Angiotensin-Converting Enzyme and Dipeptidyl Peptidase IV Inhibitors
An Increased Risk of Angioedema

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The incidence of diabetes is increasing and affects 180 million adults worldwide, including 24 million in the United States, or 7.8% of the population. In 2007, 1.6 million new cases were diagnosed in U.S. residents aged 20 years or more.1 Despite the large number of antidiabetic agents on the market, the condition is still inadequately controlled in 30% of affected patients.2

Among available therapies, dipeptidyl-peptidase IV (DPPIV) inhibitors offer a new promising alternative for the treatment of type 2 diabetes, through their ability to improve glucose tolerance and insulin response to oral carbohydrates.3 DPPIV is involved in the rapid N-terminal cleavage of incretins, ie, peptide hormones such as glucose-dependent insulinitropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), which are released from the gut in response to nutrients intake, thus enhancing glucose-stimulated insulin secretion and inhibiting glucagon secretion.4 Sitagliptin (Januvia) was the first DPPIV inhibitor marketed in the United States in 2006, subsequently received EMEA approval in 2007 but is currently not marketed in the United States. Many analogs of DPPIV inhibitors are currently under development. A metaanalysis evaluated the efficacy and safety of DPPIV inhibitors based on 17 randomized controlled clinical trials involving 7823 patients treated with vildagliptin or sitagliptin over 12 to 52 weeks; DPPIV inhibitors appear well tolerated, with, however, an increased risk of nasopharyngitis, cystitis, and headache.5

Estimating the Risk of Angioedema With DPPIV Inhibitors
Postmarketing surveillance of patients treated with sitagliptin and vildagliptin reported cases of angioedema, most often during the first 3 months of treatment, with some reactions observed already after the first dose. Consequently, the Summaries of Product Characteristics and Package Leaflets of both compounds were updated to include angioedema among potential adverse effects.6,6 Although DPPIV theoretically inactivates or interacts with a large number of biologically active peptides,7 relatively little attention was given to other potential enzymatic targets during their development. Substance P (SP), a potent proinflammatory peptide released during sensory nerves activation, causes edema and pain and may be involved in the pathogenesis of angioedema.8 SP is sequentially truncated by DPPIV into SP 5 to 11, the later being 1000-fold less potent than the native peptide.9 Nevertheless, neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE) may compensate for the blockade of DPPIV by cleaving SP at different sites (Figure).8 Plasma DPPIV activity was found decreased in patients with a history of ACE inhibitor–induced angioedema, compared with control subjects, although ACE and DPPIV activities were not correlated in those patients.8

In this issue of Hypertension, Brown et al investigated the influence of DPPIV inhibitors, with or without ACE inhibitors, on angioedema formation. They present the results of a thorough premarketing surveillance program aimed at defining the frequency of angioedema during clinical trials on vildagliptin, and emphasize the interaction with ACE inhibitors.10 Additionally, they looked for information from the Adverse Events Reporting System of the FDA on about 14 cases of angioedema reported under sitagliptin between February 2006 and June 2007, including 5 requiring admission into an intensive care unit. However, the true number of sitagliptin-related angioedema cases is probably much higher, as adverse drug events are usually underreported.

Nevertheless, the numbers of patients affected by angioedema have little chance to exceed those reported in the OCTAVE study, a multicenter randomized controlled 24-week trial comparing omapatrilat (a dual NEP and ACE inhibitor) with enalapril as initial therapy for hypertension. This trial found 274 cases of angioedema among 12 745 patients under dual ACE-NEP inhibition (2.17%), versus 86 among 12 557 under ACE inhibition alone (0.68%).11 Among the 5799 patients receiving vildagliptin for 12 to 52 weeks without ACE inhibitors, Brown et al found no association with angioedema; only 5 patients receiving vildagliptin (0.09%) developed this complication versus 7 among the 3549 receiving the comparator (0.20%). This observation is reassuring and suggests that enzyme redundancy is normally sufficient to prevent SP accumulation during DPPIV inhibition.

Estimating the Risk of Angioedema in Patients Treated by DPPIV and ACE Inhibitors

On the other hand, Brown et al report a significant increase in the incidence of angioedema in vildagliptin-treated patients.
also receiving ACE inhibitors. Indeed, 14 cases of angioedema were observed among those 2754 patients receiving both agents (0.51%), whereas only 1 patient of 1819 in the comparator group exposed to ACE inhibitors alone developed this complication (0.09%). The odds ratio versus comparator rose to 4.57 with an apparent dose-effect relationship for vildagliptin. The incidence of angioedema reported by Brown et al with ACE inhibitors alone was lower than in the controls of the OCTAVE study (0.68%)\textsuperscript{11} and in U.S. veterans starting ACE inhibitors (0.2%).\textsuperscript{12} This observation might owe something to the fact that in both of these trials, ACE inhibitors were administered to untreated hypertensive patients, whereas in the study by Brown et al the patients had been previously exposed to ACE inhibitors for prolonged time periods. This may have filtered out cases intolerant to ACE inhibition. Moreover, the OCTAVE study was designed to take into account all cases of angioedema including milder forms, whereas the U.S. veteran study incorporating 600 000 might have underestimated incidence rates because of inaccuracies in case ascertainment.\textsuperscript{11,12} (Although 55% of cases occurred within 90 days of ACE inhibitor introduction, the event rate declined gradually over the following year but still remained elevated, even after 1 year of ACE inhibition, because of delayed symptoms\textsuperscript{13}).

Adverse events monitoring during clinical trials faces 2 opposite threats, both leading to the loss of essential information: missing noteworthy events through under-reporting, and hiding key observations in a magma of insignificant events through overreporting and overfragmenting. The approach of Brown et al, supported by the manufacturer, tries to avoid either of those traps, and should inspire similar efforts on other gliptins.

Messerli et al estimated in 2000 that 40 million patients worldwide were exposed to ACE inhibitors,\textsuperscript{13} and concluded that this drug class could account for 1200 deaths per year because of angioedema. Would the generalization of gliptins use amplify those numbers to an extent that might jeopardize the benefits of treatment? Remarkably, the study by Brown et al presents some similarities with the OCTAVE trial, in which the addition of NEP inhibition to ACE inhibition raised the relative risk to develop angioedema by 3.17. A subgroup analysis of the OCTAVE trial indicated that patients with diabetes mellitus were relatively protected from angioedema (absolute frequency 0.43%).\textsuperscript{14} Similarly, a 12% lower rate of angioedema was found in the U.S. veterans study patients receiving ACE inhibitors,\textsuperscript{12} most probably because of a higher expression of DPPIV in diabetic patients.\textsuperscript{15} The mechanism involved in dual NEP and ACE inhibition could be attributed to the exhaustion of alternative pathways for SP and bradykinin (BK) degradation (the latter was initially presented as the peptide responsible of angioedema induced by ACE inhibitors). During concomitant inhibition of NEP and ACE, the sole enzymes remaining for inactivating BK are aminopeptidase P and kininase I, whereas SP is degraded only by DPPIV. Unfortunately, investigations are lacking to establish the relative contribution of NEP and DPPIV in comparison to ACE for SP degradation. However, ACE remains the common link between BK and SP metabolism (Figure). Therefore, it is conceivable that dual enzyme inhibition of ACE and DPPIV, or of ACE and NEP, may prolong BK and SP half-lives to a larger extent than observed with ACE inhibitors alone. This might raise the risk of angioedema to an unacceptable level with regard to the benefit of lowering blood pressure or glucose level. Such mechanisms finally led to the withdrawal of omapatrilat.

**Perspectives and Unsolved Questions**

The results of Brown et al call for caution when gliptins are combined with ACE inhibitors, because the risk of causing angioedema is significantly increased. No data are yet available regarding DPPIV inhibitors other than vildagliptin, to assess whether this complication represents a class effect or is specific to vildagliptin. Similarly, no studies have evaluated whether the relative efficacy of ACE inhibitors in blocking the renin–angiotensin system influences the rate of angioedema, though a study suggested that captopril may be safer than the long-lasting inhibitors.\textsuperscript{12} Blacks have a 4-fold higher basal risk than whites to develop angioedema under ACE inhibition,\textsuperscript{12,14} but it is unclear whether additional DPPIV inhibition may further increase this risk. A similar question applies to women, who are at higher risk than men to suffer from angioedema induced by ACE inhibition.\textsuperscript{11} The class of ACE inhibitors ranked 4th in the total U.S. prescription market, with 157 millions prescriptions dispensed in first half 2007.\textsuperscript{16} Within the past 10 years, the cardioprotective benefits of ACE inhibition have been abundantly established in high-risk patients, including those with comorbidities such as diabetes.\textsuperscript{17} This reflects well in the study by Brown et al, where about one third of the patients enrolled in vildagliptin phase III trials received ACE inhibitors concomitantly. Sitagliptin is presently the second leading branded oral antidiabetic agent in terms of new prescriptions in the United States,

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**Figure.** Schematic showing cleavage of substance P by peptidases. Specific propeptidases inhibition. Various combinations of enzyme inhibitors are depicted and affect the cleavage of substance P. ACE indicates angiotensin converting enzyme; NEP, neutral endopeptidase, DPPIV, dipeptidyl peptidase IV; APN, aminopeptidase N.
with $411.1 million revenue in the first quarter of 2009. European sales of vildagliptin reached $26 million in the first quarter of 2009, compared with $6 million for the first quarter of 2008. Therefore, the risk of facing an outbreak of angioedema under combined ACE and DPPIV inhibition should be considered. In this context, the recent FDA cardiovascular risk assessment guideline for antidiabetic drugs, imposed to investigate hard cardiovascular outcomes during their development,\textsuperscript{18} should perhaps also take angioedema outcome into consideration. In the meantime, substituting ACE inhibitors with angiotensin II–receptor blockers (or even renin inhibitors?) in diabetic patients receiving a gliptin may represent a prudent alternative to minimize such a risk. The issue of lower cardio-renal benefits, because of the absence of elevated BK or SP concentrations with this alternative, remains to be clarified.

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\textbf{References}

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