Combining incretin-based drugs and RAAS inhibitors: more cons than pros?

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Two novel antihyperglycaemic drug classes for the treatment of type 2 diabetes might have important, clinically relevant off-target effects. The so-called incretin-based drugs—ie, glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors—mainly reduce glucose concentration by improving pancreatic islet-cell function. However, findings from clinical trials and preclinical studies suggest that incretin-based drugs have extra-pancreatic actions that interact with the renin-angiotensin-aldosterone system (RAAS; Figure), inhibitors of which are antihypertensive drugs taken daily by patients with type 2 diabetes.

Evidence from model systems suggests that GLP-1 receptor activation inhibits intracellular signaling of the angiotensin II type 1 receptor, which mediates harmful effects of RAAS—such as inflammation and hypertension. In healthy people, acute GLP-1 infusion lowers circulating angiotensin II concentrations by 15–19% and leads to a non-significant reduction in plasma renin activity. In one study that included obese patients with glomerular hyperfiltration, 25% of whom had type 2 diabetes, GLP-1 infusion reduced plasma renin activity by 25% (Figure). The reduced renin secretion might be accounted for by a direct effect of GLP-1 on the juxtaglomerular cells, via atrial natriuretic peptide, or through inhibition of tubuloglomerular feedback by inhibition of proximal sodium reabsorption. Skov and colleagues hypothesised that many GLP-1-mediated effects on RAAS—including glucose-dependent insulin secretion, renoprotection, and inhibition of the Na⁺/H⁺ exchanger isoform 3 in the proximal tubule—are partly caused by decreased angiotensin-II signalling. Stronger inhibition of the RAAS cascade by GLP-1 receptor agonists might further increase the protective effects of compounds that interact with RAAS. However, the clinical benefit of such augmented inhibition could be questionable in view of the results of the ONTARGET, ALTITUDE, and the recently stopped VA NEPHRON-D trials, which showed increased risk of adverse events, including hyperkalaemia and renal failure, when two different drugs that synergistically inhibit RAAS were combined. As a result, dual RAAS blockade in patients with diabetes is currently not recommended. Notably, the authors of several case reports have described acute renal failure in patients who received a GLP-1 receptor agonist in combination with a RAAS inhibitor in the context of dehydration and use of diuretic drugs. However, the results of phase 3 studies of GLP-1 receptor agonists have not given rise to concerns, although these studies were of a fairly short duration and did not include subgroup analyses for the use of concurrent RAAS inhibitors.

Inhibitors of DPP-4 are used in diabetes management with the aim of reducing the rate of GLP-1 cleavage. Besides GLP-1, DPP-4 cleaves several vasoactive substrates, and is the main enzyme to cause substance P inactivation during angiotensin-converting enzyme (ACE) inhibition. Substance P is a potent vasodilator but, when released from primary afferent sensory nerve fibres, it also increases sympathetic activity. During concurrent use of ACE and DPP-4 inhibitors, intra-arterial substance P administration activates the sympathetic nervous system in healthy people. Notably, in one study in individuals with metabolic syndrome, sitagliptin attenuated the systemic hypotensive response to an acutely administered ACE inhibitor with concomitant increases in heart rate and noradrenaline concentrations. The investigators postulated that increased concentrations of active substance P, although not measured, could have mediated the observed unfavourable effects. Additionally, DPP-4 degrades neuropeptide Y.
(NPY), a neurotransmitter in postganglionic sympathetic nerves. Since NPY is released with noradrenaline and augments its vasoconstrictor responses via Y1-receptor activation, reduced NPY degradation could enhance the negative vascular effect of concurrent DPP-4 and ACE inhibition (Figure). Based on these mechanistic data, combining DPP-4 and ACE inhibitors might result in augmented vasopressor response and increased heart rate. Indeed, in the DPP-4 inhibitor cardiovascular outcome trials SAVOR-TIMI 53 (saxagliptin) and EXAMINE (alogliptin), the incidence of hospital admission for heart failure increased relative to placebo, significantly by 27% (95% CI 6–51) for SAVOR-TIMI 53 and non-significantly by 19% (–11 to 58) for EXAMINE; a pooled analysis of both trials showed an overall significant increase of 24%. Notably, 54% of the patients at high risk of cardiovascular events with type 2 diabetes in SAVOR-TIMI 53 used ACE inhibitors, and 82% of such patients in EXAMINE used RAAS inhibitors (not specified). A post-hoc analysis of SAVOR-TIMI 53 showed a similar risk of heart failure across subgroups, although no subgroup analysis for drugs used in combination was done. In the VIVIDDD trial, which compared vildagliptin with placebo in patients with type 2 diabetes and established heart failure—26% of whom used ACE inhibitors—patients in the intervention group unexpectedly showed increased stroke volume and left-ventricular end-
Combining incretin-based drugs and RAAS inhibitors

diastolic and end-systolic volume. Moreover, the investigators noted a non-significant increase in mortality in the vildagliptin group.

Full characterisation of the potential adverse effects of incretin-based drugs is crucially important. We encourage investigators of long-term randomised controlled trials to specifically address the mechanistically plausible unfavourable drug–drug interactions between incretin-based drugs and RAAS inhibitors.
References


