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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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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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