

**ORIGINAL
ARTICLE**

The impact of age and sex on the reporting of cough and angioedema with renin–angiotensin system inhibitors: a case/noncase study in VigiBase

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ABSTRACT

The purpose of this study was to assess the impact of age and sex on the reporting of cough and angioedema related to renin–angiotensin system (RAS) inhibitors. A case/noncase study was performed in VigiBase. Two case groups were identified, reports of cough and reports of angioedema, and noncases were all reports of all other adverse events. Logistic regression analysis was used to assess the association between reporting of cough and angioedema with each class of RAS inhibitors stratified by age/sex and to control for confounding. The reporting of cough with angiotensin-converting enzyme (ACE) inhibitors was significantly higher in women than in men [adjusted reporting odds ratio (ROR): 44.0, 95% CI (43.2–44.8) for women vs. 29.2, 95% CI (28.5–29.9) for men]. There was no difference in reporting of cough linked to angiotensin receptor blockers (ARBs) and aliskiren between men and women. In contrast, the reporting of angioedema with ACE inhibitors and ARBs was significantly higher in men than in women, but for aliskiren, women had a significantly higher ROR than men [adjusted ROR: 5.20, 95% CI (4.18–6.46) for women vs. 3.04, 95% CI (2.30–4.02) for men]. The reporting of cough with ACE inhibitors was increased with age until reaching a plateau at middle adulthood (40–59 years) and the reporting of angioedema with ACE inhibitors was increased with age until elderly (60–79 years). Age had only a slight effect on the reporting of cough and angioedema with ARBs and aliskiren. Both age and sex have substantial effects on the reporting of cough and angioedema with RAS inhibitors and in particular ACE inhibitors. Further study is needed to determine whether these differences mainly express different adverse drug reaction risks in subgroups or also can be explained by factors influencing reporting.

INTRODUCTION

Cough and angioedema are adverse drug reactions (ADRs) associated with especially angiotensin-

converting enzyme (ACE) inhibitors but also reported with other renin–angiotensin system (RAS) inhibitors [angiotensin receptor blockers (ARBs) and a direct renin inhibitor (DRI), aliskiren] [1]. The mechanism

causing these ADRs while using ACE inhibitors is not completely clear, but accumulation of bradykinin is thought to be involved. Accumulation of bradykinin can cause symptoms of inflammation, including vasodilation and pain by activating bradykinin receptors. In normal human physiology, bradykinin is metabolized by ACE to inactive peptides. Some animal and human studies found that ARBs may increase bradykinin levels by reducing its metabolism and as consequence may cause cough and angioedema [2,3]. Most studies concluded that the incidence of cough and angioedema is higher in users of ACE inhibitors compared to users of ARBs, DRI, and placebo [4–6]. However, in a study using pediatric hypertension patient-level data from eight randomized controlled trials conducted by Smith et al. [7], it was found that there was no significant difference of cough incidence in children using ACE inhibitors compared to ARBs users [(17/524 (3.2%) and 4/224 (1.8%), respectively; P -value = 0.34)]. Moreover, most studies have observed that women have a higher incidence of cough than men in patients using ACE inhibitors [8–12]. Only a few studies observed that the incidence of ACE inhibitors–angioedema is higher in female patients than in male as well as in elderly patients [6,13]. To our knowledge, there are no published studies that assessed the influence of sex and age on the occurrence of cough and angioedema with aliskiren and the literature on effects of sex and age on cough and angioedema occurrence with ACE inhibitors and ARBs is limited. Therefore, the objective of our study was to assess the impact of age and sex on the reporting of cough and angioedema related to RAS inhibitors using information reported to the World Health Organization (WHO) global database of individual case safety reports (ICSRs), VigiBase.

METHODS

Study setting

The WHO Programme for International Drug Monitoring was established in 1968 in Geneva, Switzerland. Since 1978, the Uppsala Monitoring Centre (UMC) in Sweden has the technical and operational responsibility of the WHO Programme, including the maintenance of VigiBase. One of the main tasks of the UMC is to collect and analyze data on reported ICSRs from worldwide [14]. VigiBase contains more than 14 million ICSRs and is maintained and improved by the UMC [14,15]. These reports are forwarded by national pharmacovigilance centers from

over 120 countries [16]. The ICSRs contain information about patients, suspected and concomitant drugs, suspected ADRs, the reporter, and other relevant clinical information. In the VigiBase system, drugs are coded by WHO Drug Dictionary that includes the WHO Anatomical Therapeutic Chemical (ATC) classification system while ADRs are coded by medical Dictionary for Regulatory Activities (MedDRA) or by the WHO Adverse Reaction Terminology (WHO-ART) [14]. VigiBase is compliant with both MedDRA and WHO-ART.

Study design

A case/noncase study was performed in VigiBase to assess the impact of age and sex on the reporting of cough and angioedema. Two case groups were identified, reports of cough and reports of angioedema, containing all coded ICSRs with WHO-ART preferred terms cough and angioedema and noncases were all reports of all other adverse events terms.

Definition of exposure

The exposure of each of RAS inhibitors (ATC code C09; ACE inhibitors: C09A/C09B, ARBs: C09C/C09D, aliskiren: C09XA) was defined as the reporting of these drugs as suspected for an ADR.

Covariates

Sex, age, fentanyl, methotrexate, nitrofurantoin, propofol, and drugs for obstructive airway diseases (OADs) – adrenergics (inhalants) and other OADs (inhalants) – were considered as possible risk factors for cough [17–19]. For angioedema, sex, age, nonsteroidal anti-inflammatory drugs, contrast agents, and opioids were considered as possible risk factors [20]. The exposure of these concomitant medications was defined as the reporting of these drugs as co-suspected or co-mediations for an ADR.

Data analysis

We used drug–ADR pair as unit of the analysis. In our study using data from VigiBase, an ICSR can contain one or more suspected drugs related to one or more ADRs. For example, we counted two drug–ADR pairs for an ICSR containing two ADRs related to one suspected drug and four drug–ADR pairs for an ICSR containing two suspected drugs related to two different ADRs.

Our statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, IBM

Corporation, Armonk, NY, USA) version 23. Age was summarized using mean \pm standard deviation. Other baseline characteristics for cases and noncases are presented as numbers and percentages. Logistic regression analysis was used to assess the association between the reporting of cough/angioedema with each class of RAS inhibitors stratified by sex/age and to control for covariates (fully adjusted model).

Main analysis

We stratified for sex and age to assess the impact of age and sex on the reporting of cough and angioedema related to RAS inhibitors worldwide. Age was divided either into two categories: <65 and ≥ 65 years old, including only adults (≥ 18 years old), or into six categories: infant and childhood (0–11 years), adolescence (12–19 years), young adulthood (20–39 years), middle adulthood (40–59 years), elderly (60–79 years), and late elderly (≥ 80 years).

Secondary analysis

In our secondary analyses, we stratified for sex and age (two categories) to assess the impact of age and sex on the reporting of cough and angioedema related to individual ACE inhibitors and ARBs that were in the top fifth of highest reporting numbers of cough and angioedema for each class.

Sensitivity analysis

We did two sensitivity analyses to test the robustness of our main results: (i) We included only cases of ICSRs that were reported by healthcare professionals and (ii) we restricted the analysis to ICSRs having one ADR and one suspected drug.

RESULTS

Main analysis

We included 24 574 952 drug–ADR pairs after excluding missing data on age and sex (8 368 826 drug–ADR pairs), unusual age numbers (0 and >120 years) (62 210 drug–ADR pairs), and unidentifiable RAS inhibitors for drugs named angiotensin ii (8 drug–ADR pairs). These drug–ADR pairs were from 6 153 145 unique ICSRs and entered in Vigibase between November 14, 1967, and January 22, 2014, from 118 countries worldwide (*Figure 1*). The main characteristics of all cases and noncases are shown in *Table I* for cough and *Table II* for angioedema.

Impact of sex

The reporting of cough related to ACE inhibitors was significantly higher in women than in men [adjusted reporting odds ratio (ROR): 44.0, 95% CI (43.2–44.8) for women vs. 29.2, 95% CI (28.5–29.9) for men, P -value < 0.0005]. There was no difference in reporting of cough related to ARBs and aliskiren between men and women (*Figure 2*). In contrast, the reporting of angioedema related to ACE inhibitors and ARBs was significantly higher in men than in women [for ACE inhibitors: adjusted ROR: 20, 95% CI (19.5–20.6) for men vs. 14.1, 95% CI (13.7–14.5) for women, P -value < 0.0005 ; and for ARBs: adjusted ROR: 3.82, 95% CI (3.54–4.13) for men vs. 3.20, 95% CI (2.98–3.43) for women, P -value < 0.0005]. However, for aliskiren, women had significantly higher ROR than men [adjusted ROR: 5.20, 95% CI (4.18–6.46) for women vs. 3.04, 95% CI (2.30–4.02) for men, P -value = 0.018] (*Figure 3*).

Impact of age

The RORs of cough with ACE inhibitors and ARBs were significantly higher in the 18- to 64-year-old group than in the ≥ 65 -year-old group [for ACE inhibitors: adjusted RORs: 45.6, 95% CI (44.7–46.5) and 30.7, 95% CI (30–31.4), P -value < 0.0005 , respectively, and for ARBs: adjusted RORs: 4.65, 95% CI (4.38–4.94) and 3.23, 95% CI (3.05–3.43), P -value < 0.0005 , respectively] (*Figure 4*). In contrast, the RORs of angioedema with ACE inhibitors were significantly higher in the ≥ 65 -year-old group than in the 18- to 64-year-old group [adjusted RORs: 20.7, 95% CI (20.1–21.4) and 13.3, 95% CI (12.9–13.7, respectively), P -value < 0.0005] (*Figure 5*). There was no difference in the reporting of cough related to aliskiren and also in the reporting of angioedema related to ARBs and aliskiren when the 18- to 64-year-old group was compared with the ≥ 65 -year-old group (*Figures 4* and *5*).

When stratifying according to six age categories, the reporting of cough related to ACE inhibitors was increased with age until reaching a plateau at middle adulthood (40–59 years) and the reporting of angioedema with ACE inhibitors was increased with age until elderly (60–79 years) (*Figures 6* and *7*). Age had only a slight effect on reporting of cough and angioedema with ARBs and aliskiren (*Figures 6* and *7*).

Secondary analysis

We included captopril, enalapril, lisinopril, perindopril, and ramipril from the ACE inhibitor group and losartan, valsartan, candesartan, irbesartan, and

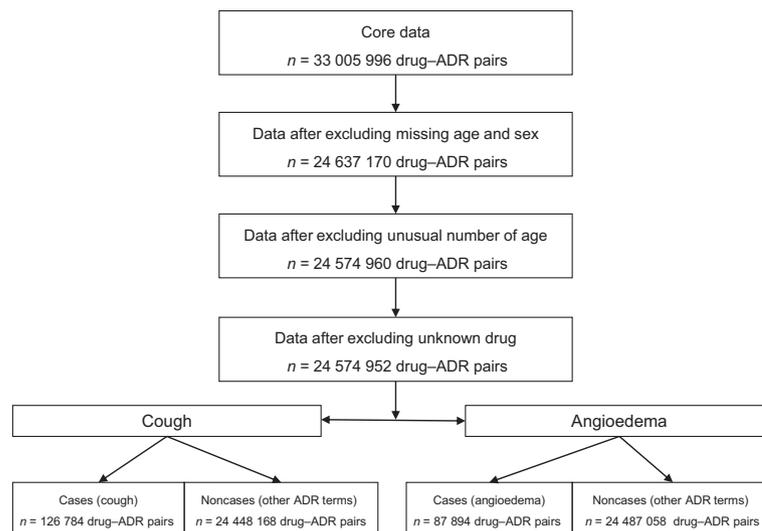


Figure 1 Flowchart illustrating the included data. ADR, adverse drug reaction.

Table 1 Baseline characteristics of cases (cough) and noncases.

	Total drug-ADR pairs (n = 24 574 952)	
	Cases (cough) N = 126 784	Noncases (other ADR terms) N = 24 448 168
Mean age, years (SD)	44.3 (26.7)	41.9 (25.8)
Age groups		
Infant and childhood	27 569 (21.7%)	4 723 386 (19.3%)
Adolescence	3834 (3.0%)	1 212 823 (5.0%)
Young adulthood	13 208 (10.4%)	4 481 799 (18.3%)
Middle adulthood	36 028 (28.4%)	6 725 685 (27.5%)
Elderly	40 261 (31.8%)	6 049 266 (24.7%)
Late elderly	5884 (4.6%)	1 255 209 (5.1%)
Sex		
Male	50 365 (39.7%)	10 111 116 (41.4%)
Female	76 419 (60.3%)	14 337 052 (58.6%)
RAS inhibitors		
ACE inhibitors	28 620 (22.6%)	215 809 (0.9%)
ARBs	2371 (1.9%)	117 370 (0.5%)
Aliskiren	73 (0.1%)	8808 (0.0%)
Co-medications		
Fentanyl	187 (0.1%)	152 831 (0.6%)
Methotrexate	711 (0.6%)	144 623 (0.6%)
Nitrofurantoin	630 (0.5%)	40 928 (0.2%)
Propofol	122 (0.1%)	55 737 (0.2%)
Adrenergic drugs for OADs (inhalants)	4729 (3.7%)	236 545 (1.0%)
Other drugs for OADs (inhalants)	1727 (1.4%)	113 292 (0.5%)

ADR, adverse drug reaction; SD, standard deviation; RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; OADs, obstructive airway diseases.

telmisartan from the ARB group. These drugs were in the top five of most frequent reporting of cough and angioedema related to these drugs.

Impact of sex

The reporting of cough related to individual ACE inhibitors was higher in women than in men, and there was no difference in reporting of cough related to individual ARBs between men and women (Figures S1 and S2). Furthermore, the reporting of angioedema related to captopril, enalapril, and lisinopril was significantly higher in men than in women but for perindopril, women had a significantly higher ROR than men. There was no difference in reporting of angioedema related to ramipril and individual ARBs between men and women (Figures S3 and S4).

Impact of age

The reporting of cough related to individual ACE inhibitors and ARBs was significantly higher in the 18- to 64-year-old group than in the ≥ 65 -year-old group except for candesartan and telmisartan (Figures S5 and S6). In contrast, the RORs of angioedema related to individual ACE inhibitors were significantly higher in the ≥ 65 -year-old group than in the 18- to 64-year-old group. However, for valsartan, the 18- to 64-year-old group had significantly higher RORs of angioedema than the ≥ 65 -year-old group. There was no difference in the reporting of angioedema related to other individual ARBs between the 18- to 64-year-old group and the ≥ 65 -year-old group (Figures S7 and S8).

Table II Baseline characteristics of cases (angioedema) and noncases.

	Total drug-ADR pairs (n = 24 574 952)	
	Cases (angioedema) N = 87 894	Noncases (other ADR terms) N = 24 487 058
Mean age, years (SD)	45.1 (22.5)	41.8 (25.8)
Age groups		
Infant and childhood	8523 (9.7%)	4 742 432 (19.4%)
Adolescence	4870 (5.5%)	1 211 787 (4.9%)
Young adulthood	20 936 (23.8%)	4 474 071 (18.3%)
Middle adulthood	27 065 (30.8%)	6 734 648 (27.5%)
Elderly	22 327 (25.4%)	6 067 200 (24.8%)
Late elderly	4173 (4.7%)	1 256 920 (5.1%)
Sex		
Male	36 413 (41.4%)	10 125 068 (41.3%)
Female	51 481 (58.6%)	14 361 990 (58.7%)
RAS inhibitors		
ACE inhibitors	11 605 (13.2%)	232 824 (1.0%)
ARBs	1478 (1.7%)	118 263 (0.5%)
Aliskiren	133 (0.2%)	8748 (0.0%)
Co-medications		
NSAIDs	9572 (10.9%)	940 586 (3.8%)
Contrast agents	2100 (2.4%)	306 628 (1.3%)
Opioids	1950 (2.2%)	920 384 (3.8%)

ADR, adverse drug reaction; SD, standard deviation; RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

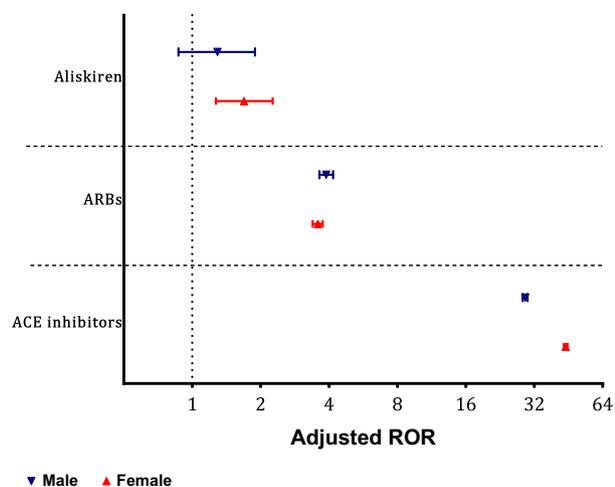


Figure 2 The impact of sex on the reporting of cough with renin-angiotensin system inhibitors. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ROR, reporting odds ratio.

Sensitivity analysis

In our sensitivity analyses, it appeared that the results were similar to our findings in the main analyses

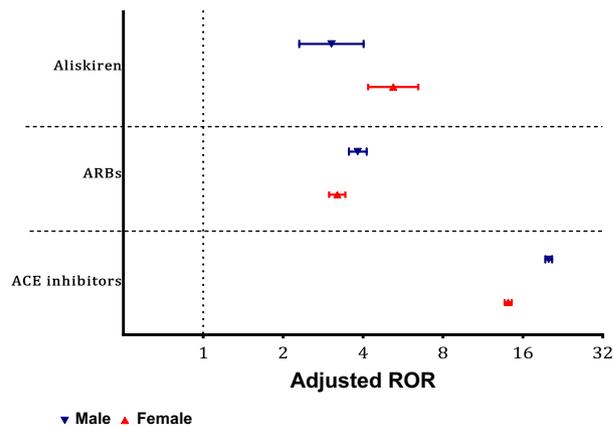


Figure 3 The impact of sex on the reporting of angioedema with renin-angiotensin system inhibitors. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ROR, reporting odds ratio.

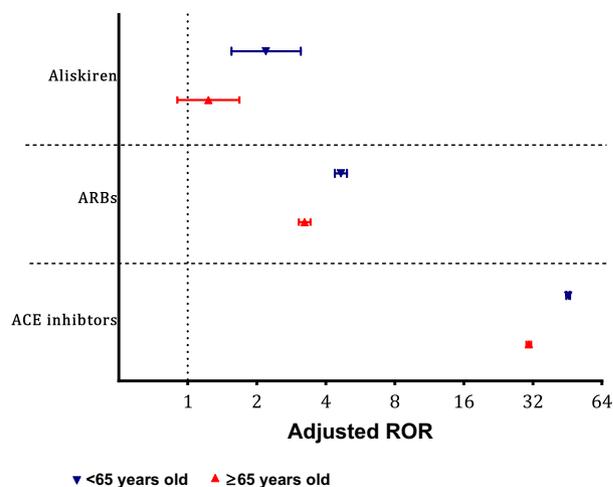


Figure 4 The impact of age (two categories) on the reporting of cough with renin-angiotensin system inhibitors. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ROR, reporting odds ratio.

except that the ROR of angioedema related to ARBs and aliskiren did not differ between men and women when we restricted our analysis to ICSRs that reported with only one ADR related to only one suspected drug.

DISCUSSION

Our study shows that the reporting of cough during the use of ACE inhibitors was significantly higher in women than in men and the reporting of angioedema in association with ACE inhibitors and ARBs was significantly higher in men than in women. However, for

aliskiren, women had significantly higher ROR of angioedema than men. For the effect of age, the reporting of cough related to ACE inhibitors and ARBs was

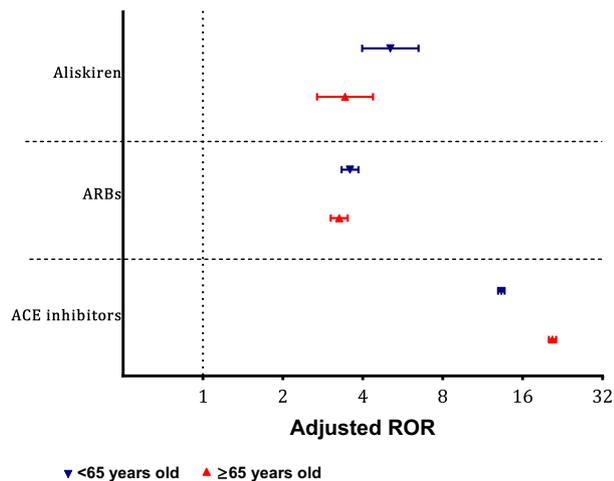


Figure 5 The impact of age (two categories) on the reporting of angioedema with renin–angiotensin system inhibitors. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ROR, reporting odds ratio.

significantly higher in the group aged 18–64 years compared to the group aged ≥65 years and the reporting of angioedema with ACE inhibitors was significantly higher in the group aged ≥65 years than in the group aged 18–64 years. The reporting of cough related to ACE inhibitors was increased with age until reaching a plateau at middle adulthood (40–59 years) and the reporting of angioedema related to ACE inhibitors was increased with age until elderly (60–79 years).

Our study is the first study that assessed the impact of age and sex on the reporting of cough and angioedema related to RAS inhibitors using VigiBase.

An important question is whether these different findings in the reporting of cough and angioedema related to RAS inhibitors reflect causal differences in ADR risk by sex and age groups or are caused by factors influencing ADRs reporting or both. Further insight can be obtained by comparing our results with randomized and observational studies that present cough and angioedema events during RAS inhibitor use stratified by sex and age.

Our finding of higher reporting of cough related to ACE inhibitors in women than in men was consistent

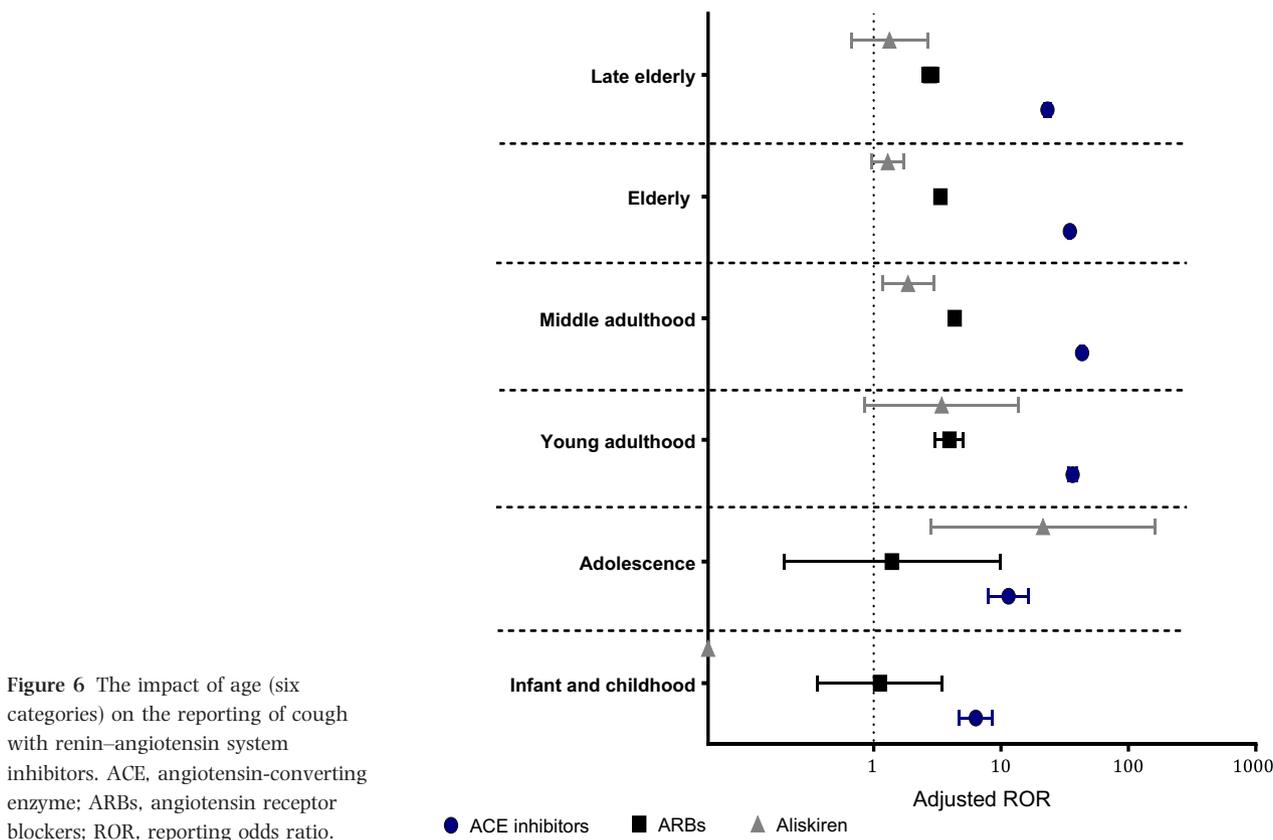


Figure 6 The impact of age (six categories) on the reporting of cough with renin–angiotensin system inhibitors. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ROR, reporting odds ratio.

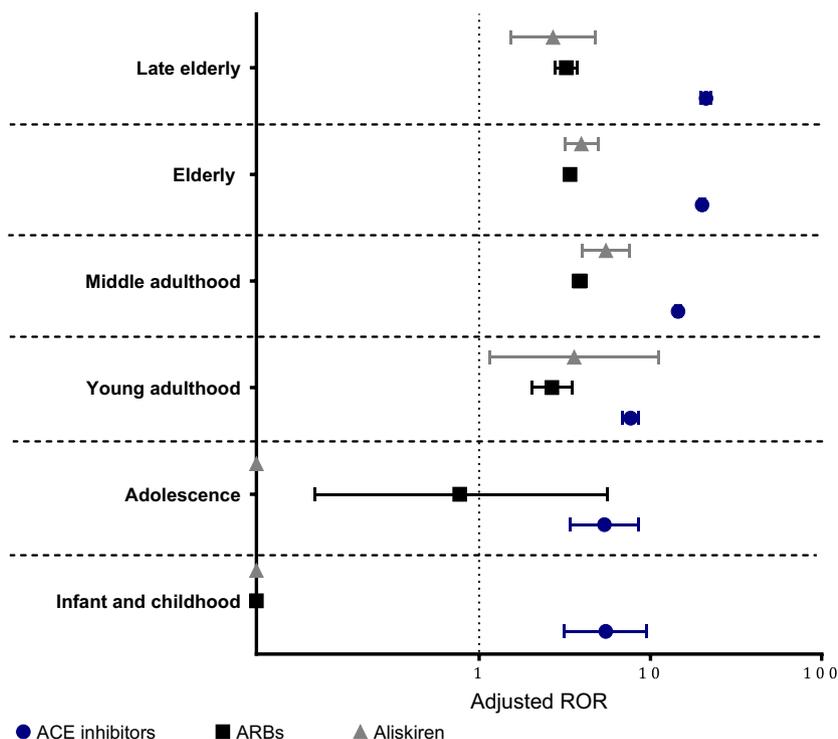


Figure 7 The impact of age (six categories) on the reporting of angioedema with renin–angiotensin system inhibitors. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ROR, reporting odds ratio.

with previous results in interventional and observational studies in literature [8–11]. Also, our finding of a higher reporting of angioedema related to ACE inhibitors in men was consistent with the Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study that found the incidence of angioedema with lisinopril was slightly higher in men (0.49%) than in women (0.31%) [21]. Moreover, Woodard-Grice *et al.* [22] found that black male patients who had the XPNPEP2 -2399A genotype had an increased risk of developing angioedema with ACE inhibitors. However, in contrast to our findings, in two cohort studies, the incidence of angioedema in users of ACE inhibitors was higher in women [6,13]. For ARBs, our finding of higher reporting of angioedema in men is in line with Toh *et al.* [6] who found in a cohort study that men had a slightly higher hazard ratio (HR) compared to women [adjusted HR 1.29, 95% CI (1.03–1.63) and 1.13, 95% CI (0.94–1.37), respectively]. Moreover, we found that there was no difference in the reporting of cough related to ARBs between men and women, which is not consistent with findings of a small randomized clinical trial in patients who had experience of cough with ACE inhibitors. This study found that the incidence of cough with losartan is higher in women than in men [20%, (4/20), and 12%, (1/8), respectively] [23].

With regard to the influence of age, we found a higher reporting of cough with ACE inhibitors in the 18- to 64-year-old group compared to the ≥ 65 -year-old group. This is in contrast with findings of Brugts *et al.* [11] that found the risk of developing of cough increases in patients who were above 65 years old. This study analyzed individual data from three large randomized clinical trials of patients who had cough due to ACE inhibitors. On the other hand, our findings regarding the reporting of angioedema related to ACE inhibitors were consistent with previous results in interventional and observational studies in literature, suggesting that the risk of developing angioedema increases in elderly people [6, 24]. Also, we found a higher reporting of cough with ARBs in the 18- to 64-year-old group compared to the ≥ 65 -year-old group, which is in line with Argenziano and Trimarco [25] who found in a randomized clinical trial that the 18- to 64-year-old group had a slightly higher incidence of cough with eprosartan compared to the ≥ 65 -year-old group (11.2% and 9.7%, respectively). Moreover, we found that age did not modify the reporting of angioedema related to ARBs, which is consistent with findings in a cohort study of Toh *et al.* [6].

We did not find information in literature to compare our findings stratified by sex and age for the reporting of cough and angioedema related to aliskiren.

We believe that our stratified findings by sex and age of the reporting of cough and angioedema related to RAS inhibitors mostly reflect causal differences in ADR risk by sex and age groups of these medications in clinical practice, as most of our findings were consistent with observations in interventional and observational studies. However, in spontaneous reporting system databases, disease prevalence, drug utilization, cultural influences on reporting behavior, and other differences within countries and between countries may also lead to discrepancies in the occurrence or the reporting of ADRs between men and women and between different age groups. Therefore, the differences we found in the reporting of cough and angioedema related to RAS inhibitors probably reflect a mix of true different ADR risks in various sex and age groups and differences in ADR reporting.

In general, occurrence of ADRs can be different between sex and age groups due to differences in pharmacokinetics and/or pharmacodynamics sometimes related to pharmacogenetic differences. For example, with regard to cough and angioedema related to ACE inhibitors, two recent studies found sex-specific differences of the effect of a polymorphism of the ABO gene (related to ACE levels; rs495828) with cough and a polymorphism of aminopeptidase P activity (XPNPEP2 gene; rs3788853) with angioedema among ACE inhibitors users [22, 26].

Our study may be helpful in therapeutic decision making in clinical practice, for example, for the starting, stopping, switching, or avoiding of RAS inhibitors in patients who are more likely to experience cough or angioedema when taking these drugs. Moreover, our findings suggest that using subgroup analyses, in addition to crude analyses in Vigibase or other spontaneous reporting system databases in data mining, may be beneficial for enhancing the sensitivity of detecting drug safety signals and/or identifying subgroups of patients who are at a higher risk of developing an ADR. This may lead to the provision of important information with regard to drugs safety and public health.

There are some strengths and limitations in our study. A strong point is that our data were retrieved from Vigibase, which contains suspected ADR reports from most countries in the world. In our study, we included ICSRs from 118 countries in all regions of the world. However, there are also limitations. Well-established risk factors for cough or angioedema such as smoking and comorbidities were not available in our database. Other general limitations are that Vigibase,

as any ICSRs spontaneous reporting database, is known to be affected by variable under-reporting, and that causality is often unsure in the collected case reports.

CONCLUSION

Both age and sex have substantial effects on the reporting of cough and angioedema with RAS inhibitors and in particular ACE inhibitors. Further study is needed to determine whether these differences mainly express different ADR risks in subgroups or also can be explained by factors influencing reporting.

CONFLICT OF INTEREST

Fawaz Alharbi, Anzhelika Kholod, Patrick Souverein, Ronald Meyboom, Mark de Groot, Anthonius de Boer, and Olaf Klungel declare that they have no conflict of interest.

CAVEAT STATEMENT

We used data provided by the UMC. However, the study results and conclusions are those of the authors and do not represent the opinion of the UMC, National Centers, or WHO. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1 and S2. The impact of sex on the reporting of cough with individual ACE inhibitors and ARBs.

Figure S3 and S4. The impact of sex on the reporting of angioedema with individual ACE inhibitors and ARBs.

Figure S5 and S6. The impact of age (two categories) on the reporting of cough with individual ACE inhibitors and ARBs.

Figure S7 and S8. The impact of age (two categories) on the reporting of angioedema with individual ACE inhibitors and ARBs.