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Cardiovascular Effects of Anti-Diabetic Agents: Focus on Blood Pressure Effects of Incretin-Based Therapies

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Abstract

Hyperglycemia is associated with increased risk of cardiovascular disease. Nevertheless, results of large clinical trials suggest that tight glucose control does not reduce the risk of macrovascular cardiovascular events in type 2 diabetes mellitus and may cause harm. This may reflect the adverse consequences of increased hypoglycemia or the adverse effects of many anti-diabetic agents on weight gain. The consequences of intensive therapy may also depend on the mechanism of the anti-diabetic agent(s) used to achieve tight control. Metformin, an anti-diabetic agent that reduces weight and activates AMP-activated protein kinase, reduces risk of cardiovascular events in overweight diabetics. In contrast, the thiazolidinedione rosiglitazone increases cardiovascular risk. Sulfonylureas may increase the risk of cardiovascular events through effects on the SUR1 of the cardiac KATP channel. Stable analogues of glucagon-like peptide-1 reduce body weight and blood pressure, and have favorable effects on ischemia following reperfusion in animal models. The dipeptidyl peptidase IV inhibitors prevent the breakdown of GLP-1 and GIP, but also decrease the degradation of several vasoactive peptides. Dipeptidyl peptidase IV inhibitors have favorable effects in animal models of ischemia/reperfusion. They have been reported both to decrease and to increase blood pressure. Clinical trials will address the effect of the incretin-based agents on macrovascular cardiovascular events.

Keywords

glucose; diabetes; heart; glucagon-like peptide

Introduction

Eight per cent of Americans are affected by diabetes. Approximately 246 million adults have diabetes worldwide.(1) This number is expected to grow to 380 million by the year 2025.(1, 2) Diabetes is associated with a dramatically increased risk of heart attack, stroke, and renal failure, as well as disability.(3) Indeed the cost of diabetes-related health care was estimated to be \$232 billion in 2007. While many classes of drugs are now available for the

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treatment of diabetes, most glucose-lowering agents do not reduce the risk of cardiovascular events in type 2 diabetes mellitus (T2DM).

This paper will briefly review the effects of intensive glycemic control with older classes of anti-diabetic agents on the risk of cardiovascular events, in the context of the mechanisms of action of these agents. The author will discuss recent evidence regarding cardiovascular effects of the incretin-based anti-diabetic therapies, with particular focus on blood pressure effects.

Cardiovascular Effects of Intensive Glucose Control Using Older Oral Anti-Diabetic Agents

Population studies indicate that there is a linear relationship between hyperglycemia and cardiovascular mortality.(4) Long-term glucose control reduces cardiovascular mortality in type 1 diabetes.(5) Nevertheless, while the beneficial effect of lowering glucose with anti-diabetic agents on microvascular complications such as retinopathy and nephropathy has been proven,(6, 7) randomized clinical trials using sulfonylureas, thiazolidinediones, and insulin do not provide clear evidence for a beneficial effect of reducing glucose on macrovascular complications in type 2 diabetes.

In the United Kingdom Prospective Diabetes Study (UKPDS), reduction of hemoglobin (Hb) A_{1C} from 8 to 7% in non-overweight patients with type 2 diabetes did not reduce cardiovascular events;(8) long-term follow-up of the study participants suggests there be a beneficial “memory effect” of tight glucose control on cardiovascular risk, however.(9) The same phenomenon has been reported with long-term follow-up of patients with type 1 diabetes who participated in the Diabetes Control and Complications Trial (DCCT).(5) More recently, the Veterans Affairs Diabetes Trial (VADT) found no benefit of tight glucose control on the risk of cardiovascular events.(10) The Action in Diabetes and Vascular disease: PreterAx and DiabmicroN Modified Release Controlled Evaluation (ADVANCE) trial compared standard therapy of type 2 diabetes with intensive, gliclazide-based therapy. (11) Intensive control did not reduce the risk of cardiovascular events, but did reduce the incidence of microalbuminuria and nephropathy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared intensive glucose control versus standard therapy. (12) Although intensive glucose control reduced the incidence of non-fatal myocardial infarction, the study was stopped early due to an increase in overall mortality.

Increased risk of hypoglycemia may contribute to increased mortality in patients at risk for coronary artery disease.(11) In addition, treatment with sulfonylurea or insulin increases weight and negative effects on these agents on risk factors for cardiovascular could offset beneficial effects of glucose lowering. In the UKPDS, for instance, intensive treatment with glibenclamide (1.7 kg), chlorpropamide (2.6 kg), and insulin (4.0 kg) was associated with significant weight gain compared to conventional therapy.(8) In ACCORD, the mean weight gain in the intensive therapy group was 3.5 kg.(8)

Alternatively, adverse cardiovascular effects could derive from the specific mechanism of action of anti-diabetic agents used. In this regard, metformin stands alone among the oral anti-diabetic agents that have been shown to reduce cardiovascular mortality. In UKPDS, in a subset of overweight (>120% ideal body weight) patients, treatment with metformin reduced any diabetes-related endpoint (0.003), all-cause mortality (0.02) and stroke (0.03) compared to intensive therapy with chlorpropamide, glibenclamide, or insulin.(12) A meta-analysis of clinical trials using metformin suggested a favorable effect on cardiovascular risk compared to placebo.(13)

Metformin suppresses hepatic gluconeogenesis and increases glucose uptake. Until recently, these effects were presumed to be mediated by the activation of AMP-activated protein kinase (AMPK). A study in wild-type, AMPK-deficient, and liver kinase B1 (LKB1)-deficient hepatocytes indicates that LKB1 is involved in the control of basal hepatic glucose production, whereas metformin inhibits gluconeogenesis through LKB1- and AMPK-independent pathways.(14) Activation of AMPK likely contributes to the beneficial cardiovascular effects of metformin, though.(15) For example, activation of AMPK increases nitric oxide formation, triggers mitochondrial biogenesis, and down regulates cholesterol synthesis, fatty acid synthesis and the formation of reactive oxygen species.(16)

In contrast, sulfonylureas were associated with adverse cardiovascular outcomes as early as 1970. The University Group Diabetes Project (UGDP) randomization to tolbutamide was associated with increased cardiovascular mortality compared to treatment with either insulin or placebo.(17) Sulfonylureas increase insulin secretion by binding to the SUR1 subunit and promoting the closure of the K_{ATP} channel in pancreatic beta cells.(18) In contrast, agents that open cardiac K_{ATP} mimic ischemic preconditioning and protect the heart from ischemic injury. While sulfonylureas differ in their specificity for the beta cell versus cardiac K_{ATP} channel, sulfonylurea-induced closure of cardiac K_{ATP} channels could worsen myocardial injury. Epidemiologic studies have provided conflicting data regarding the effect of sulfonylureas on cardiovascular morbidity and mortality.(19, 20) In UKPDS, cardiovascular mortality was similar in patients randomized to chlorpropamide and insulin.(8) In the substudy of patients treated with metformin, however, the combination of metformin and sulfonylurea was associated with increased mortality.(8)

Although all classes of anti-diabetics were used significantly more frequently in the intensive treatment group in ACCORD trial, ninety-two percent of patients were given a thiazolidinedione versus fifty-eight percent in the standard treatment group.(21) Several meta-analyses raised concerns about the cardiovascular safety of the rosiglitazone.(22, 23) The prospective Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial found no adverse effect of rosiglitazone on the combined outcome of cardiovascular death or hospitalization but did report an increased risk of hospitalization for congestive heart failure (hazard ratio 2.10, 95% CI 1.35–3.27) in patients taking rosiglitazone versus active comparator.(24)

Whether all peroxisome proliferator-activated receptor (PPAR) γ agonists increase cardiovascular mortality has been the subject of some debate. As a class, the PPAR γ agonists cause fluid retention and this effect has been attributed to increased expression of the epithelial sodium channel (ENaC) and amiloride-sensitive salt-retention in the collecting duct.(25) In a retrospective, observational trial, rosiglitazone use was associated with an increased risk of stroke (adjusted hazard ratio of 1.27, 95% CI 1.12–1.45), heart failure (1.25, 95% CI 1.16–1.34), death (1.14, 95% CI 1.05–1.24), and a composite endpoint of acute myocardial infarction (AMI), stroke, heart failure or death (1.18, 95% CI 1.12–1.23) compared to pioglitazone use, but not for AMI alone (1.06, 95% CI, 0.96–1.18).(26)

Incretin-Based Therapies

The recognition that the gut-derived incretins, glucagon-like peptide (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), stimulate insulin secretion following an oral glucose load led to the development of incretin-based therapies. GLP-1 decreases appetite and increases satiety, decreases gastric emptying, increases insulin secretion and β cell mass, decreases glucagon secretion and stimulates glucose uptake and glycogen synthesis in muscle and fat.(27) GLP-1 is rapidly inactivated by dipeptidyl peptidase IV, a serine exopeptidase which cleaves amino terminus dipeptide from peptides in which the

penultimate amino acid is a proline or alanine. The half-life of native GLP-1 in the human circulation is minutes.(28) Two pharmacological approaches have been developed to increase incretin effects for the treatment of diabetes. The first is the development of the stable GLP-1 analogues exenatide and liraglutide, and the second is the development of pharmacological inhibitors of dipeptidyl peptidase IV (DPPIV inhibitors).

GLP-1 acts through a classical seven transmembrane G protein-coupled receptor to activate cyclic adenosine monophosphate (cAMP) and phosphatidylinositol 3-kinase (PI3 kinase). Activation of PI3 kinase decreases apoptosis of myocytes and activated PI3 kinase contributes to ischemic preconditioning.(29) Stable GLP-1 analogues and DPPIV inhibitors limit myocardial injury and improve function following ischemia and reperfusion in animal models.(30–32) Several small studies in humans suggest that infusion of native GLP-1 improves cardiac function(33) or decreases inotrope use(34) following ischemia and reperfusion. In a large retrospective study, patients who were treated with exenatide were less likely to be hospitalized for cardiovascular disease even though they were more likely to have coronary artery disease and risk factors for coronary disease than those patients who were not treated with exenatide.(35)

GLP-1 causes vasodilation in animal models. Ban et al identified GLP-1 receptors in endothelium and cardiac and vascular myocytes.(36) They showed that both GLP-1 and exenatide improved cardiac function following ischemia/reperfusion in an isolated mouse heart preparation. Unexpectedly, the cardioprotective effects of GLP-1 were, in part, GLP receptor-independent and depended on degradation to GLP-1 (9–36). Moreover, the metabolite GLP-1 (9–36) improved ischemic injury and caused coronary vasodilation through a nitric oxide-dependent, GLP-1 receptor-independent mechanism.

GLP-1 also improves endothelial function in humans. Basu et al reported that administration of GLP-1 enhanced the forearm vasodilator response to intra-arterial acetylcholine but not to nitroprusside, consistent with a nitric oxide synthase-dependent effect.(37) The authors did not investigate whether these effects were mediated by GLP-1 or its degradation product. Several studies have examined the effect of stable GLP analogues on blood pressure in humans. Okerson et al reported that six-month treatment with exenatide reduced systolic blood pressure to a greater extent than did treatment with insulin or placebo.(38) In the Lead-3 mono trial, treatment with liraglutide 1.8 mg decreased blood pressure to a greater extent than did treatment with glimepiride 8 mg.(39) Changes in weight among the treatment groups may have confounded the observed changes in blood pressure in these two studies. Weight loss is known to reduce blood pressure and, in the study by Okerson et al, the reduction in SBP correlated with weight loss.(38) In Lead-3 liraglutide treatment significantly reduced weight, whereas glimepiride did not.(39)

Dipeptidyl peptide IV cleaves a number of vasoactive peptides and could either raise or lower blood pressure based on these actions (Table). For example, as mentioned earlier, GLP-1 enhances endothelium-dependent vasodilation in humans. Studies in mice suggest that the degradation product GLP-1 (9–36) contributes to this effect, and that stable analogues of GLP-1 do not cause vasodilation.(37) If this is the case, then inhibition of GLP-1 degradation by dipeptidyl peptidase IV inhibition might decrease vasodilation as well. Likewise, Yamamoto et al reported that GLP-1 receptor stimulation increases blood pressure and heart rate due to activation of autonomic regulatory neurons,(40) an effect that could be potentiated by DPPIV inhibition.

The vasodilator brain natriuretic peptide (BNP) is also cleaved by DPPIV;(41) the degradation product is a less potent vasodilator and natriuretic peptide in a dog model.(42) Thus, a DPPIV inhibitor might be expected to increase vasodilation due to endogenous

BNP. Substance P, another vasodilator, is normally inactivated by angiotensin-converting enzyme (ACE); when ACE is inhibited, however, cleavage by DPPIV becomes a major pathway for inactivation.(43) In contrast, DPPIV metabolizes the vasoconstrictors neuropeptide Y and peptide YY to vasodilator metabolites; DPPIV inhibition might be expected to *increase* blood pressure by preventing the degradation of these endogenous Y1 receptor agonists.(44)

Early reports indicated that DPPIV inhibitors decreased blood pressure in clinical trials in diabetes but these studies were not designed to assess blood pressure or to consider interactions with other agents.(45) Marney et al examined the interactive effect of acute ACE inhibition and DPPIV inhibition on blood pressure in individuals with the metabolic syndrome.(46) During placebo or incomplete ACE inhibition, sitagliptin lowered blood pressure. During maximal ACE inhibition, sitagliptin increased blood pressure. This effect was accompanied by an increase in heart rate and circulating norepinephrine concentrations. These findings are remarkably similar to the findings of Jackson and co-workers in the rat. (44) The investigators reported that the DPPIV inhibitor P32/98 decreased blood pressure in a dose-dependent manner. When rats were pretreated with the ACE inhibitor captopril, however, P32/98 increased blood pressure. This effect was prevented by administration of an NPY1 receptor antagonist, suggesting a NPY1-dependent effect on blood pressure in this rodent model. Alternatively, combined inhibition of ACE and DPPIV could raise blood pressure through their synergistic effects on substance P degradation. Endogenous substance P increases the sympathetic response to upright posture in humans.(47) Clearly, studies are needed to clarify the mechanism of such interactions.

Sodium glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors represent a new class of anti-diabetic agents under development for the treatment of diabetes.(48) By blocking SGLT-2 in the renal tubule, these agents promote the loss of glucose in the kidney, without affecting insulin secretion. Like the GLP-1 agonists, SGLT-2 inhibitors promote weight loss.(49) Blood pressure also decreases.(49) This decline in blood pressure is dose-independent and likely results from weight loss. These agents have yet to be approved by the FDA. In 2011, an FDA advisory panel expressed concern regarding a reported increased incidence of breast cancer in patients treated with the SGLT-2 inhibitor dapagliflozin.(50) SGLT-2 inhibitor treatment has also been associated with an increased risk of fungal urinary tract infection. (49)

Conclusion

While hyperglycemia predicts risk of cardiovascular events, clinical trials of intensive glucose control using standard anti-diabetic agents in patients with type 2 diabetes have proven disappointing and, in some cases, intensive glucose control increased the risk of mortality. Metformin stands out as an agent that reduces cardiovascular mortality in overweight diabetics. Like metformin, and in contradistinction to sulfonylureas and insulin, stable GLP-1 analogues cause weight loss in type 2 diabetics. Native GLP-1 has favorable effects on the myocardium and causes vasodilation. DPPIV inhibitors would be expected to potentiate those effects mediated by native GLP-1 but decrease effects attributable to its metabolite GLP-1 (9–36). The cardiovascular effect of DPPIV inhibitors will reflect the integrated effect of these agents on several vasoactive peptides, and may depend on interactions with cardiovascular drugs such as ACE inhibitors. Finally, beneficial vascular effects observed in animal models or even small mechanistic studies in humans do not necessarily translate into favorable cardiovascular outcomes in clinical trials. Numerous such studies demonstrated that rosiglitazone and other thiazolidinediones improve

endothelial function, reduce blood pressure, and decrease inflammation, before clinical trials revealed adverse cardiovascular effects of rosiglitazone.

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Figure.

Cardiovascular effects of glucagon like peptide-1 (GLP-1). Binding to the GLP-1 receptor in the heart induces activation of cyclic adenosine monophosphate (cAMP) and of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway contributes to ischemic preconditioning and decreases myocyte apoptosis. GLP-1 receptor in the brain leads to activation of the sympathetic nervous system. GLP-1 is degraded by dipeptidyl peptidase IV (DPPIV) to GLP-1 (9–36). GLP-1 (9–36) activates nitric oxide synthase (NOS) and causes vasodilation through a GLP-1 receptor-independent pathway. Thus, inhibition of GLP-1 degradation could reduce cardiovascular events by promoting preconditioning but could also decrease vasodilation and increase sympathetic activity. Exenatide and liraglutide are resistant to degradation by DPPIV.

Table

Vasoactive substrates of dipeptidyl peptidase IV (DPPIV)

DPPIV Substrate	Cardiovascular Actions	Metabolite	Cardiovascular Actions
GLP-1 (7–36)	Decreases apoptosis and promotes preconditioning via PI3K/akt pathway	GLP-1 (9–36)	Causes vasodilation via GLP receptor-independent activation of nitric oxide synthase
BNP	Vasodilator and natriuretic	BNP (3–36)	Less active vasodilator and natriuretic
Substance P	Causes vasodilation and increased vascular permeability, increases sympathetic activity	Substance P (5–11)	Inactive
Peptide YY (1–36)	Vasoconstrictor via Y1 receptor	Peptide YY (3–36)	Vasodilator via Y2 receptor
Neuropeptide Y (1–36)	Vasoconstrictor via Y1 receptor	Neuropeptide Y (3–36)	Vasodilator via Y2 receptor