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REVIEW TOPIC OF THE WEEK

Incretin-Based Therapy for Diabetes

What a Cardiologist Needs to Know

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ABSTRACT

Incretin-based therapies are effective glucose-lowering drugs that have an increasing role in the treatment of type 2 diabetes because of their efficacy, safety, and ease of use. Both glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors are commonly used for glycemic control as adjuncts to metformin, other oral antiglycemic agents, or insulin. Glucagon-like peptide-1 receptor agonists may have additional effects, such as weight loss, that may be advantageous in obese patients. There is a large body of evidence from randomized controlled clinical trials supporting the cardiovascular safety of dipeptidyl peptidase-4 inhibitors and some glucagon-like peptide-1 receptor agonists, at least in the short term. However, concerns have been raised, particularly regarding their safety in patients with heart failure. In this review, the authors provide a brief but practical evidence-based analysis of the use of incretin-based agents in patients with diabetes, their efficacy, and cardiovascular safety. (J Am Coll Cardiol 2016;67:1488-96)

Type 2 diabetes mellitus (T2DM) is characterized by progressive decline in beta cell function and increased risk for cardiovascular (CV) complications (1). Although diet, exercise, and weight loss are considered central tenets in the management of T2DM, pharmacological approaches are almost always required. The ease of use of incretin agents, their glycemic efficacy, low to no risk for hypoglycemia, and ancillary benefits may allow their earlier incorporation with other evidence-based therapies in the treatment of T2DM. However, recent reports of these agents being associated with heart failure (HF) have created considerable confusion (2,3). In this review we critically evaluate the evidence supporting the efficacy (glycemic control, weight loss, lipoprotein effects, blood pressure [BP], and CV events) and safety of currently available incretin agents (dipeptidyl peptidase-4 inhibitors [DPP-4i] and glucagon-like peptide-1 receptor agonists [GLP-1Ra]) from randomized controlled trials published from 2008 onward. The intent is to provide a succinct overview of the use of these agents for CV practitioners.

INCRETINS AND RELEVANCE TO TYPE 2 DIABETES MELLITUS

Incretins are gut-derived members of the glucagon superfamily, released in response to nutrient ingestion (mainly glucose and fat). Glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) are the major physiological incretins (4). Secreted by the small intestine, these peptides amplify the insulin secretory response to nutrients through their cognate G protein-coupled receptors in the pancreatic beta cell (5). Together, GLP-1 and GIP account for

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50% to 70% of total insulin secreted following an oral glucose load and contribute to the control of postprandial hyperglycemia (4). The effects on insulin secretion are maintained only until a "normal" threshold level of plasma glucose is achieved, thus minimizing risk for hypoglycemia. GLP-1 receptor signaling involves the activation of adenylyl cyclase and cyclic adenosine monophosphate-dependent activation of protein kinase A, which promote insulin secretion. Recent evidence at physiologically relevant concentrations of GLP-1 (picomolar range) provides evidence of restoration of beta cell competence by these hormones through increased membrane excitability mediated by ion channels (6). The incretin effect is markedly diminished in T2DM because of resistance at the level of the beta cell, except in late stages, when there may be a reduction in plasma GLP-1 and GIP levels. Incretins, such as GLP-1, also address hyperglucagonemia in T2DM by inhibiting glucagon secretion and reducing hepatic gluconeogenesis. Finally, pharmacological doses of GLP-1 are well known to decrease gastric emptying and appetite through central nervous system mechanisms, thus contributing to weight loss (**Figure 1**) (7).

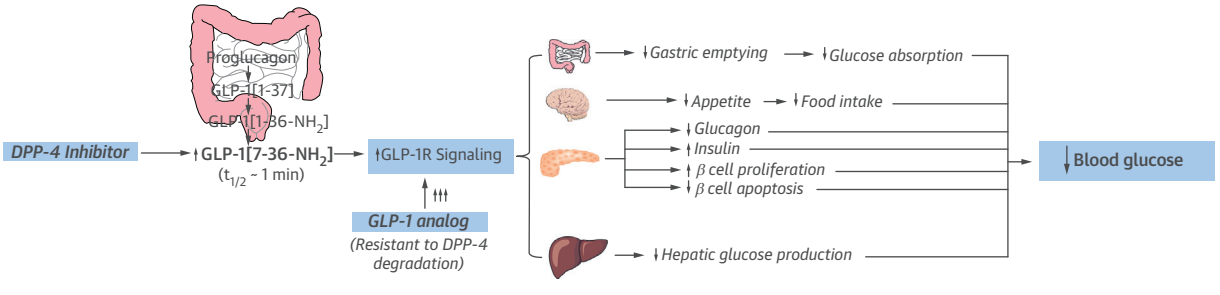
CATALYTIC DEGRADATION OF INCRETINS BY DIPEPTIDYL-AMINOPEPTIDASE-4. Both GLP-1 and GIP have short half-lives in vivo (approximately 1 to 2 min) and are rapidly degraded to their inactive forms (GLP-1 [9-36] and GIP [3-42] in humans) by the peptidase dipeptidyl-aminopeptidase-4 (DPP-4). DPP-4 is a widely expressed serine peptidase that inactivates peptides with an alanine, proline, or serine residue in the penultimate position from the N-terminus (5). DPP-4 catalytic inhibition elevates GLP-1 and GIP levels, although the extent of elevation (picomolar) is small compared with pharmacological supplementation with GLP-1 analogues (nanomolar). These pharmacokinetic considerations may in part explain effects, such as weight loss and gastric slowing, with GLP-1Ra that are not seen with DPP-4i (**Table 1**). DPP-4 is also involved in the catalytic inactivation of a number of other peptides, which may exert effects independent of GLP-1 and GIP levels (**Central Illustration**) (8).

APPROVED INCRETINERGIC AGENTS. The approved agents for the management of T2DM and their pharmacology, dosing, adverse effects, and costs are outlined in Online Table 1. Exenatide is the 39-amino acid synthetic version of exendin-4 (originally isolated from the Gila monster, a species of venomous lizard native to the southwestern United States) that is resistant to DPP-4 degradation. Exenatide long-acting release is a depot formulation of exendin-4, entrapped noncovalently into biodegradable poly-D,L-lactide-co-glycolide microspheres from which the drug is gradually released, increasing the half-life to 6 days. Liraglutide is a GLP-1 (7-37) analogue, containing a fatty acid chain at a lysine residue in position 26 through a gamma-glutamyl spacer, which facilitates binding to albumin, increasing its half-life. Albiglutide and dulaglutide are synthetic fusion proteins composed of dimers of degradation-resistant GLP-1 with a linker protein that prolongs half-life. There are currently 4 DPP-4i ("gliptins") approved by the U.S. Food and Drug Administration (FDA) (**Central Illustration**). All gliptins are orally available, low-nanomolar selective inhibitors and do not interfere with other members of the DPP family. The plasma half-lives of these agents do not reflect tissue half-life, as most DPP-4

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CI = confidence interval
CKD = chronic kidney disease
CV = cardiovascular
DPP-4 = dipeptidyl-aminopeptidase-4
DPP-4i = dipeptidyl peptidase-4 inhibitors
FDA = U.S. Food and Drug Administration
GFR = glomerular filtration rate
GIP = gastric inhibitory peptide
GLP-1 = glucagon-like peptide-1
GLP-1Ra = glucagon-like peptide-1 receptor agonists
HbA_{1c} = glycated hemoglobin
HF = heart failure
HR = hazard ratio
OAD = oral antidiabetic drug
SU = sulfonylurea
T2DM = type 2 diabetes mellitus
TZD = thiazolidinedione

FIGURE 1 Glucose-Lowering Effect of Dipeptidyl Peptidase-4 Inhibitors and Glucagon-Like Peptide-1 Analogs



Dipeptidyl peptidase-4 (DPP-4) inhibition preserves gut-derived glucagon-like peptide-1 (GLP-1), resulting in enhanced GLP-1 receptor (GLP-1R) signaling. DPP-4-resistant GLP-1 analogs directly enhance GLP-1R signaling in multiple organs and reduce glucose via multiple mechanisms. DPP-4 = dipeptidyl peptidase-4.