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Translating Experimental Evidence Into Clinical Decision Making

Emma Healy, Jason H. Wasfy *

Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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In medicine, clinicians need to interpret the results of medical research and apply those results to specific treatment decisions. Although this process is a foundational principle of evidence-based medicine, it can be exceptionally complex in practice. Many clinical decisions are not informed by adequate evidence. Other decisions are informed only by results of observational studies, which are subject to important limitations that constrain causal claims about the efficacy of therapeutic options [1]. Observational studies use a variety of approaches to minimize treatment selection bias, but this type of confounding cannot be entirely eliminated in these analyses and, as such, prospective randomized controlled trials (RCTs) are needed to make rigorous causal claims about treatment efficacy [2].

Unfortunately, even when RCTs have been performed, the results can still leave questions about the efficacy of treatment strategies. RCTs are prone to questions about external validity – whether an observed treatment effect applies to populations not included in the trial. In that setting, particularly in cardiology, a field rich with RCTs, multiple RCTs can provide discordant results. In these situations, making practical clinical decisions is more difficult. This exact dilemma has occurred over many years for clinicians implementing strategies to prevent contrast-induced acute kidney injury (CIAKI) after coronary angiography.

CIAKI has been a recognized risk of administering contrast media for decades. Although risk of CIAKI is practically negligible for patients without risk factors such as chronic kidney disease (CKD) [3,4], development of CIAKI is associated with increased short- and long-term morbidity and mortality, longer hospital stays, and higher costs [5–8]. Validating effective prevention strategies has been difficult despite many published papers. Even as of 2006, 12 years ago, 19 RCTs, 4 prospective non-randomized analyses, and 11 meta-analyses had been published to evaluate the potential role of N-acetylcysteine in CIAKI prevention [9]. The exceptional number of RCTs on CIAKI may have occurred because the topic is relatively easy to assess in single-center studies – angiography is common, and the outcome is easily measurable [9]. Despite that, the results were discordant: Some meta-analyses of RCTs suggested benefit of N-acetylcysteine in preventing CIAKI [10–12], while others did not [13–15]. Eventually, in 2018, with 5177 patients at 53 sites, the PRESERVE trial demonstrated no benefit for N-acetylcysteine in preventing CIAKI [16]. The experience with N-acetylcysteine illustrates a common problem in this space – a tremendous amount of data to inform this important clinical question but not a lot of clarity about how to proceed clinically.

In this issue of *Cardiovascular Revascularization Medicine,* Khan et al. present results of a Bayesian network meta-analysis to compare preventative strategies for CIAKI, including normal saline, sodium bicarbonate, N-acetylcysteine, statin, placebo, or combinations of these treatments [17]. The authors included 49 randomized controlled trials in their analysis, capturing a total of 28,063 patients undergoing cardiac catheterization. Trials were only included if they enrolled at least 100 patients and compared two or more preventative strategies for CIAKI that are widely practiced and clinically applicable. The authors found that statins were associated with 51% relative risk reduction for CIAKI compared with normal saline alone. No significant differences were found across treatment groups for the secondary outcomes: risk of hemodialysis and all-cause mortality.

This new meta-analysis is consistent with the substantial number of previous meta-analyses supporting the efficacy of statin therapy to reduce CIAKI [18–24]. The effect estimate of about 50% is consistent with the effect estimate observed in RCTs [25]. As the authors note, however, a large degree of heterogeneity complicates interpretation of this meta-analysis and other meta-analyses. Studies led in diverse settings with variable methods and patient populations may reasonably produce different results if the quality of studies, assessed outcomes, or true intervention effects are different. Whether the data can appropriately be pooled for meta-analysis, then, depends on the degree of heterogeneity and what is understood about its source [26–28].

Reporting a high level of statistical heterogeneity for CIAKI ($\tau^2 = 0.66$), the authors acknowledge some of its potential sources, including both methodological diversity (e.g., differing definitions of CIAKI) and clinical diversity (e.g., variable patient characteristics, procedural settings, treatment doses, and contrast agents, strengths, or volumes). In this analysis, the authors investigate subgroups based on the type of contrast media administered and the setting for cardiac catheterization, finding that statins only reduced CIAKI risk in patients receiving low-osmolar contrast or requiring emergent catheterization, not in those receiving iso-osmolar contrast or elective catheterization.

The largest limitation, in our opinion, is a lack of nuanced understanding of how statins affect different populations. Risk for CIAKI depends heavily on a patient's prior health status [3,4]. Studies that enroll a low-risk population may not find CIAKI in a significant number of cases, regardless of their chosen intervention, and the analysis can be

* Corresponding author at: Massachusetts General Hospital, Bulfinch 2, 55 Fruit Street, Boston, MA 02114.
E-mail address: jwasfy@mgh.harvard.edu (J.H. Wasfy).

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underpowered to detect the efficacy of an intervention [29]. Combining studies that include at-risk populations, such as patients with diabetes or renal insufficiency, with those that lack such inclusion criteria may produce results without clinical applicability. Furthermore, certain interventions may affect patients differently depending on their characteristics and comorbidities. For example, a meta-analysis on preventative strategies for CIAKI demonstrated that no intervention reduced risk in diabetic patients [30]. Gender may influence CIAKI incidence and response to treatment [19].

Twelve years ago, Bagshaw et al. wrote an editorial on the excessive number of publications exploring N-acetylcysteine in the prevention of CIAKI, highlighting a series of studies and analyses that found conflicting results [9]. They identified factors that contributed to the rapid proliferation of inconclusive research, discussed the limitations of meta-analyses, and critiqued the lack of coordination among groups, pointing out the missed opportunity for a more robust multicenter trial.

Years later, we see this trend continue. More randomized trials have been published, and as a response, several meta-analyses have arisen to address these studies' conflicting results. Differences among patient clinical characteristics and treatment administration patterns, however, continue to prevent these analyses from generating meaningful pooled estimates. We commend Khan et al. for their contribution to the field and agree with their conclusion that statins merit further study for the prevention of CIAKI. But we question the value that additional meta-analyses will add to this topic. Ideally, as in the case of PRESERVE, a large multicenter RCT will be performed. But since that is unlikely, clinicians should recognize that this new work by Khan et al. is consistent with prior meta-analyses in implying a benefit of statin therapy in preventing CIAKI among patients undergoing cardiac catheterization.

This is important, particularly because other evidence-based prevention strategies are dwindling. The PRESERVE trial has now shown no benefit for either sodium bicarbonate (relative to sodium chloride) or N-acetylcysteine [16]. Even hydration itself with sodium chloride has been called into question after a negative non-inferiority trial [31]. The 2011 percutaneous coronary intervention guidelines list hydration and minimization of contrast dye as class 1 recommendations for prevention of CIAKI but do not directly address statin use, at least for the purpose of preventing CIAKI [32]. Statins may also be a reasonable strategy worthy of consideration by clinicians. Furthermore, many patients undergoing coronary angiography will have an alternative strong indication for statin therapy, such as acute myocardial infarction or either past or present revascularization. For many of these patients, the decision to continue or initiate statin therapy at time of angiography will be straightforward.

Disclosures

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