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Potential Cardiovascular Effects of the Glucagon-like Peptide-1 Receptor Agonists

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Abstract

In patients with type 2 diabetes, cardiovascular risk reduction represents an important clinical goal in light of the elevated risk of cardiovascular mortality in this patient population; thus, it is important that glucose-lowering drugs have no negative effects and potentially some positive effects on cardiovascular risk. The glucagon-like peptide-1 receptor agonists (GLP-1RAs), which were designed to resist degradation by the enzyme dipeptidyl peptidase-4, are among the newer glucose-lowering agents for the treatment of type 2 diabetes. There are a number of agents within this class, including exenatide, liraglutide, albiglutide, lixisenatide, and dulaglutide. Preclinical research efforts in animal models have identified a number of favorable cardiovascular effects of GLP-1RAs beyond glucose lowering. Although the underlying basis for these cardiovascular effects has not yet been elucidated, a number of potential mechanisms have been suggested. Accumulating data from randomized clinical trials and retrospective/post hoc pooled analyses of clinical trials support the favorable effects of GLP-1RAs on blood pressure and lipid profiles. Although some observations have suggested that GLP-1RAs may lead to an increase in heart rate, a recent post hoc analysis including 11 studies of exenatide once weekly versus active comparators or placebo shows that mean increases in heart rate are small and transient, increases are more common in patients with low baseline heart rate, and that heart rate elevations become less prevalent over time. In addition, no association was observed between major adverse cardiac events and small mean increases in heart rate. Individual clinical trials in patients with type 2 diabetes also have provided evidence of protection against post-myocardial infarction ischemic damage, as well as the ability to improve circulating biomarker levels. Forthcoming data from phase 3 and 4 cardiovascular outcome trials of GLP-1RAs will provide further insight into their cardiovascular safety and cardioprotective potential in various settings.

Keywords: Albiglutide; Blood pressure; Cardiovascular disease; Dulaglutide; Exenatide; Glucagon-like peptide-1 receptor agonists; Liraglutide; Lixisenatide

Abbreviations: BNP: B-type (brain) Natriuretic Peptide; BP: Blood Pressure; bpm: beats per minute; DBP: Diastolic Blood Pressure; DPP-4: Dipeptidyl Peptidase-4; GLP-1: Glucagon-Like Peptide-1; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; HDL: High-Density Lipoprotein; hsCRP: high-sensitivity C-Reactive Protein; LDL: Low-Density Lipoprotein; LS: Least Squares; LV: Left Ventricular; MACE: Major Adverse Cardiac Events; MDI: Multiple Daily Insulin; MI: Myocardial Infarction; pPCI: primary Percutaneous Coronary Intervention; SBP: Systolic Blood Pressure; STEMI: ST-Segment–Elevation Myocardial Infarction; VLDL: Very Low-Density Lipoprotein

Introduction

Cardiovascular risk reduction is a fundamental component of the management of type 2 diabetes, with the recognition that cardiovascular disease accounts for more than half of the mortality in this patient population [1-4]. The development and progression of cardiovascular disease are particularly aggressive in patients with type 2 diabetes, for which proposed mechanisms include an underlying effect of hyperglycemia on endothelial cell dysfunction, development of a prothrombotic state, and/or negative arterial modeling [5]. In patients with diabetes, a 3-fold increase in cardiovascular mortality and significantly higher 30-day and 1-year mortality after presentation with acute coronary syndrome, have been reported, compared with patients without diabetes [6]. Specifically, glycemic control has been shown to be a key element in reducing cardiovascular risk in patients with type 2 diabetes [7,8]. Long-term randomized controlled trials studies such as VADT (Veterans Administration Diabetes Trial) [9], ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) [10] and ACCORD (The Action to Control Cardiovascular Risk in Diabetes) [11] have shown that strict glycemic control is not associated with significant benefit in terms of cardiovascular outcomes in patients with type 2 diabetes and may even increase the risk of adverse cardiovascular outcomes and mortality in elderly patients at high cardiovascular risk [12]. Although increased incidence of hypoglycemia was observed with intensive anti-glycemic treatment in all three studies, there is insufficient data to show causality between it and higher cardiovascular mortality in patients under strict glycemic control [12]. Notably, in 2007, rosiglitazone was shown to be associated with increased risk of myocardial infarction and cardiovascular-related mortality [13] and, as a result, changes were made to the regulatory requirements for development of anti-diabetic drugs in 2008 requiring that clinical studies ruled out excess cardiovascular risk [14].

Overall, it is apparent that diabetes can be regarded as a cardiovascular disease, not just a comorbid condition that often coexists with cardiovascular disease [15]. Accordingly, it is critical that

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glucose-lowering agents do not increase cardiovascular risk, and the ability to produce positive cardiovascular effects beyond those afforded by glucose control would be optimal [16].

Glucagon-like peptide-1 (GLP-1) is released into the circulation as an effect of food intake and is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), with a reduced postprandial response to this peptide hormone implicated in the pathogenesis of type 2 diabetes [17]. GLP-1 receptor agonists (GLP-1RAs) are resistant to the effects of DPP-4 and represent a relatively new class of glucose-lowering agents [18,19]. In patients with diabetes, these agents act to lower glucose by enhancing pancreatic β-cell–mediated glucose-dependent insulin secretion, suppressing glucagon secretion in the setting of abnormally high levels, delaying gastric emptying, and reducing food intake. Some potential benefits over other glucose-lowering agents have been recognized, including weight loss and a lower (albeit not eliminated) risk of hypoglycemia [18]. A number of GLP-1RAs are currently available or under investigation [20], including exenatide (twice daily or once weekly), liraglutide (once daily), and albiglutide (once weekly), which are indicated with diet and exercise for the improvement of glycemic control in adults with type 2 diabetes in the United States. Lixisenatide (once daily) is available in countries outside the United States, and other agents are in late-stage development (eg, dulaglutide). Effects of this class are known to extend beyond glucose lowering and include a number of potential cardiovascular benefits including small reductions in blood pressure (BP), potential effects on lipid and circulating biomarker profiles, and protection against post-myocardial infarction (MI) damage, which are discussed herein.

Materials and Methods

A series of literature searches were conducted of the PubMed.gov database in November 2013 (with no limits on publication dates) to identify both preclinical and randomized clinical trials of the GLP-1RAs with the most extensive clinical experience, exenatide and liraglutide. For this review, focus was placed on the key Phase 3 clinical trial data for the GLP1-RAs, although all clinical data with cardiovascular outcomes were considered for inclusion. The search terms used were: 1) (randomized controlled trial) and (glucagon-like peptide-1 receptor agonist OR GLP-1RA or exenatide OR liraglutide) and (type 2 diabetes) and (cardiovascular), human only; and 2) (preclinical OR animal) and (glucagon-like peptide-1 receptor agonist OR GLP-1RA or exenatide OR liraglutide); with no other limits applied. In June 2014, a new search was conducted to capture additional clinical trials for GLP-1RAs, specifically albiglutide, lixisenatide, and dulaglutide using the same search strategy. Another supplementary literature search was performed in November 2014 to update the literature immediately prior to publication. After a manual review of the search results and selection of individual articles providing cardiovascular data, results were supplemented with reports of interest from bibliographies of published papers or key data from published abstracts or associated presentations.

Ongoing trials relevant to this topic were identified using the U.S. National Institutes of Health ClinicalTrials.gov registry.

Preclinical data and potential mechanisms for the cardiovascular effects of GLP-1RA agents

Substantial preclinical evidence supports that GLP-1RAs improve BP, with additional effects that may include improved myocardial metabolism, coronary blood flow, pre-/post-ischemic conditioning, Left Ventricular (LV) remodeling, and LV performance (as recently reviewed elsewhere) [15]. A vast amount of preclinical literature derived from animal models collectively supports that GLP-1 receptor (GLP-1R) stimulation may culminate in a broad range of physiological effects involving the blood vessels (and the heart , as well as the nervous system, intestines, and kidneys [17]. Importantly, the effects of GLP-1RAs on blood vessels and the heart appear to be reflective of the localization of GLP-1 receptors and direct effects on these organs.

Preclinical trials focused on elucidating the effects of GLP-1 on BP and heart rate collectively support significant effects on these parameters [21-26]. An early study in male Sprague-Dawley rats found dose-dependent increases in BP (including systolic BP (SBP) and diastolic BP (DBP)) as well as heart rate with both GLP-1 (7-36) amide and exendin-4, with more rapid and strong effects for the former and more prolonged effects for the latter [21]. Exendin-(9-36) exhibited antagonist effects, blocking the increases in both BP and heart rate, when co-administered with GLP-1 (7-36) amide and exendin-4— supporting the hypothesis that this effect is receptor mediated.

Numerous preclinical investigations of the effects of GLP-1 in animal models of MI have provided evidence of improvements in infarct size and cardiac function [27-33], with no deleterious histopathological effects on the pancreas [34-36].

Some findings may provide insight into the cardioprotective mechanisms underlying the changes in infarct size and cardiac function, including increased myocardial expression of phosphorylated protein kinase B (pAkt), reduction in active caspase 3 expression, increased antioxidant enzyme activity and reduced nuclear oxidative stress with active treatment [31]. One of the more recent trials focused on elucidating the effects of GLP-1 in neutrophil-mediated reperfusion injury, with GLP-1 administration immediately prior to reperfusion resulting in a significant reduction in infarct size as well as neutrophil activation in blood and myocardial accumulation [33].

In addition to those described above, a number of potential cardioprotective mechanisms for GLP-1 have been described (Figure 1) [37], such as a potential effect on myocardial glucose uptake and a number of other myocardial and systemic effects that may stem from its activity in the gastrointestinal system, adipose tissue, and/or vascular system [37,38]. GLP-1 has been proposed to have a direct influence on endothelial cells by means of GLP-1R, with anti-inflammatory effects reflecting a reduction in expression of the receptor for advanced glycation end products [39,40]. The mechanism(s) of BP reduction for GLP-1RAs, involve GLP-1R activation leading to atrial natriuretic peptide secretion and subsequent BP reduction (Figure 2) [41]. Anti-atherosclerotic effects of GLP-1 may be mediated via reduced monocyte/macrophage accumulation in the arterial wall, by inhibiting the inflammatory response in macrophages [42], whereas effects on survival and infarct remodeling post-MI may reflect activation of cardioprotective signaling pathways in the heart [29].

Clinical Trial Data: Cardiovascular Effects

Vital signs

BP data from the Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly (DURATION) trials of exenatide once weekly [43-52] and the Liraglutide Effect and Action in Diabetes (LEAD) studies of liraglutide [53-60] are summarized in Table 1. Overall, the DURATION and LEAD studies collectively support that exenatide once weekly and liraglutide confer SBP reductions from baseline,
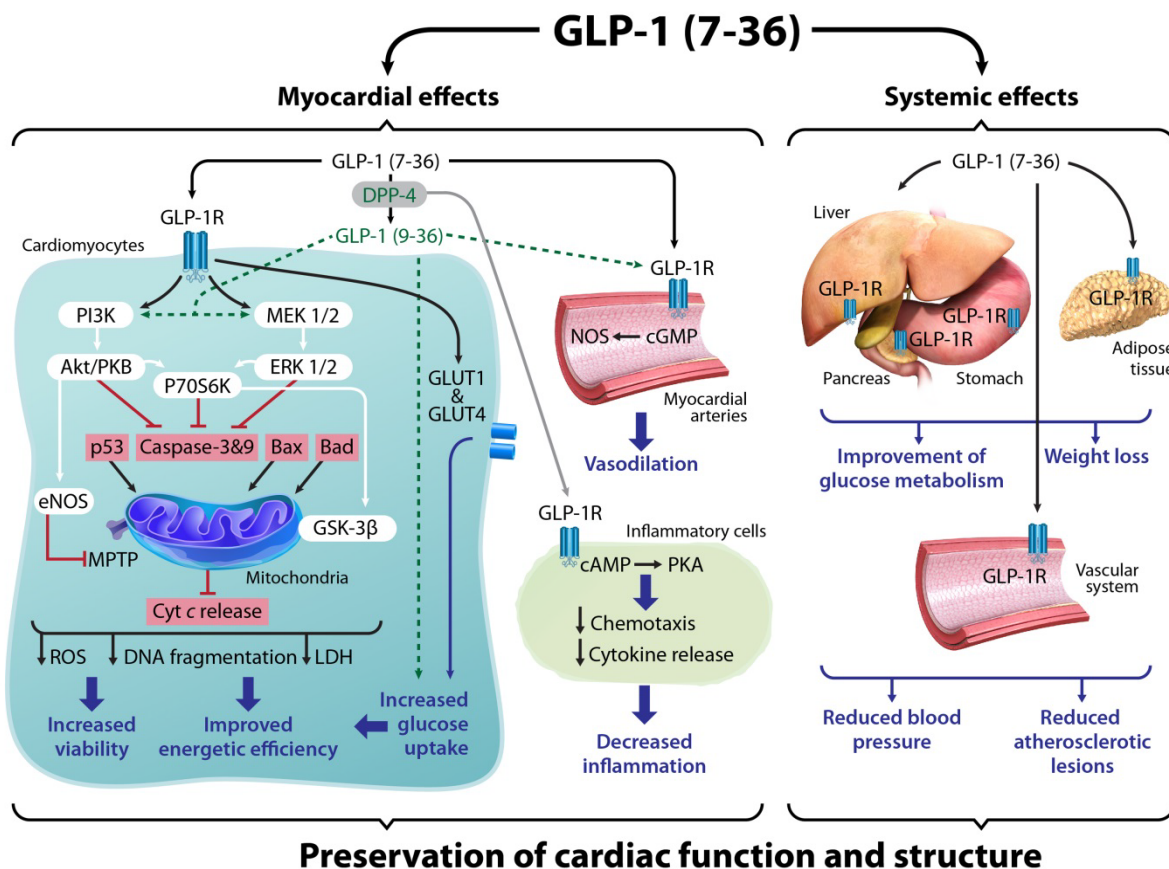
Figure 1: Schematic representation of the proposed pathways by which GLP-1 may exert its cardiovascular actions. The combination of GLP-1 effects on the myocardium (ie, apoptosis and necrosis prevention in cardiomyocytes through the activation of the RISK pathway, increased glucose metabolism, vasodilatory and anti-inflammatory actions) with GLP-1 metabolic and vascular effects at the systemic level contributes to cardiac survival and function improvement. cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; Cyt c: cytochrome c; DPP-4: dipeptidyl peptidase-4; ERK: extracellular signal-regulated kinase; GLP-1: glucagon-like peptide-1; GLP-1R: GLP-1 receptor; GLUT: glucose transporter; GSK: glycogen synthase kinase; LDH: lactate dehydrogenase; MEK1/2: MAP kinase; MPTP: mitochondrial permeability transition pore; NOS: nitric oxide synthase; PI3K: phosphatidylinositol 3-kinase; PKA: protein kinase A; PKB: protein kinase B; ROS: reactive oxygen species. Reprinted with permission from Ravassa et al. Cardiovasc Res. 2012;94(2): 316–323 [37].
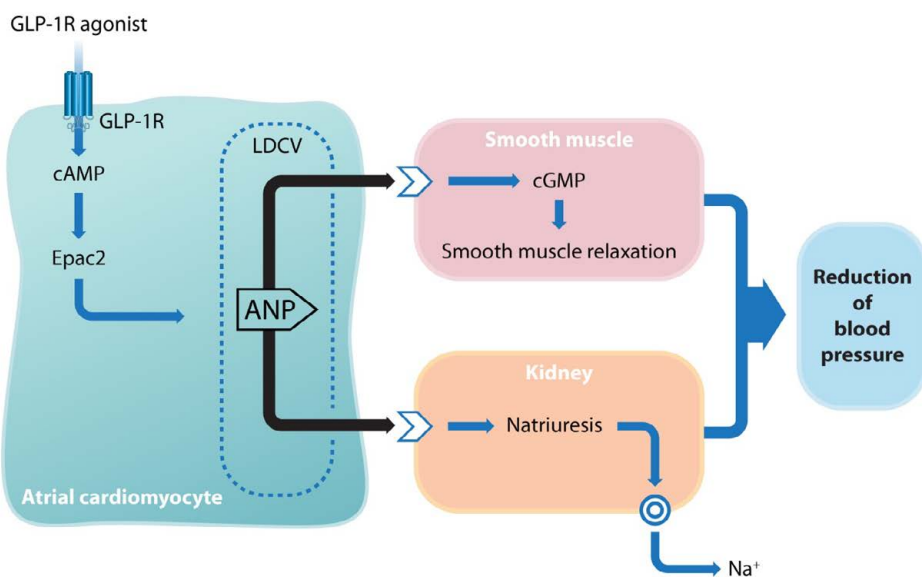

Figure 2: Mechanism of action for GLP-1 regulation of blood pressure. Reprinted with permission from Kim et al. Nat Med. 2013;19 (5):567–575 [41].

Study	Design	Heart rate	SBP	DBP
DURATION trials of exenatide				
Drucker 2008 (DURATION-1) [43]	30-week study, monotherapy or adjunct to oral agents	Not reported	Exenatide QW: –4.7 mmHg Exenatide BID: –3.4 mmHg	Exenatide QW: –1.7 mmHg Exenatide BID: –1.7 mmHg
Buse 2010 (DURATION-1 extension) [51]	22-week extension of DURATION-1 study (52 weeks total), monotherapy or adjunct to oral agents; after initial 30 weeks, switch from exenatide BID to QW or continued exenatide QW	Not reported	Exenatide QW: –6.2 mmHg (p<0.05 vs. baseline) Exenatide BID→QW: –3.8 mmHg	Exenatide QW: –2.8 mmHg Exenatide BID→QW: –1.8 mmHg
MacConell 2013 (DURATION-1 extension) [52]	Extension of DURATION-1 study to 3 years (reported for completer population); all patients receiving exenatide QW after initial 30 weeks	Not reported	–2.14 mmHg	–2.0 mmHg (p<0.05 vs. baseline)
Bergenstal 2010 (DURATION-2) [44]	26-week study, adjunct to metformin	Not reported	Improvements in patients receiving exenatide QW and pioglitazone (exenatide QW p=0.0055 vs. sitagliptin)	Changes did not differ significantly between groups
Diamant 2010 (DURATION-3) [45]	26-week study, adjunct to oral agents	Exenatide QW: +4.0 bpm (p<0.05 vs. baseline) Insulin glargine: 0 bpm	Exenatide QW: –3.0 mmHg (p<0.05 vs baseline) Insulin glargine: –1.0 mmHg	Exenatide QW: –1.0 mmHg Insulin glargine: –1.0 mmHg
Diamant 2012 (DURATION-3 extension) [49]	84-week study, adjunct to oral agents	Exenatide QW: +1.97 bpm (p<0.05 vs. baseline) Insulin glargine: –0.79 bpm	Exenatide QW: –4.2 mmHg (p<0.05 vs. baseline) Insulin glargine: –0.8 mmHg	Exenatide QW: –1.5 mmHg (p<0.05 vs baseline) Insulin glargine: –1.4 mmHg (p<0.05 vs. baseline)
Diamant 2014 (DURATION-3 extension) [50]	156-week study, adjunct to oral agents	Exenatide QW: +2 bpm Insulin glargine: –1 bpm	Exenatide QW: –2 mmHg Insulin glargine: +2 mmHg	Exenatide QW: –2 mmHg Insulin glargine: –2 mmHg
Russell-Jones 2012 (DURATION-4) [48]	26-week study, monotherapy	Exenatide QW: +1.5 bpm Metformin: +0.3 bpm Sitaglipin: +0.5 bpm Pioglitazone: –1.7 bpm	Exenatide QW: –1.3 mmHg Pioglitazone: –1.7 mmHg Sitagliptin: –1.8 mmHg	Pioglitazone: –2.5 mmHg
Blevins 2011 (DURATION-5) [47]	24-week study, monotherapy or adjunct to oral agents	Exenatide QW: +4.1 bpm (p<0.05 vs. baseline) Exenatide BID: +2.1 bpm (p<0.05 vs. baseline)	Exenatide QW: –2.9 mmHg (p<0.05 vs. baseline) Exenatide BID: –1.2 mmHg	Exenatide QW: +0.2 mmHg Exenatide BID: –0.1 mmHg
Buse 2013 (DURATION-6) [46]	26-week study, adjunct to oral agents	Not reported	Exenatide QW: –2.48 mmHg (p<0.05 vs. baseline) Liraglutide QD: –3.45 mmHg (p<0.05 vs. baseline)	Exenatide QW: –0.49 mmHg Liraglutide QD: –0.51 mmHg
LEAD studies of liraglutide				
Marre 2009 (LEAD-1 SU) [58]	26-week study, adjunct to sulfonylurea	Liraglutide (3 doses): +2–4 bpm (all 3 doses p ≤ 0.002 vs. placebo; 1.8 or 1.2 mg p<0.01 vs rosiglitazone) Rosiglitazone: +1 bpm Placebo: –1 bpm	Liraglutide (2 doses): –2.6 to –2.8 mmHg Rosiglitazone/placebo: –0.9 to –2.3 mmHg	Across the 4 arms: –0.7 to –1.4 mmHg
Nauck 2009 (LEAD-2) [59]	26-week study, adjunct to metformin	Liraglutide (3 doses): +2–3 bpm (0.6 mg p=0.012, 1.2 mg p=0.024 vs. glimepiride) Glimepiride: +1 bpm Placebo: +1 bpm	Liraglutide 0.6 mg: –0.6 mmHg Liraglutide 1.2 mg: –2.8 mmHg (p=0.0128 vs. glimepiride) Liraglutide 1.8 mg: –2.3 mmHg (p=0.0467 vs. glimepiride) Glimepiride: +0.4 mmHg Placebo: –1.8 mmHg	Specific data not reported (qualitatively, there was no apparent change in DBP from baseline in any group)
Garber 2009 (LEAD-3 [Mono]) [57]	52-week study, monotherapy	Liraglutide 1.2 mg: +3.2 bpm (p=0.0027 vs. glimepiride) Liraglutide 1.8 mg: +1.6 bpm Glimepiride: +0.4 bpm	Liraglutide 1.2 mg: –2.1 mmHg Liraglutide 1.8 mg: –3.6 mmHg (p<0.0118 vs. glimepiride) Glimepiride: –0.7 mmHg	Specific data not reported (qualitatively, all groups had slight, nonsignificant DBP reductions)
Garber 2011 (LEAD-3 [Mono]) [56]	1-year extension of LEAD-3, monotherapy	Liraglutide 1.2 mg: +2.04 bpm Liraglutide 1.8 mg: +0.92 bpm Glimepiride: +0.67 bpm	Liraglutide 1.2 mg: –1.35 mmHg Liraglutide 1.8 mg: –2.37 mmHg Glimepiride 8 mg: –0.49 mmHg	Liraglutide 1.2 mg: –0.58 mmHg Liraglutide 1.8 mg: –0.81 mmHg Glimepiride 8 mg: –0.44 mmHg
Russell-Jones 2009 (LEAD-5 [met+SU]) [60]	26-week study, adjunct metformin and glimepiride	Liraglutide 1.8 mg: +2.62 bpm (p=0.0006 vs. insulin glargine) Insulin glargine: +0.08 bpm Placebo: +0.93 bpm	Liraglutide 1.8 mg: –4.0 mmHg (p=0.0001 vs. insulin glargine) Insulin glargine: +0.54 mmHg Placebo: –1.4 mmHg	Specific data not reported; no significant difference in reductions between treatment groups

| Buse 2009 (LEAD-6) [55] | 26-week study, adjunct to oral agents | Liraglutide: +3.28 bpm (p=0.0012 vs. exenatide) Exenatide: +0.69 bpm | Liraglutide: –2.51 mmHg Exenatide: –2.00 mmHg | Liraglutide: –1.05 mmHg Exenatide: –1.98 mmHg |
| Buse 2010 (LEAD-6) [54] | 14-week extension of LEAD-6, switch from exenatide BID to liraglutide 1.8 mg QD or continued liraglutide | Not reported | Exenatide→Liraglutide: –3.8 mmHg (p<0.0001 vs. Week 26) Liraglutide: –2.2 mmHg (p=0.0128 vs. Week 26) | Specific data not reported; no significant changes observed in either treatment group |

BID: twice daily; bpm: beats per minute; DBP: diastolic blood pressure; DURATION: Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly; LEAD: Liraglutide Effect and Action in Diabetes; QD: once daily; QW: once weekly; SBP: systolic blood pressure.

Table 1: Blood Pressure and Heart Rate Data from DURATION Trials of Exenatide and LEAD Trials of Liraglutide.

ranging from –1.3 to –6.2 mmHg in the DURATION trials of exenatide and from –0.6 to –4.0 mmHg in the LEAD trials of liraglutide. DBP reductions have also been observed, but these have been smaller and typically consistent with the observed reductions in the comparator groups; changes range from +0.2 to –2.8 mmHg with exenatide QW and from –0.6 to –1.1 mmHg with liraglutide. Other randomized studies of exenatide twice daily and once weekly [61-65] have yielded similar findings, with significant SBP reductions ranging from –3 to –9 mmHg and smaller (and significant in some but not all cases) DBP reductions of –0.4 to –3 mmHg. In a randomized comparison of liraglutide versus sitagliptin, SBP/DBP changes were –0.55/–0.71 mmHg with liraglutide 1.2 mg and –0.72/+0.07 mmHg with liraglutide 1.8 mg after 26 weeks and –0.37/–0.53 mmHg and –2.55/–0.87 mmHg, respectively, after 1 year; these changes did not represent significant benefits over the comparator sitagliptin [66,67]. Similar 52-week SBP reductions were seen for dulaglutide once weekly in the Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes (AWARD)-3 study (dulaglutide 1.5 mg, –0.1 mmHg; dulaglutide 0.75 mg, –2.7 mmHg; metformin, –1.0 mmHg) [68] and the AWARD-5 trial (dulaglutide 1.5 mg, –0.8 mmHg; dulaglutide 0.75 mg, –0.5 mmHg; sitagliptin, –0.5 mmHg) [69]. The AWARD-1 trial showed no benefit in terms of 52-week SBP and DBP results for dulaglutide once weekly [70]. The AWARD-6 open-label non-inferiority study showed that once-weekly dulaglutide and once-daily liraglutide had similar reductions in SBP/DBP of –3.36/–0.22 mmHg and –2.82/–0.31 mmHg, respectively, over 26 weeks [71].

Albiglutide once weekly added to background metformin was associated with reductions in SBP and DBP (–1.0 mmHg and –0.7 mmHg, respectively) in the HARMONY 3 study, with small increases observed in the placebo, sitagliptin, and glimepiride arms [72]. In HARMONY 7, which evaluated albiglutide once weekly versus liraglutide once daily in patients with inadequate control from oral anti-glycemic agents, SBP and DBP changes did not exceed 1 mmHg in either treatment group [73]. In the 1-year HARMONY-4 study, patients with type 2 diabetes uncontrolled on metformin were randomized to albiglutide 30 mg once weekly or insulin glargine [74]. Mean SBP decreased in the albiglutide group (–1.4 mmHg) and increased slightly in the insulin group (0.3 mmHg) and DBP decreased slightly in both groups (–0.8 mmHg and –1.8 mmHg, respectively) [74].

Heart rate data were reported for some of the DURATION [47-50] studies of exenatide once weekly and LEAD [56-58,60] studies of liraglutide, which revealed numerical increases in heart rate versus some of the comparator agents (Table 1). In a randomized comparison against sitagliptin, at 26 weeks both liraglutide 1.2 mg and 1.8 mg were associated with significant mean increases from baseline of 2.32 beats per minute (bpm; p=0.0002) and 3.94 bpm (p<0.0001), respectively, compared with the –0.64 bpm reduction in the sitagliptin group [66]. In AWARD-5, heart rate increases at 52 weeks were significantly higher

(p<0.0001) with dulaglutide 1.5 mg (2.4 bpm) and with dulaglutide 0.75 mg (2.1 bpm) than the –0.3 bpm reduction with sitagliptin [69]. In AWARD-1 and AWARD-3, heart rate increases ranged from 2.1 to 2.8 bpm after 26 weeks of treatment across dulaglutide doses and were lower after 52 weeks of treatment (1.6 to 1.8 bpm); increases of 1.2 bpm for once-weekly exenatide (AWARD-1) and 1.1 bpm for metformin (AWARD-3) were observed after 52 weeks [68,70]. In AWARD-6, heart rate increases of 2.37 bpm and 3.12 bpm were observed for dulaglutide and liraglutide, respectively, with no significant difference between groups [71]. In a Japanese 12-week phase 2 dose-response study, small, but significant increases (p<0.005) in heart rate were observed with dulaglutide 0.25 mg (+1.4 bpm), 0.5 mg (+1.56 bpm), and 0.75 mg (+1.32 bpm) versus a decrease with placebo (–3.44 bpm), but increases were not dose-dependent [75].

In HARMONY 3 and HARMONY 7, and HARMONY 4, heart rate increased by approximately 1 bpm with albiglutide, compared with 2 bpm and 3 bpm increases with placebo (HARMONY 3; 104 weeks) and liraglutide (HARMONY 7; 32 weeks), respectively [72,73], and no increase with insulin glargine (HARMONY 4; 52 weeks)[74]. Both GetGoal-X and GetGoal-S trials showed that heart rate changes were limited to increases or reductions of 0.1 bpm for lixisenatide as well as for the respective comparators exenatide twice daily and placebo [76,77]. In GetGoal-M-Asia, heart rate increased by 0.7 bpm with lixisenatide, but remained unchanged with placebo [78].
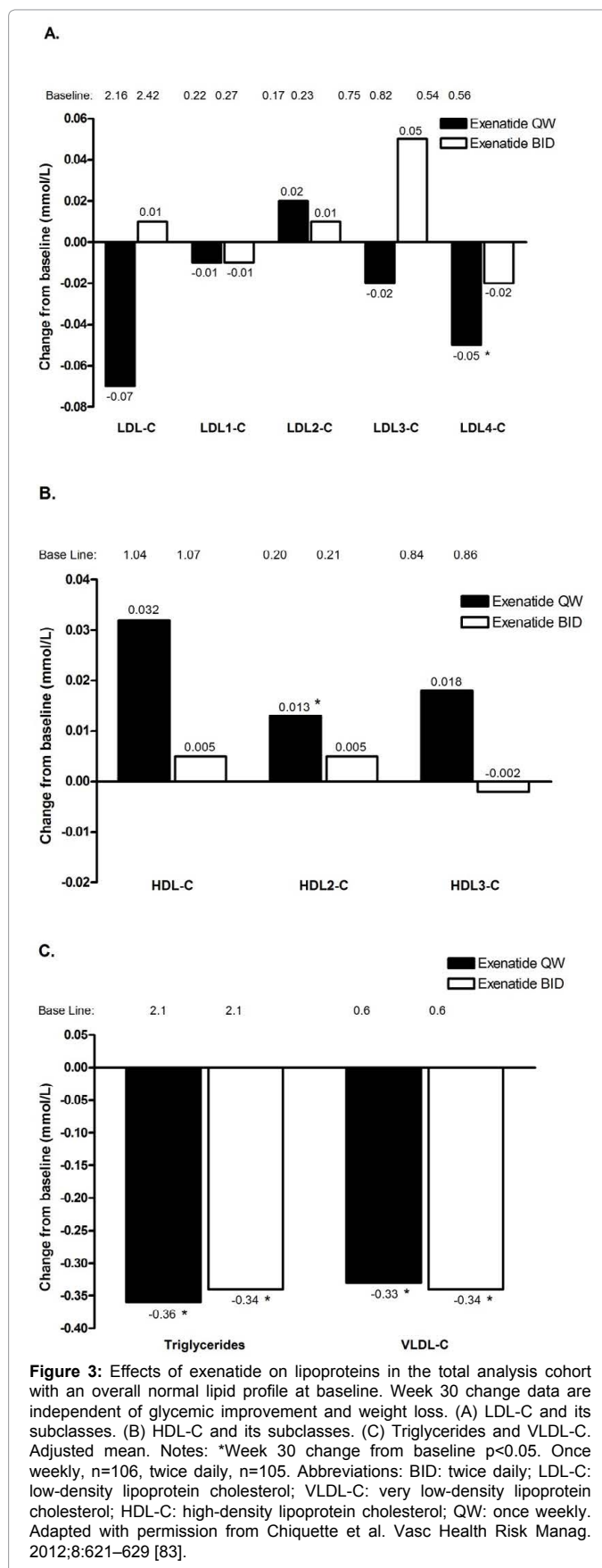
Data showing effects on BP also are available from several retrospective/post hoc combined analyses of clinical trials. In a post hoc analysis of BP-lowering effects from 6 trials of once-weekly or twice-daily exenatide versus placebo or insulin, the 6-month pooled data showed that exenatide recipients achieved SBP reductions that were significantly greater than those observed with placebo (least squares [LS] mean –2.2 vs. +0.6 mmHg; p=0.0002) or insulin (LS mean –4.5 vs. –0.9 mmHg; p<0.0001) [79]. No significant differences were observed with respect to DBP reductions from baseline, which for exenatide were –0.7 mmHg and –1.6 mmHg in the comparisons against placebo and insulin, respectively (corresponding reductions for placebo and exenatide were –0.2 and –0.8 mmHg, respectively). Exenatide-associated SBP reductions were most pronounced among patients with elevated SBP at baseline. Within this same report, analysis of treatment effects by baseline BP showed that the largest between-group differences between exenatide and the comparators were in patients with baseline SBP ≥150 mmHg. More recently, in a retrospective analysis of BP and Low-Density Lipoprotein (LDL) cholesterol from three trials of exenatide once weekly versus oral glucose-lowering medications or insulin glargine, the proportions of patients reaching goal SBP <130 mmHg were highest among the exenatide recipients [80]. Most notably, in the DURATION-2 trial, 56.9% of exenatide recipients achieved goal SBP versus 34.8% and 39.1% of sitagliptin and pioglitazone recipients, respectively. The differences in the proportions

of patients attaining a SBP goal were smaller in the other 2 trials, with a rate of 25.3% for exenatide versus 21.3% with insulin glargine in DURATION-3 and a rate of 39.7% with exenatide versus 25.0%, 31.2%, and 32.2% with metformin, sitagliptin, and pioglitazone, respectively. Recently, an analysis of 6 randomized controlled trials of liraglutide was conducted, showing that SBP reductions achieved with liraglutide after 26 weeks were significantly greater than those observed with placebo (mean –2.7 mmHg for 1.2 mg and –2.9 mmHg for 1.8 mg vs. –0.5 mmHg; p=0.0029 and p=0.0004, respectively) [81]. Reductions in SBP also were significantly greater for liraglutide (either dose) versus glimepiride and specifically for the 1.8-mg dose versus insulin glargine or rosiglitazone; only liraglutide 1.8 mg was compared with exenatide twice daily, for which there were no differences in SBP reduction. At week 26, liraglutide recipients had heart rate values that were significantly higher compared with baseline and those in the placebo group, with placebo-adjusted changes of 2.33 bpm for liraglutide 1.2 mg and 2.57 bpm for liraglutide 1.8 mg (both p<0.0001).

Data from a post hoc analysis of heart rate and Major Adverse Cardiac Events (MACE) from 11 studies comparing exenatide once weekly with an active comparator (ie, exenatide twice daily, insulin, liraglutide, metformin, pioglitazone, sitagliptin) or placebo demonstrated that heart rate variability was observed for all treatments over time; mean increases in heart rate were small and transient, and increases were not prevalent after 10 weeks [82]. In addition, most of those who experienced an increased heart rate had among the lowest baseline heart rates, such that heart rate increases were negatively correlated with baseline heart rate. No associations were observed between MACE and small mean increased heart rate, although further study is needed.

Lipids

Lipid data derived from the DURATION studies of exenatide once weekly support improvements in several parameters [43-46,83]. In a post hoc analysis of DURATION-1, a 30-week course of exenatide once weekly was associated with significant reductions from baseline in triglycerides, apolipoprotein B (–0.036%), apolipoprotein B–to–A1 ratio (–3.1%), LDL4, and very low-density lipoprotein (VLDL) (all p<0.05; Figure 3), in conjunction with a significant increase in high-density lipoprotein 2 (HDL2) (p<0.05; Figure 3). With exenatide twice daily, significant reductions were limited to triglycerides and VLDL (p<0.05; Figure 3) [83]. In DURATION-2, significant improvements in HDL from baseline were observed, albeit significantly lower than that observed with pioglitazone [44]. In DURATION-5, significant reductions were observed in mean fasting total cholesterol and LDL with exenatide once weekly; however, no significant changes in lipid parameters were observed with exenatide twice daily [47]. In DURATION-6, changes in the lipid profile were more pronounced with liraglutide versus exenatide once weekly with respect to total cholesterol, non-HDL, and LDL, with a rise in HDL of +0.02 mmol/L in both treatment groups [46]. In the LEAD-6 study, liraglutide and exenatide twice daily were associated with similar reductions in total cholesterol and LDL and increases in HDL; however, changes in VLDL, triglycerides, and free fatty acids significantly favored the liraglutide group [55]. In addition to the DURATION and LEAD studies, data derived from a number of other randomized studies of exenatide once weekly or twice daily [61,62,64,84,85], liraglutide [66,67,86], and dulaglutide [69,70] lend further support to the ability of these agents to improve some lipid profile components among patients with type 2 diabetes. Meaningful improvements in lipid parameters

Figure 3: Effects of exenatide on lipoproteins in the total analysis cohort with an overall normal lipid profile at baseline. Week 30 change data are independent of glycemic improvement and weight loss. (A) LDL-C and its subclasses. (B) HDL-C and its subclasses. (C) Triglycerides and VLDL-C. Adjusted mean. Notes: *Week 30 change from baseline p<0.05. Once weekly, n=106, twice daily, n=105. Abbreviations: BID: twice daily; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; QW: once weekly. Adapted with permission from Chiquette et al. Vasc Health Risk Manag. 2012;8:621–629 [83].

were not observed with albiglutide in HARMONY 3 or HARMONY 7 [72,73], or lixisenatide in GetGoal-S [76]. In the HARMONY-4 study, similar small reductions in LDL-cholesterol, total cholesterol, and triglycerides, and a small increase in HDL-cholesterol were observed with albiglutide added to insulin and in the standard insulin therapy group [74]. In the aforementioned retrospective analysis of three trials of exenatide once weekly versus oral glucose-lowering medications or insulin glargine, exenatide was associated with a somewhat increased propensity for achieving an LDL cholesterol level <100 mg/dL compared with sitagliptin and pioglitazone (20.2% vs. 13.8% and 13.0%, respectively, in DURATION-4; 29.8% vs. 21.6% and 19.4%, respectively, in DURATION-2) but not when exenatide was compared with metformin (20.2% vs. 23.1% in DURATION-4) [80]. In the Japanese dose-response study, two patients receiving dulaglutide 0.25 mg/week had elevated triglycerides [75].

Corrected QT interval effects

The effects of GLP-1RAs on the corrected QT interval have been examined in healthy subjects in randomized, placebo-controlled studies, which identified no evidence of clinically relevant prolongation for subjects receiving daily (subcutaneously or via infusion to reach steady state) exenatide [87,88], liraglutide [89], or albiglutide [90].

Reducing damage after MI

Exenatide (given via infusion, dosed to a prespecified target plasma concentration) was recently shown, for the first time, to increase myocardial salvage in patients with ST-segment–elevation MI (STEMI) undergoing primary percutaneous coronary intervention (pPCI) [91]. In this study of 172 patients in this setting, there were significant differences favoring exenatide versus placebo with respect to the primary end point of acute phase salvage index (0.71 vs. 0.62; p=0.003) as well as Day 90 final infarct size/myocardial area at risk ratio (0.30 vs. 0.39 g; p=0.003). Results of another randomized placebo-controlled trial of intravenous exenatide, administered prior to PCI, in 210 patients presenting with ST-segment elevation have since been published [92]. The results described the association between hyperglycemia and infarct size (related to myocardial area at risk, but not myocardial salvage), as well as the ability of intravenous exenatide to increase the salvage index, which was numerically greater in the setting of normoglycemia (0.68 vs. 0.62; p=0.08) and significant for hyperglycemia (0.73 vs. 0.64; p=0.017). Also recently, in a smaller study of 58 patients, adjunctive exenatide therapy (five subcutaneous doses over 3 days, with an initial bolus dose with the first subcutaneous dose (given before the onset of reperfusion)) with pPCI was shown to reduce infarct size while also improving subclinical LV function in patients with STEMI [93].

Circulating biomarker data

In the DURATION-3 trial of exenatide once weekly versus insulin glargine, a significant reduction from baseline in high-sensitivity C-reactive protein (hsCRP) was observed with exenatide (−2.0 mg/L; p<0.05) but not insulin glargine (−0.8 mg/L), for a mean treatment difference of −1.2 (95% confidence interval (CI), −2.8 to 0.3) [45]. Subsequently, in DURATION-6, hsCRP was reduced by −2.19 nmol/L in patients treated with exenatide once weekly versus a 0.29 nmol/L increase in patients treated with liraglutide, for a LS mean treatment difference of −2.48 (95% CI, −14.83 to 9.43) [46]. Conversely, reduction in B-type (brain) natriuretic peptide (BNP) was more pronounced with liraglutide versus exenatide once weekly (−7.32 vs −4.45 ng/L; LS mean treatment difference of 2.87; 95% CI, −0.76 to 6.51). In the

DURATION-2 trial of exenatide once weekly versus sitagliptin and pioglitazone, treatment with exenatide once weekly was associated with significant improvements in BNP, albumin to creatinine ratio, hsCRP, and adiponectin; BNP was improved significantly more than sitagliptin or pioglitazone [44]. Biomarker data from several other randomized trials of exenatide twice daily [94,95] and liraglutide [86,96] collectively support favorable effects on hsCRP and/or BNP. The most detailed report of cardiovascular risk biomarker data is based on a randomized trial in which exenatide twice daily was as effective as insulin glargine in improving glycemic control [94,97]. After 1 year of treatment, exenatide was shown to not only reduce total and trunk fat mass, body weight, and waist circumference, but also improve circulating levels of hsCRP, total adiponectin, and leptin [94]. Moreover, changes in these circulating biomarkers appeared to be independent of the observed reductions in fat mass.

Noteworthy cardiovascular adverse events

The most common adverse events reported in randomized studies of exenatide once weekly or twice daily or liraglutide were gastrointestinal, although cardiovascular events were also observed, as expected in this patient population. In the DURATION-2 study of exenatide once weekly versus sitagliptin or pioglitazone, serious adverse events included coronary artery occlusion in two patients (both in the pioglitazone group), and cerebrovascular accident in 2 patients (one in the sitagliptin group and one in the pioglitazone group) [44]. No other noteworthy cardiovascular adverse events were reported in that study. In the analysis of patients who had switched from exenatide twice daily to liraglutide once daily in the LEAD-6 study of liraglutide, serious adverse events included single reports of cardiac failure and MI in those who switched and single reports of cerebral infarction, cerebrovascular accident, transient ischemic attack, acute coronary syndrome and coronary artery occlusion in those who continued liraglutide [54]. In AWARD-1, a recipient of dulaglutide 1.5 mg had a fatal MI during the study [70]. In AWARD-6, one cardiovascular event of myocardial infarction occurred in a patient receiving liraglutide [71].

Results of a pooled analysis of 3,945 patients who participated across 12 randomized trials of exenatide twice daily versus placebo or insulin found no increased risk of MACE with exenatide and the possibility of an improved cardiovascular safety profile versus the comparator arms, with a primary MACE relative risk of 0.7 (95% CI, 0.38–1.31) [98].

Managing Modifiable Risk Factors to Reduce Cardiovascular Risk

Managing multiple risk factors in patients with type 2 diabetes is an important treatment strategy to reduce the risk of cardiovascular, as well as microvascular, events. Results from the STENO-2 trial demonstrated that intensive, targeted, long-term (7.8 years), multifactorial intervention to manage modifiable risk factors (ie, hyperglycemia, hypertension, dyslipidemia, and microalbuminuria) in patients with type 2 diabetes and microalbuminuria significantly improved patient outcomes versus conventional therapy [4]. Compared with conventional therapy, patients in the intensive therapy group (stepwise diet/behavioral modification and pharmacologic therapy to achieve targets) had a significantly lower risk of cardiovascular disease (hazard ratio, 0.47; 95% CI, 0.24–0.73), retinopathy (hazard ratio, 0.42; 95% CI, 0.21–0.86), nephropathy (hazard ratio, 0.39; 95% CI, 0.17–0.87), and autonomic neuropathy (hazard ratio, 0.37; 95% CI, 0.18–0.79). Patients from the STENO-2 study were then followed for

5.5 years in a subsequent study to determine the effect of the intensive therapy regimen on mortality [99]. The follow-up results demonstrated that after a mean study time of 13.3 years the beneficial effects of the intensive versus the conventional regimen were sustained: overall mortality was significantly reduced (hazard ratio, 0.54; 95% CI, 0.32–0.89; p=0.02) and there was a lower risk of death due to cardiovascular causes (hazard ratio, 0.43; 95% CI, 0.19–0.94; p=0.04) and a lower risk of cardiovascular events (hazard ratio, 0.41; 95% CI, 0.25–0.67; p<0.001).

The importance of aggressive pharmacologic therapy also was demonstrated in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [100]. The primary objective of the COURAGE trial was to assess whether PCI plus lifestyle intervention/intensive pharmacologic therapy (ie, medical therapy) was superior to medical therapy without PCI in reducing the risk of cardiovascular events in patients with myocardial ischemia and significant coronary artery disease. Patients were followed for 2.5 to 7.0 years (median 4.6 years) and results showed that as in initial management strategy, PCI plus medical therapy did not significantly reduce the composite end point of death and non-fatal MI (p=0.62); composite endpoint of death, MI, and stroke (p=0.62); or the end points hospitalization for acute coronary syndrome (p=0.56), death (p=0.38), total non-fatal MI (p=0.33), or stroke (p=0.19) versus medical therapy alone. Data from COURAGE showed that lifestyle intervention with intensive medical therapy to achieve aggressive targets was safe and effective in mitigating clinical events. Although COURAGE was not designed to be a diabetes study, 34% of the patient population had diabetes.

Anticipated Cardiovascular Data from Ongoing Phase 3 Trials

A number of clinical investigations of exenatide, liraglutide, dulaglutide, and lixisenatide are in progress, for which forthcoming results will provide further insight into the potential of GLP-1RAs as cardioprotective agents (Table 2). In one trial (NCT01373216), a 72-hour infusion of exenatide is being tested for its ability to improve glucose control and cardiac function among patients with type 2 diabetes, coronary atherosclerosis, and LV dysfunction who are undergoing coronary artery bypass grafting; primary outcomes are effects on cardiac function, including cardiac chamber dimensions, LV systolic function, LV diastolic function, and right ventricular systolic function. The Effect of additional treatment with EXenatide in patients with an Acute Myocardial Infarction (EXAMI) trial (NCT01254123) [101,102] is a pilot study assessing the safety and efficacy of exenatide infusion compared with placebo in patients with an acute MI undergoing pPCI. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial (NCT01144338) is a placebo-controlled phase 4 trial examining exenatide once weekly for improving cardiovascular outcomes in patients with type 2 diabetes. The primary outcome is time to first confirmed cardiovascular event in the primary composite cardiovascular endpoint.

Liraglutide is being examined for improving cardiometabolic risk markers in patients with type 2 diabetes, with a primary outcome measure of change in carotid intima-media thickness (NCT01715428). The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial (NCT01179048) is a long-term (60 months) international study designed to determine the effect of liraglutide on cardiovascular events in patients with type 2 diabetes. The primary outcome is the time from randomization to the first occurrence of the composite cardiovascular outcome of cardiovascular death, non-fatal MI, or non-fatal stroke. Liraglutide is also being investigated in the ongoing 6-month randomized AddHope2 study (NCT01595789) in patients with newly diagnosed type 2 diabetes and coronary artery disease. The study will investigate the effect of adding liraglutide to metformin on glucose metabolic and cardiovascular end points including BP, heart rate, and left-ventricular ejection fraction (LVEF) over 12 weeks [103]. In the ongoing 24-week randomized controlled LIVE study (effect of LIraglutide on left VEntricular function; NCT01472640), 240 patients with chronic heart failure (LVEF ≤45%) with and without type 2 diabetes will be randomized to liraglutide 1.8 mg once daily or placebo [104]. The primary end point will be the effect of liraglutide on left ventricular systolic function (change in LVEF assessed using three-dimensional contrast echocardiography) versus placebo. Secondary end points will include left ventricular diastolic function, functional capacity (6-minute walk test), BNP levels, BP, heart rate, weight loss, total body composition, ECG, and quality of life evaluation [104].

In the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial (NCT01394952), dulaglutide is being examined versus placebo to determine the time to first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke. Lixisenatide is being compared with placebo in patients with type 2 diabetes who recently experienced an acute coronary event in the Evaluation of Lixisenatide in acute coronary syndrome (ELIXA) trial (NCT01147250). The primary outcome is the time to first occurrence of the primary cardiovascular event (cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina).

Key Outstanding Questions and PrioritiesfFor Future Research

Results of the prospective outcome trials of the GLP-1RAs described herein are awaited to determine the extent to which the findings are supportive of published research from preclinical series. Additionally, further basic research efforts are needed to more fully characterize the mechanisms by which the GLP-1RAs exert cardioprotective benefit, and also to determine if there are any noteworthy differences between individual agents in this regard. Moreover, additional studies will help to determine if the cardiovascular safety profile of GLP1-RAs is appropriate for use in at-risk populations and define in which populations GLP1-RAs might improve cardiovascular outcomes.

Summary

The GLP-1RAs are providing the opportunity for concurrent glycemic control and reduction of specific cardiovascular risk factors, such as hypertension and hyperlipidemia, in patients with type 2 diabetes. Most of the available randomized clinical trial cardiovascular data are in support of BP- and lipid-lowering effects, but favorable findings are accumulating regarding protection from MI-induced damage and circulating improvements in levels of the cardiovascular biomarkers hsCRP and BNP. An association between increased heart rate and adverse events has not been observed. Data from ongoing phase 3 trials of exenatide, liraglutide, dulaglutide, and lixisenatide, and a phase 4 trial of exenatide are awaited, to more fully characterize the cardioprotective effects of the GLP-1RAs. The effects of GLP-1RAs on proteomics and microRNAs are undergoing extensive investigation to ascertain their effect on myocardial protection in patients with or without diabetes by improving prosurvival kinases.

Study	Study arms	Population	Primary outcome	Estimated study completion
NCT01373216	Exenatide vs. no intervention	38 patients with type 2 diabetes undergoing elective aortocoronary bypass	Cardiac function – echocardiographic parameters	April 2014
NCT01254123 (EXAMI) [101,102]	Exenatide vs. placebo	40 patients with first acute myocardial infarction undergoing primary PCI	Safety	Unknown
NCT01144338 (EXSCEL)	Exenatide vs. placebo	14,000 patients with type 2 diabetes	Time to composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	April 2018
NCT01715428	Liraglutide	300 patients with type 2 diabetes	Carotid intima-media thickness	December 2015
NCT01179048 (LEADER)	Liraglutide vs. placebo	9,340 patients with type 2 diabetes	Time to composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	October 2015
NCT01595789 (AddHope2) [103]	Liraglutide vs. placebo	40 patients with coronary artery disease and newly diagnosed type 2 diabetes	Beta-cell function and left ventricular ejection fraction after 12 weeks	October 2015
NCT01472640 (LIVE) [104]	Liraglutide vs. placebo	240 patients with chronic heart failure with and without diabetes	Change in left ventricular function	December 2014
NCT01394952 (REWIND)	Dulaglutide vs. placebo	9,622 patients with type 2 diabetes	Time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	April 2019
NCT01147250 (ELIXA)	Lixisenatide vs. placebo	6,000 patients with type 2 diabetes who recently experienced an acute coronary syndrome event	Time to first occurrence of the primary cardiovascular event	January 2015

ELIXA, Evaluation of Lixasenatide in Acute Coronary Syndrome; EXAMI, Effect of Additional Treatment With EXenatide in Patients With an Acute Myocardial Infarction; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1: glucagon-like peptide-1; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PCI, percutaneous coronary intervention; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes

Table 2: Ongoing Trials of the Cardioprotective Effects of the GLP-1 Receptor Agonists.

Acknowledgements

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