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INVITED COMMENTARY

Is Evidence of Absence Considered Absence of Evidence? How Negative Studies Inform Shared Decision-Making

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Medical decision-making involves balancing risks against benefits with the aim of optimizing outcomes. In clinical practice, management choices are decided among the physician, patient, and family after careful assessment of benefits, risks, and alternatives chosen from an appropriate set of options [1]. Ideally, suitable management choices offer health benefits that clearly outweigh infrequent risks that, even if they occur, would be considered clinically insignificant (i.e. reversible and without long-lasting clinical consequences). More frequently, patients and gastroenterologists face competing risks that are potentially catastrophic but statistically infrequent. Such is often the case for medically necessary gastrointestinal procedures for patients that take antiplatelet or anticoagulant therapy: Should the patient continue their antiplatelet or anticoagulation agents at the risk of hemodynamically significant bleeding, or should the patient stop these agents and face a small but potentially catastrophic risk of a thromboembolic event?

In this issue of *Digestive Diseases and Sciences*, Gangwani et al. [2] present a network meta-analysis that aimed to inform the risk of bleeding among patients who were already scheduled to undergo percutaneous gastrostomy (PEG) tube placement and subsequently randomized to continuing or temporarily stopping dual antiplatelet therapy. The authors did not find a statistically significant difference in bleeding risk between patients that continued dual antiplatelet therapy compared with patients who stopped taking at least one antiplatelet agent, a negative result.

A benefit of well-conducted studies is that negative findings are just as informative as positive findings to clinical practice [3]. To the clinical audience, a *positive* study is generally conceptualized as one that identifies a $<5\%$ likelihood of a certain event of interest occurring due to chance as assessed by an appropriate statistical test. Nevertheless, defining studies as positive or negative inherently assumes that negative findings do not inform clinical management. Furthermore, statistical analysis is based on probability and not certainty. On one hand, a positive finding may be still be due solely to chance and require larger studies to confirm or refute such findings, such as in recent studies on proton pump inhibitor safety [4]. On the other hand, a negative finding does not confirm the absence of any effect. A negative finding only suggests that such an effect has not been found to the level of power available based on sample size. As such, since a *negative* study is not a failed study, it should be interpreted in the appropriate context. Here, the finding that stopping dual antiplatelet therapy may not affect overall procedural bleeding risk is an important finding that helps inform this important decision for the gastroenterologist and patient.

Gastroenterologists and patients might be more concerned about clinically significant bleeding (requiring blood product transfusion or hospitalization), than about inconsequential or minor bleeding. Despite the more than 1800 patients included in this study, the authors found that definitions of bleeding were variable across the included published trials. Therefore, the resultant small sample size and heterogeneity were insufficient to detect differences in clinically significant bleeding with adequate power. Furthermore, the authors also found that the underlying studies did not uniformly report risk factors that are important to objectively evaluate competing bleeding and thromboembolic risks [5, 6]. This finding is important not only to point out an absence of evidence from a clinical standpoint but also to emphasize the need for more rigorous evidence from a research standpoint. Future clinical trials in this area should therefore consider adopting standard definitions of clinically significant bleeding to inform event frequency and

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appropriate management strategies, such as defined in recent clinical practice guidelines [5, 6].

Guidelines define high-bleeding risk procedures, especially quasi-surgical procedures such as PEG placement [7, 8] and endoscopic submucosal dissection as those for which the 30-day risk of clinically significant bleeding exceeds 2%. In recent recommendations, guidelines assigned a *conditional* recommendation to the most applicable statement that "for patients on direct oral anticoagulants (DOACs) who are undergoing elective/planned endoscopic GI procedures, we suggest temporarily interrupting DOACs rather than continuing DOACs" [7]. A previous clinical trial suggested a low incremental risk of bleeding among patients taking single-agent thienopyridines or aspirin/non-steroid anti-inflammatory drugs (NSAID) during PEG placement [9]. In the current network meta-analysis that evaluated dual antiplatelet therapy, the risk of bleeding exceeded 2% regardless of whether dual antiplatelet therapy was continued or held. As defined by the GRADE process that underlies the development of guidelines, conditional recommendations are made when "the panel concludes that desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident" [10]. In other words, guidelines empower gastroenterologists and patients to individualize management choices based on patients' individual values and preferences regarding competing undesirable potential outcomes of thromboembolic events or clinically significant bleeding. In the case of PEG placement for patients taking dual antiplatelet therapy that face a high risk of peri-procedural bleeding, a third alternative should also be considered: Is there a different approach than offering PEG placement at all.

The clinical relevance of negative studies depends entirely on ensuring rigorous conduct. First, the primary research question should demonstrate equipoise among competing alternatives and be clinically relevant. Second, justification for pooling clinical trials data depends on whether patient recruitment criteria, technical performance of the intervention, and definitions for outcomes are sufficiently comparable across trials with clarity on heterogeneity for readers to consider. Third, exploratory analyses may not provide definitive evidence but can be helpful to develop hypotheses for further prospective evaluation. As demonstrated here, negative trials can be clinically useful to demonstrate the complexity and nuance of individualizing management choices in real-world practice and to improve future research efforts in the field.

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Declarations

Conflict of interest EDS consulted for Salix, Mahana, Takeda, Ardelyx, Neuraxis, GI Supply.

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