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# Angiotensin-converting enzyme and dipeptidyl peptidase-4 inhibitor–induced angioedema: A disproportionality analysis of the WHO pharmacovigilance database

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1 **Title page**

2 **Angiotensin-converting enzyme and dipeptidyl peptidase-4 inhibitor induced angioedema:**  
3 **a disproportionality analysis of the WHO pharmacovigilance database**

4

5 Angiotensin-converting enzyme and dipeptidyl peptidase-4 inhibitors induced angioedema

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25

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31 Clinical Implications:

32 There is no data concerning the risk of bradykinin-mediated angioedema with dipeptidyl  
33 peptidase-4 inhibitors (DPP-4i) apart from that of vildagliptin in combination with ACEi. This  
34 disproportionality analysis demonstrates that concomitant exposure to DPP-4i and ACEi is  
35 associated with an increased reporting risk of angioedema, but not with DPP-4i without  
36 ACEi.

37

38 Angioedemas (AE) are induced by vasodilation and increased vascular permeability due to  
39 the release of inflammatory mediators, including bradykinin (BK) (1). BK-mediated  
40 angioedema (BK-AE) results from either the overproduction of BK or inhibition of its  
41 degradation. Mast cells are not thought to be involved, and pruritus and urticaria are absent  
42 in this form of AE.

43 BK is metabolized primarily by angiotensin converting enzyme (ACE), neutral endopeptidase  
44 and aminopeptidase P; and secondarily by dipeptidyl peptidase-4 (DPP-4). Moreover, BK  
45 stimulates the release of substance P, which also increases vascular permeability. Substance  
46 P is inactivated primarily by ACE and secondarily by DPP-4 and neutral endopeptidase.

47 The lack of awareness about BK-AE, as well as the inefficacy of antihistamines and  
48 corticosteroids, can delay its management and potentially lead to a fatal outcome (2).

49 The main etiologies of BK-AE are hereditary, acquired or drug-induced. Among drugs able to  
50 induce BK-AE, angiotensin-converting enzyme inhibitors (ACEi) are the most often reported  
51 (3). The use of ACEi contributes to the accumulation of BK and substance P which can lead to  
52 the onset of BK-AE. This rare adverse drug reaction (ADR) occurs in 0.1 to 0.7% of patients  
53 treated with ACEi (3). African-Americans, smokers, and females are at increased risk of ACEi-  
54 induced BK-AE (4).

55 DPP-4 degrades BK and substance P when ACE is inhibited (1). Furthermore, DPP-4 activity  
56 decreases during ACEi-associated BK-AE (5). Thus, concomitant use of ACEi and DPP-4  
57 inhibitors (DPP-4i) could have a synergistic effect on the accumulation of BK and substance  
58 P. To date, an increased risk of BK-AE has only been described with the concomitant use of

59 vildagliptin and ACEi (6). However, the risk of BK-AE with DPP-4i therapy without ACEi and  
60 with DPP-4i drugs, other than vildagliptin, in combination with ACEi is unknown.

61 The aim of this study was to evaluate whether the combination of ACEi and DPP-4i is  
62 associated with an increased AE reporting risk, compared to ACEi alone or to DPP-4i alone, in  
63 the World Health Organization's (WHO) pharmacovigilance database, Vigibase®, using  
64 disproportionality analysis. When we refer to ACEi or DPP-4i as taken alone, we mean that  
65 ACEi is taken without DPP-4i, or DPP-4i is taken without ACEi. The patient may have been on  
66 additional medications besides these two classes.

67 We extracted from VigiBase® all reports of "angioedemas", according to the high level term  
68 of the Medical Dictionary for Regulatory Activities (MedDRA), from November 14<sup>th</sup> 1967 to  
69 December 14<sup>th</sup> 2017. Given the absence of the term "bradykinin-mediated angioedema" in  
70 the MedDRA, we excluded all reports associated with symptoms suggesting another  
71 underlying mechanism such as histamine-mediated AE (urticaria, pruritus, rash, rash  
72 erythematous, rash maculo-papular).

73 We selected reports involving at least one ACEi, coded as a suspect drug; or at least one  
74 DPP-4i, coded as a suspect or concomitant drug.

75 We performed a disproportionality analysis in which we calculated the reporting odds ratio  
76 (ROR) of AE involving ACEi alone, DPP-4i alone and ACEi+DPP-4i, if the number of reports  
77 was  $\geq 5$ . A signal was considered significant if the lower boundary of the 95% confidence  
78 interval (95%CI) was  $> 2$  (7). According to the additive interaction model, a ROR value for co-  
79 exposure that exceeds the sum of the RORs estimated for each individual class of drug  
80 supports a potential drug-drug interaction (8). Details on the Anatomical Therapeutic  
81 Chemical codes and ROR calculation used for drug selection are provided in the Online  
82 Repository Text (APPENDICES A1 and A2).

83 In order to assess the robustness of the results, we conducted complementary analyses with  
84 drugs known not to induce BK-AE, as negative controls: dihydropyridine calcium channel  
85 blockers (CCB) and glucagon-like peptide-1 (GLP-1) analogues.

86

87 We extracted 340,686 reports of BK-AE from Vigibase<sup>®</sup>. Patient characteristics are  
88 summarized in TABLE 1. Among them, 19,997 were attributed to ACEi, with a corresponding  
89 ROR of 5.69 (95%CI 5.61-5.78) (TABLE 2). Individually, every ACEi was associated with a  
90 disproportionality signal, though the ROR could not be calculated for 3 ACEis (TABLE E1 in  
91 the Online Repository Text). The DPP-4i drug class was involved in 677 reports of AE with a  
92 corresponding ROR of 0.43 (95%CI 0.40-0.47). Individually, no DPP-4i drug was associated  
93 with an AE disproportionality signal, though the ROR could not be calculated for 5 DPP-4is  
94 (TABLE E2 in the Online Repository Text). Concomitant exposure to ACEi and DPP-4i was  
95 involved in 345 reports of AE with a corresponding ROR of 42.77 (95%CI 36.93-49.53), which  
96 supports the hypothesis of a drug-drug interaction between ACEi and DPP-4i. No AE  
97 disproportionality signal was associated with the use of dihydropyridine CCB, nor with GLP-1  
98 analogues.

99 To our knowledge this is the first international pharmacovigilance study exploring the  
100 reporting risk of AE induced by the interaction between DPP-4i and ACEi. Concomitant  
101 exposure to DPP-4i and ACEi was associated with an increased reporting risk of AE.  
102 Numerous cases of AE in patients treated concomitantly with an ACEi and a DPP-4i have  
103 been reported in the literature. A meta-analysis of phase III studies of vildagliptin showed an  
104 increased risk of AE among patients taking an ACEi and vildagliptin at a daily dosage of 100  
105 mg (6). Here we demonstrate a possible class effect of DPP-4i.

106 In this study, exposure to DPP-4i alone was not associated with a disproportionality signal for  
107 AE. Nevertheless, this result does not completely eliminate the risk of an AE with DPP-4i.  
108 Under-reporting, well described in pharmacovigilance, could have led to an underestimation  
109 of the number of cases of AE with DPP-4i alone. Case reports have been reported in the  
110 literature, but to date, clinical trials and epidemiological studies have failed to demonstrate  
111 an increased risk of AE with DPP-4i alone (6).

112 This disproportionality analysis had several limitations. ADR reporting rate may be  
113 influenced by media coverage, the ADR severity, and the number of patients using the drug.  
114 Moreover, the lack of detailed patient data in Vigibase<sup>®</sup> prevented appropriate adjustments  
115 on potential confounders, such as ethnicity, sex and smoking status. Furthermore, the fact  
116 that the term “bradykinin-mediated angioedema” does not exist in the MedDRA might have  
117 resulted in our including misclassified AE cases. Nevertheless, we found that exposure to

118 ACEi was associated with an increased reporting risk of AE whereas dihydropyridine CCB and  
119 GLP-1 analogues were not, supporting the robustness of the results (9). This study indicates  
120 that the increased reporting risk of BK-AE due to pharmacodynamic drug-drug interaction  
121 between ACEi and vildagliptin applies to all DPP4i, though DPP4i does not increase the  
122 reporting risk of BK-AE without concomitant ACEi.

123

124

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130

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157 42.

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159

160 **Tables**

161 Table 1. Characteristics of patients with BK-AE

<b>Characteristics</b>	<b>ACEi N = 19 997</b>	<b>DPP-4i N = 677</b>	<b>ACEi + DPP-4i N = 345</b>
Female (%)	8725 (44%)	414 (61%)	156 (45%)
Male (%)	10482 (52%)	218 (32%)	485 (54%)
Unspecified (%)	790 (4%)	45 (7%)	4 (1%)
Mean age ± SD (years) (min-max) Unspecified (%)	64.1 ± 13.5 (0-103.5) 2010 (10%)	65.3 ± 11.8 (25.0-91.7) 199 (29%)	66.7 ± 11.5 (30.0-91.1) 30 (9%)
Severe (%)	8600 (43%)	297 (44%)	264 (77%)
Death (%)	226 (1%)	14 (2%)	14 (4%)
Origin of report			
- North America	8543 (43%)	387 (57%)	148 (43%)
- South America	48 (0%)	2 (0%)	0 (0%)
- Africa	1162 (6%)	6 (1%)	1 (0%)
- Europe	7765 (39%)	153 (23%)	176 (51%)
- Asia	928 (5%)	118 (17%)	9 (3%)
- Oceania	1551 (8%)	11 (2%)	11 (3%)

162

163 Table 2. Disproportionality analysis of AE reports associating with ACEi and DPP-4i

<b>Drugs</b>	<b>Cases (N)</b>	<b>Non-cases (N)</b>	<b>ROR [95% CI]</b>
ACEi	19997	168673	5.69 [5.61-5.78]
DPP-4i	677	71233	0.43 [0.40-0.47]
ACEi + DPP-4i	345	369	42.77 [36.93-49.53]
<i>Details of DPP-4i associated:</i>			
<i>Sitagliptin</i>	225	213	48.30 [40.05-58.26]
<i>Linagliptin</i>	37	55	30.75 [20.27-46.64]



<i>Vildagliptin</i>	40	30	60.94 [37.96-97.83]
<i>Saxagliptin</i>	43	102	19.27 [13.49-27.52]
<i>Alogliptin</i>	3	7	NA
Dihydropyridine calcium channel blockers	3155	165896	0.87 [0.84-0.90]
GLP-1 analogues	388	102224	0.17 [0.16-0.19]

164 NA = not available (due to numbers of cases < 5)

165

166