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Insulin and Its Cardiovascular Effects: What Is the Current Evidence?

Sahana Pai Dongerkery[1] · **Pamela R. Schroeder**[1] · **Mansur E. Shomali**[1]

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Abstract
Purpose of Review In this article, we examine the nature of the complex relationship between insulin and cardiovascular disease. With metabolic abnormalities comes increased risk for cardiovascular complications. We discuss the key factors implicated in development and progression of cardiovascular disease, its relationship to insulin therapy, and what can be learned from large, recent cardiovascular outcome studies.
Recent Findings Preclinical studies suggest that insulin has positive effects of facilitating glucose entry into cells and maintaining euglycemia and negative effects of favoring obesity and atherogenesis under certain conditions. Confounding this relationship is that cardiovascular morbidity is linked closely to duration and control of diabetes, and insulin is often used in patients with diabetes of longer duration. However, more recent clinical studies examining the cardiovascular safety of insulin therapy have been reassuring.
Summary Diabetes and cardiovascular outcomes are closely linked. Many studies have implicated insulin resistance and hyperinsulinemia as a major factor for poor cardiovascular outcomes. Additional studies link the anabolic effects of therapeutic insulin to weight gain, along with hypoglycemia, which may further aggravate cardiovascular risk in this population. Though good glycemic control has been shown to improve microvascular risks in type 1 and type 2 diabetes, what are the known cardiovascular effects of insulin therapy? The ORIGIN trial suggests at least a neutral effect of the basal insulin glargine on cardiovascular outcomes. Recent studies have demonstrated that ultra-long-acting insulin analogs like insulin degludec are non-inferior to insulin glargine with regard to cardiovascular outcomes.

Keywords Insulin resistance · Insulin · Diabetes · Cardiovascular outcomes

Introduction

The relationship between insulin and cardiovascular disease is complex. Patients with diabetes are at increased risk for cardiovascular disease and associated clinical complications. Although type 2 diabetes has become an increasingly common disease and is predicted to affect 380 million people worldwide by 2025, the incidence of myocardial infarction and stroke has declined in these patients during the past few decades [1]. Nevertheless, cardiovascular disease is the most common cause of death for individuals with diabetes [2].

Cardiovascular disease and related morbidity and mortality continue to be studied as primary outcomes for major trials in patients with type 2 diabetes. From multiple clinical studies in individuals with type 1 and type 2 diabetes, hemoglobin A1C reduction as a measure of improvements in average blood glucose correlates with reductions in microvascular

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✉ Mansur E. Shomali
Mansur.Shomali@medstar.net

Sahana Pai Dongerkery
Sahana.P.Dongerkery@medstar.net

Pamela R. Schroeder
Pamela.R.Schroeder@medstar.net

[1] MedStar Union Memorial Hospital, 201 East University Parkway, 33rd Street Professional Building, Baltimore, MD 21218, USA

complications such as nephropathy and retinopathy, but the relationship between macrovascular complications and glucose control is complicated. Large clinical studies, such as the VADT [3], ADVANCE [4], and ACCORD [5] trials have shown mixed results for cardiovascular outcomes (Table 1).

The Veterans Affairs Diabetes Trial (VADT) examined 1791 individuals with poorly controlled type 2 diabetes treated with maximal doses of an oral agent or insulin therapy [3]. Subjects were randomized to an intensive group in which the goal was an absolute reduction of 1.5 percentage points in the A1C as compared with the standard therapy group. After a mean follow-up of 5.6 years, there was no difference between the two groups for the primary outcome of time to first major cardiovascular event, though there was more frequent hypoglycemia in the intensive group (17.6 vs. 24.1%).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) studied 11,140 patients with T2DM and cardiovascular disease. Intensive glucose control, targeting an HbA1c $\leq$ 6.5%, significantly reduced the primary composite outcome of major macrovascular and microvascular events, mainly as a consequence of a reduction in nephropathy, again indicating that intensive control of glucose has an important role in the prevention of microvascular complications of type 2 diabetes [4].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial studied 10,251 patients with type 2 diabetes to determine whether intensive glycemic control targeting A1C < 6% vs. standard glycemic control targeting 7–7.9% reduces the risk of cardiovascular events. The study found that intensive control did not significantly reduce major cardiovascular events, but did increase mortality compared to standard control [5]. Several factors have been implicated as potential contributors to this unexpected result. Subjects in the intensive group were treated with more insulin and non-insulin medications, had disproportionate weight gain, were less likely to be treated with ACE inhibitors, and were associated with an increase in hypoglycemia [16].A post hoc analysis of the ACCORD results suggested that persisting higher A1C levels in the intensive group likely contributed to the excess mortality [17]. The authors speculated that participant characteristics that were not measured, such as lack of adherence to treatment plans, social crises, depression, and other psychiatric conditions, may have contributed to the persistently high A1C levels.

Molecular Mechanisms

A brief review of the basic science of insulin action may help generate hypotheses regarding any potential cardiovascular effects of insulin therapy. Insulin receptors are widely represented on the surface of cells lining the vascular walls. The binding of insulin to insulin receptors triggers its phosphorylation and activation via intrinsic kinase activity, leading to tyrosine phosphorylation of insulin receptor substrate proteins and to activation of two major pathways: the phosphatidylinositol 3-kinase (PI3K) pathway and the mitogen-activated protein kinase (MAPK) pathway.

The PI3K pathway is responsible for the metabolic actions of insulin and the activation of endothelial nitric oxide (NO) synthase (eNOS) [18]. The NO produced by eNOS decreases vascular tone and vascular smooth muscle cell proliferation and diminishes adhesion of inflammatory cells and platelet aggregation at the endothelium. Insulin also increases eNOS phosphorylation in human endothelial cells, improving eNOS activity and significantly reducing the production of reactive oxygen species. Furthermore, insulin modulates production of prostaglandins and endothelium-derived factors, which play a critical role as additional active vasodilators [19].

The MAPK pathway mediates the effects of insulin on growth, mitogenesis, and differentiation [20]. In addition, the MAPK pathway promotes multiple atherothrombotic effects such as upregulation of plasminogen activator inhibitor type 1 (PAI-1) and increased expression of vascular cell adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1). The balance between the pro-atherogenic and anti-atherogenic effects of insulin showed significant differences based on the experimental model. In healthy individuals, insulin exerts a preponderance of vasodilatory and vasoprotective actions, but in insulin-resistant conditions, the opposite vasoconstrictive effects seem to prevail [20]. A key feature of insulin resistance is selectivity of resistance to the PI3K pathway. Therefore, PI3K-dependent processes such as NO-mediated vasodilation will be reduced and insulin will drive MAPK-dependent atherothrombotic effects [20]. This imbalance in insulin signaling thus has the potential to be exaggerated even further by insulin therapy.

Metabolic Syndrome/Insulin Resistance

Individuals with metabolic syndrome have an increased risk of cardiovascular disease [21]. Risk factors such as visceral adiposity, insulin resistance, dyslipidemia, and hypertension are common to metabolic syndrome and type 2 diabetes. Endothelial dysfunction is an important characteristic of metabolic syndrome [21]. This is demonstrated by inadequate vasodilation and/or paradoxical vasoconstriction in coronary and peripheral arteries in response to stimuli that release NO. Moreover, endothelial dysfunction contributes to impaired insulin action by altering the trans-capillary passage of insulin to target tissues. This establishes a cycle in which progressive endothelial dysfunction and disturbances in glucose and lipid metabolism develop secondary to the insulin resistance. Vascular damage, which results from lipid deposition and oxidative stress to the vessel wall, triggers an inflammatory

Table 1 Selected clinical trials discussed in the text[a]

Study	Year	Mean follow-up	No. of subjects	Diabetes type	Study intervention	Primary outcome
DCCT [6]	1993	6.5 years	1441	Type 1	Intensive insulin therapy vs. conventional insulin therapy	Intensive insulin therapy reduced the occurrence or progression of retinopathy, nephropathy, and neuropathy
UKPDS [7]	1998	10.0 years	3867	Type 2	Intensive therapy with sulphonylurea or insulin vs diet therapy and less intensive use of drugs	Intensive therapy decreased the risk of microvascular complications but not macrovascular disease
EDIC [8]	2005	11.0 years	1394	Type 1	Observational follow-up of the DCCT cohorts	Overall mortality in the DCCT intensive group was similar to the general population; overall mortality in the conventional group was greater than the general population
PROactive [9]	2005	138 weeks	5238	Type 2	Pioglitazone vs placebo added to other glucose-lowering drugs	There was no difference in the primary composite endpoint; pioglitazone treatment reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke
ACCORD [5]	2008	3.5 years	10,251	Type 2	Intensive therapy (targeting an A1C < 6.0%) vs. standard therapy (targeting an A1C from 7.0 to 7.9%)	As compared with standard therapy, the use of intensive therapy increased mortality
ADVANCE [4]	2008	5 .0 years	11,140	Type 2	Standard glucose control vs. intensive glucose control, defined as the use of gliclazide plus other drugs as required to achieve an A1C of 6.5% or less	Intensive control resulted in a reduction in the combined outcome of macrovascular and microvascular events, primarily due to a reduction in nephropathy
VADT [3]	2009	5.6 years	1791	Type 2	Intensive vs. standard glucose control	No significant difference between the 2 groups in

Table 1 (continued)

Study	Year	Mean follow-up	No. of subjects	Diabetes type	Study intervention	Primary outcome
						cardiovascular events
ORIGIN [10]	2012	6.2 years	12,537	Type 2	Insulin glargine U100 vs standard of care in prediabetes or early diabetes	No significant difference between the 2 groups in cardiovascular events
EMPA-REG [11]	2015	3.1 years	7020	Type 2	Empagliflozin vs. placebo added to other drugs	Empagliflozin treatment was associated with lower rates of cardiovascular outcomes
LEADER [10]	2016	3.8 years	9340	Type 2	Liraglutide vs. placebo added to other drugs	Liraglutide treatment was associated with lower rates of cardiovascular outcomes
CANVAS [12]	2017	188.2 weeks	10,142	Type 2	Canagliflozin vs. placebo added to other drugs	Canagliflozin treatment was associated with lower rates of cardiovascular outcomes
SWITCH-1 [13••]	2017	64 weeks	501	Type 1	Insulin degludec vs. insulin glargine U100	Treatment with insulin degludec was associated with a reduced rate of hypoglycemic episodes
SWITCH-2 [14••]	2017	64 weeks	721	Type 2	Insulin degludec vs. insulin glargine U100	Treatment with insulin degludec was associated with a reduced rate of hypoglycemic episodes
DEVOTE [15]	2017	1.99 years	7637	Type 2	Insulin degludec vs. insulin glargine U100 in a cardiovascular safety trial	Treatment with insulin degludec was non-inferior to glargine with respect to the incidence of cardiovascular events

[a] The order of the studies is by year of publication

reaction, and the release of chemo-attractants and cytokines worsens the insulin resistance and endothelial dysfunction [21].

The "inflammation hypothesis" [22] proposes links between pro-inflammatory cytokines and tumor necrosis factor alpha produced by adipose tissue and increased insulin resistance, which contributes to vascular endothelial dysfunction and poor cardiovascular outcome. Inflammatory mediators play a paramount role in the initiation, progression, and rupture of atherosclerotic plaques. There is accumulating evidence suggesting that inflammation is the bridging link between atherosclerosis and the metabolic syndrome [23]. In summary, complex interactions between endothelial function, abnormal skeletal muscle blood flow, and reduced insulin-mediated glucose uptake may be central to the link between insulin resistance, hypertension, impaired glucose tolerance,

and vascular disease [21]. Given these multiple metabolic abnormalities that cannot be corrected by glycemic control alone and the potential for insulin therapy to drive MAPK-dependent pathways, adverse cardiovascular effects of insulin therapy may be a concern.

Dysglycemia as a Contributor to Cardiovascular Risk

Individuals with type 1 diabetes also have an increased risk for cardiovascular disease [24]. Generally, these people do not have the similar cardiovascular risk factors as patients with type 2 diabetes. Their only therapy is insulin. This supports the role of dysglycemia in the development of cardiovascular disease. In experimental models, hyperglycemia itself has been shown to have multiple adverse effects such as reducing eNOS activation [25].

The Diabetes Control and Complications Trial (DCCT) [6] and the similarly designed but smaller Stockholm diabetes intervention study [26] have shown unequivocally that lowering blood glucose delays onset and slows the progression of microvascular complications in individuals with type 1 diabetes. In the DCCT study, the fewer cardiovascular events in the improved glycemic control group was not statistically significant in this relatively young population which had a very low event rate. When the DCCT ended in 1993, researchers continued to study more than 90% of participants in a follow-up study, called Epidemiology of Diabetes Interventions and Complications (EDIC), to assess incidence and predictors of cardiovascular disease events as well as diabetic complications. They found that with intensive blood glucose control during the DCCT, the risk of any cardiovascular disease event was reduced by 42% [8]. These findings suggest that intensive glucose control, even during the relatively short period of time of the initial DCCT study period, had a significant effect on the eventual development of cardiovascular disease.

The Role of Hypoglycemia in Cardiovascular Risk

In the large studies investigating intensive therapy and health outcomes, increased hypoglycemia has been associated with intensive intervention. In the DCCT study, the chief adverse event in the intensive insulin group was a two- to threefold increase in severe hypoglycemia [8]. In the ACCORD trial, the incidence of hypoglycemia in the intensive group was greater than in the conventional group (3.1 vs. 1.0%) [5]. As discussed previously, no clear link was found between hypoglycemia and mortality in ACCORD. In the ADVANCE study, severe hypoglycemia was associated with a significant increase in the adjusted risk of major macrovascular events (hazard ratio, 2.88; 95% confidence interval [CI], 2.01 to 4.12), death from a cardiovascular cause (hazard ratio, 2.68; 95% CI, 1.72 to 4.19), and death from any cause (hazard ratio, 2.69; 95% CI, 1.97 to 3.67) ($P < 0.001$ for all comparisons) [27].

In a small but important study of 25 insulin-treated individuals with type 2 diabetes and cardiovascular disease, the authors, by means of continuous glucose monitoring and Holter monitoring, found that hypoglycemia was associated with an increase in cardiac arrhythmia [28]. Bradycardia and atrial and ventricular ectopic counts were significantly higher during nocturnal hypoglycemia. The authors suggested that excessive compensatory vagal activation after the counterregulatory phase may account for bradycardia and associated arrhythmias. Prolonged QT intervals and abnormal T wave morphology were observed during hypoglycemia in some participants. Therefore, cardiac arrhythmia, provoked by insulin-induced hypoglycemia, is a plausible mechanism for cardiovascular mortality in susceptible individuals.

Insulin-Sparing Therapies for Type 2 Diabetes

As previously discussed, the hyperinsulinemia in insulin-resistant individuals might have deleterious effects. The concern of using insulin as a therapy is that, though it may lower blood glucose, it may compound the negative effects of MAPK-dependent processes. Insulin-sparing medications for type 2 diabetes, such as metformin, thiazolidinediones, sodium-glucose transport inhibitors, and glucagon-like peptide 1 agonists have been proposed as therapies which would reduce the need for insulin as therapy. In fact, studies such as PROACTIVE [9], EMPA-REG [11], LEADER [10], and CANVAS [12] have demonstrated cardiovascular benefit (Table 1). Furthermore, the drugs used in these studies do not confer an increased risk of hypoglycemia.

New Clinical Trial Evidence

Results from previous studies, including UKPDS [7], VADT [3], and ADVANCE [4], have not shown a significant benefit of reducing glycemic levels on the risk of cardiovascular events, whereas ACCORD [5] has demonstrated significantly increased risk of death both from cardiovascular causes and from any cause associated with more intensive glycemic control. Newer studies specifically examining the cardiovascular safety of insulin therapy have recently been completed. In addition, newer insulin formulations are now available which are associated with a lower risk of hypoglycemia.

The ORIGIN Trial

The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial [29••] involved 12,537 people 50 years of age or older with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes in addition to other

cardiovascular risk factors. There were two co-primary composite cardiovascular (CV) outcomes. The first was death from CV causes, non-fatal myocardial infarction, or non-fatal stroke, and the second was a composite of any of these events, plus a revascularization procedure or hospitalization for heart failure. The incidence of both co-primary outcomes did not differ significantly between treatment groups with hazard ratios of 1.02 (95% CI, 0.94 to 1.11; $P = 0.63$) and 1.04 (95% CI, 0.97 to 1.11; $P = 0.27$), respectively. The intervention with basal insulin glargine U100 reduced diabetes incidence in subjects who did not have diabetes, and this occurred despite weight gain. The incidence of a first episode of severe hypoglycemia was 1.00 per 100 person years in the insulin glargine group and 0.31 per 100 person years in the standard care group ($P < 0.001$).

The ORIGIN trial had several strengths. The trial duration of more than 6 years, the high rates of follow-up and treatment adherence, the large number of cardiovascular outcomes, and their prospective adjudication ensured sufficient power to detect a clinically important cardiovascular effect. In addition, the prospective collection of data pertaining to hypoglycemia and weight gain ensured that potential harms were quantified [30]. In summary, therapy with basal insulin glargine for more than 6 years had a neutral effect on cardiovascular outcomes. Moreover, this therapy maintained near-normal glycemic control and slowed progression of dysglycemia, but it was associated with a significant increase in hypoglycemia and weight gain.

SWITCH 1 and SWITCH 2 Trials

Severe hypoglycemia has been associated with significant morbidity. Coma and seizures are well-recognized neurological sequelae of severe hypoglycemia, but, as discussed previously, much interest is currently focused on the potential for hypoglycemia to cause serious life-threatening cardiac complications, such as arrhythmias and myocardial ischemia [31].

The SWITCH 1 and the SWITCH 2 trials were randomized double-blind cross-over clinical trials that studied rates of overall symptomatic hypoglycemia and nocturnal hypoglycemia in subjects with type 1 diabetes (SWITCH 1) [13••] and subjects with type 2 diabetes (SWITCH 2) [14••] treated with insulin glargine versus insulin degludec. Insulin degludec is an ultra-long-acting basal insulin with low day-to-day variability in its glucose-lowering effect. Reduced rates of hypoglycemia were observed in both trials with insulin degludec. In SWITCH 1, the rate of overall symptomatic hypoglycemia during the maintenance period was significantly lower with insulin degludec (2200.9 episodes per 100 patient years of exposure (PYE) than with insulin glargine U100 (2462.7 episodes per 100 PYE), for a rate ratio of 0.89 (95% CI, 0.85–0.94; $P < .001$) [13••]. Similarly in SWITCH 2, the rate of overall symptomatic hypoglycemia during the maintenance period was significantly lower with insulin degludec as compared to insulin glargine U100 (185.6 vs 265.4 episodes/100 PYE, respectively), for a rate ratio = 0.70 (95% CI, 0.61–0.80; $P < 0.001$) [14••].

DEVOTE

The DEVOTE study examined 7637 patient with type 2 diabetes at high risk for cardiovascular events [15••]. The study compared outcomes with insulin glargine versus insulin degludec, a basal insulin which was found to be associated with lower rates of hypoglycemia as discussed above in the SWITCH trials. This study found that degludec was non-inferior to glargine with respect to the incidence of major cardiovascular events. The primary composite outcome occurred in 325 patients (8.5%) in the degludec group and in 356 patients (9.3%) in the glargine group (hazard ratio, 0.91; 95% confidence interval 0.78 to 1.06; $P < 0.001$ for non-inferiority). There was no significant difference in the incidence of adverse events between the degludec and glargine groups [15••].

The design of the DEVOTE trial differed from the ORIGIN study in important ways [15••, 29••]. The DEVOTE trial was a 2-year event-driven cardiovascular outcome trial. Subjects with diabetes either had established cardiovascular disease, chronic kidney disease, or both. The ORIGIN trial recruited subjects with prediabetes or early type 2 diabetes with cardiovascular risk factors and followed them for 6 years. In DEVOTE, all subjects in both groups were prescribed basal insulin. In ORIGIN, very few subjects in the standard care group (11%) were using insulin. Event rates for the primary cardiovascular composite endpoint were much higher in ORIGIN, potentially due to the longer duration of this study. Given these differences, direct comparisons would be difficult. However, the ORIGIN results reassure patients and providers of the cardiovascular safety of insulin glargine, and the DEVOTE results suggest that the newer basal insulin degludec has a similar cardiovascular safety profile as insulin glargine.

Conclusions

Because of the complicated cardiovascular effects of insulin, the knowledge that insulin resistance and resultant hyperinsulinemia have adverse effects on the vasculature, the failure of intensive diabetes intervention to show a cardiovascular benefit, and the cardiovascular safety of insulin therapy has been questioned. The more recent studies such as ORIGIN and DEVOTE have demonstrated the cardiovascular safety of two basal insulins. These clinical trials have been reassuring for patients and providers because insulin is an

important component of treatment for those with type 2 diabetes and an essential treatment for those with type 1 diabetes.

The challenge of insulin therapy is optimizing the dosing to minimize undesirable effects such as weight gain and hypoglycemia. In patients at risk for hypoglycemia, newer insulin analogs may be considered. In addition, newer insulin delivery systems, continuous glucose monitors, and even artificial pancreas systems have the potential to further enhance glycemic control while simultaneously reducing hypoglycemia. Finally, managing the non-glycemic cardiovascular risk factors, particularly in individuals with type 2 diabetes, is critical given the complicated nature of insulin action.

Compliance With Ethical Standards

Conflict of Interest Sahana Pai Dongerkery, Pamela R. Schroeder, and Mansur E. Shomali declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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