Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension, heart disease and diabetic nephropathy and reduce mortality. In addition to preventing the degradation of angiotensin (Ang) I to Ang II, ACE inhibitors potentiate the effects of the vasodilator and natriuretic hormone bradykinin. Studies using specific bradykinin receptor antagonists demonstrate that bradykinin contributes to favorable effects of ACE inhibitors on blood pressure and fibrinolytic balance but also to the side effect of angioedema. Neutral endopeptidase inhibitors (now given in combination with angiotensin receptor blockers to treat heart failure) are also likely to potentiate endogenous bradykinin. Dipeptidyl peptidase-4 (DPP4) inhibitors are widely used in the treatment of type 2 diabetes mellitus (T2DM) and prevent the cleavage of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic peptide (GIP). Whereas treatment with exogenous GLP-1 agonists causes weight loss and reduces mortality, treatment with DPP4 inhibitors has no effect on weight or risk of acute coronary events, and may increase the risk of heart failure. In addition to decreasing the degradation of GLP-1 and GIP, DPP4 inhibitors prevent the degradation of a number of potentially vasoactive peptides with a penultimate alanine or proline at the amino terminus including substance P, neuropeptide Y (NPY), polypeptide Y (PYY), and growth hormone releasing hormone (GHRH). Among these, substance P is also cleaved by ACE. DPP4 inhibition attenuates the acute effect of ACE inhibition on blood pressure. During combined DPP4 and ACE inhibition, intra-arterial infusion of substance P increases sympathetic activity in humans. In addition, during ACE inhibition or angiotensin receptor blockade, DPP4 inhibition potentiates the vasoconstrictor response to intra-arterial NPY in both normal controls and patients with T2DM. There is no effect of DPP4 inhibition on vasodilation in response to intra-arterial infusion of brain natriuretic peptide (BNP) in humans. GLP-1 does not cause vasodilation when infused intra-arterially. In summary, the anti-diabetic DPP4 inhibitors affect the degradation of vasoactive peptides as well as the incretin hormones. These effects may account for differential effects on cardiovascular risk compared to GLP-1 agonists.