is deemed closed, thereby warranting an "unknown status" designation.[2] This anomaly is particularly pronounced in juxtaposition with the assertion by Baldus et al.[1] that patient randomization in MATTERHORN spanned from February 2015 to December 2022, encompassing a total of 210 patients. The purportedly prolonged enrollment period starkly contrasts with the publicly available registry data,[2] underscoring a notable disparity between the two sources.

In addition, given the considerable temporal gap between the initiation of enrollment in 2015 and the publication of the study (9 years), it is striking that the follow-up period is limited to a single year. One should expect a more protracted follow-up duration, extending to five years or beyond, to provide a more comprehensive understanding of the outcomes.

Methodological concerns: the mirage of non-inferiority

The methodological design of the MATTERHORN trial reveals several significant concerns, particularly in its reliance on the intention-to-treat (ITT) principle. While ITT analysis ensures that all randomized patients are included regardless of protocol adherence or withdrawal, including even those who are deceased, it provides a pragmatic assessment. However, this approach can also dilute actual treatment effects, especially in non-inferiority designs. Baldus et al.[1] reported 19 events (18.2%) in the TEER group (out of 104 patients) and 26 events (25%) in the MV surgery group (out of 104 patients) for the primary efficacy endpoint at one year. This translated to a non-significant p-value of 0.234, with a 6.8% difference (95% confidence interval [95% CI]: -4.42% to 17.84%).

A crucial aspect of non-inferiority trials is the statistical threshold. The use of a one-sided *p*-value of 0.025, as opposed to the more common two-sided 0.05, is often employed given the directional hypothesis.[3] However, our analysis, with a *p*-value of 0.234, suggests the observed differences between TEER and MV surgery are more likely due to random variation than a statistically meaningful effect.

Furthermore, interpreting non-inferiority studies demands a careful balance between statistical significance (*p*-value) and clinical relevance (effect size and confidence interval). The non-inferiority margin itself is central to this interpretation, and its derivation warrants meticulous scrutiny. The authors assumed an average 35% incidence of adverse events for their primary endpoint, resulting int a non-inferiority margin of 0.175.[1] The lack of clarity regarding the evidence or database supporting this 35% event rate is concerning. A higher assumed event rate can artificially broaden the non-inferiority margin, potentially skewing results towards non-inferiority. This is a notable dilemma in the MATTERHORN trial. The reported Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) of 2.2%[1] indicates a low-

risk cohort. Current data, such as that from Newell et al.,[4] suggest that patients undergoing MV repair with an STS-PROM ≤2% exhibit a composite mortality and morbidity rate of 8.03%, substantially lower than the 19.24% observed in those with STS-PROM >2%. Even assuming the MATTERHORN cohort had an STS-PROM >2%, their expected event rate would still not exceed 19.24%, falling considerably short of the 35% threshold proposed by the investigators.

The inclusion of soft endpoints can inflate event rates and, consequently, widen the non-inferiority margin, potentially benefiting the trial's outcome. In MATTERHORN, the one-year primary efficacy composite endpoint was driven mainly by reintervention [7.6% for TEER versus 18.5% for MV surgery; difference in proportions = -0.12 (-0.23; -0.01)] and rehospitalization for any cause.[1] Closer examination of reintervention rates reveals inconsistencies between 30-day and one-year reporting: the MV surgery group had more reinterventions at 30 days (10 cases) than TEER (7 cases), but at one year, the pattern shifted, with only 2 cases in MV surgery versus 5 in the TEER group. The lack of specific causes for early reinterventions further diminishes confidence in the accuracy of this outcome.

Furthermore, while rehospitalization for any cause demonstrated statistical significance between TEER and MV surgery [24.7% versus 39%; difference in proportions = -0.14 (-0.28; -0.004)], a deeper dive into specific causes reveals that only "other causes" (unrelated to HF or cardiovascular issues) reached statistical significance [13.9% versus 15.9%; difference in proportions = -0.02 (-0.13; 0.09)].[1] This raises questions about the appropriateness of including such non-specific events in a primary efficacy composite. The dilution of specificity, turning HF rehospitalization (3% versus 6.9%, $p = 0.1969$ at one year) into the broader "rehospitalization for any cause" underscores the critical importance of rigorous endpoint selection and definition, particularly for non-inferiority assessments. Adding to this complexity, the disparate implications of the non-inferiority margin for MV repair versus replacement procedures make their amalgamation potentially problematic, especially given that 28% of cases required MV prostheses.[1] By the same token, the broad variability in surgical MV repair techniques further reported in this RCT introduces confounding variables that could compromise the study's internal validity.

It is widely recognized that ITT analyses, when not complemented by per-protocol analyses, can obscure genuine differences between treatment arms due to protocol deviations.[3] Non-inferiority trials typically demand consistent conclusions from both ITT and per-protocol analyses. However, the MATTERHORN trial relied solely on an ITT analysis to declare non-inferiority, a methodological choice that may compromise the study's overall validity and credibility.

Limitations in functional mitral regurgitation phenotyping

A critical limitation of this study lies in its undifferentiated inclusion criteria concerning FMR. The current criteria, encompassing echocardiographic quantitative parameters [effective regurgitant orifice area (EROA), regurgitant volume, vena contracta, and regurgitant fraction], a history of recurrent HF hospitalizations, left ventricular ejection fraction (LVEF) ≥20%, Heart Team adjudicated high surgical risk, and New York Heart Association Class II-IV symptoms despite optimal GDMT, do not adequately distinguish between atrial-type FMR and ventricular-type FMR.

The lack of precise phenotyping is significant because atrial-type and ventricular-type FMR represent distinct pathophysiological entities with divergent prognoses, especially after MV intervention, regardless of TEER or surgical MV repair/replacement. Patients diagnosed with ventricular-type FMR demonstrate significantly poorer clinical outcomes compared to those with atrial-type FMR. Specifically, ventricular-type FMR is associated with a higher incidence of all-cause mortality [adjusted hazard ratio (HR) = 1.73, 95% confidence interval (CI 95%): 1.54-1.94, $p < 0.001$], and HF hospitalization (adjusted HR = 1.23, 95% CI: 1.15-1.32, $p < 0.001$).[5] The echocardiographic assessment utilized in this RCT does not facilitate this crucial differentiation, potentially obscuring the actual impact of interventions on specific FMR subtypes.

The patient demographic of the MATTERHORN trial is complex. While 43.7% had ischemic heart disease not requiring coronary artery bypass grafting (CABG), suggesting ischemic dilated cardiomyopathy, the extent of non-ischemic dilated cardiomyopathy remains unclear. Mitral regurgitation mechanisms were split: 46.9% exhibited LV tethering (Carpentier type IIIb), while 53.1% had annular dilation (Carpentier type I).[1] The latter group likely overlaps with 51% with a history of atrial fibrillation, indicating atrial-type FMR. This distinction is vital, as atrial-type FMR typically carries a more favorable prognosis than ventricular-type FMR, especially

post-intervention. Therefore, the high proportion (53.1%) of presumptive atrial-type FMR cases detected in the MATTERHORN trial, representing a lower-risk population, likely favored a non-inferiority finding, thereby limiting and essentially precluding the applicability of its results to the more common ventricular-type FMR secondary to ischemic heart disease requiring CABG.

High surgical risk: misused as a treatment rationale

It is important to note that while high surgical risk, as determined by the Heart Team, is an inclusion criterion for MATTERHORN, it does not guide the selection of specific treatments for FMR. Indeed, neither the American Heart Association (AHA) and American College of Cardiology (ACC) 2020 guidelines (AHA/ACC 2020) for the management of patients with valvular heart disease (VHD)[6] nor the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) 2021 guidelines (ESC/EACTS 2021) for the management of VHD[7] base FMR treatment decisions on surgical risk.

Constraints on clinical applicability: a trial detached from real-world practice

The MATTERHORN trial's singular position as the only RCT comparing MV surgery with TEER for FMR prompts inquiry into its underlying rationale. The limited indications for isolated MV surgery in FMR in the absence of concomitant CABG —the specific patient population of this trial— likely explain this gap in evidence.[8]

Current clinical guidelines from both the 2020 ACC/AHA[6] and 2021 ESC/EACTS[7] for VHD clearly differentiate the management of severe FMR based on the presence of concomitant CABG. MV surgery receives a Class I indication with CABG, while TEER, which does not involve CABG, is a class IIa indication. Conversely, isolated MV surgery without CABG is merely a class IIb indication.[6,7] Astonishingly, the MATTERHORN trial enrolled no patients who underwent CABG, and those who had CABG within a month of enrollment were explicitly excluded. Essentially, the investigators sought to establish non-inferiority of a Class IIa indication (TEER) against a Class IIb indication (MV surgery without CABG) —a comparison that appears both questionable and clinically unnecessary.

Further complicating the surgical arm, Chikwe et al.[9] and García-Villarreal et al.[10] observed that while 72% of the surgical cohort underwent MV repair and 28% underwent MV replacement, no further details were provided regarding the specific prosthesis type (mechanical or biological) in 53.6 % of the series.[1] The surgeon's discretion governed the choice of surgical technique, an unstandardized and arguably lax approach for a multicenter trial where methodological consistency is paramount. The ultimate event count could be skewed by the ratio of repair to replacement procedures. Reoperation rates are expected to be higher in MV repair than in MV replacement (34% at one year, 59% at two years).[11,12] This disparity disproportionately impacts the primary composite outcome, potentially conferring an inherent advantage to TEER.

Lancellotti et al.[13] emphasized the importance of stringent echocardiographic criteria for successful MV repair in FMR. However, the MATTERHORN trial did not specify criteria for MV repair type. This is particularly critical when CABG is not part of the treatment plan, and the risk of recurrent mitral regurgitation (MR) is elevated. While LV remodeling dictates MV repair techniques (annular or subvalvular, with or without chordal/papillary muscle intervention),[8] the MATTERHORN trial provided no such details. Similarly, although the specific annuloplasty ring type may not be decisive, a strong consensus favors complete rings, especially given FMR's characteristic MV anteroposterior deformation. Etiology-specific rings have shown promise in achieving long-term freedom from MR.[14-18] Of note, the MATTERHORN trial again offered no information in this regard.

Questionable inclusion and severity criteria of MR

A further concern revolves around the inclusion criterion of EROA ≥20 mm^2.[1] Both the 2020 ACC/AHA[6] and 2021 ESC/EACTS[7] guidelines for VHD specify that only patients with severe FMR, defined by EROA ≥40 mm^2, regurgitant volume ≥60 mL, and regurgitant fraction ≥50%, are candidates for interventional treatment. In the MATTERHORN, the baseline median EROA was 20 ± 10 mm^2, ranging from 17 to 28 mm^2, indicating mild (1+) or mild-to-moderate (2+) MR. Critically, specific results coming from different MR subgroups [mild (<20 mm^2), mild-to-moderate (21-29 mm^2), moderate-to-severe (30-39 mm^2), and severe (≥40 mm^2) MR], according to Lancellotti et al.[13] and Zoghbi et al.,[19] were not provided in this RCT. At baseline, 59.8% had moderate-to-severe (3+) MR (30-39 mm^2), and only 37.3% had severe (4+) MR (≥40 mm^2).[1] Wang et al.[20] also noted that approximately 60% of MATTERHORN patients had non-severe FMR. This implies that only about one-third of the MATTERHORN participants would meet current guideline criteria for MV intervention,[6,7] thus

raising significant doubts about the trial's actual applicability to patients needing more than medical therapy.

Methodological shortcomings and missing information

Chikwe et al.[9] highlighted additional methodological shortcomings, including substantial patient dropout (11.9%) and significant missing data (e.g., 16.3% for 30-day mortality in the surgical group). Similarly, Baldus et al.[1] reported in the supplementary appendix considerable missing echocardiographic data at one year for parameters like vena contracta (62.5% for 2-chamber, 64.4% for 3-chamber), systolic pulmonary artery pressure (53.8%), LV end systolic diameter (43.2%), LV end diastolic diameter (43.2%), LVEF (43.2%), and LV end diastolic volume (44.2%). Such extensive data loss at follow-up severely compromises the study's reliability and generalizability.

Deficiencies in guideline-directed medical therapy adherence

Furthermore, the reported treatment adherence in MATTERHORN appears suboptimal. Concomitant ablation was performed in only 35.4% of patients with preoperative atrial fibrillation, and 10.5% of surgical patients received triple HF therapy.[9] The 2022 AHA, ACC and Heart Failure Society of America (HFSA) guidelines for the management of patients with HF with reduced ejection fraction (HFrEF), prevalent in more than 50% of patients with FMR, advocate for GDMT encompassing four cornerstone medication classes: mineralocorticoid receptor antagonist (MRA), beta blocker (BB), angiotensin receptor-neprilysin inhibitor (ARNi), and sodium-glucose cotransporter 2 inhibitor (SGLT2i), all with class IA recommendations.[21] Fonarow et al.[22] demonstrated that delaying or omitting GDMT in HFrEF significantly increases adverse outcomes, with omissions of SGLT2i, ARNi, and MRA linked to increased all-cause mortality and HF hospitalization. Baldus et al.[1] showed that only 19.3% of the total cohort received triple GDMT at discharge (27.5% in TEER versus 10.5% in MV surgery). MRA were prescribed in only 26.4%, ARNi proportions remain unknown, and SGLT2 inhibitors were absent,[1] despite their approval for HFrEF since May 2020[23] and the trial's enrollment extending to December 2022, according to MATTERHORN authors.[1] Furthermore, the post-procedural success of both surgical MV repair or replacement and TEER is heavily contingent upon the uptitration, continuation, and high quality of GDMT.[24]

Critical omissions, unaddressed metrics in outcome assessment

The MATTERHORN trial also failed to assess crucial post-procedural outcomes, such as residual MR or trans-mitral gradients, as primary efficacy endpoints. Optimal TEER outcomes depend on achieving specific hemodynamic targets, including residual MR ≤1+, MV area >2.0 cm^2, mean trans-mitral gradient < 5 mmHg, and pressure half-time <100 milliseconds post-procedure.[25] The absence of data on post-TEER trans-mitral gradients or MV area in the MATTERHORN study is a significant oversight.

Finally, structural failure rates of MV repair, regardless of whether the approach is surgical or percutaneous, have emerged as a more robust quality metric than reoperation rates, which are influenced by numerous patient and clinician variables.[26] The omission of structural failure rate as a hard endpoint in the MATTERHORN's primary composite outcome for efficacy is highly questionable.

Conclusion: a trial that falls short of its aspirations

While evocatively named after a mountain of great altitude, the MATTERHORN trial ultimately fails to reach equivalent scientific heights. In sum, for patients with FMR, particularly given that ischemic ventricular-type FMR is the overwhelmingly predominant phenotype encountered in clinical practice, the benefits of isolated MV surgery are largely palliative, addressing symptoms and improving quality of life. Conversely, CABG remains the primary driver of survival benefits in this population.[8] The trial excludes CABG, misclassifies MR severity, differentiates FMR phenotypes inadequately, underutilizes GDMT, and neglects critical endpoints; consequently, it offers limited guidance for real-world practice. Its methodology is undermined by significant limitations that preclude meaningful changes in clinical paradigms for managing FMR. Thus, the comparison between the majestic Matterhorn peak and the eponymous RCT appears tenuous, bearing little resemblance to the complex realities of clinical practice.

Declarations

The author declares no conflict of interest.

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