

Developments in Diabetology in 2016

Sanjay Kalra

Department of Endocrinology, Bharti Hospital, Karnal, India

<https://doi.org/10.17925/USE.2016.12.02.78>

Two major trials, LEADER and SUSTAIN 6, published in 2016, reported the cardiovascular and microvascular benefits of liraglutide and semaglutide respectively. This communication describes the results of these trials, and analyses the subtle differences in their outcomes. While semaglutide significantly reduces the risk of non-fatal myocardial infarction (primary prevention), liraglutide reduces the risk of all-cause mortality and cardiovascular mortality (secondary prevention). Both drugs significantly improve renal outcomes, but semaglutide increased the risk of retinal events. The time taken to achieve benefit was much less (4–6 months) with semaglutide than with liraglutide (12–18 months). LEADER and SUSTAIN 6 have made 2016 a landmark year in the history of diabetes care. Their positive results will help promote better, comprehensive diabetes care, using minimal drugs (therapeutic parsimony), encourage use of rational combinations to improve outcomes, and stimulate exaptation of these drugs for non-glycemic purposes.

Keywords

GLP1RA, long acting GLP1RA, liraglutide, semaglutide, LEADER, SUSTAIN6, cardiovascular outcome trials

Disclosure: Sanjay Kalra has nothing to disclose in relation to this paper. No funding was received for the publication of this article. This article is a short opinion piece and has not been submitted to external peer reviewers.

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Open Access: This article is published under the Creative Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, adaptation, and reproduction provided the original author(s) and source are given appropriate credit.

Received: October 23, 2016

Published Online: December 20, 2016

Citation: *US Endocrinology*, 2016;12(2):78–80

Corresponding Author: Sanjay Kalra, Department of Endocrinology, Bharti Hospital, Karnal, India. E: brideknl@gmail.com

2016 has been a landmark year for diabetology. While the last decade has seen various pharmacological advances, 2016 stands out for consolidation of existing drugs. Not one, but two, glucose-lowering molecules demonstrated beneficial effects on cardiovascular health this year. These drugs have also been able to show renal safety and benefit in diabetes.

A tale of two trials

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial proved the cardiovascular benefit of liraglutide when used in participants with diabetes at high risk of, or established, cardiovascular disease (CVD).¹ Liraglutide use was associated with a lower risk of cardiovascular mortality and lower all-cause mortality (see *Tables 1* and *2*). A 13% reduction of the primary endpoint (hazard ratio [HR] 0.87; 95% confidence interval [CI], 0.78–0.97; $p < 0.001$ for non-inferiority; $p = 0.01$ for superiority) for liraglutide-treated compared to placebo-treated subjects. For the individual components of the primary endpoint, 22% reduction of cardiovascular death (HR 0.78; 95% CI, 0.66–0.93; $p = 0.007$) was noted. Reduction in non-fatal stroke and non-fatal myocardial infarction (MI) was noted. Non-significant reductions of non-fatal myocardial infarction (HR 0.88; 95% CI, 0.75–1.03; $p = 0.11$) and non-fatal stroke (HR 0.89; 95% CI, 0.72–1.11; $p = 0.30$) were found. For the expanded cardiovascular (CV) endpoint, there was a 12% reduced risk (HR 0.88; 95% CI, 0.81–0.96; $p = 0.005$). There was a non-significantly reduced risk of hospitalization for heart failure (HR 0.87; 95% CI, 0.73–1.05; $p = 0.14$).

There was also a lower risk of renal events. A 16% reduction in the composite microvascular endpoint (HR 0.84; 95% CI, 0.67–0.92; $p = 0.02$) for liraglutide-treated versus placebo-treated subjects in which 22% reduction in the risk of the composite nephropathy outcome (HR 0.78; 95% CI, 0.73–0.97; $p = 0.003$) was demonstrated.

Liraglutide was able to reduce insulin requirement, reduce body weight, and reduce hypoglycemic episodes, while achieving lower glycated haemoglobin (HbA_{1c}). An estimated treatment difference (ETD) in HbA_{1c} between liraglutide and placebo of -0.40 % (95% CI -0.45 to -0.34) was observed at 36 months. Severe hypoglycemia occurred in 114 liraglutide- and 153 placebo-treated subjects, yielding a rate ratio of 0.68 (95% CI, 0.51–0.91). Similarly, the rate ratio for confirmed hypoglycemia (<56 mg/dl) was 0.80 (95% CI, 0.74–0.88), which corresponds to a 32% lower risk for severe hypoglycemia and 20% lower risk for confirmed hypoglycemia (<56 mg/dl) for liraglutide-treated subjects compared to placebo-treated subjects. An ETD in body weight between the liraglutide and placebo arm of -2.3 kg (95% CI, -2.5–2.0) was observed at 36 months. The major part of the weight loss was achieved within the first six months of the trial, and remained stable during the rest of the trial.

Table 1: Baseline characteristics of the LEADER and SUSTAIN 6 trials

Baseline characteristic	Drug	Comparator	Primary outcome	n	Follow up (years)	Mean age, years (SD)	Mean duration diabetes, years (SD)	Mean HbA _{1c} (%)	Previous CV disease
LEADER	Liraglutide	Liraglutide versus placebo	CV death, MI or stroke	9,340	3.8	64.3 (7.2)	12.7 (8.0)	8.7 (1.5)	81%
SUSTAIN 6	Semaglutide	Semaglutide 0.5 mg versus semaglutide 1.0 mg versus placebo	CV death, MI or stroke	3,297	1.99	64.6 (7.4)	13.9 (8.1)	8.7 (1.5)	83%

CV = cardiovascular; HbA_{1c} = glycated haemoglobin; MI = myocardial infarction; SD = standard deviation

Table 2: Outcomes of the LEADER and SUSTAIN 6 trials

Outcomes	LEADER Hazard ratio (95 % CI) p-value	LEADER % risk reduction (stat significant/ non-significant)	SUSTAIN 6 Hazard ratio (95% CI) p-value	SUSTAIN 6 Reduction (stat significant/non-significant)
Primary composite MACE	0.87 (0.78–0.97) 0.01	13% reduction (significant)	0.74 (0.58–0.95) 0.02	26% reduction (significant)
CV death	0.78 (0.66–0.93) 0.007	22% reduction (significant)	0.98 (0.65–1.48) 0.92	2% reduction (non-significant)
Non-fatal MI	0.88 (0.75–1.03) 0.046	12% reduction (non-significant)	0.74 (0.51–1.08) p=0.12	26% reduction (non-significant)
Non-fatal stroke	0.89 (0.72–1.11) 0.16	11% reduction (non-significant)	0.61 (0.38–0.99) p=0.04	39% reduction (significant)
Death from any cause	0.85 (95% CI, 0.74–0.97) p=0.02	15% reduction (significant)	1.05 (0.74–1.50) 0.79	5% increase (non-significant)
Hospitalization for heart failure	0.87 (0.73–1.05) 0.14	13% reduction (non-significant)	1.11 (0.77–1.61) 0.57	11% increase (non-significant)
Microvascular endpoints				
New or worsening Nephropathy	0.78 (0.67–0.92) 0.003	22% reduction (significant)	0.64 (0.46–0.88) 0.005	36% reduction (significant)
Retinopathy	1.15 (0.87–1.52) 0.33	15% non-significant increase	1.76 (1.11–2.78) 0.02	76% increase

CI = confidence interval; CV = cardiovascular; MACE = major adverse cardiac event; MI = myocardial infarction

Thus, these results support the use of liraglutide as a preferred second-line drug in diabetes care, provided it is not contraindicated and is well tolerated.

The positive results seen in LEADER were repeated in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), which assessed the cardiovascular outcomes of semaglutide, a once-weekly injectable glucagon-like peptide-1 receptor agonists (GLP1RA). Semaglutide use led to a statistically significant reduction in stroke, and a numerically significant fall in non-fatal MI.² Semaglutide demonstrated 26% reduction in composite CV outcome compared with placebo. The long-acting analogue reduced the risk of non-fatal stroke by 39%, (HR = 0.61, 95% CI [0.38; 0.99] p=0.044) and non-fatal MI by 26% (HR = 0.74 95% CI [0.51; 1.08] p=0.12). Though overall mortality did not fall, reduction in HbA_{1c}, body weight, insulin requirement and hypoglycemia were noted.

The SUSTAIN 6 results also support early use of GLP1RA in the diabetes therapeutic landscape.

Shades of gray

While both the LEADER and SUSTAIN 6 results demonstrate CV benefit, there are subtle differences in their vascular effects. Semaglutide has shown significant reduction in the risk of non-fatal MI, thus acting as a primary preventive strategy against CV events. On the other hand, liraglutide reduces the risk of all-cause mortality and CV mortality, without significantly reducing the chances of having a non-fatal MI or stroke. This implies that liraglutide works better in secondary prevention, that is, prevention of complications after an acute cardiovascular event has occurred. Semaglutide use was associated with an increase in retinal

events, while there was no change noted with liraglutide. Renal events were markedly reduced with both drugs, however. Semaglutide's benefits were visible within four to six months of the trial, while liraglutide took 12 to 18 months to demonstrate its advantage.

The differences noted between liraglutide and semaglutide may be associated with their duration of action, or with their capacity to cross the blood brain barrier and influence cerebral blood flow, either directly, or through an effect on neuronal cells and astrocytes.

Great expectations

More important, however, is the impact the trials reported in 2016 will have on future diabetes care. It is less than 20 years since the UK Prospective Diabetes Study (UKPDS) provided proof of reduction of chronic vascular outcomes with glucose-lowering therapy.³ It took another decade for regulatory authorities to ask for evidence of cardiovascular safety of anti-diabetic drugs, making cardiovascular outcome trials mandatory.⁴ Now LEADER and SUSTAIN 6 (along with the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial [EMPA REG])⁵ have raised the bar by offering CV benefit, over and above safety, with a drug primarily meant to reduce glycemia. This sets the stage for great expectations and, hopefully, better delivery of comprehensive care in diabetes.

Sense and sensibility

The data released in 2016 will stimulate and support calls for comprehensive vasculo-metabolic care using a minimal number of drugs (therapeutic parsimony).⁶ Paradoxically, at the same time, the unique vascular bed-specific benefits of various antidiabetic drugs suggest that

attention will focus on rational combinations of drugs to achieve pan-vascular safety and benefit. For example, a combination of empagliflozin and semaglutide/liraglutide may offer maximal benefit in postponing death and reducing the risk of cardiovascular events. Similarly, a combination of fenofibrate and semaglutide may provide optimal coverage against both retinopathy⁷ and stroke.

Treasure island

Exaptation of glucose-lowering drugs for non-glycemic purposes⁸ may be another spin-off from developments reported this year. Liraglutide is approved for use in obesity (in a 3.0 mg dose),⁹ and other uses are also

being explored. Semaglutide, too, has the potential to be of utility in non-diabetic indications. The next decade may see these molecules being used not only for their glucose-lowering efficacy, but also for their vasculo-protective and metabolic modulatory effects. These uses may extend from neurological conditions such as Alzheimer's disease to metabolic conditions like polycystic ovary syndrome.¹⁰

Summary

The year 2016 has been a landmark year in diabetology. Developments reported this year should help change the way in which we approach, and manage, not only diabetes, but all cardiovascular and metabolic disease. ■

1. Marso SP, Daniels GH, Brown-Frandsen K, et al., Liraglutide and cardiovascular outcomes in type 2 diabetes, *N Engl J Med*, 2016;375(4):311–22.
2. Marso SP, Bain SC, Consoli A, et al., Semaglutide and cardiovascular outcomes in patients with type 2 diabetes, *N Engl J Med*, 2016;375:1834–44.
3. UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet*, 1998;352:837–53.
4. US Food and Drug Administration Guidance for industry: Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf (accessed October 22, 2016).
5. Zinman B, Wanner C, Lachin JM, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, *N Engl J Med*, 2015;373(22):2117–28.
6. Kalra S, Gupta Y, Sahay R, The law of therapeutic parsimony, *Indian J Endocr Metab*, 2016;20(3):283.
7. Knickelbein JE, Abbott AB, Chew EY, Fenofibrate and Diabetic Retinopathy, *Curr Diab Rep*, 2016;16(10):90.
8. Kalra S, Bantwal G, John M, The exaptation of endocrine pharmacology, *Indian J Endocr Metab*, 2012;16(3):329.
9. Scott LJ, Liraglutide in obesity: a guide to its use in the EU, *Drugs & Therapy Perspectives*, 2015;31(10):334–40.
10. Kalra S, Gupta Y, Endocrine and metabolic effects of Glucagon like peptide 1 receptor agonists (GLP1RA), *J Pak Med Assoc*, 2016;6(3):357–9.