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COMMENTARY

Counterpoint—The End Point: Less Is More

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Abstract

Improving the scientific and regulatory evaluation of therapies for metabolic disorders is a necessary ongoing process dependent on accruing knowledge and improving technology. The use of a composite primary efficacy outcome consisting of hemoglobin A1c (HbA1c) and hypoglycemia rates is alluring for evaluating glucose-lowering therapies. This composite, however, provides little advantage, if not some disadvantage, over HbA1c as the primary end point. Composite end points have traditionally been used as regulatory end points when a more straightforward approach is not available or feasible. The most well-known example is the composite of major adverse cardiac events (MACE), which has long been used for cardiac drug approvals by the Food and Drug Administration and has become a primary safety outcome for oral diabetes drugs. The MACE composite is widely accepted even though the cardiac death component would provide the most persuasive and near definitive reflection of benefit. Less definitive but more frequently occurring end points—myocardial infarction and stroke—are added to the composite only to enable outcome trials that can be completed in a reasonable time and with reasonable costs. Composite end points have inherent drawbacks and challenges, which may include undue dependence on assumptions, difficulty of validation, less sensitivity to detecting clinically important effects, and oversimplifying evidence for the prescribing physician and other therapeutic decision makers. The proposed efficacy end point composed of glycemic control and hypoglycemia carries all these drawbacks for diabetes drugs. Even insulin products, for which hypoglycemia is the chief safety concern, will more feasibly continue to be developed and evaluated under a treat to glycemic target design, with glycemic control as the sole primary efficacy outcome and rates of hypoglycemia as the prime adverse measure.

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In this issue of *Journal of Diabetes Science and Technology*, Muchmore's[1] proposed composite end point for diabetes treatment trials, which integrates hemoglobin A1c (HbA1c) and hypoglycemia risk into a single measure, serves the very useful purpose of stimulating appraisal of current and candidate approaches for evaluating therapies for diabetes. Advances in the relevant sciences and technologies encourage such rethinking. Most everyone would agree with the author that clinical trials to support registration of new drugs have become arduous, lengthy, and expensive, particularly so for diabetes therapies. Challenges in type 2 diabetes mellitus (T2DM) drug development have escalated to a tipping point of diverting efforts just when they are most needed. New approaches

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Abbreviations: (ACCORD) Action to Control Cardiovascular Risk in Diabetes, (ARI) aldose reductase inhibitor, (FDA) Food and Drug Administration, (HbA1c) hemoglobin A1c, (MACE) major adverse cardiac event, (RDNS) Rochester Diabetic Neuropathy Study, (T2DM) type 2 diabetes mellitus

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are indeed required to encourage innovation and investment in this therapeutic area. My view is that the proposed composite approach will not help and could even impair T2DM therapeutic development.

As Muchmore[1] points out, multiple publications have advocated diabetes efficacy composites comprising glycemic control and rates of hypoglycemia.[2,3] This composite end point was also considered at the Food and Drug Administration (FDA) during my tenure from 1986–1998, if not before. The composite is conceptually attractive because, in addition to the primary desired effect, it includes the dose-limiting and most serious adverse effect of many, but not all, glucose-lowering therapies. This approach is most appropriately applied to insulin products and insulin secretagogues. It has less potential value for accessing incretins and other drugs with less risk of hypoglycemia.

Composite end points have traditionally been used as regulatory end points in cases when a more straightforward approach is not available or feasible. The best known example of a primary efficacy composite is major adverse cardiac events (MACE; consisting of myocardial infarction, stroke, and cardiac death). Major adverse cardiac events have long been used for cardiac drug approvals by the FDA, and they have become a primary safety outcome for oral diabetes drugs.[4] The MACE composite is widely accepted even though the cardiac death component alone would provide the most persuasive and near definitive reflection of benefit. Less definitive but more frequently occurring end points—myocardial infarction and stroke—are added to the composite only to enable outcome trials that can be completed in a reasonable time and with reasonable costs. Experience with MACE has taught us that only objectively defined events should be included, not those that are dependent on human judgment. For example, an outcome trial used, as the primary outcome, an expanded MACE composite that added coronary revascularization and unstable angina to the "hard" events of myocardial infarction, stroke, and cardiac death. No difference was seen between treatment groups in this expanded composite, but a statistically significant reduction in events was seen in the "hard" outcome composite.[5] Assessing hypoglycemia has similar challenges.

The composite end point approach may overcome the challenge of low event rates, but it has its own drawbacks and challenges. Undue dependence on assumptions is one of the major hazards. Similar to MACE, the proposed glycemic/hypoglycemic composite involves events with face validity representing real clinical benefits or close proxies of benefits. In the case of MACE, an assumption is made that myocardial infarction, stroke, and cardiac death event rates, though different by orders of magnitude, should run roughly in parallel for an anti-thrombogenic intervention. This assumption allows for pooling of these different events but also results in heavy dependence on myocardial infarction events due to a higher event rate. Correspondingly, the less frequent but more definitive cardiac death outcome will typically contribute little to the composite. Thus the current use of MACE itself is based on the assumption that interventions that lower myocardial infarction rates will ultimately lower cardiac and total death rates. This is a solid assumption, but some caution is still required given the history of ventricular anti-arrhythmics, which, as a class, eventually proved to cause harm.[6]

The composite of MACE does have clear face validity since no one would argue that each of the components do not reflect real benefit. Overall benefit would be concluded for a positive MACE composite even if the result was entirely driven by just one of the components. Likewise, both glycemic control and rates of severe hypoglycemia have individual face validity, but lumping them together raises a crucial question: how is one benefit traded off for another? Under the ideal scenario in which a therapy restores normal glycemic control without any hypoglycemia, this question becomes moot, but the question is important if less than perfect results are achieved with either or both outcomes. Because both glycemic control and hypoglycemia are two sides of the same pharmacologic coin, the quandary is in deciding how to make a tradeoff between the two outcomes. For example, if one therapy in a mega trial resulted in a treatment effect of 2.0% HbA1c units and 100 severe hypoglycemic events, would this result be considered superior to a therapy that resulted in 1.0% reduction and 10 events? As simple ratios, the latter result would win, but could we really conclude from comparing these ratios that the latter is inherently a better therapy? In fact, both results are consistent with the same therapy being evaluated under different glycemic targets.

The formal approach to this kind of quandary is to construct the composite on the basis of analyzing long-term clinical outcomes such as survival, major complications, and/or quality of life assessment from a large randomized trial or population-based longitudinal follow-up. These approaches have their own challenges. Though not designed to develop or validate a composite end point, the Action to Control Cardiovascular Risk in

Diabetes (ACCORD) study[7,8] is a good example of a large randomized trial that might have been very suitable for such a purpose. However, the perplexing results of this study are now well-known: intensive glycemic control, compared with conventional control, was associated with increased 5-year mortality, and this was not explained by hypoglycemia. These unexpected results could be explained by the population studied, which consisted of people with high cardiovascular risk and advanced T2DM. Nonetheless, in this particular case, glycemic control itself did not turn out to correlate with survival benefit. Therefore, the ACCORD study cannot validate glycemic control alone, or combined with hypoglycemia rates, as predicting benefit on survival (though myocardial infarction events were reduced).

An example of the longitudinal approach is provided by the Rochester Diabetic Neuropathy Study (RDNS), which was done as a means of accessing efficacy of therapies [largely aldose reductase inhibitors (ARIs)] aimed at preventing the progression of diabetic peripheral neuropathy.[9] A composite was devised by incorporating different aspects of this disorder, including nerve conduction, cardiac autonomic function, neurologic examination, and patient symptoms. Validity, reliability, and sensitivity to changes over time have been demonstrated for this and similar composite approaches.[10] Fatefully, the RDNS composite was accepted by the FDA as the primary regulatory efficacy end point. Of the dozen or more ARIs that have been taken to or through phase 3, not one has shown a robust effect on this composite end point and none has been approved for this or any other indication by the FDA. On the other hand, many of these compounds have had significant positive effects on nerve conduction velocity.[11] In retrospect, median nerve conduction could have been an appropriate primary regulatory end point and basis for drug approval. With approved use, one or more of these drugs could have proved to result in long-term benefit to patients. Other factors contributed to the demise of ARIs besides the RDNS composite end point, but this chapter in drug development teaches that composite end points can be less sensitive than a single end point for detecting clinically important effects.

The final drawback to a composite approach is its generally more abstract quality than that of a single palpable clinical measure such as HbA1c. A related drawback is greater complexity in analyzing and interpreting a drug effect on a composite compared with a single component. A microvascular complication benefit can be ascribed to a sustained treatment effect on HbA1c, but a glycemic control/hypoglycemic composite, without validation, cannot predict any more than just the glycemic control end point itself. Deciding whether two different trials have produced a meaningful difference in HbA1c is very straightforward. It is more difficult to discern a meaningful difference between two composite outcomes.

Clinical and regulatory assessment of insulin products will continue to depend on treat to glycemic target trials, with the outcome that is being targeted—HbA1c— as the primary efficacy end point. To the extent that the glycemic target becomes standardized and consistently achieved, HbA1c reductions, and important secondary end points such as hypoglycemia, can be directly compared across different trials or products. As HbA1c reductions in trials of different products diverge, it becomes increasingly difficult to conclude that a difference in the glycemic control/hypoglycemia composite is meaningful unless one product is clearly superior on both outcomes. Using semicategorical approaches such as "percentage of patients achieving HbA1c <7% without unacceptable hypoglycemia"[1] raises even more difficulties than a composite index or score. The proportion of patients achieving an arbitrary level of glycemic control is highly dependent on trial design and conditions. Deciding what is unacceptable hypoglycemia provides the opportunity for another debate. In summary, development, evaluation, and clinical use of insulin products is better facilitated by retaining glycemic control as the necessary and sufficient primary efficacy end point.

Disclosure:

The author is working in the field of diabetes drug development and provides advice to a number of pharmaceutical and medical device companies.

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