

Chronic Dipeptidyl Peptidase-4 Inhibition With Sitagliptin Is Associated With Sustained Protection Against Ischemic Left Ventricular Dysfunction in a Pilot Study of Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease

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Background—The incretin hormone, glucagon-like peptide-1, promotes myocardial glucose uptake and may improve myocardial tolerance to ischemia. Endogenous glucagon-like peptide-1 (7–36) is augmented by pharmacological inhibition of dipeptidyl peptidase-4. We investigated whether chronic dipeptidyl peptidase-4 inhibition by sitagliptin protected against ischemic left ventricular dysfunction during dobutamine stress in patients with type 2 diabetes mellitus and coronary artery disease.

Methods and Results—A total of 19 patients with type 2 diabetes mellitus underwent dobutamine stress echocardiography with tissue Doppler imaging on 2 separate occasions: the first (control) while receiving oral hypoglycemic agents, and the second after the addition of sitagliptin (100 mg once daily) for ≈4 weeks. Sitagliptin increased plasma glucagon-like peptide-1 (7–36) levels and, at peak stress, enhanced both global (ejection fraction, 70.5±7.0 versus 65.7±8.0%; $P<0.0001$; mitral annular systolic velocity, 11.7±2.6 versus 10.9±2.3 cm/s; $P=0.01$) and regional left ventricular function, assessed by peak systolic velocity and strain rate in 12 paired, nonapical segments. This was predominantly because of a cardioprotective effect on ischemic segments (strain rate in ischemic segments, $-2.27±0.65$ versus $-1.98±0.58$ s⁻¹; $P=0.001$), whereas no effect was seen in nonischemic segments ($-2.19±0.48$ versus $-2.18±0.54$ s⁻¹; $P=0.87$). At 30 minutes recovery, dipeptidyl peptidase-4 inhibition mitigated the postischemic stunning seen in the control scan.

Conclusions—The addition of dipeptidyl peptidase-4 inhibitor therapy with sitagliptin to the treatment regime of patients with type 2 diabetes mellitus and coronary artery disease is associated with a sustained improvement in myocardial performance during dobutamine stress and a reduction in postischemic stunning.

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As a result of heightened awareness surrounding the risks associated with iatrogenic hypoglycemia and the cardiovascular safety of some antidiabetic agents, guidelines are increasingly favoring the earlier and more frequent use of the dipeptidyl peptidase-4 (DPP-4) inhibitors for the management of type 2 diabetes mellitus (T2DM). These agents reduce the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1), resulting in an increase in the stimulation of insulin secretion, the suppression of glucagon release, a reduction in the hepatic production of glucose, and an increase in peripheral glucose uptake and metabolism. Importantly, their pancreatic effects are dependent on the prevailing glucose

concentration, so that the risk of hypoglycemia is low, and clinical studies have shown them to be safe and well tolerated, with a neutral effect on weight.¹

Although the glucoregulatory efficacy of GLP-1 modulation is now well documented, there is an increasing body of evidence to suggest several pleiotropic effects, which may have the potential to influence cardiovascular risk. The majority of these data relate to the actions of exogenous GLP-1 or GLP-1 receptor agonists, with studies specifically investigating the cardioprotective effects of DPP-4 inhibition small in number and almost exclusively restricted to animal models of ischemia.²⁻⁵ This issue however is important, given the uncertainty surrounding the cardiovascular significance of several endogenous substrates targeted by DPP-4,⁶ as well as that of the GLP-1 metabolite.⁷

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In the only study to date investigating the cardioprotective effects of DPP-4 inhibition in humans, we demonstrated an acute improvement in myocardial performance during dobutamine stress in nondiabetic patients with coronary artery disease (CAD) after a single dose of sitagliptin and an oral glucose load.⁸ However, it is not known whether these favorable cardiovascular effects also occur in patients with T2DM and, if so, whether they are sustained with regular therapy. This study was therefore undertaken to determine whether chronic DPP-4 inhibition with sitagliptin could protect the heart from ischemic left ventricular (LV) dysfunction and improve the myocardial response to demand ischemia during dobutamine stress in patients with T2DM and CAD.

Methods

Study Population

Patients with T2DM who received oral hypoglycemic agents (OHA) and obstructive CAD (at least 1 proximal stenosis >50% in at least 1 epicardial coronary artery) were invited to participate in the study. All patients had undergone recent coronary angiography before enrollment in the study. Exclusion criteria included LV dysfunction (ejection fraction <40%) or regional wall motion abnormalities at rest, a history of previous myocardial infarction within the preceding 3 months, conduction abnormalities, valvular heart disease, patients taking insulin, DPP-4 inhibitors or GLP-1 receptor agonists, and those with permanent pacemakers. The study was approved by the local ethics committee and complied with the guidelines set out in the Declaration of Helsinki. All participants gave written informed consent.

Dobutamine Stress Echocardiography

Subjects underwent dobutamine stress echocardiography (DSE) on 2 separate occasions after an overnight fast (Figure 1); the first (control) while taking their usual OHA and the second after the addition of sitagliptin (100 mg once daily) for ≈4 weeks. They were asked to omit β -blockers for 48 hours before each scan, and OHA were omitted on the morning of the study.

A standard clinical protocol for DSE was used. Dobutamine was administered intravenously using an infusion pump in incremental doses (10 μ g/kg per min initially, then increased at 3-minute intervals to 20, 30, and 40 μ g/kg per min if tolerated), and, if necessary, up to 2 mg of atropine was given to achieve the target heart rate. Criteria for stopping the test were achievement of target heart rate of (220-age) \times 0.85 bpm, ischemic ECG changes (>2 mm ST depression), angina, systolic blood pressure increase to >240 mmHg or decrease to <100 mmHg, and severe arrhythmias. Two-dimensional echocardiography (Vivid 7, GE Medical Systems) was performed with the patient in the left recumbent position, and images were recorded at rest, at peak stress, and in recovery. Three cardiac cycles of the apical 4-, 3-, and 2-chamber views were captured with tissue Doppler imaging. The image sector width was kept as narrow as possible to maximize

the frame rate. All recordings were made in gently held midexpiration to minimize beat-to-beat variability, and the data were stored for subsequent off-line analysis (EchoPac, GE Medical Systems).

Blood samples were taken to measure glucose, insulin, free fatty acids (FFA), and GLP-1 (7–36) at several time points before and after the DSE. The syringes for the collection of GLP-1 samples were preprepared with DPP-4 inhibitor (Millipore) to prevent GLP-1 degradation. Plasma GLP-1 levels were measured using a commercially available assay (Meso Scale Discovery, Rockville, MD).

Echocardiographic Analysis

The scans were analyzed off-line by a reviewer who was blinded to the treatment strategy (control versus sitagliptin). Regional wall LV motion was assessed using a 12-segment model comprising the base and mid level of six regional walls (anterior, anterolateral, antero-septal, inferior, inferolateral, and inferoseptal) obtained from the three apical views. LV volumes and ejection fraction were calculated using the Simpson biplane method according to the guidelines of the American Society of Echocardiography. Global LV function was also assessed by mitral annular systolic velocity averaged from six sites.⁹ Peak systolic tissue velocity, strain rate, and strain were calculated from tissue Doppler velocity data averaged over three consecutive beats. The timings of aortic valve opening and closure were made from the tissue Doppler waveform. The Myocardial Doppler in Stress Echocardiography study demonstrated that CAD could be diagnosed accurately and objectively from off-line measurements of myocardial velocities recorded by tissue Doppler echocardiography during dobutamine stress.¹⁰ In particular, strain rate imaging has been shown to provide objective evidence of inducible ischemia¹¹ and may be a superior parameter to peak tissue velocity.¹²

A diameter stenosis of >70% stenosis on coronary angiography was considered hemodynamically significant. Myocardial segments were assigned to the perfusion territories of stenosed vessels, considering the left anterior descending coronary artery to supply the anterior and antero-septal segments, the right coronary artery (when dominant) to supply the inferior and inferoseptal segments, and the circumflex artery to supply the anterolateral and inferolateral segments.

Statistics

The number of subjects had been calculated on the basis of previous work in patients with CAD in whom ejection fraction increased from $57.0 \pm 5.6\%$ to $66.0 \pm 6.7\%$ when dobutamine stress was performed during a hyperinsulinemic, euglycemic clamp. To detect a change in global LV ejection fraction of 5% after dobutamine stress (standardized effect size of 1), 17 patients were required (paired *t* test, $\alpha=0.05$, $\beta=0.20$). However, to allow for possible suboptimal image quality and incomplete data, we planned to recruit 20 subjects. Each patient acted as his or her own control, and comparisons were made between the sitagliptin and control DSE scans. Categorical data are expressed as numbers (percentages) and compared by use of McNemar test. Continuous and discrete variables are expressed as mean \pm SD and compared by use of the paired Student *t* test or the Wilcoxon signed-rank test where appropriate after testing for normality of distribution using the Shapiro–Wilk test. In the case of borderline significant

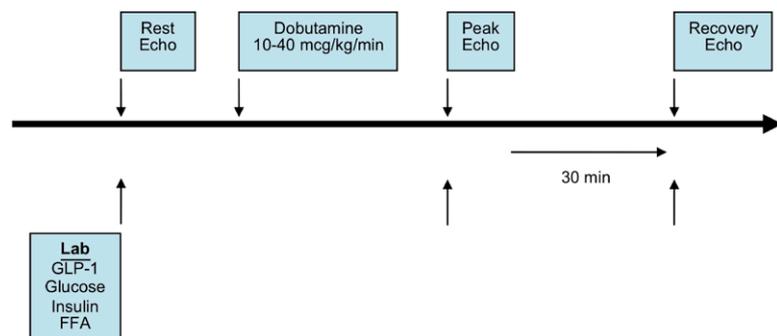


Figure 1. Flow chart illustrating the study design and timeline. FFA indicates free fatty acids; and GLP-1, glucagon-like peptide-1.

results for echocardiographic parameters, further analysis was performed using a mixed effects repeated measures model. A random intercept was included at the patient and patient–time–treatment level, and a random time effect with an unstructured variance-covariance matrix was included at the patient–segment and patient–segment–treatment level. The choice of covariance structure was determined using post hoc examination of the Akaike information criterion (AIC). Two-tailed tests were used on all occasions, and a probability value of <0.05 was considered statistically significant. Intra- and interobserver variations were calculated using the Bland–Altman method and expressed as the coefficient of variation (SD divided by the average value of the variable) \pm the 95% limits of agreement.

Results

Study Population

A total of 20 patients were assigned; however, 1 patient's images were not of sufficient quality to enable accurate assessment of myocardial deformation imaging parameters (Figure 2). Therefore, 19 patients completed the study (Table 1). Of these, 12 (63%) patients had single-vessel CAD, 4 (21%) patients had double-vessel disease, and 3 (16%) patients had triple-vessel disease. The left anterior descending artery was involved in 53%, the left circumflex artery in 47%, and the right coronary artery in 63% of patients.

Dobutamine Stress Echocardiography

The 2 DSEs were performed 30 ± 5 days apart. There was no difference in the rate–pressure products at baseline, peak stress, or recovery between the sitagliptin and control scans (Table 2). The number of patients experiencing ischemic chest pain did not differ between the 2 DSEs. Similarly, at peak stress, there was no significant difference in ST segment shift (0.95 ± 0.51

Table 1. Demographics and Clinical Data of Participants

Demographics	
Age, y	66.1 \pm 9.6
Male sex	16 (80)
BMI, kg/m ²	30.5 \pm 5.2
Type 2 diabetes mellitus	20 (100)
Active/ex-smoker	9 (45)
Hypertension	17 (85)
Hypercholesterolemia	11 (55)
FHx CAD	9 (45)
Biochemistry	
Total cholesterol, mmol/L	3.7 \pm 1.0
HbA1c, %	7.35 \pm 0.87
HOMA IR	3.27 \pm 2.16
Oral hypoglycemic agents	
Metformin	19 (95)
Sulfonylurea	7 (35)
Thiazolidinedione	4 (20)
Antianginal medications	
β -blocker	14 (70)
Calcium channel antagonist	6 (30)
Long-acting nitrate	3 (15)
Nicorandil	1 (5)

Data are presented as mean \pm SD or n (%). BMI indicates body mass index; FHx CAD, family history of coronary artery disease; HbA1c, glycosylated hemoglobin; and HOMA IR, homeostasis model assessment of insulin resistance.

[sitagliptin] versus 1.10 ± 0.47 mm [control]; $P=0.09$) or segmental motion abnormalities (5.21 ± 4.71 [sitagliptin] versus 5.63 ± 4.41 [control]; $P=0.13$) after DPP-4 inhibition.

Biochemistry

Blood samples were taken in the fasted state at baseline, during peak dobutamine stress, and in the recovery phase at 30 minutes after cessation of dobutamine. At all 3 time points, the plasma GLP-1 (7–36) concentration after sitagliptin was 5 to 8 times greater than control (baseline: 12.7 ± 9.0 versus 1.6 ± 1.4 pg/mL; $P=0.0005$; peak stress: 13.2 ± 9.9 versus 2.6 ± 2.6 pg/mL; $P=0.0005$; recovery: 9.5 ± 7.2 versus 1.3 ± 1.2 pg/mL; $P=0.007$). However, plasma glucose levels were not significantly different (Figure 3).

At baseline, there were no differences in the plasma concentrations of insulin (94.1 ± 93.2 [sitagliptin] versus 74.1 ± 55.3 pmol/L [control]; $P=0.67$) or FFA (431 ± 178 [sitagliptin] versus 483 ± 147 umol/L [control]; $P=0.48$). During a DSE, insulin is released because of the direct effect of dobutamine on the pancreatic islet cells. However, there was no difference in insulin concentration (171 ± 140 [sitagliptin] versus 201 ± 177 pmol/L [control]; $P=0.43$) or in the plasma level of FFA (900 ± 269 [sitagliptin] versus 968 ± 345 umol/L [control]; $P=0.42$) at peak stress. Similarly, in the recovery phase at 30 minutes after cessation of dobutamine, there were no differences in the concentration of insulin (74 ± 54 [sitagliptin] versus 73 ± 38 pmol/L [control]; $P=0.34$) or FFA (611 ± 238 [sitagliptin] versus 701 ± 285 umol/L [control]; $P=0.13$; Figure 3).

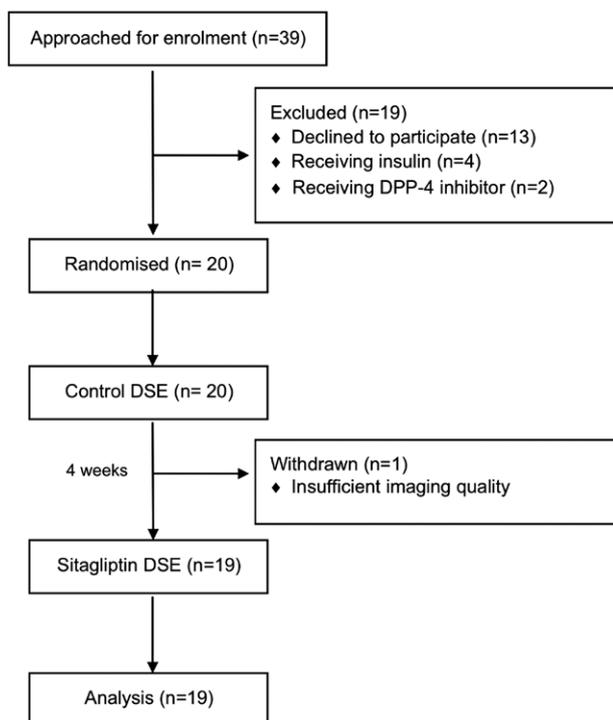


Figure 2. Consort diagram illustrating study recruitment. DPP-4 indicates dipeptidyl peptidase-4; and DSE, dobutamine stress echocardiography.

Table 2. Hemodynamic Data During DSE Scans

	Peak Stress			Recovery		
	Control	Sitagliptin	<i>P</i> Value	Control	Sitagliptin	<i>P</i> Value
Heart rate, bpm	126±9	126±11	0.93	72±10	74±10	0.23
Systolic blood pressure, mm Hg	155±32	155±28	0.96	137±22	137±18	0.90
Diastolic blood pressure, mm Hg	69±12	78±17	0.06	83±17	83±14	0.91
Rate-pressure product, mm Hg·bpm	19662±4804	19464±3218	0.83	10142±2377	10373±1913	0.89

DSE indicates dobutamine stress echocardiography.

Global LV Function

There was no difference in ejection fraction at rest before both studies (56.5±6.0 [sitagliptin] versus 56.7±5.1% [control]; $P=0.81$). At peak stress, there was a greater increase in LV function after DPP-4 inhibition (Figure 2; 70.5±7.0 [sitagliptin] versus 65.7±8.0% [control]; $P<0.0001$), and this improved performance persisted into recovery (56.0±6.2 [sitagliptin] versus 51.2±6.0% [control]; $P<0.0001$; Figure 4). During the control scan, there was evidence of postischemic LV dysfunction (stunning) compared with baseline (51.2±6.0 versus 56.7±5.1%; $P<0.0001$), but this did not occur after sitagliptin.

Assessment of global LV function by mitral annular systolic velocity confirmed these findings. At rest, LV function was similar before both studies (5.67±1.29 [sitagliptin] versus 5.70±1.28 cm/s [control]; $P=0.87$). However, after sitagliptin, myocardial performance was enhanced both at peak stress (11.69±2.64 [sitagliptin] versus 10.9±2.29 cm/s [control]; $P=0.01$) and at 30 minutes after dobutamine stress (5.81±1.16 [sitagliptin] versus 5.53±1.21 cm/s [control]; $P=0.03$).

Regional Wall LV Function

For the 12 paired, nonapical segments, DPP-4 inhibition was associated with a small increase in peak systolic tissue velocity at rest (4.59±1.68 [sitagliptin] versus 4.44±1.69 cm/s [control]; $P=0.02$), but there were no differences in strain rate or strain. At peak dobutamine stress, all 3 parameters of regional wall function were enhanced after sitagliptin, and these improvements persisted into recovery (Table 3). However, the effect of sitagliptin was greater on peak systolic tissue velocity and strain rate than for strain. To assess this in more detail and allow for differences in the variance of measures over time, further analysis was undertaken for strain using a mixed effects repeated measures model. This demonstrated that the effect of sitagliptin on peak systolic strain was borderline significant at both peak stress (estimated effect 0.83%; $P=0.06$) and 30 minutes recovery (estimated effect 0.84%; $P=0.06$; Table 4). In the control studies, there was a reduction in strain (−14.8±5.55 versus −16.2±5.51%; $P=0.03$) and strain rate (−1.03±0.29 versus −1.1±0.34 s^{−1}, $P=0.005$), and there was borderline significant difference in velocity (4.16±1.7 versus 4.44±1.69 cm/s; $P=0.06$) at 30 minutes compared with

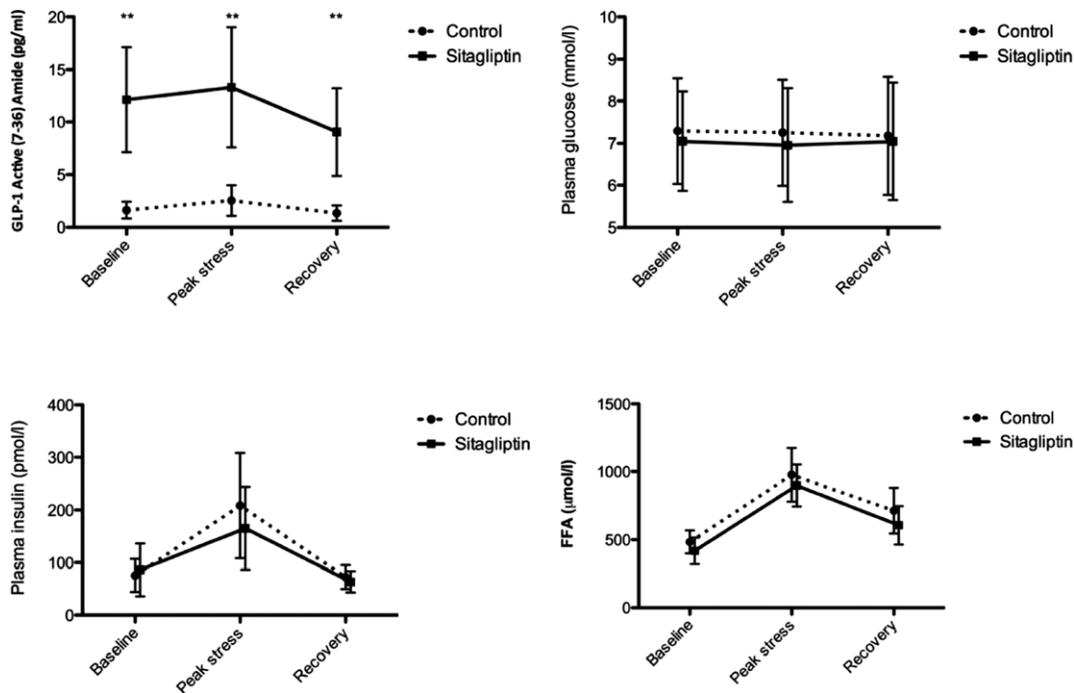


Figure 3. Biochemical data (mean±SEM) during the dobutamine stress echocardiography scans at baseline, peak stress, and 30-minute recovery. FFA indicates free fatty acids; and GLP-1, glucagon-like peptide-1. ** $P<0.001$.

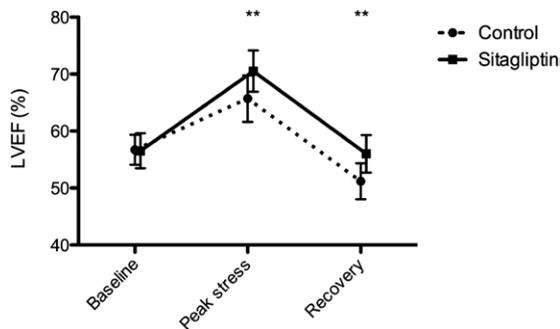


Figure 4. Global left ventricular (LV) function assessed by LV ejection fraction (LVEF; mean \pm SEM) at baseline, peak stress, and 30-minute recovery. ** $P<0.0001$.

baseline. This did not occur with sitagliptin where all 3 parameters were unchanged from baseline.

Ischemic versus Nonischemic Segments

Regions subtended by an artery with a stenosis $>70\%$ on coronary angiography were defined as potentially subject to demand ischemia during DSE. Sitagliptin had a greater beneficial effect on ischemic than on nonischemic segments (Table 5).

Reproducibility

Reproducibility was assessed in 6 randomly selected patients for the images recorded at rest, at peak stress, and in recovery. The intra- and interobserver variations for the tissue Doppler imaging parameters were $6.1\pm 1.0\%$ and $6.4\pm 1.0\%$, respectively, for mitral annular systolic velocity, $7.2\pm 1.0\%$ and $5.8\pm 0.8\%$ for tissue velocity, $11.0\pm 3.6\%$ and $12.6\pm 4.0\%$ for strain, and $9.7\pm 0.3\%$ and $11.6\pm 0.3\%$ for strain rate. For LV ejection fraction, the intraobserver variation was $5.7\pm 7.0\%$, and the interobserver variation was $6.6\pm 8.2\%$.

Discussion

In this pilot study, we have demonstrated that the addition of DPP-4 inhibitor therapy with sitagliptin to the treatment regime of patients with T2DM and CAD can protect the heart from ischemic LV dysfunction during dobutamine stress and mitigate postischemic stunning. Furthermore, these beneficial effects are sustained after a month's therapy.

Compared with control, sitagliptin was associated with improved parameters of both global and regional LV performance at peak stress and 30 minutes into recovery. These effects were predominantly driven by a reduction in contractile dysfunction in regions subject to demand ischemia. At the time of the second DSE, DPP-4 inhibitor therapy resulted in GLP-1 (7–36) concentrations that were 5 to 8 times greater

than that during the control scan. As expected, this was associated with lower fasting plasma glucose levels. However, importantly, the rise in plasma insulin was also lower after sitagliptin, suggesting that the cardioprotective effects seen were not because of insulin.

We observed that sitagliptin had a greater effect on peak systolic tissue velocity and strain rate than strain. This apparent discrepancy may represent a limitation of the velocity gradient method, whereby strain rate is calculated from the derived velocity data sets, with strain then subsequently obtained by integration over time. However, time-integration can result in drifting of the strain curve, which may be magnified further during DSE because of higher heart rates and angle changes during the cardiac cycle. It should also be noted that the effects of incremental doses of dobutamine on peak systolic strain (which either remains unchanged or demonstrates a biphasic response) are more variable than for tissue velocity and strain rate (both of which increase linearly).¹¹ As a result, differences in strain may be more difficult to detect.

In patients with T2DM, CAD continues to be a major cause of morbidity and mortality.¹³ However, with contemporary randomized studies failing to demonstrate any prognostic benefit of percutaneous revascularization over medical therapy,¹⁴ it is clear that there is an ongoing requirement for the development of new treatment strategies for these high-risk individuals. Our data indicate that DPP-4 inhibition may offer an important therapeutic adjunct as a metabolic agent for cardioprotection in patients with diabetes mellitus. However, it should be emphasized that we have demonstrated this effect using echocardiographic, and not clinical, end points. Our findings should therefore be interpreted with caution, and considered preliminary and hypothesis-generating, until the results of large, prospective randomized studies (with clinical outcome data) have been reported.

During the last decade, there has been an increasing body of evidence to indicate a cardioprotective effect of GLP-1 modulation in humans. This has been demonstrated in a variety of clinical settings, including chronic LV dysfunction,^{15,16} acute myocardial infarction,^{17,18} the perioperative period of coronary artery bypass graft surgery,^{19,20} with demand ischemia during dobutamine stress,²¹ and supply ischemia during elective percutaneous coronary intervention.²² In animal studies that have assessed cardiac metabolic alterations, GLP-1 modulation was associated with increased myocardial glucose uptake,²³ reduced myocardial levels of lactate and pyruvate,²⁴ and an increase in the relative oxidation of carbohydrate versus fat.²³ GLP-1 may therefore confer its favorable cardiovascular effects by inducing a shift toward greater myocardial glucose use, an adaptive response that is known to be more oxygen

Table 3. Regional Wall LV Function

	Baseline			Peak Stress			Recovery		
	Control	Sitagliptin	<i>P</i> Value	Control	Sitagliptin	<i>P</i> Value	Control	Sitagliptin	<i>P</i> Value
V_s , cm/s	4.44 \pm 1.69	4.59 \pm 1.68	0.02	8.98 \pm 3.62	9.44 \pm 3.81	0.0002	4.16 \pm 1.67	4.46 \pm 1.55	<0.0001
Strain rate, s ⁻¹	-1.1 \pm 0.34	-1.1 \pm 0.3	0.90	-2.08 \pm 0.57	-2.23 \pm 0.58	<0.0001	-1.03 \pm 0.29	-1.11 \pm 0.27	<0.0001
Strain, %	-16.2 \pm 5.5	-16.5 \pm 5.2	0.34	-15.3 \pm 5.9	-16.0 \pm 5.5	0.046	-14.8 \pm 5.4	-15.8 \pm 5.5	0.007

LV indicates left ventricular.

Table 4. Random Effects Repeat Measures Model Estimates of Treatment Effects (Sitagliptin–Control) for Peak Systolic Strain

Time Point	Estimate (SE)	95% Confidence Interval	Degrees of Freedom (Kenward–Roger Method)	P Value
Baseline	0.289 (0.457)	–0.629, 1.207	49.3	0.530
Peak	0.835 (0.437)	–0.047, 1.716	42.1	0.063
Recovery	0.836 (0.426)	–0.022, 1.693	46.6	0.056

efficient than fatty acid metabolism²⁵ but is impaired in the context of insulin resistance. The results of this study support this concept because ischemic segments derive more benefit than nonischemic segments. Interestingly, it has recently been reported that GLP-1 levels are lower in patients with CAD than those without, an effect that seems to be independent of the presence of diabetes mellitus.²⁶

In contrast, there are few studies investigating the cardioprotective effects of DPP-4 inhibition. In a porcine model of ischemia-reperfusion injury, pretreatment with vildagliptin was associated with a reduction in infarct size and an increase in ventricular fibrillation thresholds.⁵ DPP-4 inhibition has also been shown to limit the size of myocardial infarction in rodents.^{3,4} In the only human study to date, involving 14 patients with CAD, there was an acute improvement in parameters of both global and regional LV systolic function after a single dose of sitagliptin, when administered in conjunction with an oral glucose load. The beneficial effects were seen predominantly in ischemic segments and persisted into recovery, with mitigation of postischemic stunning. However, only 1 of these patients had diabetes mellitus.⁸ The data from our study demonstrate, for the first time, that chronic DPP-4 inhibition may also provide sustained cardioprotection in patients with T2DM and CAD.

Although it is conceivable that the cardioprotection conferred by DPP-4 inhibition is mediated solely via its effects on GLP-1, some data suggest that it may occur, at least in part, independently of incretin signaling pathways. For example, the elevation in GLP-1 levels seen with DPP-4 inhibitors is significantly lower than that with exogenous GLP-1 administration. Furthermore, there is an increasing recognition of the cardiovascular significance of several endogenous physiological substrates targeted by DPP-4 that are unrelated to incretin biology.⁶ These include stromal cell–derived factor 1- α , which enhances ischemic

neovascularization via recruitment of endothelial progenitor cells,²⁷ and substance P, which plays an important role in vascular biology and atherosclerosis through the stimulation of endothelial nitric oxide release.²⁸ Indeed, in patients with T2DM, sitagliptin has been shown to increase circulating levels of endothelial progenitor cells with concomitant upregulation of stromal cell–derived factor 1- α ²⁹ and is also associated with improved peripheral endothelial function.³⁰

Limitations

This study has several important limitations. First, the potential cardioprotective effect of DPP-4 inhibition has been assessed in an unblinded and nonrandomized fashion in only a small number of patients. Second, we have used tissue Doppler-derived indices of myocardial deformation to assess regional LV function, which has several potential pitfalls compared with two-dimensional speckle tracking echocardiography (STE). These include a high dependence on a favorable angle of incidence during image acquisition, an inability to accurately assess apical segments, and potentially high interobserver and intraobserver variations. However, because tissue Doppler-derived indices allow for measurements of strain and strain rate with excellent temporal resolution, this technique may be advantageous to STE at times of higher heart rates (eg, during dobutamine stress). Third, although all attempts were made to perform the 2 DSE scans for each patient in identical fashion and to obtain the peak stress images at the same degree of dobutamine stress, we cannot exclude the possibility of a degree of variation in the response of individual patients to dobutamine on the 2 separate study days.

Conclusions

The addition of DPP-4 inhibitor therapy with sitagliptin to the treatment regime of patients with T2DM and CAD is

Table 5. Ischemic versus Nonischemic Segments

	Peak Stress			Recovery		
	Control	Sitagliptin	P Value	Control	Sitagliptin	P Value
Ischemic segments						
V_s , cm/s	8.23±3.09	8.64±3.42	0.03	3.94±1.77	4.36±1.51	<0.0001
Strain rate, s ⁻¹	–1.98±0.58	–2.27±0.65	<0.0001	–1.0±0.29	–1.12±0.30	<0.0001
Strain, %	–14.5±5.9	–15.8±5.7	0.005	–14.0±5.0	–15.4±5.6	0.002
Nonischemic segments						
V_s , cm/s	9.76±3.98	10.3±4.0	0.001	4.38±1.56	4.54±1.60	0.08
Strain rate, s ⁻¹	–2.18±0.54	–2.19±0.48	0.87	–1.05±0.3	–1.10±0.25	0.04
Strain, %	–16.2±5.7	–16.2±5.4	0.93	–15.7±5.7	–16.1±5.4	0.36

associated with a sustained improvement in myocardial performance during dobutamine stress and a reduction in post-ischemic stunning, a response predominantly driven by a cardioprotective effect on ischemic regional wall segments. Further randomized studies involving larger cohorts of patients are required to ascertain whether these effects translate into an improvement in clinical outcomes.

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Disclosures

None.

References

- Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab*. 2011;13:7–18.
- Sauvé M, Ban K, Momen MA, Zhou YQ, Henkelman RM, Husain M, Drucker DJ. Genetic deletion or pharmacological inhibition of dipeptidyl peptidase-4 improves cardiovascular outcomes after myocardial infarction in mice. *Diabetes*. 2010;59:1063–1073.
- Ye Y, Keyes KT, Zhang C, Perez-Polo JR, Lin Y, Birnbaum Y. The myocardial infarct size-limiting effect of sitagliptin is PKA-dependent, whereas the protective effect of pioglitazone is partially dependent on PKA. *Am J Physiol Heart Circ Physiol*. 2010;298:H1454–H1465.
- Huisamen B, Genis A, Marais E, Lochner A. Pre-treatment with a DPP-4 inhibitor is infarct sparing in hearts from obese, pre-diabetic rats. *Cardiovasc Drugs Ther*. 2011;25:13–20.
- Chinda K, Palee S, Surinkaew S, Phornphutkul M, Chattipakorn S, Chattipakorn N. Cardioprotective effect of dipeptidyl peptidase-4 inhibitor during ischemia-reperfusion injury. *Int J Cardiol*. 2013;167:451–457.
- Zhong J, Rao X, Rajagopalan S. An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: potential implications in cardiovascular disease. *Atherosclerosis*. 2013;226:305–314.
- Ban K, Noyan-Ashraf MH, Hofer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation*. 2008;117:2340–2350.
- Read PA, Khan FZ, Heck PM, Hoole SP, Dutka DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. *Circ Cardiovasc Imaging*. 2010;3:195–201.
- Pellerin D, Sharma R, Elliott P, Veyrat C. Tissue Doppler, strain, and strain rate echocardiography for the assessment of left and right systolic ventricular function. *Heart*. 2003;89(Suppl 3):iii9–iii17.
- Mädler CF, Payne N, Wilkeshoff U, Cohen A, Derumeaux GA, Piérard LA, Engvall J, Brodin LA, Sutherland GR, Fraser AG; Myocardial Doppler in Stress Echocardiography (MYDISE) Study Investigators. Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography: optimal diagnostic models using off-line tissue Doppler in the MYDISE study. *Eur Heart J*. 2003;24:1584–1594.
- Voigt JU, Exner B, Schmiedehausen K, Huchzermeyer C, Reulbach U, Nixdorff U, Platsch G, Kuwert T, Daniel WG, Flachskampf FA. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. *Circulation*. 2003;107:2120–2126.
- Voigt JU, Nixdorff U, Bogdan R, Exner B, Schmiedehausen K, Platsch G, Kuwert T, Daniel WG, Flachskampf FA. Comparison of deformation imaging and velocity imaging for detecting regional inducible ischaemia during dobutamine stress echocardiography. *Eur Heart J*. 2004;25:1517–1525.
- Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;115:114–126.
- Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.
- Thrainsdottir I, Malmberg K, Olsson A, Gutniak M, Rydén L. Initial experience with GLP-1 treatment on metabolic control and myocardial function in patients with type 2 diabetes mellitus and heart failure. *Diab Vasc Dis Res*. 2004;1:40–43.
- Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail*. 2006;12:694–699.
- Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, Shannon RP. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation*. 2004;109:962–965.
- Lønborg J, Vejstrup N, Kelbæk H, Bøtker HE, Kim WY, Mathiasen AB, Jørgensen E, Helqvist S, Saunamäki K, Clemmensen P, Holmvang L, Thuesen L, Krusell LR, Jensen JS, Køber L, Treiman M, Holst JJ, Engström T. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2012;33:1491–1499.
- Sokos GG, Bolukoglu H, German J, Hentosz T, Magovern GJ Jr, Maher TD, Dean DA, Bailey SH, Marrone G, Benckart DH, Elahi D, Shannon RP. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. *Am J Cardiol*. 2007;100:824–829.
- Müssig K, Oncü A, Lindauer P, Heininger A, Aebert H, Unertl K, Ziemer G, Häring HU, Holst JJ, Gallwitz B. Effects of intravenous glucagon-like peptide-1 on glucose control and hemodynamics after coronary artery bypass surgery in patients with type 2 diabetes. *Am J Cardiol*. 2008;102:646–647.
- Read PA, Khan FZ, Dutka DP. Cardioprotection against ischaemia induced by dobutamine stress using glucagon-like peptide-1 in patients with coronary artery disease. *Heart*. 2012;98:408–413.
- Read PA, Hoole SP, White PA, Khan FZ, O'Sullivan M, West NE, Dutka DP. A pilot study to assess whether glucagon-like peptide-1 protects the heart from ischemic dysfunction and attenuates stunning after coronary balloon occlusion in humans. *Circ Cardiovasc Interv*. 2011;4:266–272.
- Bao W, Aravindhan K, Alsaid H, Chendrimada T, Szapacs M, Citerone DR, Harpel MR, Willette RN, Lepore JJ, Jucker BM. Albiglutide, a long lasting glucagon-like peptide-1 analog, protects the rat heart against ischemia/reperfusion injury: evidence for improving cardiac metabolic efficiency. *PLoS One*. 2011;6:e23570.
- Kavianipour M, Ehlers MR, Malmberg K, Ronquist G, Rydén L, Wikström G, Gutniak M. Glucagon-like peptide-1 (7-36) amide prevents the accumulation of pyruvate and lactate in the ischemic and non-ischemic porcine myocardium. *Peptides*. 2003;24:569–578.
- Liedtke AJ. Alterations of carbohydrate and lipid metabolism in the acutely ischemic heart. *Prog Cardiovasc Dis*. 1981;23:321–336.
- Matsubara J, Sugiyama S, Sugamura K, Nakamura T, Fujiwara Y, Akiyama E, Kurokawa H, Nozaki T, Ohba K, Konishi M, Maeda H, Izumiya Y, Kaikita K, Sumida H, Jinnouchi H, Matsui K, Kim-Mitsuyama S, Takeya M, Ogawa H. A dipeptidyl peptidase-4 inhibitor, des-fluoro-sitagliptin, improves endothelial function and reduces atherosclerotic lesion formation in apolipoprotein E-deficient mice. *J Am Coll Cardiol*. 2012;59:265–276.
- Yamaguchi J, Kusano KF, Masuo O, Kawamoto A, Silver M, Murasawa S, Bosch-Marce M, Masuda H, Losordo DW, Isner JM, Asahara T. Stromal cell-derived factor-1 effects on ex vivo expanded endothelial progenitor cell recruitment for ischemic neovascularization. *Circulation*. 2003;107:1322–1328.
- Napoli C, de Nigris F, Williams-Ignarro S, Pignalosa O, Sica V, Ignarro LJ. Nitric oxide and atherosclerosis: an update. *Nitric Oxide*. 2006;15:265–279.
- Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, de Kreutzenberg S, Agostini C, Tiengo A, Avogaro A. The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in

- patients with type 2 diabetes: possible role of stromal-derived factor-1alpha. *Diabetes Care*. 2010;33:1607–1609.
30. Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K, Maeda H, Fujisue K, Yamamoto E, Kaikita K, Hokimoto S, Jinnouchi

H, Ogawa H. Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. *Circ J*. 2013;77:1337–1344.

CLINICAL PERSPECTIVE

Coronary artery disease is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus, but there is uncertainty regarding the cardiovascular safety of some antidiabetic drugs. Newer classes of oral hypoglycemic agents, such as the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors, act by potentiating the glucoregulatory effects of the incretin hormone GLP-1. Besides its actions on the pancreas, GLP-1 is also increasingly recognized as having metabolic effects on the cardiovascular system. In animal studies, the peptide has been shown to induce a shift toward greater myocardial glucose use, which is more oxygen efficient than fatty acid metabolism, and therefore potentially advantageous at times of myocardial ischemia. There is increasing evidence to support a cardioprotective effect of GLP-1 in humans, although most of these data relate to the administration of exogenous GLP-1 or a GLP-1 receptor agonist. Relatively little is known regarding the effect of dipeptidyl peptidase-4 inhibitors on the myocardium. This study demonstrates that in patients with type 2 diabetes mellitus and coronary artery disease, dipeptidyl peptidase-4 inhibition with sitagliptin is associated with a sustained improvement in myocardial performance during demand ischemia induced by dobutamine stress and a reduction in postischemic stunning, a response predominantly driven by a cardioprotective effect on ischemic regional wall segments. Although these findings are encouraging, it remains to be determined whether they will translate to an improvement in clinical outcomes for patients with coronary artery disease and type 2 diabetes mellitus.