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Editorial

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**PRECISION MEDICINE, GLYCEMIC CONTROL AND THE PROBLEMS OF IDENTIFYING
FRIEND FROM FOE**

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Running title: Precision medicine problems

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“Friendly fire” is a military concept that describes risks to troops from their own weaponry during combat operations. In broad terms, knowing the target and hitting the target are key principles in avoiding collateral damages. Medicine will never be combat, but similar principles apply when one cannot identify and treat the things that matter most in disease.

The lessons of tight glycemic control in the intensive care unit are still being learned. The promise of a simple, inexpensive and initially promising therapy have devolved into uncertainties about harm. Enthusiasm for tight protocols in response to large effect sizes in a randomized, controlled trial (1) could not be replicated in larger studies (2). Explanations for the irreproducibility and the suggestion of harm focused on hypoglycemia and plasma glucose level variability (3). As enthusiasm waned, interest shifted from maximizing benefits from tight control to minimizing the harms of permissive hyperglycemia.

In this edition of the journal, two studies suggest that new approaches might overcome the faults of an earlier approach to tight glycemic control. They re-introduce the idea of benefit, not harm, from insulin therapy. Tanenberg et al., present an experience with a computer-guided glucose management system that improves the precision around a glycemic target (4). Using a computer algorithm, nurses titrated insulin to achieve a decreasing coefficients of variation for glucose measurements and rates of hypoglycemia over 7 years of use and refinement. A technological solution to glycemic variability and the risks of hypoglycemia seems closer, based on their conclusions. It would seem that by hitting a glycemic target accurately and precisely, clinicians have a tool to improve care. Krinsley and colleagues (5) describe ways to select which patients to target, building on a growing body of research that suggests patients are remarkably different in their response to insulin therapy and levels of glycemia (6).

For all the advantages of large randomized, controlled trials such as NICE SUGAR (2), important signals

can be lost when diverse patients receive strict protocolized therapies. These authors compared a singular approach to glycemic control, a tight target of 90-120 mg/dL serum glucose, to a variably permissive strategy based on the presence of diabetes and a metric of the degree of control, the level of hemoglobin A1C (A1C). In a mixed medical and surgical intensive care unit, they demonstrated an improved observed-to-expected mortality, an effect driven by patients with diabetes and an A1C level at or above 7%. These patients' glucose targets were liberalized to a range of 110-160 mg/dL, compared to 80-140 mg/dL in patients without a history of diabetes and those with diabetes and an A1C level less than 7 mg/dL. Their hypothesis, that more personalized control would improve outcomes, was supported by data suggesting that poor baseline glycemic control called for less tight control in the inpatient setting. In both articles, correlations can only be hypothesis-forming. Additional data would be needed to provide more than weak support for the studies' conclusions.

The juxtaposition of these two trials permits a deeper discussion of two complex covariates. Precision is relevant to both studies. In Tanenberg, precision applies to targeting the right level of glycemic control. Measurements with the management system were tightly clustered. In Krinsley, the issue is more about selecting the right target for individual patients, identifying the abnormality, which may be different based on a history of chronic hyperglycemia. Knowing whom to treat, to what endpoints, and then doing it with precision are sensible models for effective and targeted care.

Enthusiasm for such a rational approach must be tempered. All of this is based on important assumptions; assumptions which may be flawed. Diabetes and stress hyperglycemia are metabolic disorders that touch on more than just the disposition of carbohydrate in the plasma or the effects of a single hormone, insulin. In an insightful editorial in 1992, McGarry noted that olfactory (instead of gustatory) observations of pancreatectomized dogs' urine would have established diabetes melitis'

reputation as a disorder of lipid disposition (7). Compelling data from the large Leuvin tight glycemic control study also suggest an important role for lipid as a target for therapy (8). Availability of glucose levels and bias lead clinicians to look for the easy target. It doesn't mean it is the right one. Krinsley's study also alludes to an important point: not all patients are the same. They suggest that poorly-controlled diabetes patients respond differently to glycemic control than well-controlled diabetes patients or those without diabetes. This is plausible. It is also plausible that immediate postoperative patients are different from patients three days out from surgery, or that any critically-ill patient recovering from their stress response might be different from someone in a cycle of crescendoing inflammation. The finding that the mortality benefit in the original Leuvin study was in longer stay ICU patients supports, but does not prove, this idea. We still aren't clear what all possible phenotypes are.

What both of these studies show is interesting, but unclear. We have significant collinearity, but an unclear causation. In the Krinsley study, these include associations between glycemic variability and mortality in patients without , but not with, diabetes, and between tight control and mortality for patients with elevated A1C levels. The comparisons aren't straightforward: Tanenberg's data are descriptive, Krinsley compares targets in a before-after study. Many clinicians in intensive care units may see small differences in these thresholds and wonder if it is easy to achieve enough statistical power to find a reproducible difference. Secular trends, like the introduction of new diabetes medications (9, 10), may confound the results. Bedside glucometers are imprecise monitors (11). If targeting makes such an important difference, how is one to demonstrate improvements if the target acquisition system is inaccurate? Krinsley et al., deserve credit for pointing out these liabilities. It is up to the reader to interpret them. Finally, mortality reductions from the Krinsley study are only significant when adjusted for APACHE IV mortality. Adjusting for covariates, especially in observational studies, is reasonable, but has limitations, and clouds the interpretation of an adjusted significant result.

Bias in the case of complex matters is not straightforward. In medicine, clinicians may feel that they are above natural cognitive biases, but examples of hindsight (12) and other biases (13) are demonstrated in the medical field. Regarding risk, there is a very real risk of a visceral response to a complex problem. Margolis described this for environmental risks, but the lessons apply to medicine (14). In a spectrum of judgments, “cognitive anomalies,” or misalignments of acts and consequences, occur at narrow, artificial constraints (such as tightly controlled research) and at broad context (such as regarding social or administrative issues). The middle ground, normal daily human experience, is what our mind is tuned to and our biases support. What this means for a medical question like glycemic control is that we hazard misalignment of our idea of risk and benefit if the model is too simple or too encompassing. Simplifying the puzzle to tight control of one output or tailoring the therapy to specific populations may be valid approaches, but our risk of cognitive bias is high. These biases fuel our uncalibrated enthusiasm and dismissal of risk. Bearing in mind that it is still not clear exactly what drives the excess mortality from tight glycemic control (hypoglycemia may or may not explain the results from trials), underestimation of risk is itself a risk. This means validation of the findings is important to understand them in context.

Personalized, precise medicine only helps if we are certain we have selected the correct targets and know we can hit them and minimize secondary harm. Both studies in this edition suggest means to improve outcomes in critically ill hyperglycemic patients, but it remains unclear whether this is the right group to target. Is sugar the right endpoint? Can we measure it accurately? Do we know the right values to manage the tradeoffs between the benefits of insulin therapy and the harms? Can we adequately characterize these endpoints based on additional clinical information, such as A1C levels? Finally, what sort of data do we need to establish causality? These are relevant questions to be addressed for some of our most vulnerable patients when it comes to iatrogenic injury. Understanding what we do not know is the key to insight. It is why creating a good question is the most difficult part of

research. When it comes to the risks of friendly fire, it means that caution should prevail and new findings must be appraised in context with an expectation of follow up validation.

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