# Trading Glucose Control for Hypertension: Lessons from Mother Nature

Reviewed by Robert Chilton, DO, FACC, FAHA

## STUDY

Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA: Dipeptidyl peptidase-IV inhibitor associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension* 54:516–523, 2009

## SUMMARY

**Objective.** Dipeptidyl peptidase-4 (DPP-4) inhibitors decrease degradation of the incretins and peptides such as substance P that may be involved in the pathogenesis of ACE inhibitor–associated angioedema. This study sought to determine the effect of DPP-4 inhibition on patients' risk of developing clinical angioedema.

**Design.** The authors compared the incidence of angioedema in patients treated with the DPP-4 inhibitor vildagliptin to that of patients treated with a comparator in phase 3 randomized clinical trials. Prospectively defined angioedema-related events in these trials were adjudicated by a blinded internal medicine committee and an expert reviewer. Patients' concurrent use of ACE inhibitors or angiotensin-receptor blockers (ARBs) was ascertained from case report forms. Odds ratios (ORs) and 95% confidence intervals (CIs) comparing the angioedema risk in vildagliptin- and comparator-treated patients were calculated for the full population as well as for the subset of patients taking ACE inhibitors or ARBs, using both an analysis of pooled data and a meta-analysis.

**Results.** Overall, the researchers found no association between vildagliptin use and angioedema. However, meta-analysis revealed that, among individuals taking an ACE inhibitor, vildagliptin use was associated with an increased risk of angioedema (14 cases among 2,754 vildagliptin users vs. 1 case among 1,819 comparator users, OR 4.57, 95% CI 1.57–13.28).

**Conclusion.** Vildagliptin use may be linked with an increased risk of angioedema among patients who also take ACE inhibitors, although the absolute risk is small. Health care providers confronted with angioedema in a patient taking an ACE inhibitor and a DPP-4 inhibitor should consider this possible drug-drug interaction.

## COMMENTARY

It is estimated that the number of people with diabetes will approach 366 million by 2030.[1] This not only increases the risk of cardiovascular events, but also implies the need for earlier treatment of younger patients than in previous decades. This situation will have a major and unprecedented impact on health care costs.

Recently, researchers such as Brown et al. have raised concerns about possible off-target cardiovascular effects of DPP-4 inhibition. This discussion focuses on new information relating to drug treatment of hyperglycemia and potential concerns about lowering blood glucose at the expense of blood pressure control in hypertensive diabetic patients with metabolic syndrome.[2]

### Beneficial Effects of Glucose Lowering

Boussageon et al.[3] completed an updated meta-analysis of randomized controlled trials in type 2 diabetes patients with glucose-lowering agents. Their primary endpoints were all-cause mortality and death from cardiovascular causes. Secondary endpoints were severe hypoglycemia and macro- and microvascular events. This meta-analysis included 13 studies with 34,533 patients, 18,315 of whom received intensive glucose-lowering treatment and 16,218 of whom received standard treatment.

Their results found no significant effect on all-cause mortality (risk ratio [RR] 1.04, 95% CI 0.91–1.19) or cardiovascular death (RR 1.11, 95% CI 0.86–1.43). This study also found that intensive treatment resulted in a 15% reduction in nonfatal myocardial infarctions (MIs) (RR 0.85, 95% CI 0.74–0.96, $P < 0.001$). Another important finding was a significant reduction in microalbuminuria (RR 0.90, 95% CI 0.85–0.96, $P < 0.001$). Unfortunately, the price of these improvements was a doubling of severe hypoglycemia (RR 2.33, 95% CI 1.62–3.36).

Translating these results to clinical practice, in a 5-year period, one would need to treat ~ 117–150 patients to avoid one MI and 32–142 patients to avoid one episode of microalbuminuria, whereas one severe episode of hypoglycemia

would occur for every 15–52 patients. Unfortunately, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study,[4] severe hypoglycemia was related to macrovascular events, including cardiovascular death (RR 2.68, 95% CI 1.72–4.19) and all-cause mortality (RR 2.69, 95% CI 1.79–3.67). Thus, intensive treatment of hyperglycemia with current medications carries some major clinical concerns.

One other important finding from this article[3] was a 47% increase in the risk for congestive heart failure ($P < 0.001$). The risk for nonfatal strokes (RR 1.00, 95% CI 0.83–1.21) was not found to clinically benefit from intensive treatment.

Another area that is frequently considered to benefit from treatment of hyperglycemia is the risk for retinopathy. Unfortunately, intensive treatment did not significantly reduce the rate of retinopathy (RR 0.85, 95% CI 0.71–1.03), photocoagulation (RR 0.91, 95% CI 0.71–1.17), or visual deterioration or blindness (RR 1.00, 95% CI 0.96–1.05). Intensive treatment also was not found to reduce the incidence of renal failure or the doubling of serum creatinine levels (RR 1.03, 95% CI 0.98–1.08).

There are two important takeaway messages from this meta-analysis: *1*) intensive treatment of elevated glucose did not show a benefit in lowering all-cause mortality or deaths from cardiovascular causes in patients with type 2 diabetes, and *2*) intensive treatment increased the likelihood of severe hypoglycemia and bestowed unclear benefits in terms of prevention of microvascular disease. Clearly, more randomized, controlled trials are needed to further elucidate these important questions.

**Benefits of Lowering Blood Pressure in Patients With Type 2 Diabetes**

Lowering blood pressure in type 2 diabetes patients seems beneficial and was recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in patients with diabetes and a systolic blood pressure > 130 mmHg.[5] However, the data to support this recommendation have been unclear.

The prospective Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial[6] tested the effect of a target systolic blood pressure of < 120 mmHg on major cardiovascular events among high-risk patients with type 2 diabetes. The two large arms of this trial enrolled a total of 4,733 patients with type 2 diabetes. These patients were randomized to either intensive (systolic blood pressure < 120 mmHg) or standard (systolic blood pressure < 140 mmHg) blood pressure control. The primary composite endpoint was nonfatal MI, nonfatal stroke, or death from cardiovascular causes, and the study had a mean follow-up period of 4.7 years.

Twelve months from the time the study started, the mean systolic blood pressure was 119.3 mmHg in the intensive arm and 133.5 mmHg in the standard-treatment group. The results for the primary endpoint were not significant (RR 0.88, 95% CI 0.73–1.06, $P = 0.20$). However, the yearly rates of stroke, a pre-specified secondary outcome, were 0.32 and 0.53% in the two groups, respectively (hazard ratio [HR] 0.59, 95% CI 0.39–0.89, $P = 0.01$).

The ACCORD investigators concluded that treating type 2 diabetic patients to a systolic blood pressure < 120 mmHg did not reduce the rate of fatal or nonfatal major cardiovascular events. However, 36 patients in the intensive-treatment arm suffered a stroke compared to 62 in the standard-treatment arm (HR 0.59, 95% CI 0.39–0.89, $P < 0.01$).

In many clinical trials, antihypertensive therapy has been associated with 35–40% mean reductions in stroke incidence and 20–25% reductions in MIs.[5] Similar findings were seen in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).[7] These findings suggest that blood pressure reduction in patients with type 2 diabetes is more important for stroke prevention than for prevention of MIs.

**Translating Research to Clinical Practice**

Recently introduced DPP-4 inhibitors for the treatment of type 2 diabetes reduce blood glucose and are well tolerated by patients. Agents in this drug class increase levels of the incretins glucagon-like peptide-1 and gastric inhibitory peptide and thereby increase insulin secretion, inhibit glucagon release, slow gastric emptying, and decrease blood glucose levels. In addition, many patients with type 2 diabetes have underlying hypertension, which is treated, according to American Diabetes Association guidelines,[8] with either an ACE inhibitor or an ARB (Table 1).

A study by Marney et al.[9] highlighted an important clinical concern with the use of high-dose ACE inhibitors with DPP-4 inhibitors in patients with metabolic syndrome. Although DPP-4 inhibitors are used in type 2 diabetes to control blood glucose, they also have systemic effects related to substance P and neuropeptide Y. Substance P is a potent vasodilator, and substance P–induced vasodilatation is dependent on nitric oxide release.[10] Neuropeptide Y is a brain peptide that can augment vasoconstriction through noradrenergic neurons. Both of these substances

**Table 1. ADA Guidelines for Blood Pressure Control in Diabetes[8]**

- Patients with diabetes who are found to have a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg should have blood pressure confirmed on a separate day.
- Repeat systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg confirms a diagnosis of hypertension.
- A goal systolic blood pressure of < 130 mmHg is appropriate for most patients. However, based on patient characteristics and responses to therapy, a higher or lower systolic blood pressure target may be appropriate.
- Patients with diabetes should be treated to a diastolic blood pressure of < 80 mmHg.
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg may be given lifestyle therapy alone for 3 months and then, if targets are not achieved, should be treated with pharmacological agents.
- Patients with more severe hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) at diagnosis or follow-up should receive pharmacological therapy in addition to lifestyle therapy.
- Pharmacological therapy should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted.
- Multiple drug therapy is generally required to achieve blood pressure targets.

may affect blood pressure when a DPP-4 inhibitor is used in conjunction with a high-dose ACE inhibitor. Concerns about increases in blood pressure with high-dose ACE inhibitors and DPP-4 inhibitors have been reported.[11,12]

Animal studies have provided some elucidation. Normally, vascular tone in hypertensive animals is high; thus, administration of a weak vasoconstrictor may not increase vascular tone or blood pressure. However, if one lowers vascular tone with high doses on an ACE inhibitor, the weak pressor effect of the DDP-4 inhibitor may become evident.[13]

A second consideration from animal studies is the effect of DDP-4 inhibition on the renal vasculature by enhancing the response to angiotensin II.[14] Angiotensin II is a well-known vasoconstrictor related to hypertension and atherosclerosis.

The previously mentioned study by Marney et al.[9] evaluated the use of DDP-4 inhibition in patients with metabolic syndrome and looked specifically at the hemodynamic effects of DPP-4 inhibition in combination with an ACE inhibitor. This well-designed study employed a parallel group crossover design to evaluate 16 patients using sitagliptin and enalapril.

Patients were randomized to receive placebo or sitagliptin, 100 mg/day, for 5 days before each of two study days in a crossover design. They were then randomized in parallel to receive an acute dose of placebo (Group A, referred to as "enalapril 0 mg" to avoid confusion with the placebo for sitagliptin), enalapril 5 mg (Group B), or enalapril 10 mg (Group C). The primary endpoint was blood pressure measured by automatic cuff. In addition, heart rate and norepinephrine levels were measured each day.

The researchers found that in patients receiving the placebo (0 mg of enalapril) or the low-dose ACE inhibitor (5 mg of enalapril), sitagliptin lowered blood pressure. However, in patients receiving the higher-dose ACE inhibitor (10 mg of enalapril), sitagliptin increased blood pressure.

There were two additional important findings. Only the group receiving high-dose enalapril with sitagliptin had increases in heart rate and blood pressure. Second, norephinephrine levels were elevated only in the group taking the high-dose ACE inhibitor and the DDP-4 inhibitor. This suggests that the antihypertensive effect of a high-dose

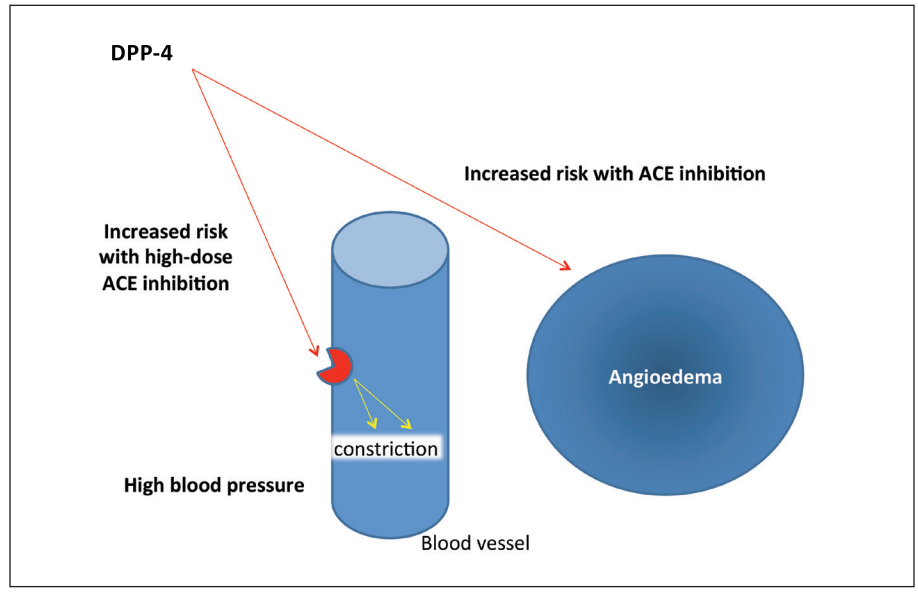


*Figure 1. Two potential clinical concerns with DPP-4 inhibition.[9,14]*

ACE inhibitor is lost, in part because of activation of the sympathetic nervous system.

Translating basic science to clinical practice is not easy and always needs to be confirmed with evidence from large, double-blind, randomized trials. The article by Marney et al.[9] is one small look at a potentially important group of high-risk patients who require careful attention.

In conclusion, this relatively new DPP-4 class of drugs for the treatment of type 2 diabetes does come with concerns, although it is well tolerated by most patients. The article by Brown et al., reviewed here, found a slight increased risk of angioedema among patients using an ACE inhibitor with vildagliptin. Studies from Marney et al. reported that a high-dose ACE inhibitor with the DPP-4 inhibitor sitagliptin increases blood pressure (Figure 1). However, all of these studies have had a small number of patients and should be viewed as early research requiring additional study.

## REFERENCES

[1]Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004

[2]Laasko M: Benefits of strict glucose and blood pressure control in type 2 diabetes: lessons from the U.K. Prospective Diabetes Study. *Circulation* 99:461–462, 1999

[3]Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, Erpeldinger S, Wright JM, Gueyffier F, Cornu C: Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 343:d4169, 2011

[4]Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S; ADVANCE Collaborative Group: Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 363:1410–1418

[5]Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289:2560–2572, 2003

[6]ACCORD study group: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008

[7]ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002

[8]American Diabetes Association: Standards of medical care in diabetes—2012. *Diabetes Care* 35(Suppl. 1):S11–S63, 2012

[9]Marney AM, Kunchakarra S, Byrne L, Brown NJ: Interactive hemodynamic effects of DPP-4 inhibition and ACE inhibition in humans. *Hypertension* 56:728–733, 2010

[10]Bossaller C, Reither K, Hehlert-Friedrich C, Auch-Schwelk W, Graf K, Gräfe M, Fleck E: In vivo measurement of endothelium-dependent vasodilation with substance P in man. *Herz* 17:284–290, 1992

[11]Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ: Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care* 30:890–895, 2007

[12]Nathwani A, Lebeaut A, Byiers S, Gimpelewicz C, Chang I: Reduction in blood pressure in patients treated with vildagliptin as monotherapy or in combination with metformin for type 2 diabetes [abstract]. *Diabetes* 55(Suppl. 1):A113, 2006

[13]Jackson EK, Dubinion JH, Mi Z: Effects of dipeptidyl peptidase-IV inhibition on arterial blood pressure. *Clin Exp Pharmacol Physiol* 35:29–34, 2008

[14]Jackson EK, Mi Z: Sitagliptin augments sympathetic enhancement of the renovascular effects of angiotensin II in genetic hypertension. *Hypertension* 51:1637–1642, 2008

*Robert Chilton, DO, FACC, FAHA, is a professor of medicine and director of the catheterization lab at the University of Texas Health Science Center in San Antonio.*