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COMMENTARY

The End Point Is Just the Beginning

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Abstract

Clinical trials to support registration of new drugs are arduous, lengthy, and expensive. Diabetes treatment trials intended to seek indications for glycemic control are facilitated by the regulatory acceptance of glycosylated hemoglobin (A1C) as a validated intermediate efficacy end point. However, A1C outcomes are not meaningful when taken outside of the context of hypoglycemia risks. Current regulatory guidance indicates that A1C efficacy end points and hypoglycemia safety end points be considered separately. A composite end point for diabetes treatment trials that integrates A1C and hypoglycemia risk into a single measure is proposed. An example would be "percentage of patients achieving A1C <7% without unacceptable hypoglycemia." The benefits and limitations of such an approach are discussed.

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Drug development, like life itself, is a balancing act. Does a new agent have enough efficacy to offset its safety concerns? Or is it so safe that its marginal efficacy can be excused? Does it treat a serious condition for which no alternatives exist? Is it a "me too" in a crowded field? Answers to these questions can provide a basis for defining an overall benefit/risk ratio and, in so doing, guide the development team down a logical and coherent path toward product registration and commercialization. To this end, a predefined objective needs to be stated, and a statistically valid analysis plan needs to be developed. The latter depends on choosing relevant end points that can support a test of the objective. The choice of end points is thus a critical step in the overall process.

How can the investigator identify the right end points? At first blush, it would seem that following regulatory guidance should suffice. Indeed, ignoring regulatory guidance is a perilous strategy. In the case of diabetes drug development, regulatory guidance is generally clear: glycosylated hemoglobin (A1C) is accepted as a validated intermediate end point marker of clinically relevant outcomes. To wit, the Food and Drug Administration Draft Guidance for Diabetes Drug Development[1] indicates that "for purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in hemoglobin A1c, which will support an indication of glycemic control."

On the other hand, hypoglycemia is considered in the draft guidance only in the context of safety: "new antidiabetic agents … should be assessed for their tendency to cause or augment hypoglycemia …. Acceptable hypoglycemia, although not defined in absolute terms, usually is a risk that is comparable to existing therapies to which the new drug is directly compared, when both drugs are used in

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Abbreviations: (A1C) glycosylated hemoglobin, (NPH) neutral protamine Hagedorn

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trials in which subjects are treated to identical glycemic goals with comparable glycemic outcomes." This leaves the drug development team with some difficult choices: should a new therapy be tested in a way that results in comparable control of A1C in order to demonstrate adequate hypoglycemia safety? And does that mean that another trial needs to be done if the product development goal is to demonstrate A1C superiority over existing treatments? And what does it really mean if the efficacy trial demonstrates superior A1C outcomes at the expense of an incremental worsening of hypoglycemia rates even if a safety trial has shown comparable A1C and hypoglycemia rates?

These issues beg the question of whether hypoglycemia is simply a safety signal or rather an outcome that is inseparable from efficacy assessment. It is well established that there is in inverse relationship between A1C and hypoglycemia for many diabetes treatments, in particular for insulin therapies as demonstrated in the Diabetes Control and Complications Trial.[2] Analyses performed by Mullins and colleagues[3] have quantified this relationship for both insulin glargine and neutral protamine Hagedorn (NPH) insulin in clinical trials involving both type 1 and type 2 diabetes. Importantly, these analyses demonstrated an intrinsic difference between these two insulin products, such that, at any given A1C outcome, insulin glargine is associated with lower rates of hypo-glycemia when compared with NPH insulin. Taking this to a logical conclusion, one could envision a clinical trial comparing two different insulin products that specifies an end point of A1C-adjusted hypoglycemia rates (or, equally logically, hypoglycemia-rate-adjusted A1C outcomes).

If further studies validate the analytic methods proposed by Mullins and colleagues,[3] then we may see a new approach to assessing safety/efficacy in diabetes clinical trials that recognizes and leverages the intimate inter-relationships between A1C and hypoglycemia by recognizing them as opposites of the same spectrum. But where do we stand in the meantime? And what about other treatment comparisons apart from two basal insulins? Another approach would be to combine A1C and hypoglycemia in a way that does not rely on a mathematical model, and this can be done by use of a composite end point that integrates information from both outcomes into a single end point. A modest proposal would be to use an end point that looks at A1C outcomes (either absolute or percentage of subjects reaching a specific treatment target level) among the efficacy evaluable population who did not experience "unacceptable" hypoglycemia.

Composite end points are commonly used in cardio-vascular outcomes and other trials to increase power by increasing the number of end point events that can be observed in a given population in a given time frame. This composite end point strategy has been subject of recent commentaries,[4–7] and it had been noted that it may predispose to misleading conclusions if the end points that are combined are of unequal importance to patients. Guidelines for valid use of composite end points have been put forth.[4,5] The composite end point that one could consider for diabetes treatment trials is fundamentally different from the commonly employed variety. The objective of a "percentage to target without unacceptable hypoglycemia" end point is not to amplify study power; if anything, it will diminish power by excluding subjects from the A1C outcomes comparison. Rather, its intention is to refine our interpretation of clinical trial A1C outcomes by factoring in the importance of hypoglycemia. If drug A allows 70% of the population to reach A1C <7% but only 20% can do so without hypoglycemia, then it would stand to reason that drug B might be considered to be superior even if only 50% of the population can reach the A1C target but all of them do so without unacceptable hypoglycemia. This sort of analysis has been applied prospectively in a trial involving pramlintide[8] and in a *post hoc* fashion to trials involving sitagliptin[9] and liraglutide.[10]

There are, of course, issues to be resolved before this composite end point approach can enjoy widespread acceptance. Although A1C treatment targets are reasonably well established, the fraction of subjects achieving a specific cut point threshold (e.g., <7%) will depend on the population studied, the starting A1C value, and the specific intervention employed. Moreover, this new approach will depend on acceptance of hypoglycemia as a clinically relevant outcome. In particular, the definition of "unacceptable hypoglycemia" needs to be determined, and this is probably different for different populations (type 1 diabetes, type 2 diabetes, pediatrics, adolescents, adults, elderly). We have initiated a pair of insulin clinical trials in adults and predefined "unacceptable hypoglycemia" as one or more episodes of glucose <56 mg/dl during the last 4 weeks of treatment in type 2 diabetes and five or more such episodes in type 1 diabetes. Admittedly, these initial definitions are arbitrary. When trials are completed, we will conduct a variety of exploratory analyses using other cut points to get a

better idea of what the "best" definition of unacceptable hypoglycemia might be.

As Fleming[11] points out, it is difficult to reach consensus on the definition of something with as many dimensions (medical, economic, psychological, and social) as are subsumed under the label of "unacceptable hypoglycemia" without anchoring the definition to data from an outcomes trial. Lacking such data, discourse on this topic may help focus discussion on how best to evaluate diabetes treatments by simultaneously considering A1C and hypoglycemia outcomes. My modest proposal is thus to suggest that drug developers begin to include the composite end point concept into relevant clinical trials so that its utility can be assessed as more data are collected and reviewed.

Conclusions

Current regulatory guidance regarding glucose control outcomes in diabetes trials does not directly integrate A1C outcomes with hypoglycemia rates. Using a composite end point that combines these measures into a single end point (e.g., percentage of subjects achieving A1C < 7% without unacceptable hypoglycemia) could improve the characterization of the total treatment effects of a drug that would better serve the needs of patients, providers, and drug developers without the need to validate complex modeling approaches to data analyses. In the end, clinicians will decide how and when to use approved therapies; if drug developers and regulators provide them with relevant and understandable data and analyses, then their tasks will be simplified and patients will be the better off for it.

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References:

1. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Guidance for industry. Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf. Accessed September 17, 2010.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New Engl J Med. 1993;329(14):977–86.
3. Mullins P, Sharplin P, Yki-Jarvinen H, Riddle MC, Haring HU. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. Clin Ther. 2007;29(8):1607–19.
4. Montori VM, Permanyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant D, Alonso J, Akl EA, Domingo-Salvany A, Mills E, Wu P, Schünemann HJ, Jaeschke R, Guyatt GH. Validity of composite end points in clinical trials. BMJ. 2005;330(7491):594–6.
5. Ferreira-González I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, Alonso-Coello P, Alonso J, Worster A, Upadhye S, Jaeschke R, Schünemann HJ, Permanyer-Miralda G, Pacheco-Huergo V, Domingo-Salvany A, Wu P, Mills EJ, Guyatt GH. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007;334(7597):786.
6. Tomlinson G, Detsky AS. Composite end points in randomized trials: there is no free lunch. JAMA. 2010;303(3):267–8.
7. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ. 2010;341:c3920.
8. Riddle M, Frias J, Zhang B, Maier H, Brown C, Lutz K, Kolterman O. Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. Diabetes Care. 2007;30(11):2794–9.
9. Seck TL, Engel SS, Williams-Herman DE, Sisk CM, Golm GT, Wang H, Kaufman KD, Goldstein BJ. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide. Diabetes Res Clin Prac. 2011.Epub ahead of print.
10. Charbonnel B, Thiriet C, Guerci B. Reaching a clinically relevant compostite end point of HbA1c target < 7% - no hypoglycaemia - no weight gain, with liraglutide vs other T2D therapies. Presented at: American Diabetes Association Annual Meeting, Orlando, FL, June 25–29, 2010. Abstract 593-P.
11. Fleming A. Counterpoint—the end point: less is more. J Diabetes Science Technol. 2011;5(5):1290–3.