Is It Time to Change the Type 2 Diabetes Treatment Paradigm? Yes! GLP-1 RAs Should Replace Metformin in the Type 2 Diabetes Algorithm

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Most treatment guidelines, including those from the American Diabetes Association/European Association for the Study of Diabetes and the International Diabetes Federation, suggest metformin be used as the first-line therapy after diet and exercise. This recommendation is based on the considerable body of evidence that has accumulated over the last 30 years, but it is also supported on clinical grounds based on metformin's affordability and tolerability. As such, metformin is the most commonly used oral antihyperglycemic agent in the U.S. However, based on the release of newer agents over the recent past, some have suggested that the modern approach to disease management should be based upon identification of its etiology and correcting the underlying biological disturbances. That is, we should use interventions that normalize or at least ameliorate the recognized derangements in physiology that drive the clinical manifestation of disease, in this circumstance, hyperglycemia. Thus, it is argued that therapeutic interventions that target glycemia but do not correct the underlying pathogenic disturbances are unlikely to result in a sustained benefit on the disease process. In our field, there is an evolving debate regarding the suggested first step in diabetes management and a call for a new paradigm. Given the current controversy, we provide a Point-Counterpoint debate on this issue. In the point narrative below that precedes the counterpoint narrative, Drs. Abdul-Ghani and DeFronzo provide their argument that a treatment approach for type 2 diabetes based upon correcting the underlying pathophysiological abnormalities responsible for the development of hyperglycemia provides the best therapeutic strategy. Such an approach requires a change in the recommendation for first-line therapy from metformin to a GLP-1 receptor agonist. In the counterpoint narrative that follows Drs. Abdul-Ghani and DeFronzo's contribution, Dr. Inzucchi argues that, based on the medical community's extensive experience and the drug's demonstrated efficacy, safety, low cost, and cardiovascular benefits, metformin should remain the "foundation therapy" for all patients with type 2 diabetes, barring contraindications.

—William T. Cefalu
Chief Scientific, Medical & Mission Officer, American Diabetes Association

The modern approach to disease management is based upon identification of its etiology and correcting the underlying pathophysiological disturbances with interventions that ameliorate/normalize known defects responsible for the clinical manifestation of the disease, i.e., hyperglycemia. Therapeutic interventions that simply target hyperglycemia but do not correct the underlying pathogenic disturbances are unlikely

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to result in a sustained reduction in HbA_{1c}. It is well established that type 2 diabetes (T2D) is a complex metabolic/cardiovascular disorder with at least eight distinct pathophysiological disturbances, referred to as the Ominous Octet (1). Hyperglycemia is a manifestation of these eight pathophysiological abnormalities. Nonetheless, the current recommended approach in T2D management still focuses on lowering the plasma glucose concentration rather than correcting the underlying metabolic abnormalities that cause the hyperglycemia (2–4). Therefore, it is not surprising that current therapeutic guidelines (2–4) do not result in a sustained HbA_{1c} reduction (5–8). In this Point-Counterpoint, we argue that it is time to apply the modern concepts of clinical practice to diabetes management and base therapy on pathophysiology. Thereby, GLP-1 receptor agonists (GLP-1 RAs), which *1*) correct six of the eight components of the Ominous Octet, *2*) prevent/reverse the progressive β-cell failure and rise in HbA_{1c}, and *3*) lower cardiovascular risk in T2D independent of their glucose-lowering ability (9,10), should replace metformin as the recommended first-line therapy in newly diagnosed T2D patients.

PATHOPHYSIOLOGY OF T2D

The etiology of T2D is complex and involves multiple pathophysiological disturbances involving multiple organs (1) (Fig. 1). Insulin resistance in skeletal muscle, liver, and adipocytes (11–15) and β-cell dysfunction (16–22) remain the major core defects responsible for the development and progression of hyperglycemia. Insulin resistance is also associated with multiple metabolic abnormalities, e.g., hypertension, dyslipidemia, endothelial dysfunction, procoagulant state, inflammation, and visceral obesity, which collectively are known as the insulin resistance (metabolic) syndrome (23–25). Each individual component of the insulin resistance syndrome, as well as the basic molecular etiology of the insulin resistance (25), is causally related to the development of atherosclerotic cardiovascular disease (CVD) and contributes to the increased risk for CVD in T2D patients.

Because progressive β-cell failure is the principal factor responsible for the development and progression of hyperglycemia in T2D patients (1,16–19), only therapies that halt/reverse the progressive β-cell failure will be effective in lowering and maintaining HbA_{1c} at the target level, and ideally this should be accomplished without increasing the risk of hypoglycemia.

In addition to insulin resistance and β-cell dysfunction, impaired incretin effect in T2D plays a major role in the progression of β-cell failure and hyperglycemia (26,27). Further, T2D patients have elevated fasting plasma glucagon levels that fail to suppress normally after a meal and enhanced hepatic sensitivity to glucagon (28,29), in part due to resistance to GLP-1 (26,30); these pathophysiological abnormalities can be reversed with GLP-1 RA therapy (26,31).

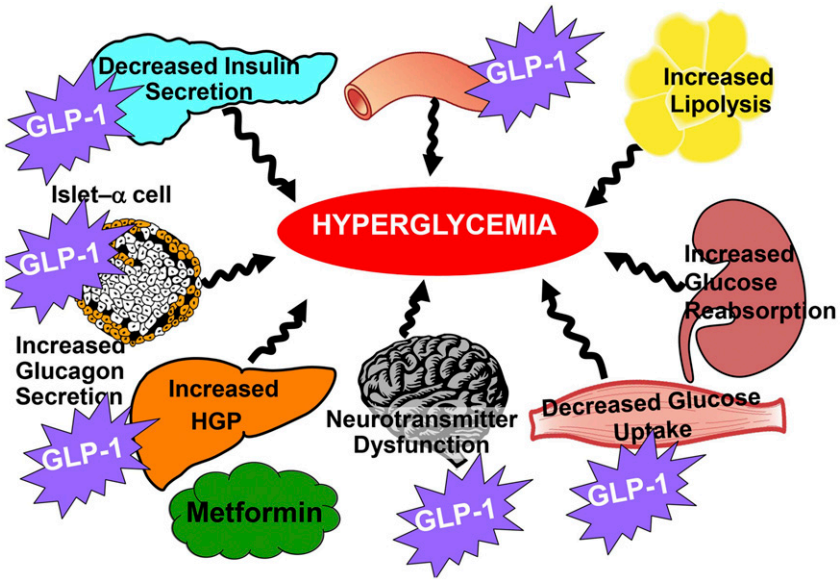

Figure 1—GLP-1 RAs correct six components of the Ominous Octet, whereas metformin corrects only one component.

BIOLOGICAL ACTIONS OF GLP-1 RAs

Activation of GLP-1 receptors in the β-cell amplifies glucose-stimulated insulin secretion but only under conditions of hyperglycemia (26,32), whereas in the α-cell, GLP-1 suppresses glucagon secretion, leading to correction of postmeal hyperglycemia in T2D (26,27,30). GLP-1 RAs improve β-cell function by enhancing β-cell responsiveness to glucose, i.e., improving β-cell glucose sensitivity; this beneficial effect on the β-cell can be observed within 8 h after a single injection of the GLP-1 RA (liraglutide) (33), is maintained at 3 months (semaglutide) (34), and persists for at least 3 years (exenatide) (35). Thus, GLP-1 RAs produce a rapid and durable reduction in HbA_{1c} with low risk of hypoglycemia (36,37).

GLP-1 also exerts multiple nonglycemic actions, all of which improve metabolic control in T2D patients (Table 1), including *1*) delayed gastric emptying, which slows the absorption of ingested glucose (32), *2*) appetite suppression, which promotes weight loss (26,38,39), *3*) reduction of hepatic and visceral fat content (40), making them an attractive intervention to prevent/reverse nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (41), and *4*) prevention of diabetic nephropathy in Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) (42). Recent evidence suggests that gut stimulation of GLP-1 secretion by the L cells is an important mechanism via which metformin suppresses hepatic glucose production (43,44).

GLP-1 RAs AND CVD

CVD is the leading cause of death in T2D patients (45), accounting for ~80% of mortality, and T2D is best viewed as a cardiometabolic disorder (25,46). Thus, reducing CVD risk is a high priority in T2D management, and reduction in blood pressure and correction of diabetic dyslipidemia are essential components of diabetes management. Considerable evidence documents that hyperglycemia is a weak risk factor for cardiovascular

Table 1—Metabolic actions of GLP-1 RAs

- Pancreas
  - Potentiate glucose-mediated insulin secretion
  - Preserve β-cell function/reverse β-cell failure
  - Inhibit glucagon secretion in a glucose-dependent fashion
- Cardiovascular system
  - Reduce MACE
  - Reduce systolic blood pressure
  - Reduce pulmonary capillary wedge pressure
  - Increase myocardial salvage following myocardial infarction
  - Improve endothelial dysfunction
- GI
  - Slow gastric emptying
  - Inhibit hepatic glucose production
  - Decrease liver fat content
  - Decrease visceral fat
- Central nervous system
  - Suppress appetite
- Kidney
  - Preserve renal function
  - Increase sodium excretion
- General
  - Promote weight loss

complications and improving glucose control has little benefit on macrovascular disease risk (UK Prospective Diabetes Study [UKPDS], Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], Veterans Affairs Diabetes Trial [VADT]), especially when it is well established. Numerous clinical trials have demonstrated that antidiabetes agents that reduce plasma glucose without altering other cardiovascular risk factors fail to reduce CVD risk in T2D patients. Conversely, antidiabetes medications that in addition to lowering the plasma glucose concentration also improve cardiovascular risk factors, e.g., GLP-1 RAs (9,10), pioglitazone (47,48), and SGLT2 inhibitors (49,50), significantly reduce cardiovascular events in T2D with established CVD. Thus, these agents should be favored over agents that lower plasma glucose but have no effect on cardiovascular risk factors or CVD, e.g., sulfonylureas (51,52), DPP-4 inhibitors (53–55), and insulin (56) (Fig. 2). GLP-1 RAs consistently have been shown to reduce many CVD risk factors (Table 2) (25,34,57–60). Thus, it is not surprising that two large, prospective, randomized, double-blind, placebo-controlled trials (9,10) have demonstrated that liraglutide and semaglutide significantly lower the incidence of 3-point MACE (major adverse cardiovascular events), which includes nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death, by 13% and 24%, respectively, in T2D patients with existing CVD. Of note, despite the high CVD risk in the patient populations in both LEADER and Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6), all cardiovascular risk factors, including blood pressure and LDL cholesterol, were well controlled at baseline, consistent with the high number of patients receiving statins, ACE inhibitors, angiotensin receptor blockers, and aspirin therapy. Addition of the GLP-1 RA to the patients' antidiabetes treatment resulted in only modest reductions in HbA_{1c} (0.4%) and systolic blood pressure (~2–3 mmHg) in LEADER and SUSTAIN-6; these glucose- and blood pressure–lowering effects are quite modest and unlikely to explain the CVD benefit of liraglutide and semaglutide. This suggests the GLP-1 RAs may have a direct beneficial action to slow the atherosclerotic process, independent of their effect to reduce glycemia and improve traditional cardiovascular risk factors (59).

The above review demonstrates that GLP-1 RAs directly and/or indirectly correct/improve six of the eight pathophysiological defects responsible for hyperglycemia in T2D, improve cardiovascular risk factors, and reduce MACE in two large, well-designed, prospective cardiovascular intervention trials.

GLP-1 RAs, NOT METFORMIN, SHOULD BE THE FIRST-LINE THERAPY IN T2D

GLP-1 RAs correct six members of the Ominous Octet, whereas the only known action of metformin is to inhibit hepatic glucose production (61) (Fig. 1 and Table 2). Contrary to common belief, metformin is not an insulin sensitizer in muscle or adipocytes (61–63) in the absence of weight loss, which is a frequent occurrence in patients treated with the biguanide (Fig. 3*A*). Consistent with this, following intravenous administration of ^{11}C-metformin, none of the biguanide can be detected in muscle (64). Most importantly, and in direct contrast to the GLP-1 RAs, metformin lacks any effect on β-cell function (61,62) (Fig. 3*B*), which is the primary pathophysiological disturbance responsible for progressive hyperglycemia in T2D patients (1). This is most graphically demonstrated in the UKPDS (65) and A Diabetes Outcome Progression Trial (ADOPT) (5) (Fig. 3*D*) in which, after an initial decline during the first year, HbA_{1c} rose progressively because of progressive β-cell failure. This stands in marked contrast to the GLP-1 RAs, which exert a potent protective effect on the β-cell that persists for at least 3 years (34). Because the GLP-1 RAs cause significant weight loss, they also improve insulin sensitivity in muscle. Thus, GLP-1 RAs, but not metformin, correct the two

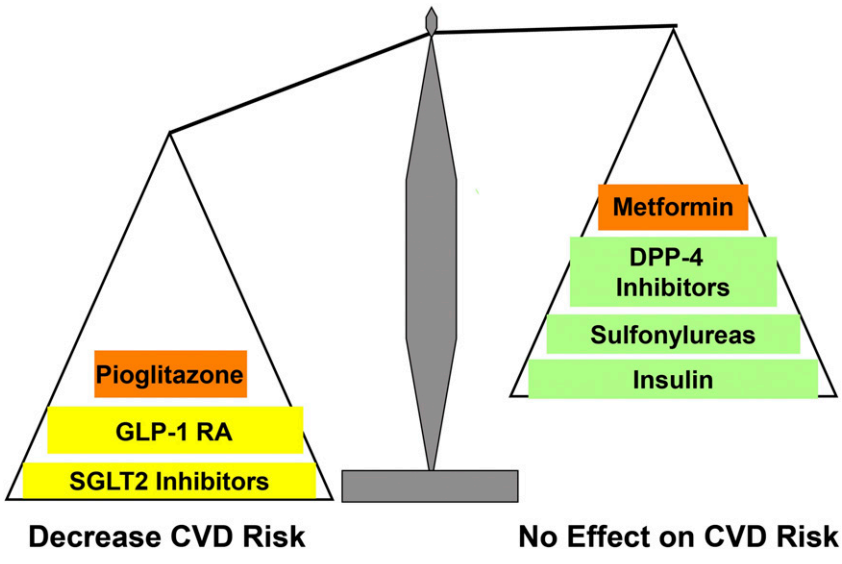

Figure 2—Not all antidiabetes agents are equal in their ability to reduce cardiovascular risk.

Table 2—Benefits of GLP-1 RAs far outweigh those of metformin

	GLP-1 RAs	Metformin
Pathophysiological defects in T2D (see Fig. 1)	Corrects six of the defects	Corrects only one of the defects
Glucose-lowering efficacy	Strong	Strong
Durability of HbA_{1c} reduction	Strong	None
Weight loss	3–4 kg	1–2 kg
Blood pressure	~2–3 mmHg reduction	Neutral
Lipid profile	Lowers triglycerides, increases HDL cholesterol	Neutral
Cardiovascular protection (MACE)	Reduction by 13–26%	Neutral
Renal protection	Reduction by 22%	Neutral
Tolerability	~10–15% GI side effects	~10–15% GI side effects
Dosing	Weekly subcutaneous injection	Once to twice daily oral administration
Cost	High	Low

major core defects in T2D patients, i.e., β-cell dysfunction and muscle insulin resistance. The major mechanism of action of metformin to reduce glycemia is inhibition of hepatic gluconeogenesis (61,62) (Fig. 3*C*), whereas the GLP-1 RAs also effectively reduce hepatic glucose production but by multiple other mechanisms, i.e., inhibition of glucagon secretion, stimulation of insulin secretion, direct effect on the liver, and depletion of liver fat (26,27,30,59,66–68).

Although the UKPDS demonstrated that metformin caused a reduction in cardiovascular events in T2D patients (65), the patient population consisted of a small number of obese T2D subjects ($n = 342$); these results, by today's standards, would never be accepted as evidence for a cardiovascular benefit of the biguanide. Moreover, a beneficial

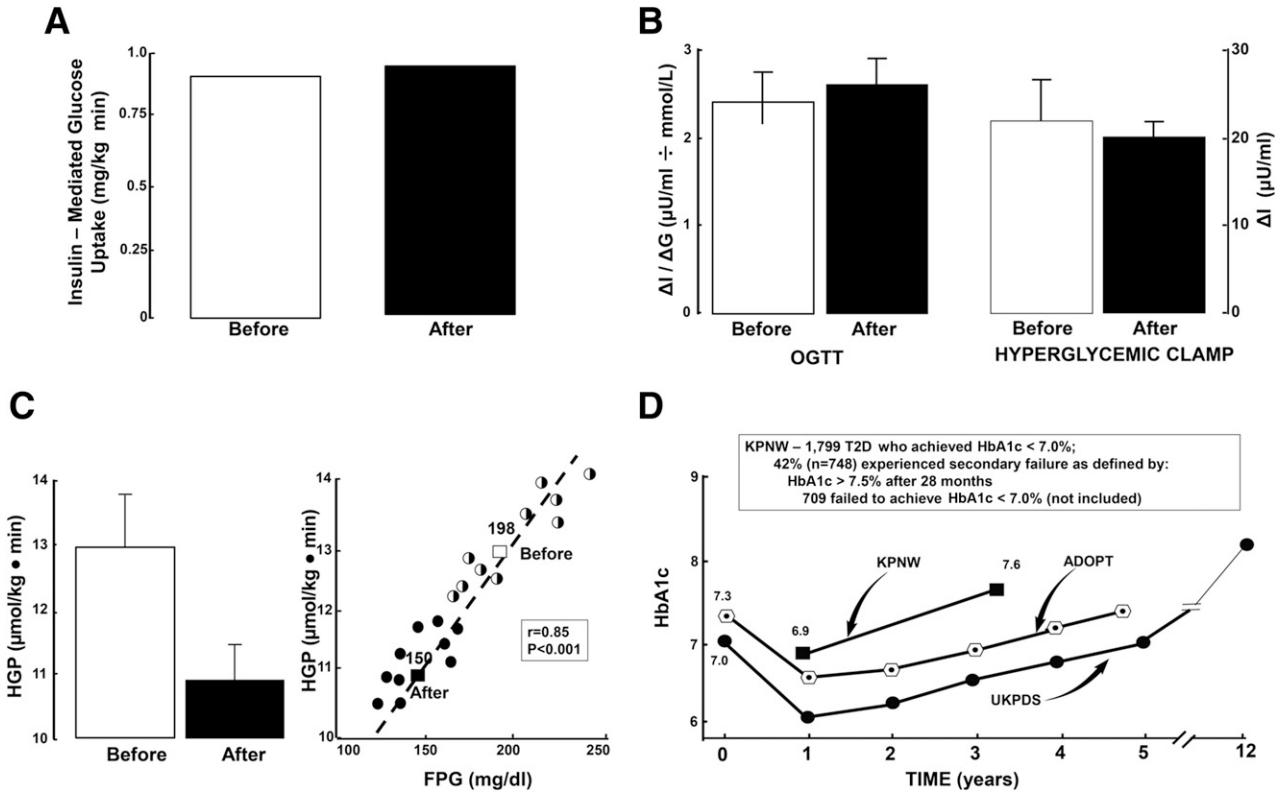

Figure 3—Effect of metformin on glycemic control, insulin secretion, and insulin sensitivity in T2D. *A*: Metformin does not improve muscle insulin sensitivity (measured with euglycemic insulin clamp) in T2D individuals ($n = 20$) in the absence of weight loss (72). *B*: Metformin has no effect on β-cell function in T2D individuals ($n = 14$) (measured with an oral glucose tolerance test [OGTT] and hyperglycemic clamp) (73). *C*: The primary effect via which metformin reduces the HbA_{1c} in T2D is related to the suppression of hepatic glucose production (HGP) via inhibition of gluconeogenesis (72). FPG, fasting plasma glucose. *D*: Effect of metformin on HbA_{1c}. Because metformin does not affect muscle insulin sensitivity or β-cell function, following an initial decline after metformin administration, the HbA_{1c} rises progressively in T2D patients (5,6,74). KPNW, Kaiser Permanente Northwest.

effect on cardiovascular events was not observed in other clinical studies with metformin, i.e., the ADOPT study (5), which included twice the number of patients as the UKPDS ($n = 818$). To the contrary, subjects receiving metformin in ADOPT experienced more cardiovascular events than subjects receiving glyburide, although this difference was not statistically significant. This emphasizes the problem of interpreting results from studies that are markedly underpowered to detect clinically significant differences in cardiac event rates. Conversely, the CVD benefit of GLP-1 RAs has conclusively been demonstrated in two very large, prospective cardiovascular intervention trials, LEADER and SUSTAIN-6 (9,10).

With regard to safety, both metformin and GLP-1 RAs are associated with gastrointestinal (GI) adverse events. Approximately 15–20% of T2D patients do not tolerate metformin because of GI side effects (66). The incidence of GI side effects with the long-acting GLP-1 RAs is similar to that of metformin. Further, and unlike those with metformin, the GI side effects usually are mild to moderate, waning over the first 4–6 weeks of initiating therapy. The percentage of patients who discontinue long-acting GLP-1 RAs because of GI side effects is significantly lower than that of metformin (67). Some postmarketing reports have suggested an increased risk of acute pancreatitis with GLP-1 RA use. However, three large, prospective, double-blind, placebo-controlled clinical trials including ~20,000 patients followed for 2–4 years have demonstrated no increased risk of acute pancreatitis with GLP-1 RA use (9,10,68).

Metformin is administered orally versus via injection for GLP-1 RAs. However, intermediate-acting metformin requires multiple daily dosing, whereas two long-acting GLP-1 RAs (exenatide and dulaglutide) are available as weekly injections and a third (semaglutide) is under review by the U.S. Food and Drug Administration. A subcutaneously implanted osmotic mini pump that continuously delivers exenatide for 6 months is expected to be approved within the next year (69), and an oral formulation of the GLP-1 RA semaglutide is in phase 3 trials (70) and is anticipated to be available within 3–4 years. These modern delivery methods will improve patient compliance for GLP-1 RAs versus metformin.

Lastly, metformin is generic and inexpensive, whereas GLP-1 RAs are still under patent and, therefore, expensive. However, most large health care plans have at least one GLP-1 RA on formulary with a modest copay. Moreover, liraglutide (Victoza) is expected to become generic by the end of 2017, and this should significantly reduce its cost. A cost-effective analysis is beyond the scope of this discussion, and the appropriate long-term, clinical, real-world studies to perform such an analysis are not available. However, a recent cost analysis for the treatment of T2D patients in the U.S. by the American Diabetes Association (71) demonstrated that only a small portion (12%) of the cost of T2D is due to the direct cost of antihyperglycemic medications. The vast majority of the cost of diabetes care is related to the development of diabetic vascular complications, with CVD disease contributing 50% of that cost, and two recent studies, LEADER and SUSTAIN-6, have demonstrated that GLP-1 RAs decrease cardiovascular events. Further, the cost of medications to treat the complications of diabetes is 50% greater than the cost of antihyperglycemic medications. It remains to be determined whether, on a long-term basis, the use of GLP-1 RAs, which in addition to causing a durable reduction in the plasma glucose concentration (thereby decreasing microvascular complications) also reduce cardiovascular events, will be cost-effective.

In summary, the currently available clinical and scientific evidence (Table 2) is overwhelmingly in favor of the use of GLP-1 RAs over metformin as first-line therapy in newly diagnosed T2D patients.

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