



Anti-Diabetic Agents and Heart Failure

— Response to the CARMELINA Study —

Motoaki Sano, MD, PhD

According to cardiovascular outcome trials, some anti-diabetic drugs can improve cardiovascular outcomes in patients with type 2 diabetes. Sodium glucose cotransporter 2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) have a strong preventive effect on both hospitalization for heart failure and the decline in kidney function in patients with type 2 diabetes, while glucagon-like peptide-1 receptor agonists, especially human glucagon-like peptide-1 receptor agonists (liraglutide, semaglutide, and albiglutide), suppress arteriosclerotic diseases (stroke and myocardial infarction). Using these medications in combination could possibly prevent both hospitalization for heart failure and arteriosclerotic events. Dipeptidyl peptidase 4 (DPP-4) inhibitors are preferentially used as add-on therapy for type 2 diabetes. Cardiovascular outcome trials conducted so far suggest that DPP-4 inhibitors (sitagliptin, alogliptin, and saxagliptin) do not promote arteriosclerotic disease, but there may be a difference between these drugs with regard to safety for heart failure. Previous cardiovascular outcome trials have mainly focused on type 2 diabetes patients with established cardiovascular disease. In contrast, the CARMELINA study investigated the cardiovascular safety of linagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes and kidney dysfunction.

Key Words: Cardiovascular outcome; Dipeptidyl peptidase 4 inhibitor; Heart failure; Sodium glucose cotransporter 2 inhibitor; Type 2 diabetes mellitus

The main objectives of diabetes mellitus treatment are to allow patients to live their daily lives like healthy persons and to achieve a normal lifespan, with good glycemic control merely being one of the methods for achieving these objectives. To achieve these treatment goals, it is important to avoid progression to end-stage renal disease or dialysis and to prevent the onset and progression of macroangiopathy that leads to complications such as angina pectoris, myocardial infarction, cerebrovascular disease, and arteriosclerosis obliterans.

Patients with diabetes have an elevated risk of developing heart failure (HF). According to recent clinical studies on cardiovascular outcomes in diabetes, HF is a more frequent complication than myocardial infarction or stroke.^{1–3} In patients with diabetes, HF impairs the quality of life⁴ and is the morbidity most directly linked to death.⁵ HF is a disease in which shortness of breath and peripheral edema occur, owing to poor cardiac function, and it progresses gradually, shortening the lifespan. If patients have had diabetes for a long time, they often also have organic or functional cardiac impairment. Even if patients do not have ischemic heart disease or left ventricular hypertrophy secondary to hypertension, diastolic function is generally reduced due to diabetic cardiomyopathy. Considering that the 5-year survival rate of patients with diabetes complicated by HF is only 20%, while that of general HF patients is

50%, diabetes associated with HF has an extremely poor prognosis.

Therefore, to improve the quality of life and prognosis of patients with diabetes, it is not only essential to prevent end-stage renal disease and suppress macroangiopathy (myocardial infarction and stroke), but also to ensure that the therapeutic strategy takes the potential impact on HF into account. In this context, the recent availability of new classes of anti-diabetic agents has led to suggestions that treatment of diabetes should be reconsidered.

These new agents include glucagon-like peptide-1 receptor agonists,^{6,7} which are reported to suppress the onset and progression of macroangiopathy, and sodium glucose cotransporter 2 (SGLT2) inhibitors that improve hard renal endpoints (composite of dialysis/renal transplantation, doubling of serum creatinine, and renal death/cardiovascular death) and prevent hospitalization due to HF.

SGLT2 Inhibitors

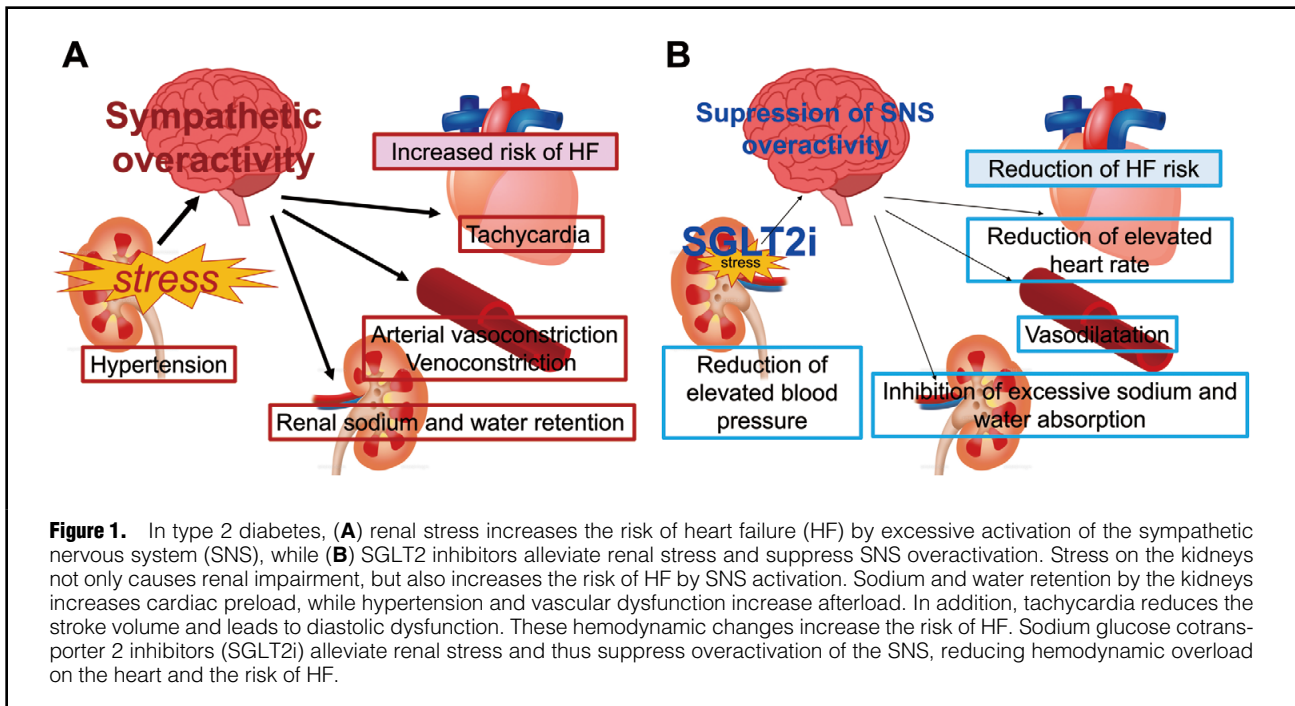
In patients with diabetes, the kidneys (especially the glomeruli and proximal tubules) are under severe stress. SGLT2 inhibitors prevent excessive sodium reabsorption in the proximal tubules, restoring the tubuloglomerular feedback mechanism and thus correcting glomerular hypertension and glomerular hyperfiltration.⁸ This mechanism is

Received November 9, 2018; accepted November 9, 2018; J-STAGE Advance Publication released online December 11, 2018
Time for primary review: 1 day

Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

Mailing address: Motoaki Sano, MD, PhD, Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: msano@a8.keio.jp

ISSN-2434-0790 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cr@j-circ.or.jp

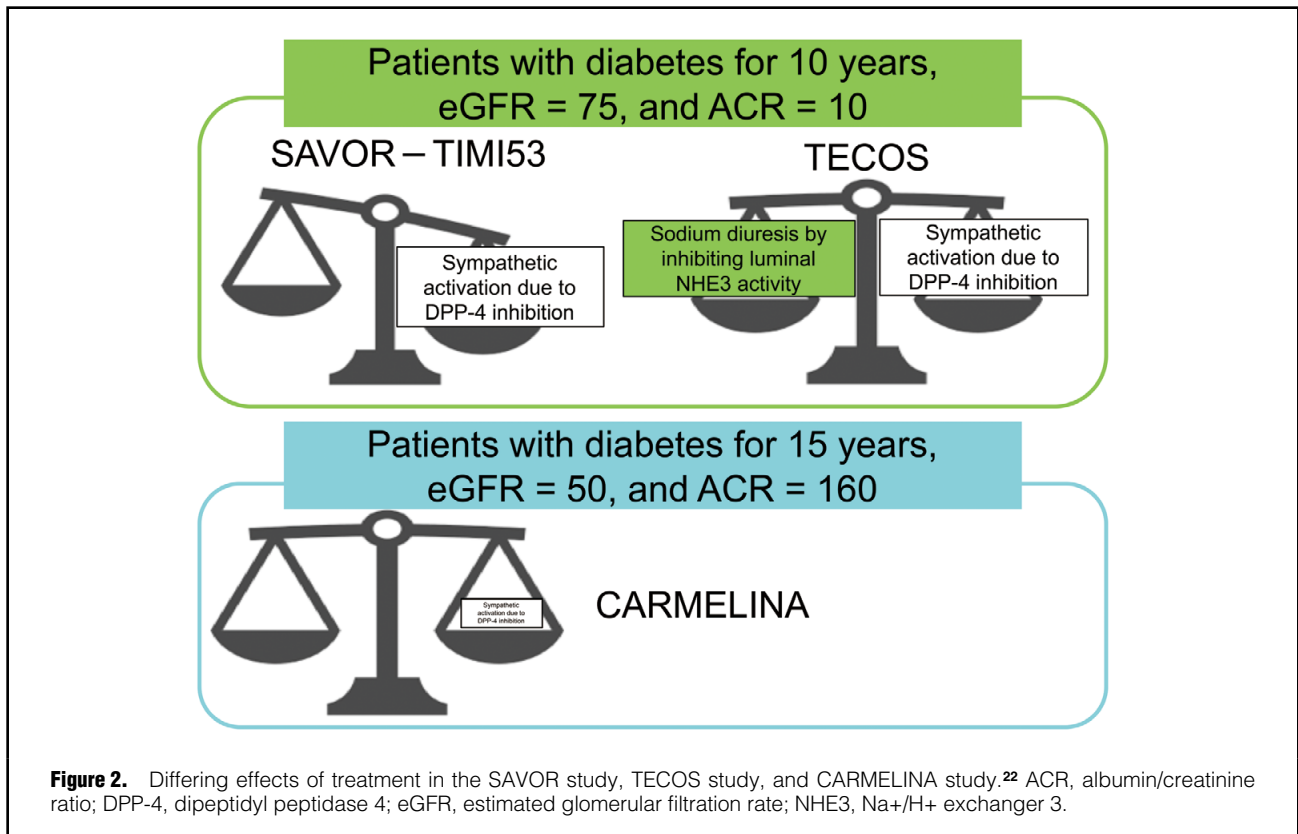


supported by detection of an initial dip in the estimated glomerular filtration rate (eGFR) as early as 4 weeks after the start of SGLT2 inhibitor therapy. Oxygen consumption by epithelial cells in the proximal convoluted tubules is increased due to reabsorption of excess glucose, which reduces the partial pressure of oxygen in the kidney cortex. The exhausted proximal convoluted tubular epithelial cells are rested by SGLT2 inhibition, allowing restoration of the tubulointerstitial environment.⁹⁻¹¹ The CREDENCE study examined the effect of canagliflozin vs. placebo on hard renal endpoints in diabetic patients with overt albuminuria and reduced eGFR, and it was terminated early due to positive findings.

When the kidneys are affected by glomerular/tubular stress due to excessive reabsorption of sodium and glucose in the proximal tubules, it is thought that the afferent renal nerves send signals to the brain, which provoke systemic activation of the sympathetic nervous system (SNS). The result is increased reabsorption of sodium and water by the kidneys, along with vasoconstriction, a higher pulse rate, and elevation of the blood pressure. This loss of homeostasis leads to hemodynamic imbalance that increases the cardiac workload and the risk of HF. By alleviating stress on the kidneys, SGLT2 inhibitors suppress overactivation of the SNS and reduce hemodynamic stress on the heart, thus preventing hospitalization due to HF. The unique finding of heart rate reduction after initiation of SGLT 2 inhibitor therapy in patients with type 2 diabetes is evidence that these drugs suppress systemic overactivation of the SNS by alleviating stress on the kidneys.¹² SGLT2 inhibitors reduce the heart rate in diabetic patients with a rapid resting heart rate, decreasing it by approximately 10 beats/min when the resting heart rate is ≥ 80 beats/min. In contrast, SGLT2 inhibitors do not reduce the heart rate in patients with a resting rate of around 60 beats/min. These data suggest that the renoprotective effect of SGLT2 inhibitors is linked to their preventive effect on HF (Figure 1).

DPP-4 Inhibitors

It has been estimated that dipeptidyl peptidase 4 (DPP-4) inhibitors are prescribed for $>60\%$ of the patients using anti-diabetic agents in Japan. In the kidneys, DPP-4 is expressed by tubular luminal cells of the proximal tubules,¹³ and it forms a complex with Na⁺/H⁺ exchanger 3 (NHE3) that is involved in sodium reabsorption.¹⁴ Inhibition of DPP-4 in tubular luminal cells also blocks the action of NHE3 and suppresses sodium reabsorption, resulting in the promotion of sodium diuresis. In order to inhibit DPP-4 in the tubular luminal cells, however, it is necessary for a DPP-4 inhibitor to be excreted in the primitive urine as the active compound, and the urinary excretion rate of the active compound varies substantially between these drugs. Urinary sodium excretion is significantly increased by sitagliptin, which is excreted in the urine.¹⁵ In the TECOS study, eGFR was decreased as early as 4 weeks after the start of sitagliptin treatment only in patients with baseline eGFR ≥ 90 mL/min/1.73 m².¹⁶ When ambulatory blood pressure monitoring was performed before and after 5 days of treatment with sitagliptin or placebo, significant reduction of blood pressure by sitagliptin was seen.¹⁷ In patients with a 10-year duration of diabetes, mean eGFR=75 mL/min/1.73 m², and mean albumin/creatinine ratio (ACR)=10, different results were obtained by the TECOS study of sitagliptin (excreted in the urine)¹⁸ and the SAVOR study of saxagliptin (not excreted in the urine).¹⁹ Although both sitagliptin and saxagliptin did not increase cardiovascular mortality or cardiovascular events (myocardial infarction and stroke), saxagliptin significantly increased hospitalization for HF by 1.28-fold (95% CI: 1.07–1.51). It was reported that the elevated risk of HF associated with saxagliptin therapy was abolished in patients using β -blockers, confirming that activation of the SNS by DPP-4 inhibition increases the risk of HF.²⁰ Based on these observations, the following hypothesis can be proposed for the mechanism



underlying the difference in HF risk between sitagliptin and saxagliptin. DPP-4 inhibitors tend to increase the risk of HF by SNS activation as a class effect, but sitagliptin may not have done so because it inhibits NHE3 activity in the proximal tubules after excretion in the urine. In contrast, saxagliptin is not excreted in the urine and it increased hospitalization for HF, reflecting the class risk of DPP-4 inhibitors.²¹

CARMELINA Study

The risk of HF is elevated in patients with type 2 diabetes and renal dysfunction or increased urinary albumin excretion.²⁰ The results of the CARMELINA study were presented at the recent conference of the European Association for the Study of Diabetes (October 2018, Berlin). That study assessed the cardiovascular safety of using linagliptin, a DPP-4 inhibitor that is not excreted in the urine, to treat patients with a high risk of HF (15-year duration of diabetes; mean eGFR, 50 mL/min/1.73 m²; mean ACR, 160). Linagliptin can be given at identical doses regardless of kidney/liver function because it undergoes minimal metabolism in the liver and is mainly excreted in the bile as the unchanged compound. The primary efficacy endpoint of the CARMELINA study was the “time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (3-point MACE),” but because it had already been announced that safety was confirmed, attention focused on the composite renal endpoint (a secondary endpoint) and the influence of linagliptin on hospitalization for HF. Based on the data presented, linagliptin was equivalent to placebo with

respect to its influence on HF and the renal prognosis in patients with kidney dysfunction. It should be noted that concomitant use of SGLT2 inhibitors was not allowed in the CARMELINA study.

TECOS and SAVOR vs. CARMELINA

These three studies were conducted in very different patient populations. While TECOS and SAVOR enrolled patients with a 10-year duration of diabetes, mean eGFR, 75 mL/min/1.73 m²; and mean ACR, 10, the CARMELINA study targeted patients with a 15-year disease duration, mean eGFR, 50 mL/min/1.73 m²; and mean ACR, 160, who had a high risk of developing HF (Figure 2).²² Thus, of the DPP-4 inhibitors with confirmed safety for patients who have diabetes and cardiovascular disease including HF, sitagliptin can be used when kidney function is normal, and linagliptin is preferable for patients who have progressed to stage IIIb chronic kidney disease.

Hospitalization for HF and death were respectively 3-fold and 2-fold more frequent in the CARMELINA study than in the TECOS study. Why did linagliptin, a DPP-4 inhibitor that is not excreted in the urine and has a neutral renal composite endpoint, not increase hospitalization for HF in patients with a high risk of HF? Given that SNS activation associated with chronic kidney disease has a significant impact in patients with kidney dysfunction,²³ it is possible that the potential (weak) sympathetic activating effect of DPP-4 inhibitor therapy was masked. In fact, stratified analysis of hospitalization for HF in the SAVOR study indicated disappearance of the elevated risk of HF associated with saxagliptin in patients with a long duration

of diabetes, high ACR, or no use of metformin (probably due to renal dysfunction). Accordingly, it is speculated that activation of the SNS by DPP-4 inhibition is relatively weak in patients with renal dysfunction, such as those targeted in the CARMELINA study. Also, the risk of hospitalization for HF as an adverse event becomes less visible vs. placebo in patients with a high risk of developing HF.

Use of insulin is more likely in diabetic patients with impaired renal function, but insulin activates the SNS and also promotes fluid retention. It is possible that treatment with linagliptin led to reduction of the insulin dosage, thus lowering the risk of HF. Alternatively, in the patients with eGFR <45, linagliptin may have protected the kidneys via a different mechanism to its natriuretic effect mediated by NHE 3 inhibition,^{24,25} thus reducing the risk of HF.

Conclusions

Publication of the EMPA-REG OUTCOME study on SGLT2 inhibitor therapy²⁶ led to proactive participation in the treatment of diabetes by cardiologists for the first time in 10 years since the PROactive study of pioglitazone.²⁷ In addition, it led them to recognize anew that renal metabolic stress in patients with diabetes leads to loss of homeostasis and hemodynamic imbalance, increasing the risk of HF. Development of SGLT2 inhibitors has provided the opportunity to discuss treatment of diabetes from the perspective of both the nephrologist and the cardiologist. For HF, we have also reached the stage where drugs should be selected from among several treatment options according to the pathogenesis and stage, while seeking advice about multimodal therapy from specialists in diabetes, endocrinology, and metabolism, as well as nephrologists.

Disclosures

The author declares no conflict of interest.

References

- Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; **355**: 253–259.
- ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560–2572.
- Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL 2 Study. *J Am Coll Cardiol* 2018; **71**: 2628–2639.
- Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, et al. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: Insights from Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial. *Circ Heart Fail* 2016; **9**: e002560.
- Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; **367**: 2204–2213.
- Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**: 311–322.
- Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**: 1834–1844.
- Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; **129**: 587–597.
- Sano M, Takei M, Shiraishi Y, Suzuki Y. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. *J Clin Med Res* 2016; **8**: 844–847.
- Sano M. Hemodynamic effects of sodium-glucose cotransporter 2 inhibitors. *J Clin Med Res* 2017; **9**: 457–460.
- Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. *J Cardiol* 2018; **71**: 471–476.
- Sano M, Chen S, Imazeki H, Ochiai H, Seino Y. Changes in heart rate in patients with type 2 diabetes mellitus after treatment with luseogliflozin: Subanalysis of placebo-controlled, double-blind clinical trials. *J Diabetes Investig* 2018; **9**: 638–641.
- Nistala R, Savin V. Diabetes, hypertension, and chronic kidney disease progression: Role of DPP4. *Am J Physiol Renal Physiol* 2017; **312**: F661–F670.
- Alexander RT, Grinstein S. Tethering, recycling and activation of the epithelial sodium-proton exchanger, NHE3. *J Exp Biol* 2009; **212**: 1630–1637.
- Lovshin JA, Rajasekaran H, Lytvyn Y, Lovblom LE, Khan S, Alemu R, et al. Dipeptidyl peptidase 4 inhibition stimulates distal tubular natriuresis and increases in circulating SDF-1 α -67 in patients with type 2 diabetes. *Diabetes Care* 2017; **40**: 1073–1081.
- Cornel JH, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: Outcomes from TECOS. *Diabetes Care* 2016; **39**: 2304–2310.
- Mistry GC, Maes AL, Lasseter KC, Davies MJ, Gottesdiener KM, Wagner JA, et al. Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. *J Clin Pharmacol* 2008; **48**: 592–598.
- Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; **373**: 232–242.
- Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369**: 1317–1326.
- Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: Observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014; **130**: 1579–1588.
- Sano M. Mechanism by which dipeptidyl peptidase-4 inhibitors increase the risk of heart failure and possible differences in heart failure risk. *J Cardiol*, doi:10.1016/j.jcc.2018.07.004.
- Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA Randomized Clinical Trial. *JAMA*, doi:10.1001/jama.2018.18269.
- Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912–1918.
- Kanasaki K, Shi S, Kanasaki M, He J, Nagai T, Nakamura Y, et al. Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. *Diabetes* 2014; **63**: 2120–2131.
- Tanaka Y, Kume S, Chin-Kanasaki M, Araki H, Araki SI, Ugi S, et al. Renoprotective effect of DPP-4 inhibitors against free fatty acid-bound albumin-induced renal proximal tubular cell injury. *Biochem Biophys Res Commun* 2016; **470**: 539–545.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117–2128.
- Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): A randomised controlled trial. *Lancet* 2005; **366**: 1279–1289.