The Impact of Guideline-Directed Medical Therapy Adherence on Cardiovascular Outcomes: A Critique of Recent Trials

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INTRODUCTION

This review scrutinises the role of guideline-directed medical therapy (GDMT) adherence in some studies and how it influenced cardiovascular outcomes. Furthermore, it explicates the methodology, outcomes, and clinical implications of the ISCHEMIA trial, emphasising the necessity of achieving optimal adherence in clinical practice. Numerous landmark clinical trials in recent years have had profound implications on interventional practice in cardiovascular medicine. Among these, the COAPT and ORBITA trials warrant mention. A consistent element in such investigations is the implementation of GDMT, a key factor often not given due emphasis while appraising trials with potential practice-changing outcomes.

GUIDELINE-DIRECTED MEDICAL THERAPY

Recent interventional trials, including cardiovascular outcomes assessment of the MitraClip percutaneous therapy for patients with heart failure and functional mitral regurgitation (COAPT) and percutaneous coronary intervention in stable angina (ORBITA), have demonstrated significant influences on clinical practice. A pivotal feature of such studies is GDMT, which is often neglected in trial evaluations.[1,2] The ISCHEMIA trial stands as a watershed study in the field of cardiovascular medicine. Its central focus lay on the outcomes of patients with stable coronary artery disease (CAD) and moderate or severe ischaemia. The pivotal comparison was between an invasive strategy encompassing GDMT with possible revascularisation, and a conservative strategy consisting solely of GDMT.[3]

The relevance of GDMT in this context cannot be overstated. GDMT refers to a therapeutic approach that utilises established medications and lifestyle interventions in accordance with medical guidelines. It typically includes anti-platelet drugs, statins, angiotensin-converting enzyme inhibitors, β-blockers, and lifestyle changes, such as regular exercise, dietary modifications, and smoking cessation. In the ISCHEMIA trial, GDMT was administered equally to both intervention groups, highlighting its importance in contemporary cardiovascular care.[3]

The ISCHEMIA trial provided a novel perspective on the role of GDMT in managing patients with ischaemic heart disease. It indicated that, in many instances, an initial conservative strategy using optimal GDMT alone can yield outcomes comparable with those from an initial invasive strategy. This finding was pivotal, as it emphasised the critical role of GDMT in managing ischaemic heart disease, and the potential to achieve substantial patient benefits, even without resorting to invasive interventions.

Historical studies evaluating coronary artery bypass grafting and percutaneous coronary intervention in CAD, such as the MASS-2 trial, were also conducted in the context of GDMT.[4] However, the evolution of medical therapy for heart failure and risk factor modification over time has rendered these trials obsolete. Therefore, a more contemporary study, such as the ISCHEMIA trial, becomes the cornerstone of this discussion.

The ISCHEMIA trial implemented a methodology involving enrolling individuals with moderate or severe ischaemia, excluding those with significant left main CAD, or other particular conditions. The trial conducted a pre-specified subanalysis, hypothesising better outcomes for non-adherent patients randomised to an invasive strategy. It utilised a modified four-item Morisky–Green–Levine Adherence Scale to capture medication-taking behaviour, and a seven-item Seattle Angina Questionnaire (SAQ-7) summary score to assess health status. Subsequent analysis of adherence and outcomes was conducted using Bayesian proportional odds models. The study found that 27.8% of patients were non-adherent at the start. Non-adherence was correlated with worse symptoms and a decline in health status in both trial arms.[5] In-depth analysis also suggested a potential benefit from an invasive strategy for these patients.[5]

Adherence, or the lack thereof, poses a persistent challenge in clinical practice. Although the appeal for selecting an invasive strategy for patients with lower probabilities of medication adherence is tempting, this study demonstrated no apparent benefits in pursuing such an approach. What becomes alarming is the worse outcomes experienced by both adherent and non-adherent groups, emphasising the importance of optimising medical therapy.

However, the ISCHEMIA trial also revealed some critical challenges.[3,6,7] For one, adherence to GDMT in real-world settings is often lower than in the context of a clinical trial, which can potentially limit the effectiveness of a GDMT-based approach.[3,7]

In response to these challenges, the trial underscored the significance of not solely granting patients access to healthcare providers throughout the entire care continuum, but also equipping them with a more profound comprehension of their treatment regimen and its advantages to enhance adherence. The ISCHEMIA trial also laid the foundation for future investigations. It underscores the need for future studies to focus not only on clinical outcomes, but also on patient-oriented outcomes, such as quality of life and cost-effectiveness. With an increasing emphasis on value-based healthcare, these considerations are becoming increasingly important.

EVIDENCE GAP AND BARRIERS

The ISCHEMIA trial, while instrumental in refining the management strategy for stable ischaemic heart disease, has left certain evidence gaps, and posed questions that need to be addressed by future research. These questions and gaps pertain to the trial design, execution, and its external validity. The trial's patient population selection is a notable limitation. Particularly, the exclusion of patients with the most severe form of ischaemia, including those with left main CAD, which raises the question of the trial's applicability to this high-risk patient group. Another evidence gap emerges in the context of the timing of the invasive strategy. The trial did not directly compare an immediate invasive strategy with a deferred one, which is only undertaken upon the failure of GDMT.

Another significant area where the ISCHEMIA trial falls short is the optimisation of GDMT. The trial underscored the importance of GDMT, but did not delve into the specifics of how it could be tailored for individual patients with CAD. The optimisation of medical therapy, taking into account patient characteristics, tolerance, and response, can significantly impact outcomes, and necessitates more focused research.

The ISCHEMIA trial rightly emphasised the importance of medication adherence, but failed to investigate measures to enhance it. A deeper understanding of factors affecting adherence, such as medication cost, regimen complexity, patient education, and socioeconomic factors, is needed.

Quality of life assessment in the trial could also be enhanced. Although the SAQ-7 was used to assess health status, future studies could consider including more objective assessments, such as exercise capacity, hospitalisation rates, and more specific angina measures. Such assessments would provide a more holistic view of the impact of different strategies on patients' quality of life. Therefore, a better understanding and application of GDMT in real-world settings is crucial.

CONCLUSIONS

The new sub-study of ISCHEMIA opens up new avenues for exploration, especially in regard to quality of life and cost-effectiveness, and raises crucial questions for future trials. It highlights that non-adherence in CAD could significantly contribute to increased morbidity, hospitalisation, and mortality. Consequently, it underscores the imperative to address medication adherence in patients with CAD in both invasive and non-invasive groups, with the aim of reducing hospitalisation, improving clinical outcomes, and reducing healthcare costs. This ISCHEMIA sub-analysis highlights that the implementation of a simple GDMT protocol is vital for improving health outcomes, and is practical for real-world settings. It paves the way for future investigations to consider how GDMT optimisation and medication adherence can be incorporated in clinical studies involving invasive strategies.

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