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GLP-1 agonists for the treatment of type 2 diabetes: Hype or hope?

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Abstract
The incretin system has become an crucial target in the treatment of type 2 diabetes in modern years, and glucagon-like peptide 1 (GLP-1) is of particular interest for its glucose-lowering effects. Glucagon-like peptide-1 (GLP-1)–based therapy betters glycaemic control through multiple mechanisms, with a low risk of hypoglycaemia and the additional benefit of clinically relevant weight loss. Since Starling and Bayliss first proposed the existence of intestinal secretions that stimulate the pancreas, tremendous progress has been made in the area of incretins. Proper patient selection and education can assist in achieving positive treatment outcomes.

Keywords: Comparison of glucagon-like peptide-1 receptor agonists, efficacy, glucagon-like peptide-1

Introduction
The development of glucagon-like peptide-1 (GLP-1) receptor agonists was first initiated when it was established that impaired insulin secretion and exaggerated glucagon secretion are the key drivers of hyperglycemia in type 2 diabetes (T2D). This combined islet defect is an early phenomenon in the development of T2D and is present before the onset of the disease in individuals at risk [1].

GLP-1, a gut incretin hormone that is released during meal ingestion, was first discovered in 1983. The key islet effects of GLP-1 are stimulation of insulin secretion and inhibition of glucagon. In addition, GLP-1 is known to delay gastric emptying, and induce satiety and lead to weight reduction [2]. Indeed, GLP-1 fulfils the criteria of being a physiological endogenous factor that has the ability to be antidiabetic through several of the above-mentioned actions in T2D.

Drugs belonging in the GLP-1 receptor agonist (RA) class, mimic endogenous GLP-1, and reduce glucose levels by augmenting insulin secretion and suppressing glucagon release in a glucose-dependent manner, by virtue of their action on GLP-1 receptors [3].

The physiological effects of GLP-1 RAs are summarized in Table 1 [3].

Table 1: The physiological effects of glucagon-like peptide-1 receptor agonist (GLP-1RA)

Location	Increased	Decreased
Brain	Neuroprotection (preclinical)	Appetite
Cardiovascular system	Regional and global LV function	Blood pressure
	Heart rate (Clinical)	Endothelial dysfunction (Preclinical)
Muscle	– Glucose uptakea	Ischemia-induced myocardial damage –
Adipose tissue	Glucose uptake	–
Liver	Lipolysis –	– Glucose productiona
		Lipid profile
Stomach	–	Gastric emptying (Clinical)
Kidney	Natriuresis	–
Pancreas	Glucose-dependent insulin secretion (Clinical) Beta cell proliferationb	Glucose-dependent glucagon secretion (Clinical) Beta cell apoptosi

LV left ventricular
a Indirect action
b In animal models

Several GLP-1 RAs are available -all share the same underlying mechanism of action, but differ in terms of formulations, administration, injection devices and dosages. The first available GLP-1 RA, was immediate-release, twice daily exenatide, additional agents subsequently gained regulatory approval and are currently being marketed, including once-daily lixisenatide and liraglutide, and once-weekly prolonged-release exenatide, dulaglutide and semaglutide. Although all the known GLP-1 RAs produce clinically significant reductions in HbA1c levels and body weight, some differences between them have been reported in head-to-head studies, including their impact on cardiovascular (CV) risk factors and gastrointestinal tolerability (Fig 1) [3].

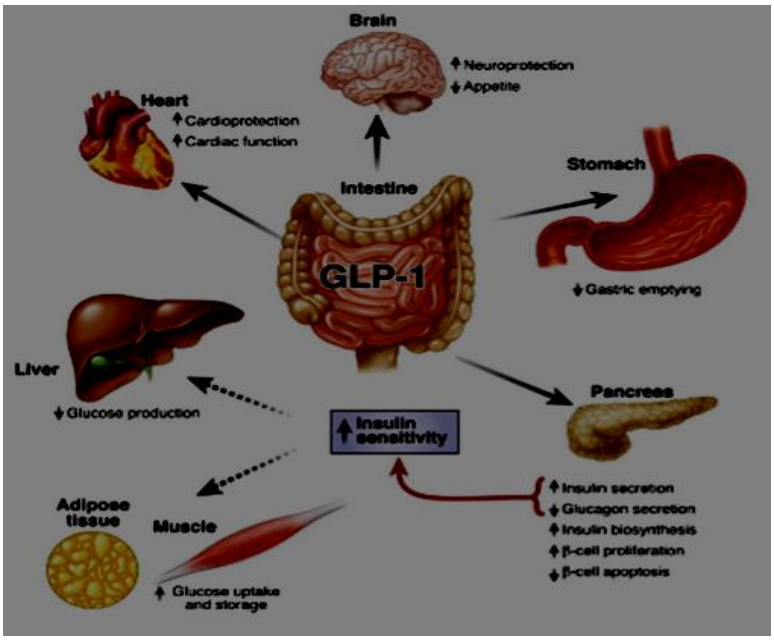

Fig 1: Mechanism of action of GLP1 RAs

Place of GLP-1RA in therapy

In the last two decades, the role of GLP-1 RAs has been well established as effective treatments for patients with T2D for whom lifestyle management (e.g. weight control, increased exercise) and antihyperglycemic monotherapy are insufficient to achieve glycemic targets [3]. Guidelines recommend GLP-1 RAs as second-line treatment after metformin in dual therapy and as part of triple therapy and in combination with insulin [4]. Liraglutide, dulaglutide and semaglutide have been approved for use as monotherapy options when treatment intensification is required.

Randomised clinical trials (RCTs) have shown that the GLP-1 RAs produce significant reductions in HbA1c and fasting plasma glucose levels, both in patients with T2D of recent onset and in those with disease of long duration [3]. The phase III studies that have compared GLP-1 RA agents head-to-head have demonstrated that all GLP-1 RA agents are effective therapeutic options at reducing A1C.(Fig 2) In addition to consistent glycemic control achieved with a low rate of hypoglycaemia, GLP-1RAs also induce weight loss. Thus, GLP-1 RAs could be a preferred option when weight control or prevention of hypoglycemia is particularly important.[5] Dose adjustment in elderly patients or in patients with mild to moderate renal impairment is not a requirement for most members of the class and can therefore be a useful option in these patients.

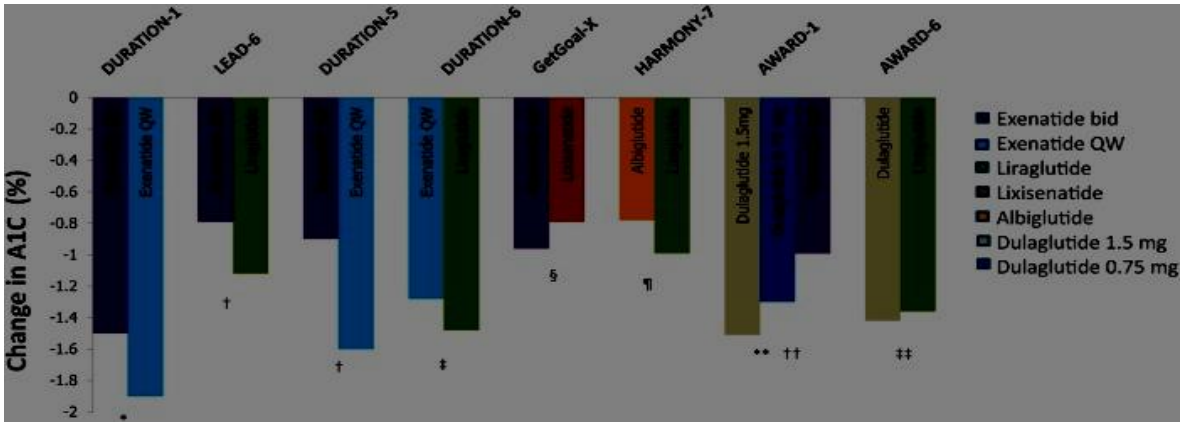

Fig 2: Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority unless otherwise noted as noninferiority; *p < 0.0025, †p < 0.0001, ‡p = 0.02, §p = not significant, noninferiority p-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶ noninferiority p-value = 0.846 (not meeting predefined noninferiority margin), **p < 0.001 for

both doses of dulaglutide versus exenatide bid, ††p = not significant, noninferiority p-value < 0.0001 (Meeting predefined noninferiority margin). (Ther Adv Endocrinol Metab. 2015 Feb; 6(1): 19–28).

CV outcome trials with GLP-1 RAs: main results

GLP-1RAs have been known to possess multiple cardiovascular protective properties that potentially have a beneficial impact on atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality [6].

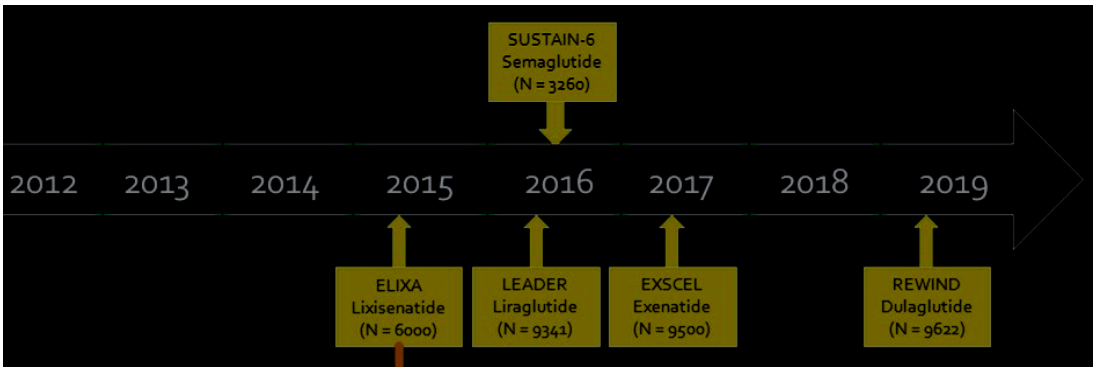

Fig 3: CV outcomes and GLP-1RA

Compared to standard-of-care antidiabetic therapies, GLP-1 RAs have revealed statistically significant non-inferiority (p < 0.001), among CV outcome trials (CVOTs) thus far completed. Once-daily liraglutide and once-weekly semaglutide demonstrated significant superiority (p = 0.01 and p = 0.02, respectively), reducing 3-point composite major adverse cardiovascular events (MACE) in extreme risk secondary prevention adults with T2D. Once-weekly exenatide demonstrated a non-significant (p = 0.06) favorable trend for CV superiority. The short half-life lixisenatide was neutral (p = 0.81) in reducing MACE, the neutral effects attributed to ineffective once-daily dosing [6].

The pleiotropic actions of these agents are mediated through CV risk factor modification along with direct effects on the CV system. (Fig 4).

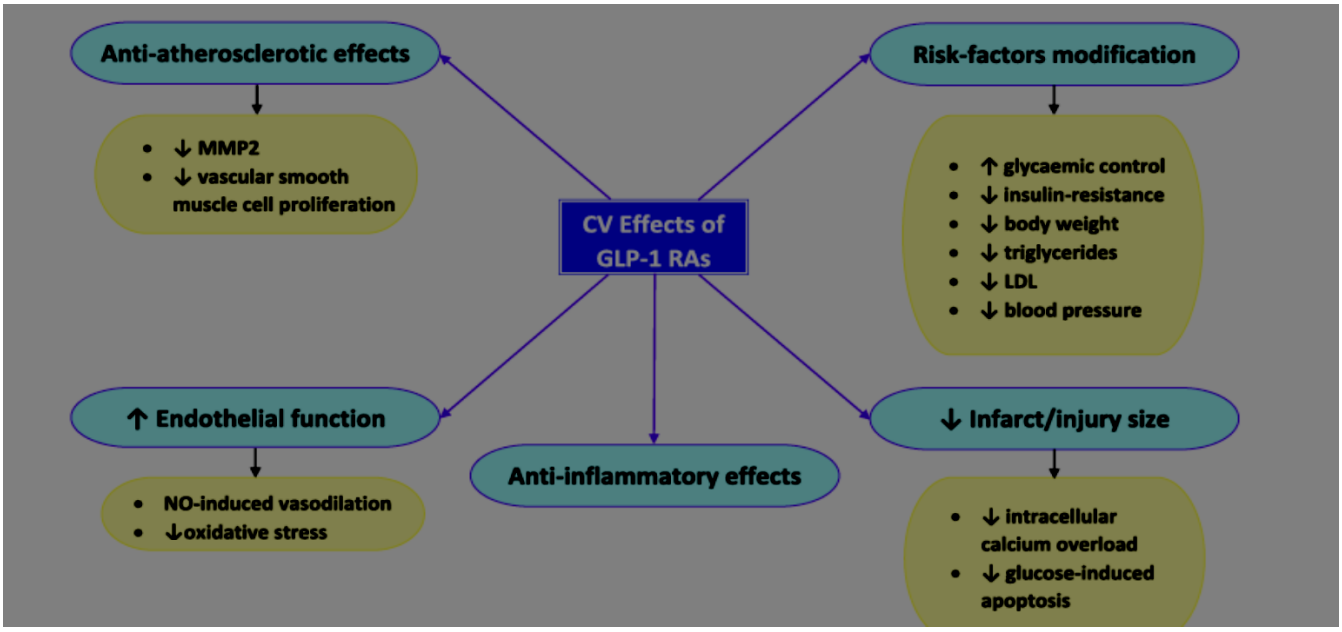

Fig 4: CV system

Impact on other diabetes complications

Meta analyses of RCTS indicate that GLP1-RA may reduce the incidence and/or progression of nephropathy and to have no specific effect on retinopathy-with the notable exception of semaglutide, which could have a negative impact on the retina [8].

Tolerability of GLP-1 RAs

As a class, the GLP-1 RAs are generally well tolerated, with nausea and vomiting being the most common adverse events, occur initially but are transient and are typically mild to moderate in nature [3].

GLP-1 receptor agonists vs. DPP-4 inhibitors T2D

Both incretin based therapies namely, GLP-1 RAs and dipeptidyl peptidase-4 (DPP-4) inhibitors have been beneficial in diabetes management, by virtue of the properties related, not only to glycemic control, but also weight loss and lower incidence of hypoglycemic episodes. DPP-4 I am administered orally and provide a physiological increase in glucagon-like peptide-1 (GLP-1) levels, while GLP-1 receptor agonists (GLP-1RAs) are injectable and deliver pharmacological levels of GLP-1RA [9].

In head-to-head clinical trials, GLP-1RAs have been shown to provide superior glycaemic control and weight loss as

compared to DPP-4 inhibitors in patients with T2D. DPP-4 inhibitors may sometimes be preferred to a GLP-1RA if weight is not a concern, oral administration is a desirable feature or when a GLP-1RA cannot be tolerated [9].

Conclusion

GLP-1 receptor agonists show a distinctive and innovative method for the treatment of diabetes due to advantages other than glucose control, such as clinically relevant weight loss, blood pressure control, cholesterol levels management, and preserving beta-cell function. They imitate the effects of the incretin hormone GLP-1, which is secreted from the intestine responding to food ingestion. Their effects comprise of increasing insulin secretion, lowering glucagon release, increasing satiety, and slowing gastric emptying. Clinical research studies have found GLP-1 to be beneficial in losing weight, when utilized in combination with diet and exercise. Furthermore, patients with type 2 diabetes have a higher risk of developing cardiovascular diseases and often have co-morbidities, including obesity, hypertension, and hyperlipidemia.

Therefore, the ideal means to manage type 2 diabetes should have positive effects on weight, blood pressure, and lipids. GLP-1 receptor agonists thus, have an advantageous effect in the treatment of type-2 diabetes.

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