Review

Blood Pressure-Lowering Effects of Incretin-Based Diabetes Therapies

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ABSTRACT

Glucagon-like peptide-1 receptor (GLP-1) agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors are therapies that are used to treat hyperglycemia in patients with type 2 diabetes mellitus. Although both of these medication types primarily lower prandial and fasting blood glucose levels by enhanced GLP-1 receptor signalling, they have distinct mechanisms of action. Whereas DPP-4 inhibitors boost patient levels of endogenously produced GLP-1 (and glucose-dependent insulinotropic peptide) by preventing its metabolism by DPP-4 enzymatic activity, GLP-1 receptor agonists are either synthetic analogues of human GLP-1 or exendin-4 based molecules. They are tailored to resist hydrolysis by DPP-4 activity and to provide longer durability in the circulation compared with native GLP-1. Several roles for incretin-based diabetes therapies beyond the endocrine pancreas and their glycemic-lowering properties have now been described, including attenuation of cardiac myocyte injury and reduction in post-ischemic infarction size after cardiovascular insult. Favourable outcomes have also been observed on systolic blood pressure reduction, postprandial intestinal lipoprotein metabolism, endothelial cell function, modulation of innate immune-mediated inflammation and surrogate markers of renal function. As hypertension is an independent risk factor for premature death in patients with type 2 diabetes, potential favourable extrapancreatic actions, particularly within the heart, blood vessels and kidney, for this drug class are of considerable clinical interest. Herein, we highlight and provide critical appraisal of the clinical data supporting the antihypertensive effects of GLP-1 receptor agonists and DPP-4 inhibitors and link possible mechanisms of action to clinical outcomes reported for this drug class.

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RESUMÉ

Les agonistes des récepteurs du GLP-1 (glucagon-like peptide—1) et les inhibiteurs de la dipeptidyl-peptidase—4 (DPP—4) sont des traitements utilisés pour traiter l’hyperglycémie des patients souffrant du diabète sucré de type 2. Bien que ces deux types de médicaments abaissent principalement les glycémies prandiale et à jeun en améliorant la signalisation des récepteurs du GLP-1, leurs mécanismes d’action sont distincts. Tandis que les inhibiteurs de la DPP-4 stimulent les concentrations du GLP-1 endogène des patients (et du GIP [glucose-dependent insulinotropic peptide]) en empêchant son métabolisme par l’activité enzymatique de la DPP-4, les agonistes des récepteurs du GLP-1 sont soit des analogues synthétiques du GLP-1 humain ou des molécules de l’exendine-4. Ils sont en mesure de résister à l’hydrolyse par l’activité de la DPP-4 et d’avoir une plus longue durabilité dans la circulation comparativement au GLP-1 natif. Les nombreux rôles des traitements à base d’incretine, outre le pancréas endocrine et leur propriétés hypoglycémiates, ont maintenant été décrits, à savoir l’atténuation des lésions cardiomypocytaires et la réduction de la taille de l’infarctus postischémique après l’agression cardiovasculaire. Des résultats favorables ont également été observés sur la réduction de la pression artérielle systolique, le métabolisme postprandial des lipoprotéines élaborées par l’intestin, le fonctionnement des cellules endothéliales, la modulation de la réaction inflammatoire de l’immunité innée et les marqueurs de substitution de la fonction rénale. Comme l’hypertension est un facteur de risque indépendant de la mortalité prématurée des patients souffrant du diabète de type 2, les actions extrapancréatiques potentiels favorables, particulièrement sur le cœur, les vaisseaux sanguins et les reins,

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de cette classe de médicaments présentent un intérêt clinique considérable. Dans cet article, nous soulignons et donnons une appréciation critique des données cliniques appuyant les effets anti-hypertenseurs des agonistes des récepteurs du GLP-1 et des inhibiteurs de la DPP-4, et nous faisons le lien entre les mécanismes d’action possibles et les résultats cliniques de cette classe de médicaments.

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Introduction

Glucagon-like peptide-1 receptor (GLP-1) agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors are therapies that are used to treat hyperglycemia in patients with type 2 diabetes mellitus (1,2). Although both of these medication types primarily lower prandial and fasting blood glucose levels by enhanced GLP-1 receptor signalling, they have distinct mechanisms of action (1,2). Whereas DPP-4 inhibitors boost patient levels of endogenously produced GLP-1 (and glucose-dependent insulinotropic peptide [GIP]) by preventing its metabolism by DPP-4 enzymatic activity, GLP-1 receptor agonists are either synthetic analogues of human GLP-1 or exendin-4-based molecules. They are tailored to resist hydrolysis by DPP-4 activity and to provide longer durability in the circulation compared with native GLP-1 (1,2).

Several roles for incretin-based diabetes therapies beyond the endocrine pancreas and their glycemic-lowering properties have now been described, including attenuation of cardiac myocyte injury and reduction in post-ischemic infarction size after cardiovascular insult. Favourable outcomes have also been observed on systolic blood pressure reduction, postprandial intestinal lipoprotein metabolism, endothelial cell function, modulation of innate immune-mediated inflammation and on surrogate markers of renal function (3,4). As hypertension is an independent risk factor for premature death in patients with type 2 diabetes, potential favourable extraprancreatic actions, particularly within the heart, blood vessels and kidney, for this drug class are of considerable clinical interest. Herein, we highlight and provide critical appraisal of the clinical data supporting the antihypertensive effects of GLP-1 receptor agonists and DPP-4 inhibitors as well as link possible mechanisms of action to clinical outcomes reported for this drug class.

Biology of glucagon-like peptide-1

Two distinct groups of medications, the glucagon-like peptide-1 receptor (GLP-1R) agonists and the DPP-4 inhibitors, comprise the class of agents known as incretin-based diabetes therapies (Table 1) (5). These medications have overlapping mechanisms of action for glycemic reduction through either potentiation of endogenous GLP-1 levels or through direct activation of the GLP-1 receptor (a 7-transmembrane, g-protein coupled receptor) to promote insulin secretion, inhibit glucagon secretion, and delay gastric emptying (5). Glucagon-like peptide-1 is an endogenously produced hormone of the distal human gut, synthesized within specialized enteroendocrine cells embedded in the intestinal mucosa known as L cells (6). Although intestinal GLP-1 secretion is triggered by a diverse variety of factors (metformin, interleukin-6, bile acids, and so forth), the classical view is that GLP-1 is secreted in the gut in response to nutrient ingestion as part of the enterointrinsic axis (7).

The half-life of GLP-1 in human plasma is very short owing to the proteolytic actions of DPP-4, and DPP-4 is the principle regulator of GLP-1 activity in humans (8). DPP-4 is also known as CD26 (cluster of differentiation 26) or adenosine deaminase complexing protein 2, and occurs in 2 principle forms: 1) as a membrane-bound glycoprotein in immune cell types, and 2) as a circulating serine exopeptidase that inactivates circulating polypeptides (9). In addition to GLP-1, DPP-4 regulates the activity of a number of substrates, including the insulinotropic factor GIP, GLP-2 (an intestinal growth factor), B-type natriuretic peptide (a ventricular-derived peptide secreted in response to cardiomyocyte stretch), stromal-derived growth factor-1-alpha (a homing factor for endothelial progenitor cells) and several other neuropeptides, growth factors and chemokines with varied functions (10). Although GLP-1 is considered the predominant incretin hormone responsible for blood glucose-lowering effects in humans, GIP is also an endogenous incretin hormone with insulinotropic properties whose bioactivity is regulated through DPP-4 (for this review, we will focus primarily on the effects of GLP-1). In the absence of small-molecule inhibitors of DPP-4 activity (DPP-4 inhibitors), the half-life of biologically active GLP-17-36amide in humans is less than 2 minutes (11). GLP-1 concentrations are also regulated by renal excretion, and this has pharmacokinetic implications for administration of GLP-1R agonists in the setting of renal dysfunction (12).

GLP-1 is also synthesized from the proglucagon gene in the brain (hypothalamus, brainstem) where it potently activates central satiety centres that express the GLP-1R, regulating appetite and food intake in humans (13). Body weight losses in the range of 3 kg to 5 kg are typically observed following chronic GLP-1R agonist administration, whereas the currently available DPP-4 inhibitors are weight neutral irrespective of the dose administered. Of those studied, it has been reported that GLP-1R agonists cross the blood-brain barrier (14,15) and some have been associated with neuroprotective effects in the central nervous system in different preclinical models of neurodegeneration (16), and more recently, in improving clinical performance scales in the setting of Parkinson disease (17). In addition to neuroprotection, GLP-1R signaling in the central nervous system may

### Table 1

<table>
<thead>
<tr>
<th>Incretin-based therapy</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1R agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.2–1.3 mg</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Exenatide</td>
<td>5–10 μg</td>
<td>SC, twice daily</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>20 μg</td>
<td>SC, once daily</td>
</tr>
<tr>
<td>Exenatide extended release</td>
<td>2 mg</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Albilglutide</td>
<td>30 mg</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>1.5 mg</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>0.8–1.6 mg</td>
<td>SC, once weekly</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>50–100 mg</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5–5 mg</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Albigluride</td>
<td>25 mg</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50 mg</td>
<td>Oral, once/daily</td>
</tr>
</tbody>
</table>

SC: subcutaneous.
The antidiabetes drug class known as incretin-based diabetes therapies consists of 2 distinct categories: 1) the GLP-1R agonists, which are administered once (or twice) daily subcutaneously for the shorter-acting agents or once weekly subcutaneously for the longer-acting agents, lower blood glucose levels through direct activation of the GLP-1 receptor; and 2) the DPP-4 inhibitors, which are administered once daily by mouth, primarily lower blood glucose levels through preventing the breakdown of the incretin hormones GLP-1 and GIP.  
* Approved for use by Health Canada for the treatment of type 2 diabetes.  
* Approved for use by the Food and Drug Administration for the treatment of type 2 diabetes.
regulate peripheral cardiovascular function. Preclinical investigation in rodents has demonstrated that brain GLP-1R signalling through the hypothalamus regulates femoral artery blood flow and heart rate; accordingly, central GLP-1R signalling may regulate cardiovascular function and peripheral responses to hypoglycemia (18,19).

**GLP-1 in the heart and cardiovascular system**

Although the classical appreciation of GLP-1 biology is that the biological actions of GLP-1 are transduced through binding of GLP-1-7-36amide to its cognate GLP-1 receptor, GLP-1R-independent vasodilatory actions on blood vessels have been reported (20). Moreover, truncated forms of GLP-1 (GLP-1-9-36amide, which were traditionally viewed as inactive hydrolyzed remnants) are associated with vasodilatory actions and may have other functional activities within compartments of the cardiovascular system (21,22). Hence, further study of GLP-1 metabolites, particularly within the cardiovascular system, may expand our knowledge of GLP-1 biology and unmask unrecognized activities of these metabolites that may be related, distinct or compensatory, to the actions of GLP-1-7-36amide. In addition to cardiomyocyte protection, GLP-1R signalling has other favourable effects in the cardiovascular system and the endovascularature, including blood pressure reduction, which may be particularly advantageous in the treatment of type 2 diabetes. In this context, we review the existing clinical data supporting the hemodynamic effects of GLP-1R agonists and DPP-4 inhibitors in patients with type 2 diabetes.

**Hemodynamic effects of GLP-1R agonists**

Much of the recent literature describing the hemodynamic effect(s) of GLP-1R agonists on systolic blood pressure (SBP) reduction are derived from large, phase III clinical studies (or meta-analysis thereof) that were primarily designed to evaluate the blood glucose-lowering effects of GLP-1R agonists. When interpreting these data, it is important to appreciate that these studies were designed a priori to evaluate glyceremic effects rather than hemodynamic effects of GLP-1R agonists. Nevertheless, consistent but modest SBP reductions—ranging from −2.1 mm Hg to −6.7 mm Hg for liraglutide in the Liraglutide Effect and Action in Diabetes (LEAD) 1-6 trials (23)—in office SBP measurement at study end as compared with study baseline are routinely observed in clinical studies of 12, 24 and 52 weeks duration with GLP-1R agonist therapy (Table 2).

Few studies report repeat office SBP readings throughout the course of these clinical studies. Detailed office BP data are available for meta-analysis from the LEAD 1-6 studies. The data demonstrate that with liraglutide administration (1.2 mg and 1.8 mg), SBP reduction occurs early (at 2 weeks, peaking at 4 weeks), preceding reductions in body weight (24). Presently, there is at least 1 registered clinical trial, Liratime (www.clinicaltrials.gov NCT01499108), prospectively evaluating the time course to blood pressure reduction for liraglutide. Once complete, this study should better characterize the onset of the antihypertensive effect(s) of GLP-1R agonists, in addition to providing other associative mechanistic information.

Interestingly, a study of acute administration of exenatide (a GLP-1R agonist) (10 μg subcutaneously) in non-diabetic volunteers was associated with a rapid rise in heart rate (+8.2 beats/min), an increase in mean cardiac output (1.2 L/min) and a fall in total peripheral resistance measured by venous occlusion plethysmography and Doppler ultrasonography, which is consistent with an acute vasodilatory effect for exenatide (25). Although the urinary sodium-to-creatinine ratio was significantly increased in this study, unexpectedly, no acute changes in BP were observed for exenatide administration vs. placebo. Accordingly, the acute effects of GLP-1R agonists on SBP may differ from the effects of chronic GLP-1R agonist administration. To account for these differences, it has been postulated that an acute rise in SBP (rather than reduction in SBP) in response to GLP-1R agonists may represent a compensatory sympathoadrenal response to the GLP-1R agonist-induced insulin release and blood glucose drop, or possibly is due to the sodium-retaining properties associated with insulin itself (which is released in response to GLP-1R agonist administration).

The effect(s) of GLP-1R agonists on SBP reduction is not transient or intermittent, but appears to be continuous and durable in long-term studies. Although there are few details available regarding the number or subclass (e.g. calcium channel antagonists, angiotensin-converting enzyme inhibitors) of concomitant antihypertensive agents used by trial participants, it is reasonable to expect that a significant proportion of these trial participants were likely receiving renin-angiotensin-aldosterone system (RAAS) blockade given their diagnosis of type 2 diabetes. It is worthwhile to emphasize that the antihypertensive effect(s) of GLP-1R agonists is additive, even in combination with antihypertensive monotherapy and polytherapy. This raises the possibility that the SBP-lowering effect of GLP-1R agonists may be even more pronounced in patients who are naïve to antihypertensive therapy. Whether the SBP-lowering effect of GLP-1R agonists is dependent or proportional to the amount of glycemic reduction achieved with GLP-1R agonist administration is unknown. The available data would suggest otherwise, given that GLP-1R agonists reduce SBP in obese euglycemic patients in the absence of significant glycemic reduction (26).

Several meta-analyses of the hemodynamic effect(s) of GLP-1R agonists have now been reported (24,27–31). These studies, although comprising heterogenous pooled data, substantiate a modest SBP-lowering classwide effect for GLP-1R agonists. A recent extensive systematic meta-analysis and meta-regression by Katout et al (30) of GLP-1R agonists in 12, 469 patients demonstrated that a greater reduction in SBP is achieved with GLP-1R agonists than with active comparator therapy (weighted mean difference, −2.22 mm Hg; −2.97 to −1.47 mm Hg). As expected, the SBP-lowering effect was associated with a small increase in heart rate (weighted mean difference, +1.30 beats/min; 0.26 to 2.33 beats/min). These results are in keeping with another recent meta-analysis by Robinson et al (27), who demonstrated that GLP-1R agonist administration was associated with a reduction in SBP by −1.79 mm Hg (−2.94 to −0.64 mm Hg) vs. placebo.
and $-2.39$ mm Hg ($-3.35$ to $-1.42$ mm Hg) vs. active control. Small increases in heart rate of $+1.86$ beats/min vs. placebo and $+1.90$ beats/min vs. active comparator were also observed in their analyses.

Although some individual phase III clinical studies report a reduction in diastolic blood pressure (DBP) for GLP-1R agonists, this is less consistently reported, and the effect is of a lesser magnitude. In a recent analysis, Robinson et al. (27) demonstrated that the effect of GLP-1R agonists on DBP failed to reach statistical significance $-0.54$ mm Hg (vs. active control), $-0.5$ mm Hg (vs. placebo). Whether a more marked effect on DBP will be observed in specific patient populations, such as hypertensive patients, patients who are naïve to antihypertensive therapy or obese patients (who might experience more substantial changes in body weight and fat loss), requires further investigation.

### Limitations of studies

Although the available clinical data that associate a small yet consistent reduction in SBP for chronic GLP-1R agonist therapy are supported by exposure in a large number of patients with type 2 diabetes, there are limitations and weaknesses of the clinical studies from which these conclusions are drawn (Table 3). Of note, although these studies included a large number of patients (e.g. LEAD trial, 4400 patients), the majority of patients in these trials were normotensive (baseline SBP typically 120 to 130 mm Hg) at study baseline. Accordingly, extrapolation of these data to the hypertensive type 2 diabetic population are inferential and are not based on evidence derived from exclusive study in trial patients with uncontrolled hypertension. Further evaluation, then, of the antihypertensive effect of GLP-1R agonists is warranted in patients with type 2 diabetes and arterial hypertension.

The rationale for the concept that GLP-1R agonists may be associated with a more robust antihypertensive effect in hypertensive patients is supported by results of 6 randomized clinical trials that prospectively compared the glycemic effects at 1 year of exenatide vs. placebo or insulin (32). These studies demonstrate that, in post-hoc subgroup analysis of patients stratified by baseline blood pressure, the most robust effect on SBP reduction is observed in patients who are in the highest BP category at baseline. Although there is presently no evidence to suggest a graded antihypertensive effect for GLP-1R agonists (which is dependent upon the magnitude of an individual patient’s BP), more focused studies comparing the amount of SBP reduction achieved by these agents in patients in various stages of hypertension (prehypertension and stages 1, 2, 3), as compared to the BP reduction achieved in patients with normal BP ($<140$ mm Hg) would be of interest. Furthermore, given the heterogeneity in mechanisms of action among the various antihypertensive classes (e.g. diuretics, calcium channel antagonists, RAAS-interfering agents, vasodilators), further clarification of the mechanisms mediating the antihypertensive effects of GLP-1R agonists is warranted and may allow for a more effective pairing of these drugs with antihypertensive agents.

Remarkably, few studies have used 24-hour ambulatory BP monitoring as a tool to accurately quantify hemodynamic changes associated with GLP-1R agonist administration. Therefore, there is presently little information regarding chronobiological factors on the antihypertensive effect(s) of GLP-1R agonists over a 24-hour period. To provide insight into how GLP-1R agonists may influence nocturnal SBP, nocturnal dipping status, pulse pressure and early morning blood pressure rises, and so forth, we and fellow investigators are carrying out the Blood Pressure Outcomes With Liraglutide Therapy (BOLT) trial (www.clinicaltrials.gov NCT01755572), a prospective, randomized, placebo-controlled, cross-over experimental study. Given the recognized link between nocturnal dipping status and cardiac risk, this exploratory study and others will provide a better understanding of how GLP-1R agonists influence nocturnal BP fluctuations and other relevant hemodynamic parameters through repeated 24-hour ambulatory BP measures in a hypertensive population of patients with type 2 diabetes.

### Hemodynamic effects of DPP-4 inhibitors

In a small exploratory study by Mistry et al. (33), the acute hemodynamic effects of the DPP-4 inhibitor sitagliptin (100 mg twice daily) were studied by 24-hour ambulatory BP monitoring. Surprisingly, a significant difference was observed in mean 24-hour SBP after a single dose ($-2.9$ mm Hg vs. placebo) of sitagliptin, and this effect was sustained at day 5 ($-1.6$ mm Hg vs. placebo). However, variable and inconsistent results for SBP reduction with DPP-4 inhibitors have been observed in larger clinical trials (>$100$ patients) with longer exposure to sitagliptin therapy (26 weeks or longer). Although some clinical studies show a neutral effect on DBP (34), others demonstrate a significant reduction in both SBP and DBP (35–37). Given that the majority of the data for DPP-4 inhibitors on BP reduction are also derived from phase III clinical trials designed to demonstrate the glycemic-lowering effects of DPP-4 inhibitors, we would suggest that the same limitations apply to the clinical data for DPP-4 inhibitors, as we noted in Table 3 for GLP-1R agonists.

### Mechanisms Mediating Hemodynamic Effect(s) of Incretin-Based Diabetes Therapies

A variety of mechanisms may contribute to the antihypertensive effect(s) of GLP-1R agonists and DPP-4 inhibitors (Table 4). As GLP-1 acutely raises insulin levels and insulin is known to have a mild vasodilatory effect (21,37,38), some suggest that insulin may mediate the antihypertensive effect(s) of GLP-1. Insulin also has sodium-retaining properties, however, and a vast proportion of patients with type 2 diabetes are obese, which predisposes them to sodium reabsorption in the proximal tubule and salt-sensitive hypertension. There is growing evidence from preclinical studies of rodents (39,40) and from clinical studies of GLP-1$^{7-36}$amide infusion in humans (41,42) that supports a role for GLP-1 in regulating water and salt homeostasis through effects on the kidney to...
stimulate urinary sodium excretion. Accordingly, 1 unifying hypothesis that may partially account for the antihypertensive effect(s) of GLP-1R agonists and DPP-4 inhibitors in humans is through the stimulation of natriuresis. A small series of preclinical and clinical studies have demonstrated that urinary sodium excretion is triggered in response to short-term infusion of GLP-17-36amide and volume expansion by hypertonic saline infusion. Gutzwiller et al (42) observed significant, dose-dependent increases in urinary sodium excretion in healthy subjects (143 nmol/L per 180±18 min [GLP-1] vs. 74 nmol/L per 180±8 min [placebo], p = 0.0013), and in obese, insulin-resistant subjects urinary sodium excretion increased 60% vs. placebo (p = 0.015) in response to native GLP-1 infusion. This effect was observed in parallel with increased chloride ion and calcium ion filtration, suggesting a GLP-1-inhibitory effect at the level of the proximal tubule. Additionally, urine volume was also increased (343±35 mL to 454±62 mL, p = 0.028) in response to GLP-17-36amide infusion. As Muskiet et al (43) eloquently pointed out, a more profound natriuretic response after oral salt loading as compared with intravenous salt loading were observed in humans, however both oral and intravenous salt loads were observed to evoke similar rises in the fractional excretion of sodium in male volunteers in response to short-term GLP-1 infusion. Therefore, although a GLP-1-mediated gut-renin effect on water and ion homeostasis after a meal seems reasonable (and is in keeping with the predominately GLP-1-mediated incretin-effect on insulin secretion and glucose homeostasis after food intake), the available data for GLP-1, although limited, do not presently support this concept.

Whereas Gutzwiller et al (42) observed modest changes on glomerular filtration rate (6% decrease, p = 0.022), Skov et al (44) did not report significant changes in glomerular filtration rate or plasma renal flow with GLP-1 infusion when using sensitive quantification techniques for these parameters. This group, however, did observe relative increases in renal sodium ion (40%, p = 0.007), calcium ion (67%, p = 0.011) and osmolar clearance rates (27%, p = 0.021). Although these studies support a natriuretic effect for GLP-1, it should be noted that in these acute studies, natriuresis was not paired to measurement of SBP; hence, the relevance of these findings to SBP reduction is unknown. Skov et al (44) recently reported a reduction in systemic levels of the potent vasoconstrictor angiotensin II with acute GLP-1 infusion; however, urinary angiotensinogen expression (a biomarker of renal tissue RAAS activity) was unchanged in this same study; therefore, the effect of GLP-1 on tissue intrarenal RAAS activity remains unclear.

More recently, a novel link between BP reduction and cardiac atrial natriuretic peptide (ANP) secretion in response to GLP-1R activation (liraglutide) was demonstrated in rodents rendered hypertensive by ANG-II (angiotensin II) infusion (45). Although previously unrecognized, Kim et al (45) importantly localized GLP-1R expression in the heart to the cardiac atrium but, interestingly, not to the ventricles (where the majority of the cardioprotective effect of GLP-1R agonists are thought to be targeted). Activation of the atrial-GLP-1R through liraglutide administration was associated with increased ANP secretion, a reduction in ANG-II-mediated hypertension and urinary sodium excretion in rodents, setting the stage for an ANP-GLP-1R-mediated gut-heart-renal axis.

Although this effect has yet to be extensively studied in human patients with type 2 diabetes and hypertension, in single-day, crossover studies investigating the effect of short-term (3-hour) continuous GLP-1 infusion in normotensive non-diabetic humans, Skov et al (46) did not report any effect of native GLP-1 on concentrations of pro-ANP. In contrast, more recently, a small study involving Chinese patients with type 2 diabetes and pre-hypertension found significant increases in ANP levels after 12 weeks of liraglutide administration. While these findings were coupled to moderate reductions in both SBP (−5.3 mm Hg, −7.9 to −2.6; p=0.001) and DBP (−2.5 mm Hg, −4.2 to −0.8; p=0.0005), these studies were not paired to changes in urinary sodium excretion (47). Surprisingly, an increase in B-type natriuretic peptide levels was also observed in this study; however, no reduction in low-density lipoprotein cholesterol lowering (−0.11 mmol/L, −0.45 to −0.23; p = 0.511) was reported. Furthermore, the majority of patients in this cohort were prehypertensive (SBP 138.2±11.2 mm Hg, DBP 85.9±6.4 mm Hg) at study baseline rather than in more advanced stages of hypertension, where the antihypertensive effect(s) of GLP-1R agonists could be more potent and ANP secretion more pronounced. At present, there are mixed data supporting the relevance of a potential ANP-mediated gut-heart-renal axis for GLP-1R agonist-dependent reductions in BP in humans.

Multiple mechanistic links between DPP-4 inhibitors and the stimulation of natriuresis have also been postulated (43). Specifically, correlations between DPP-4 inhibition and the modulation of specific renal sodium ion exchanger activities have been observed in several preclinical rodent studies. Vallon et al (48) demonstrated that administration of the DPP-4 inhibitor vildagliptin was associated with increased urinary sodium excretion, and remarkably, the observed vildagliptin-mediated stimulation of natriuresis was preserved in GLP-1R null mice. Hence, separate antihypertensive mechanisms may be at play for mediating the BP-lowering effect(s) of GLP-1R agonists as compared to DPP-4 inhibitors, consistent with the overlapping yet subtle differences in the mechanisms of action for these 2 medication types.

### Cardiovascular Outcome Studies With Incretin-Based Diabetes Therapies

To establish cardiovascular safety for this drug class, several international, multicentre, randomized, double-blind, placebo-controlled phase IIIb cardiovascular outcome studies with long-term follow up are either actively recruiting or have completed enrolment for efficacy and safety assessment of GLP-1R agonists in patients with type 2 diabetes and stable cardiovascular disease (or patients at high risk for cardiovascular events) or after a recent acute coronary syndrome. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results - A Long Term Evaluation (LEADER) trial (NCT01179048) is a noninferiority trial that began in 2010 and completed enrolment of 9340 patients. Eligibility for the LEADER trial includes patients with type 2 diabetes and cardiovascular disease (age ≥50 years plus established atherosclerosis or renal failure or heart failure, or age ≥60 years plus prespecified vascular risk factors) and patients were randomly assigned to either liraglutide (1.8 mg) or placebo. The primary endpoint is time to first occurrence of composite cardiovascular death, nonfatal myocardial infarction or nonfatal stroke, with a
minimum 3.5 years follow up to a maximum of 5 years follow up, the results of which will likely be reported in 2016.

The Researching Cardiovascular Events With A Weekly Incretin in Diabetes (REWIND) trial (NCT01394952) started in 2011. It is a trial evaluating the once-weekly GLP-1R agonist dulaglutide (1.5 mg) compared with placebo and has an estimated enrolment of 9622 patients. Eligibility for the REWIND study includes patients with type 2 diabetes (glycated hemoglobin [A1C] 9.5% or less) at age ≥50 years plus clinical vascular disease, age ≥55 years with subclinical vascular disease or age ≥60 years with multiple cardiovascular risk factors; the composite primary endpoint is time to first occurrence of major adverse cardiovascular event.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial (NCT01144338) began in 2010; it compares exenatide once weekly (2 mg) vs. placebo in patients with type 2 diabetes (age ≥18 years, A1C 6.5% to 10%) receiving oral hypoglycemic agents or insulin, and has a projected enrolment of 14,000 patients. Similar to the LEADER and REWIND studies, the EXSCEL trial has a composite primary endpoint of time to first occurrence of major adverse cardiovascular event.

The Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE00101 (lixisenatide) (ELIXA) trial (NCT01147250) is designed to evaluate whether treatment with the GLP-1R agonist lixisenatide (20 μg), compared to placebo, reduces cardiovascular morbidity and mortality (composite primary endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina) after hospitalization for acute coronary syndrome, defined as ST-segment or non-ST-segment elevation myocardial infarction or unstable angina with an elevated cardiac biomarker (troponin or creatine kinase—myocardial band), in patients with type 2 diabetes (newly diagnosed or established disease) within 180 days of hospital admission. The active double-blind treatment study period is approximately 10 months, with follow up occurring until the accrual of approximately 844 positively adjudicated primary cardiovascular outcome events.

The Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) trial (NCT01720446) will evaluate the time to major adverse cardiovascular events with semaglutide, a once-weekly GLP-1R agonist, at 0.5 mg or 1.0 mg doses vs. placebo. The SUSTAIN-6 study is an event-driven trial (with an estimated enrolment of 3260 patients) that became active in 2013. Eligibility for the SUSTAIN-6 trial includes patients with type 2 diabetes and high baseline cardiovascular disease (age ≥50 years plus clinical cardiovascular disease or age ≥60 plus subclinical cardiovascular disease).

At present, there are no registered cardiovascular outcomes studies for albiglutide in public clinical trial registries in North America. Although no cardiovascular safety studies have been reported for GLP-1R agonists, results of 2 studies were recently reported for DPP-4 inhibitors.

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction-53 trial (SAVOR-TIMI 53) (49) enrolled 16 494 patients with type 2 diabetes (median duration 10 years, mean A1C 8.0%) with established atherosclerotic disease (78%). Eligibility criteria included age ≥40 years plus clinical events (coronary, cerebrovascular or peripheral vascular system), or age ≥55 years (males) or age ≥60 years (females) with either dyslipidemia or hypertension or active smoking. SAVOR-TIMI 53 was an event-driven trial with a median follow up of 2.1 years. Compared with placebo, the number of ischemic events (7.3% vs. 7.2%) were neither increased nor decreased with saxagliptin 5 mg therapy (hazard ratio 1.00, 95% confidence interval, 0.89 to 1.12; p = 0.99 inferiority, p < 0.001 noninferiority). A 27% (hazard ratio 1.27, 95% confidence interval, 1.07 to 1.51; p = 0.007 for superiority) increased rate of hospitalization for heart failure was observed with saxagliptin as compared with placebo. While these data are presently under re-evaluation by the United States Food and Drug Administration, several key questions have ensued since the publication of these findings, including identification of a unifying mechanism to link these results specifically to saxagliptin and determination of whether this is a classwide effect for all DPP-4 inhibitors.

The Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) trial (50) was a double-blind, noninferiority trial that enrolled 5380 patients with type 2 diabetes within 15 to 90 days of hospitalization for acute myocardial infarction or hospitalization for unstable angina and randomly assigned them to either alogliptin (25 mg) or placebo. The median follow up was 18 months, at which time there were no statistically significant differences observed in the cumulative incidence of the primary outcome (percentage of patients with primary major adverse cardiac event) for alogliptin (11.3%, compared with placebo 11.8%; hazard ratio 0.96 (percentage of patients with primary major adverse cardiac event), confidence interval [upper boundary 1-sided repeated], 1.16; p = 0.32 for superiority).

Although efficacy for the reduction of cardiovascular events in type 2 diabetes patients with stable (or at high risk for the development of) cardiovascular disease or after acute coronary syndrome has yet to be demonstrated for DPP-4 inhibitors, there are other ongoing cardiovascular outcome studies evaluating other DPP-4 inhibitors, for example, the Trial to Evaluate Cardiovascular Outcomes After Treatment With Sitagliptin (TECOS). The results of these trials may either substantiate or differ from those of the SAVOR-TIMI 53 or EXAMINE studies, and either way, will broaden and extend our knowledge of this drug class in the setting of type 2 diabetes and cardiovascular disease.

Considerations for special patient populations

Clinicians should be aware that positive chronotropic effects (2 to 4 beats/min) are consistently observed following GLP-1R agonist administration but not with DPP-4 inhibitors in patients with type 2 diabetes. Accordingly, use of GLP-1R agonists is not recommended for patients with a heart rate >100 beats/min. Although extensive studies of specific patient groups potentially at risk for tachycardia (e.g. atrial and ventricular arrhythmias or the elderly) are lacking, caution in their use is suggested, given the association between elevations in heart rate and increased cardiovascular mortality.

Paradoxically, although GLP-1R agonists reduce SBP and have been associated with renoprotection preclinically, administration of exenatide has been associated with several cases of acute renal failure (ARF), including acute interstitial nephritis and acute tubular necrosis, with diagnoses substantiated by renal biopsy (51). As no causal link has been established between exenatide and ARF, these occurrences are presently only associative. Nevertheless, clinicians should be mindful of the possibility of ARF with exenatide use, and must be attentive to acute changes in renal function or to clinical presentations consistent with ARF (proteinuria or hematuria) in patients taking this medication. Although ARF has not been associated with liagliptide use, it should be noted that there is less clinical experience with the use of this entire drug class for patients with renal dysfunction. Although there are several ongoing safety trials for GLP-1R agonists and DPP-4 inhibitors in the setting of various stages of renal dysfunction, clinicians must be aware of specific dosing indications presently advised for some of these medications for patients with renal impairment.

Finally, although the intention of this article was to review and comment on the antihypertensive effect(s) of incretin-based diabetes therapies, we wish to emphasize that, at present, the
clinical indication for these medications is exclusively for the treatment of type 2 diabetes. To our knowledge, this drug class is not indicated or approved anywhere in the world for the treatment of hypertension and should not be used off-label in lieu of conventionally prescribed antihypertensive agents for patients with hypertension, with or without type 2 diabetes.

Conclusion

In summary, incretin-based medications are a newer class of diabetes therapies that are used worldwide for the treatment of type 2 diabetes. There is growing interest in their use for high-risk patients with type 2 diabetes, given their association with several favourable nonglycemic effects that extend to the cardiovascular, endovascular and renovascular systems. Although we highlight the limitations of the current literature, these data support a modest yet significant lowering effect on SBP with chronic (but not with acute) use of this drug class (particularly for GLP-1R agonists). Nevertheless, physicians should be mindful that this SBP-lowering effect is paired with small yet positive chronotropic effects (for GLP-1R agonists); and furthermore, precaution should be taken for use of this drug class in patients with renal impairment until further clinical studies are available.

While natriuresis remains a unifying mechanism to explain the antihypertensive effect(s) of this drug class, further study is required with diabetic hypertensive models for complete characterization. Accordingly, future preclinical and clinical studies designed to investigate the natriuretic and the natriuretic-independent mechanisms that regulate the SBP-lowering effect(s) of these medications are warranted. Given that repair and remodelling of the heart and blood vessels occurs during sleep, an understanding of the influence of GLP-1R agonists on diurnal BP variation is of interest. Moreover, as left ventricular size is a major risk predictor, prospective evaluation of how GLP-1R agonist therapy might influence the regression of left ventricular hypertrophy in the setting of chronic hypertension would be key in appreciating whether the antihypertensive effect of this drug class can modify hard vascular outcomes.

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