

# Glycemic equipoise

Sanjay Kalra, Mathew John<sup>1,2</sup>, A. G. Unnikrishnan<sup>2</sup>

Department of Endocrinology, Bharti Hospital, Karnal, Haryana, <sup>1</sup>Department of Endocrinology, Providence Clinic, Trivandrum, Kerala, <sup>2</sup>C.E.O, Chellaram Diabetes Institute, Pune, Maharashtra, India

## DEFINITIONS

The term “equipoise,” defined as “a state of equilibrium,” is a noun as well as a verb.<sup>[1]</sup> Clinical (or community) equipoise, which implies that there is uncertainty among the medical fraternity regarding the benefit, or otherwise, of a clinical intervention, provides the basis for conducting clinical trials.<sup>[2]</sup> Equipoise is also used as a guiding tool for patient–physician interactions, which involve shared decision-making.<sup>[3]</sup> Such interaction is possible only if equipoise is achieved in information and knowledge: we term this “communication equipoise.”

Theoretical equipoise is a separate concept related to evidence-based medicine.<sup>[4]</sup> This describes the state of uncertainty that exists in a medical professional regarding a particular diagnostic interventional tool. A similar term is personal equipoise, which alludes to the personal opinion of an investigator, if she or he feels that there is difference between two opposing modes of therapy.<sup>[5]</sup> Although criticism has been leveled against these concepts,<sup>[6]</sup> clinical, communication, theoretical, and personal equipoise are salient features to be considered while planning randomized controlled trials. Clinical and theoretical equipoise are of equal relevance to all fields of medicine; communication equipoise relates to studies involving education, counseling, and support; while personal equipoise must be addressed in trials of surgical procedures and manual maneuvers.

## CARDIOVASCULAR OUTCOME TRIALS IN PERSPECTIVE

Recent years have seen the design, conduct, and publication of various cardiovascular outcome trials (CVOTs) in diabetes. These trials have been necessitated by the need to assure long-term vascular safety of glucose-lowering therapies.<sup>[7]</sup> Recently, three trials have reported cardiovascular benefit, as opposed to safety, of glucose-lowering drugs.

These include the Empagliflozin Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) trials, which studied empagliflozin, liraglutide and semaglutide, respectively.<sup>[8–10]</sup> Extensive discussion has followed the publication of these trial results, attempting to explain the positive benefits reported by the authors.<sup>[11,12]</sup>

## GLYCEMIC EQUIPOISE

A characteristic, highlighted by some, is the lack of glycemic equipoise between various arms of these trials. This is proposed both as a limiting factor of the study and as an explanation of the cardiovascular benefits of empagliflozin and liraglutide. The glycemic equipoise hypothesis or theory states that two opposing arms in a CVOT of an antidiabetic drug should maintain and achieve similar glycemic levels during and at the end of the trial. This will allow the assessment of whether the drug can achieve cardiovascular safety/benefit, independent of its glucose-lowering efficacy.<sup>[13]</sup>

## CARDIOVASCULAR OUTCOME TRIAL DESIGN

Modern CVOTs are designed as per guidance from the United States Food and Drug Administration.<sup>[14]</sup> This guidance does not mention the concept of glycemic equipoise as a desired strategy or outcome of CVOT. The aim of such CVOT is neither to demonstrate glucose-lowering efficacy nor to assess the risk of hypoglycemia or extent of glycemic variability. Thus, ideally one should not consider the degree of glucose control achieved by study drugs in CVOT. Modern antidiabetic drugs are efficient in controlling glucose, but they also have pleiotropic effects which contribute to their overall benefit. Therefore, it becomes difficult to assess the impact of these effects in isolation.

## MECHANISMS OF ACTION

The cardiovascular safety or benefit of a particular molecule is mediated through the modulation of multiple

**Corresponding Author:** Dr. Sanjay Kalra,  
Department of Endocrinology, Bharti Hospital, Karnal,  
Haryana, India.  
E-mail: brideknl@gmail.com

pathophysiologic processes, which are intricately linked with each other. Analysis of these separate processes does make sense from a mechanistic or biochemical viewpoint, but may not be feasible (or desirable) from a clinical standpoint. This is because the primary and secondary end points laid down in CVOT (major adverse cardiovascular events) are more relevant, for both patient and prescriber.

## PREVIOUS TRIALS AND LACK OF EQUIPOISE

There are a number of other CVOTs in high-risk cohorts of patients with type 2 diabetes, in which similar magnitude effects on glycemic control have been shown, without significant benefits with respect to rates of cardiovascular events or death. Detailed analysis<sup>[15]</sup> reveals that glycemic equipoise could not be achieved in major CVOT, including those on saxagliptin, alogliptin, and sitagliptin. Yet, their results, when compared, show significant differences<sup>[15]</sup> which do not seem to be linked to the degree of glycosylated hemoglobin (HbA1c) reduction.

## THE LEADER RESULTS AND EQUIPOISE

In the LEADER trial, cardiovascular benefit was noted after 12–18 months of therapy with liraglutide.<sup>[9]</sup> In contrast, reduction in HbA1c was evident 3 months after the onset of therapy. Simultaneously, a reduction in insulin dose requirement was noted within the first few months' treatment. Therefore, it makes it highly unlikely that cardiovascular benefits could be directly attributed to the glucose-lowering efficacy of liraglutide.

In the current diabetes treatment scenario, it would be virtually impossible to have a treat to target design superimposed upon a long-term CVOT framework. An exception, the Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events

(DEVOTE) trial protocol provided an algorithm for basal insulin titration to achieve prespecified glycemic targets, which could be reassessed during the duration of the trial. Titration adequacy was monitored centrally and feedback was provided to encourage adherence to the protocol.<sup>[16]</sup>

Fifty percent of LEADER participants were on concomitant sulfonylurea therapy, 45% on insulin, and 75% on metformin. The LEADER study protocol suggested broad guidelines of targets to be achieved, and no specific guidelines other than uptitration of liraglutide were proposed. Adjusting the doses of multiple drugs, based on rigid self-titration regimens, over such a long period of time, is unrealistic.

At the same time, the minor improvement in glycemic control (0.4%), if compared with the differences noted in the UKPDS trial,<sup>[17]</sup> cannot explain the significant vascular benefits noted with liraglutide, semaglutide, or empagliflozin [Table 1].

## THE LEADER RESULTS AND LEGACY

There is a case for glycemic legacy as a contributor to cardiovascular benefit. In other trials where this term has been used, the duration of follow-up was much longer, and the initial improvement noted in glycemia was not sustained.<sup>[18]</sup> The same is true in trials documenting vascular legacy, where initial blood pressure control helped achieve long-term cardiovascular protection, even though differences in blood pressure were not sustained over time.<sup>[19]</sup> In LEADER, glucose control was maintained over the entire duration of the study, and this negates the legacy theory, at least during the duration of the study.

## THE LEADER RESULTS AND WEIGHT

Loss of weight, a documented pleiotropic effect of the molecule, was noted within 6 months of treatment and

**Table 1: Degree of glycemic control and cardiovascular benefit**

Study	Difference in HbA1c between study group and placebo group	Vascular outcomes
UKPDS	0.9%	16% reduction in cardiovascular events; $P=0.052$
TECOS	0.29%, $P<0.0001$	NS; HR: 0.98
SAVOR TIMI	0.20%, $P<0.001$	Increased hospitalization for heart failure; HR: 1.00
EXAMINE	0.36%, $P<0.001$	NS; HR: 0.95
ELIXA	0.27%, $P<0.001$	NS; HR: 1.02
EMPA REG	0.24% in 10 mg group and 0.36% in 25 mg group	Improved outcomes; HR: 0.86
LEADER	0.4%	Improved outcomes; HR: 0.87
SUSTAIN 6	0.7% in 0.5 mg group, 1.0% in 1.0 mg group, $P<0.001$	Improved outcomes; HR: 0.74

NS: Not significant, HR: Hazard ratio for primary outcome, HbA1c: Glycosylated hemoglobin, LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, SUSTAIN 6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes, EMPA REG: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

persisted till the end of the trial. If glycemic control can be defended as a mechanism of action for cardiovascular benefit to liraglutide, so can weight reduction. Weight loss, however, was unable to achieve a significant improvement in cardiovascular outcomes in the LOOK AHEAD (Action for Health in Diabetes) trial.<sup>[20]</sup> This implies that other, or multiple, factors played in role in improving cardiovascular health.

## ALL-ROUND LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS

The multiple beneficial effects of liraglutide seen to have worked simultaneously, in conjunction with each other, to achieve stabilization of atherosclerotic plaques and halt the progression of atherosclerotic coronary vascular disease. This, rather than “lack of glucose-lowering equipoise,” explains the positive results of LEADER.

### REFERENCES

1. Equipoise. Available from: <http://www.merriam-webster.com/dictionary/equipoise>. [Last accessed on 2016 Sep 05].
2. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-5.
3. Elwyn G, Edwards A, Kinnorsley P, Grol R. Shared decision making and the concept of equipoise: The competences of involving patients in healthcare choices. *Br J Gen Pract* 2000;50:892-9.
4. Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? *J Med Ethics* 1991;17:30-4.
5. Alderson P. Equipoise as a means of managing uncertainty: Personal, communal and proxy. *J Med Ethics* 1996;22:135-9.
6. Chiong W. The real problem with equipoise. *Am J Bioeth* 2006;6:37-47.
7. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. *Lancet* 2014;383:2008-17.
8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28.
9. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-22.
10. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016. DOI: 10.1007/s13300-016-0197-4. [Epub ahead of print].
11. Kalra S. One small step for empagliflozin, one giant leap for diabetology. *Diabetes Ther* 2015;6:405-9.
12. Kalra S. Follow the LEADER-Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results Trial. *Diabetes Ther* 2016. DOI: 10.1007/s13300-016-0197-4. [Epub ahead of print].
13. John M, Gopalakrishnan Unnikrishnan A, Kalra S, Nair T. Cardiovascular outcome trials for anti-diabetes medication: A holy grail of drug development? *Indian Heart J* 2016;68:564-71.
14. Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Silver Spring, MD: Food and Drug Administration; 2008. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>. [Last accessed on 2016 Sep 15].
15. Ghosal S, Sinha B. Gliptins and cardiovascular outcomes: A comparative and critical analysis after TECOS. *J Diabetes Res* 2016;2016:1643496.
16. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) – DEVOTE 1. *Am Heart J* 2016;179:175-83.
17. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* 2000;321:405-12.
18. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
19. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hiraoka Y, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392-406.
20. Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: A post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016. pii: S2213-858730162-0.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Access this article online	
<b>Quick Response Code:</b>	<b>Website:</b> <a href="http://www.ijem.in">www.ijem.in</a>
	<b>DOI:</b> 10.4103/2230-8210.194361

**Cite this article as:** Kalra S, John M, Unnikrishnan AG. Glycemic equipoise. *Indian J Endocr Metab* 2017;21:18-20.