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EDITORIAL | OPEN ACCESS

Bridging the gap between basic and clinical research in cardioprotection: The imperative to publish neutral studies

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In the pursuit of scientific advancement, the integrity of our research methods and the transparency of our publication practices are of paramount importance. I would like to echo the concerns raised by Skyschally et al. (2024) in their recent article, "Expression of concern: Publication bias for positive preclinical cardioprotection studies." The authors highlight a critical issue in the field of cardioprotection: the publication bias favoring positive preclinical studies and the reluctance to accept neutral or negative results.

Skyschally et al. (2024) begin their article with an anecdotal event: they submitted a well-designed study to a prestigious cardiovascular journal, examining the effects of a pharmacological agent on reducing infarct size. Their prospective study, based on power analysis, aimed to validate previous positive results from another laboratory. Despite their rigorous methodology, they did not find a significant reduction in infarct size. This was in contrast with a previous exploratory study. Skyschally et al. (2024) report that the reviewers appreciated the meticulousness of their work but requested a mechanistic explanation for the discrepancy, which the authors could not provide. This inability to identify a specific mechanism led to the rejection of their study, as the editors considered it low priority.

This experience is not isolated but symptomatic of a larger issue within cardioprotection and conditioning research. The field, particularly in conditioning, faces a worrying translational gap. Indeed, numerous positive preclinical studies fail to translate into successful phase III clinical trials. Preclinical studies are often reductionist in nature, as they focus on identifying mechanisms of cardioprotection. The various laboratories tend to report studies that produce positive results in their specific conditions, while failed attempts remain unpublished. This selective publication pumps up the scientific literature, creating an illusion of consistent efficacy and fueling unrealistic clinical expectations.

The reluctance to publish neutral or negative results perpetuates this somewhat “doped” situation. Positive results are celebrated and disseminated, while null results are swept under the carpet, considered inconclusive or uninteresting. This bias misleads the scientific community and influences the direction of subsequent research and clinical trials. The consequences are clear: numerous phase III studies, based on promising preclinical results, have produced disappointing results.

These experiences raise a crucial question: Why is the burden of explaining discrepancies placed on studies with neutral findings, particularly when these studies are rigorously designed? It seems to me unreasonable to demand mechanistic explanations for negative results, as well as for findings that contradict less robust, exploratory studies. Instead, the scientific community should welcome the neutral findings as essential contributions to a balanced understanding of cardioprotective interventions.

Recent efforts have begun to address this issue, with guidelines for rigorous studies (Bøtker et al., 2018; Bolli & Tang, 2022) and with an increasing number of neutral studies on cardioprotective conditioning interventions being published (Skyschally et al., 2024, and references therein). However, these published neutral studies may represent only a small fraction of the neutral findings that are not reported or even submitted to a journal by researchers. A significant change in publication practices is necessary to fully appreciate the true effectiveness of cardioprotective strategies. Recognizing and addressing publication bias is critical to refining our approach to preclinical research and ensuring that clinical trials are built on a foundation of complete and accurate data from rigorously designed research studies.

The path from the laboratory to the bedside is full of challenges, and the journey to successful cardioprotection is no exception. The issues extend beyond the bias discussed in this editorial/commentary (see for example Heusch, 2017 and Kleinbongard et al., 2020). However, by promoting a more inclusive publishing culture that values neutral outcomes with appropriate power analysis, we can better address these

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challenges. This change will not only improve the robustness of preclinical research but also mitigate the translational gap, paving the way for more reliable and effective clinical interventions.

As mentioned, researchers are aware that this bias is not the only problem we need to address. Additionally, for instance, clinical trials have yet to adopt the approach advocated by Brutsaert over a decade ago (Brutsaert, 2010). Future clinical trials should be multidisciplinary and translational and should incorporate non-linear complex systems biology instead of relying solely on traditional linear feedback methods. Myocardial ischemia/reperfusion and subsequent heart failure are multifactorial syndromes with multiple co-morbidities and result from failing complexity rather than a failing individual component. Biomedical sciences need to advance and integrate approaches from physics and engineering sciences after lagging behind for a long time now (Brutsaert, 2010).

At *Conditioning Medicine*, we are dedicated to disseminating high-quality studies in basic, translational, and clinical investigations. Our field encompasses the cellular and organ response to stress and injury, how the body adapts to these conditions, the cellular mechanisms underlying this response, and therapeutic approaches to harness this response, including conditioning strategies. We welcome original research reports, review articles, and commentaries. We are particularly open to publishing neutral findings in our field of interest. Our editorial board includes world-renowned research experts committed to promoting a balanced and comprehensive understanding of cardioprotection (http://www.conditionmed.org/).

In conclusion, improved reporting of both positive and neutral data will enhance the rigor and robustness of preclinical cardioprotection studies, facilitating their translation into patient benefits. Let us commit to a more transparent and balanced approach to scientific publishing. Embracing the full spectrum of research findings, including neutral or negative ones, will ultimately strengthen the field of cardioprotection and improve research for patients' benefit. In an effort to capture a balanced scientific and clinical assessment of the field, *Conditioning Medicine* equally welcomes positive, neutral, or negative protection studies.

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Conflict of interest

The author declares that there is no conflict of interest related to the content of this manuscript.

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