It is now more than 18 years of repeated publication since the appearance of the first TRICC trial and we are finally presented with another well-designed and large randomized controlled trial. Mazer et. al., have undertaken an unprecedented effort enrolling 5243 adult patients undergoing cardiac surgery in 73 centers across 19 countries in Transfusion Requirements in Cardiac Surgery III (TRICS-III) trial.[5] Patients were randomized into either a restrictive transfusion strategy (hemoglobin <7.5 g/dL during or after surgery) or a liberal transfusion strategy (a hemoglobin <9.5 g/dL in the operating room or post-surgical critical care unit or <8.5 g/dL on the ward). The primary outcome of this trial was a composite of all-cause mortality, myocardial infarction, stroke or renal failure anytime during hospitalization and up to 28 days after the surgery.(ref)

Results of this trial showed a composite adverse outcome of 11.4% in the restrictive arm versus 12.5% in those assigned to the liberal arm, amounting to an absolute risk difference of 1.11% (95% confidence interval 0.72 to 2.93) and a non-significant odds ratio of 0.90 favoring the restrictive arm. The results positively show that restrictive transfusion strategy is not inferior to liberal transfusion strategy.

Although the TRICC trial was credited as a pioneer in the now common liberal and restrictive transfusion strategy trials, it was not the first study to address the impact of lowering the hemoglobin triggers (better referred to as thresholds") for transfusion.(ref) After decades of many other studies, it might help to reconsider the driver for designing that study and those that followed. As stated by Hebert et.

al., the key issue was the opposing views on the risks of low hemoglobin (anemia) and benefits of allogeneic blood transfusion.(ref) This prevailing and current view, is essentially an acceptance of red cell transfusion as the only viable and possibly the best treatment for low hemoglobin levels.

The Figure 1 in the paper of the study by Mazer et. al. depicts the changes of hemoglobin level in the study arms during the hospital stay and it is quite telling.[5] In both study arms, patients enter the operating room with similar average hemoglobin levels of about 13 g/dL but end up with hemoglobin below 9 g/dL during surgery. The restrictive arm ends with hemoglobin of 9.5 g/dL and the liberal at approximately 10.5 g/dL as expected with more transfusions. Of interest, the patients' average hemoglobin concentrations hover around these same levels for the rest of their stay and never fully recover at discharge. This phenomenon is pervasive throughout these genera of trials.

While surgical blood loss might be inevitable in open heart surgery, we cannot understand what appears to be acceptance of anemia without active therapy during the pre and postoperative period. In the TRICS-III trial and similar to most of patients who undergo cardiac surgery, the vast majority of the patients are discharged well within a week of the surgery and do not receive proper further treatment of anemia.

Prior to the TRICS-III study, Transfusion Indication Threshold Reduction (TITRe2) trial showed no difference between the liberal and the restrictive arms except for a statistically significant increase in 90 day mortality rates (4.2% in

restrictive vs. 2.6% in liberal transfusion arm).(ref) Although no sound physiologic explanation was offered by the investigators as to why this increase only occurred (or became statistically detectable) at 90 days but not earlier, a closer examination of the mortality causes may reveal that the deaths may have nothing to do with restrictive transfusions or anemia. In addition, the liberal and restrictive transfusion groups both received substantial amounts of blood transfused with hemoglobin as the only indicator whilst all patients had been revascularized and their coronary disease was surgically treated, suggesting a significant bias toward liberal use of blood components regardless of study arm allocation. This recurring theme is seen in most other transfusion trials in which both study arms receive large amounts of blood and TRICS-III trial is no exception.[5]

Despite all the issues and shortcomings that affect transfusion trials in general, the TRICS-III trial has many strong points in addition to its large patient cohort. The trial was conducted across multiple hospitals in different countries. The trial included much higher acuity patients and more closely resembled the real life practice of medicine as opposed to ideal and “sanitized” patient populations studied in many randomized trials. It accounted for all red blood cell transfusions occurring during the course of care in the operating room, ICU and ward except prior to randomization, and it showed reduction in transfusion as a group and per patient a salient point considering the dose-dependent effects of transfusion.

All of the randomized trials discussed (and others) do not begin by identifying a disease to be treated, but instead focus on addressing the adverse

events and risks of allogeneic blood transfusion. When reverting back to the basis of medical intervention (disease management), proper diagnosis is required, seeking the appropriate treatment for individual patient rather than offering just one short term treatment for all despite the many treatment modalities that are available for treatment and making a concerted effort to introduce modes of prevention. Anemia - especially in this population - has been largely ignored and is generally only addressed if a certain hemoglobin threshold is reached for a transfusion decision.(ref) No attempt at identifying the etiology of anemia, i.e., iron deficiency is sought since the only response is treatment with an allogeneic transfusion regardless of the, yet unknown, impact on outcome.

The average preoperative hemoglobin level of 13 g/dL in the patients participating in the study by Mazer et. al. suggests that many entered the operative room while anemic.

In their conclusions, Mazer et. al. allude to the existence of treatment modalities other than transfusion but reverts to suggest that more trials with different thresholds might be suitable to conduct. Repeating the same activity over and over again expecting different results may not be a fruitful activity. It is time to examine transfusion versus other proper management of anemia in a randomized controlled trial that is structured to not only look at survival or other severely morbid events but improvement in the patients' health and quality of life.