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Commentary: In pursuit of the truth for applying randomized controlled trial results to individual patients

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In the recent *Journal* publication “Randomized Trials, Observational Studies, and the Illusive Search for the Source of Truth,” Gaudino and colleagues¹ open an important discussion regarding strengths and limitations of randomized controlled trials (RCTs) and observational studies using large electronic health record databases vis-à-vis the illusive search for truth. Adding to the appeal of a large quantity of data in a broad or specific patient population of interest, machine learning² can be used to digest such large datasets to identify patterns, even in the absence of an a priori hypothesis. However, observational studies are susceptible to inherent biases and unmeasured or hidden confounding, which no statistical or machine-learning approach can resolve.³ While large databases can be used to assess trends and associations, it is not possible to determine how every individual patient was treated based on surgeon-specific practices. RCTs are performed with the intention to account for hidden confounding by controlling allocation across treatment groups to obtain balance for all measured and unmeasured baseline covariates.⁴ RCTs are less common than observational studies in the surgical literature as they are not always feasible in certain surgical settings.⁵

One shared limitation of traditional RCTs and observational database analyses in cardiothoracic surgery is that, although the effects on individual subgroups of patients

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Advantages and Limitations of Randomized Controlled Trials and Observational Studies in Cardiovascular Surgery		
Criteria	Advantages	Limitations
Randomized Controlled Trials (RCTs)	<ul style="list-style-type: none"> Randomization provides an opportunity to reduce imbalances in baseline covariates and hidden confounding by controlling allocation across treatment groups At specified data are collected Treatment effects of interest can be estimated 	<ul style="list-style-type: none"> Sample sizes may be small leading to low statistical power May not be feasible in certain surgical settings Treatment effect estimates for subgroups remain at risk from imbalances in baseline covariates at the subgroup level
Observational Studies	<ul style="list-style-type: none"> Large sample sizes (big data) can be collected and analyzed Feasible for all surgical treatments and settings Machine learning can be used to uncover patterns without a priori hypotheses 	<ul style="list-style-type: none"> Unmeasured confounding is not controlled There may be missing data for important patient characteristics and outcomes Treatment effect estimates for subgroups remain at risk from imbalances in baseline covariates at the subgroup level

Covariate imbalances at the subgroup level may create biased treatment effect estimates.

CENTRAL MESSAGE

Ensuring balance of baseline risk factors by randomization at the subgroup level is crucial for unbiased assessment of treatment effects to best inform clinical decisions for individual patients.

may be studied, they are at risk from subgroup imbalances in baseline covariates that are truly predictive of the outcome. Thus, subgroup results from RCTs can be overinterpreted as informative to decision-making for individual patients. Because we rarely have unbiased effect estimates of treatments or surgical interventions at the patient level, the fundamental question becomes how to design and conduct RCTs to best inform clinical decision-making for individual patients, given that subgroups of patients may have different risks for developing the outcome of interest.

Often, predictor type variables that represent individual patient factors are not handled in the design of the randomization scheme for an RCT. Block randomization has been presumed to ensure an equal distribution of certain patient factors between treatment groups to achieve balance⁶; however, this strategy may not be implemented at a granular level for key patient characteristics. Problematically, block randomization only ensures balance between the treatment and control groups across the health care site—rather than on patient characteristics—and this is only a first step in estimating a treatment effect within certain subgroups. Although sample size feasibility will continue to be an issue in RCTs in cardiothoracic surgery,⁷ data obtained from randomized trials can be most impactful for individualized patient care by ensuring that patient factors are balanced as robustly as possible. To provide unbiased information regarding how a treatment may affect an individual patient, randomization procedures need to incorporate control of

baseline predictors at the subgroup level. Past the research challenges outlined by Gaudino and colleagues, considerable work remains to optimize randomized trials to best inform surgical and medical care decisions for individual patients. This work must go beyond conversation in the pursuit of the truth.

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