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Reply: Cardiac surgeons as innovative researchers

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Word Count: 969
Central message: Cardiac surgeons have a long history of utilizing innovative statistical analysis to maintain high standards for clinical research.

Central Figure:
Modulated renewal analysis: associated mortality with repeated bleeding after VAD implant.

Figure 1:
Survival among patients stratified by number of bleeding events after left ventricular assist device implantation. The survival curves are based on modulated renewal analysis. Each curve represents the freedom from death based on the number of bleeding events after LVAD placement (reprinted with permission: Bunte MC, Blackstone EH, Thuita L, et al.).

1
The aggregate effect of clinical research has a large impact on patient care. Clinical research is used to develop evidence-based protocols, draft society guidelines, and help develop best practice recommendations. Despite the importance in maintaining high-quality, accurate, and up-to-date research, it is not uncommon to see complex clinical questions answered with outdated statistical methodology. Although it may seem trivial, selecting the appropriate study design and statistical analysis is critically important for producing accurate results, and ultimately, guiding clinical decision making. As physician scientists it is important to review, analyze, and interpret clinical outcomes with some degree of skepticism, especially when studies are conducted using unfamiliar analytic techniques. Conversely, it is equally important to acknowledge that advanced analytic strategies, even if they are not clearly understood, may provide the most accurate results.

The letter to the editor, ‘Rethinking traditional survival analysis: Modulated renewal analysis with competing risks regression’ by Van den Eynde et al.\(^2\) offered important insight and perspective with regard to how advanced statistical methodology can help answer difficult clinical questions. The authors’ letter was in response to a recently published manuscript in the *Journal of Thoracic and Cardiovascular Surgery* studying risk factors associated with mortality and reintervention after complete repair of truncus arteriosus over a 35-year period.\(^3\) In the study, Guariento *et al.* were tasked with the complex problem of how to statistically account for the inherent risk that occurs in patients who require multiple interventions throughout follow-up. The complexity of their study stems from the fact that their analysis had to accurately adjust for the risk incurred with each subsequent operation, the effect of interstage duration, and additional clinical risk factors - both pre and post-index operation. As Van den Eynde and the authors of the commentary note, Guariento and the team’s use of modulated renewal with competing-risks analysis was an excellent strategy to account for the complexity of the analysis. The authors went on to point out a number of additional clinical questions that would benefit from using a
modulated renewal statistical analysis, including the example of patients with HIV and coronary artery disease being at increased risk for recurrent cardiovascular events after coronary revascularization.²

I would like to reiterate the point made by Van den Eynde and colleagues regarding the usefulness and many applications of advanced survival (time-to-event) analysis. Although the current commentary focused on modulated renewal, an alternative, but parallel strategy used to adjust for post-intervention risk factors is the technique of incorporating time-varying covariates. In fact, there are many examples of advanced survival analyses used in congenital and adult cardiac surgery outcomes research. A few examples include, the use of modulated renewal to study the risk of subsequent procedures after interrupted arch repair,⁴ and to evaluate the burden of bleeding complications after ventricular assist device implantation (Figure.1).¹ Time-varying covariable survival analysis has been used to study the durability of right-ventricle to pulmonary artery conduits in patients with congenital heart disease,⁵ and to develop a decision aid to help identify patients at increased risk of mortality while awaiting transplantation.⁶

The true merit of this reply is not to detail the specifics of advanced survival analysis, but rather to acknowledge the role cardiac surgeons have had in promoting better outcomes research. Cardiac surgeons have long history of being data collectors, realizing early on the need to accurately analyze and evaluate their outcomes. Renè Favaloro, a pioneer in coronary artery bypass surgery notably commented “just when we have accumulated enough data over a sufficient time period, we find that surgical technique has improved or medical therapy has changed, or both, and the conclusions no longer apply,”⁷ a statement that seeming set the stage for the development of multi-institutional collaboration and data pooling. Subsequently in the in the mid-to-late 1980’s, cardiac surgery became the first specialty mandated to publicly report surgical outcomes.⁸ The response was an understanding of the need to develop a strong, robust research platform that would accurately adjust for confounding risk factors in order to generate reliable, unbiased outcomes. The result of these efforts has led to coronary artery
bypass grafting becoming the most widely studied operation in the history of surgery.\textsuperscript{9} Similar efforts to accrue data based on combined experiences were also seen in congenital heart surgery. Until the mid-1980’s the Congenital Heart Surgeons’ Society (CHSS) was primarily an informal meeting of a small group of surgeons who came together to discuss their surgical experiences. However, Drs. Eugene Blackstone and John Kirklin proposed that the CHSS pool their data together, resulting in the formation of the CHSS Data Center. The CHSS currently represents over 80 centers world-wide, has contributed to over 60 publications, numerous national and international presentations, and is the sponsor of the CHSS Data Center, a thriving congenital research database.\textsuperscript{10}

From a historical perspective cardiac surgeons have consistently advocated for the most innovative and advanced research methodology. With that said, as clinicians it is not incumbent upon us to become experts in data collection and analysis, or complex statistical theory. In fact, I would argue that the field of biostatistics has become too expansive and progressing too rapidly for practicing physicians to claim expertise in this realm. However, we should continue the legacy of our predecessors and retain the motivation to produce the most robust, accurate, and unbiased results possible. A realistic objective should be to maintain a fundamental understanding of statistical techniques in order to accurately communicate with statisticians and direct appropriate study designs. It is also important that we avoid answering complex questions simple or antiquated analytic tools. As the clinical problems we are treating become more complex, and the questions we are asking become more nuanced, it is increasingly important to retain our roots as “data collectors” seeking the best tools to produce accurate results. In doing so, we should rely on the best analytic tools at our disposal.
References:

Estimated Survival After HeartMate II Implantation by Bleeding Status