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# Impact of ACE Inhibitors and ARBs-related Adverse Drug Reactions Consultations on Patients' Clinical Outcomes: A Cohort Study in UK Primary Care


## Abstract

### Background

Adverse drug reactions (ADRs) related to angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) may negatively affect patients' treatment outcomes. There is limited evidence on the impact of these ADRs in a real-world clinical setting.

### Aim

To investigate the impact of ACEI/ARB-related ADRs consultations in primary care on patients' clinical outcomes.

### Design and Settings

Propensity score-matched cohort study of ACEI/ARB users during 2004-2019 using UK IQVIA medical research data.

### Methods

ACEI/ARB-related ADRs consultations were identified using standardised designated codes in primary care medical records data. Propensity scores were calculated based on comorbidities, concomitant medications, frailty index, polypharmacy, and interval between ACEI/ARB initiation and index date. The outcomes of interest were cardiovascular disease (CVD) events and all-cause mortality. Cox proportional hazard

regression models were used to compare the outcomes between ADRs and non-ADRs group. In secondary analysis, treatment pattern changes following ACEI/ARB-related ADRs were examined and the subsequent outcomes were compared.

**Results**

Among 1,471,906 eligible ACEI/ARB users, 13,652 patients (0.93%) had ACEI/ARB-related ADRs consultation in primary care. Mean follow-up duration were 6.57 and 4.84 years for the CVD primary (n=6,196) and secondary (n=14,238) prevention cohorts, respectively. ACEI/ARB-related ADRs consultations were associated with subsequent CVD events and all-cause mortality in both primary (adjusted HR. 1.22, 95%CI 1.05,1.43 and 1.14,95%CI 1.01,1.27) and secondary prevention cohort (adjusted HR. 1.13, 95%CI 1.05,1.21 and 1.15, 95%CI 1.09,1.21), respectively. Half (50.19%) patients with ADRs consultations continued to use ACEI/ARB and these patients had a reduced risk of mortality (adjusted HR. 0.88, 95% CI 0.82, 0.95) compared to those who discontinued ACEI/ARB.

**Conclusions**

This study provides information on the burden of ADRs on patients and the health system. Patients with ACEI/ARB-related ADRs consultation had an increased risk of subsequent CVD events and mortality, indicating additional monitoring and treatment strategies by healthcare professionals for patients affected by ADRs are needed to mitigate the risks of adverse clinical outcomes.

**Keywords:** adverse drug reactions, drug-related side effects and adverse reactions, primary health care, hypertension

## How this fits in

Adverse drug reactions (ADRs) represent considerable burden for patients and health care system. ADRs related to angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were among the most frequent ADRs in primary care setting. However, there is limited information on the impact of ACEI/ARB-related ADRs on patients outcome and treatment pattern changes following the ADRs in this setting. In this study, we found that ACEI/ARB-related ADRs consultations were associated with subsequent major cardiovascular event and all-cause mortality, indicating the affected patients should be monitored more closely by healthcare professionals to mitigate the risk of adverse clinical outcomes.

## Introduction

Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) are two renin-angiotensin-aldosterone system inhibitor (RAASI) which are among the most frequently prescribed drugs worldwide.[1-3] These medications are commonly indicated for a number of conditions, including hypertension, chronic kidney diseases (CKD), and heart failure (HF).[4-9] Treatment with ACEI/ARB has been shown to reduce morbidity and mortality.[10-12]

Previous studies reported that up to 3.9% of ACEI/ARB users may develop adverse drug reactions (ADRs), including persistent dry cough, hyperkalaemia, dizziness, hypotension, gastrointestinal symptoms, palpitation, excessive urination, and angioedema.[13, 14] A UK-based study by Tsang et al found that ACEI was among the most common drugs class involved in ADRs in primary care.[15] Risk of ACEI/ARB-related ADRs increased with dual RAASI combination, history of smoking, progression of CKD stages, hypoaldosteronism, and the use of concomitant medication such as other anti-hypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), heparin, and immunosuppressants.[16-19]

In addition to direct physiological impact, ADRs may have negative consequences on patients' treatment outcomes.[20] Previous studies showed that up to a third of patients with hypertension had their treatment reduced and/or interrupted owing to ADRs, and thus precluded treatment options to achieve blood pressure target.[14, 21] Clinical guidelines indicate that depending on the severity of the reactions and underlying comorbidities, management of ACEI/ARB-related ADRs may vary between patients,

which include altering the dosage regimen, switching between ACEI/ARB and/or other drug classes, and necessary monitoring e.g., renal functions and electrolytes.[22, 23]

There is limited information on the impact of ACEI/ARB-related ADRs on patients' clinical outcomes. Such findings may help to improve understanding of the burden of ADRs and better inform patient care and monitoring for individuals at high risk of untoward clinical outcomes. The objectives of this study were to examine the impact of ACEI/ARB-related ADRs consultation on subsequent cardiovascular disease (CVD) events and all-cause mortality and investigate treatment pattern changes following these ADRs in UK primary care settings.

## Methods

### Data Source

This study was conducted using IQVIA Medical Research Data UK that incorporates data from The Health Improvement Network (THIN).[24] The data contains de-identified information provided by patients as part of their routine primary care. UK primary databases have been previously used to investigate ADR-related consultations.[15, 25-27] The study protocol was approved by IMRD Scientific Review Committee (reference number:21SRC008).

### Study Design

This cohort study included ACEI/ARB users during 2004-2019. Patients with missing date of birth, sex, aged <18 years at the date of first ACEI/ARB prescription, had a previous ACEI/ARB-related ADR before 2004, were registered less than one year before the index date, and had a history of cancer were excluded. As a previous history

of CVD increases the risk of recurrent CVD events and mortality, we stratified the analysis based on CVD primary prevention and secondary prevention,i.e.,without and with a history of CVD, respectively. CVD was defined as coronary heart disease (angina and myocardial infarction), cerebrovascular disease (stroke and transient ischemic attack), and peripheral arterial disease. Patients with HF were included in the secondary prevention due to their equivalent level of risk as people with an established CVD.[28, 29] Study design is presented in the Supplementary Figure 1.

**Exposed cohort**

The exposed cohort comprised of patients with ACEI/ARB-related ADRs consultation in primary care. ACEI/ARB-related ADRs consultation was defined using standardised designated codes, e.g., Read code chapter TJ (*adverse drug reactions*), as previously examined.[15, 25-27] This study used designated codes specific to ACEI/ARB-related ADRs consultation, thus it is estimated that the ADRs consultation is attributed to ACEI/ARB therapy. The index date was defined as the date of the first ACEI/ARB-related ADRs consultation (Supplementary Table 1).

**Control cohort**

The control cohort comprised of ACEI/ARB users who did not have ACEI/ARB-related ADRs consultation in primary care. To generate a control cohort, we assigned an index date at random to a sample of 30% of unexposed patients by incidence density sampling from the distribution of index dates in the exposed cohort.[30] After excluding patients who died/transferred before or at the index date, registered less than one year, or had history of cancer, propensity score matching (1:1) was used to select the

control group using the greedy matching algorithm.[31] Patients with history of any cancer were excluded as cancers negatively affect survival.

**Covariates**

The covariates measured were age, sex, interval between ACEI/ARB initiation date and index date, comorbidities (recorded at any time before or on the index date), i.e., hypertension, CKD, type 1 and type 2 diabetes mellitus, dyslipidaemia, chronic liver disease, chronic obstructive pulmonary disease, rheumatic disease; the use of concomitant medications (recorded ≤ 180 days before the index date), i.e., calcium channel blockers (CCBs), diuretics, β-blockers, statins, antiplatelets/anticoagulants, antidiabetics, nitrates, and NSAIDs; electronic frailty index (eFi), comprising 36 health conditions as developed and validated by Clegg et al;[32] and polypharmacy. Frailty index was categorized as i) fit, ii) mild, iii.) moderate, and iv) severe frailty. Polypharmacy was defined as the use of 5-9 medications and excessive polypharmacy as the use of ≥ 10 medications.[33]

**Propensity Score**

Propensity score is defined as the probability of receiving the exposure (ACEI/ARB-related ADRs) estimated from a logistic regression model based on all covariates at baseline.[34] It was used to control for confounding due to nonrandomised exposure allocation by generating comparable distribution of measured covariates across exposed and control groups. In the matched sample, the balance of covariates was assessed using standardised mean difference (SMD). SMD of less than 0.2 indicates a negligible difference in covariates between both groups.[35]

## Outcomes and follow-up period

The primary outcome was the first composite CVD events (myocardial infarction, stroke/TIA) and the secondary outcome was all-cause mortality. The follow-up for each patient commenced from the date of ACEI/ARB-related ADRs/index date until the occurrence of the outcome or at the earliest of any censoring event (patient transferred out, death, study end date).

## Secondary, subgroup, and sensitivity analysis

In the secondary analysis, treatment pattern changes within 12 months following the ADRs consultation were examined and the subsequent outcomes were compared. The continued ACEI/ARB prescription was defined as any prescription within 12 months after ADR consultation, as used in previous study examining continued drug prescription following ADRs.[36] Patients who died, transferred, had last day of follow up, and CVD events within 1-year after the ADR date were excluded to reduce immortal time bias. The eligible patients were classified as:i) Continued ACEI/ARB, either continuing the current treatment or switching to another ACEI/ARB; ii) Discontinued ACEI/ARB. The subsequent outcomes were compared between those who continued and discontinued ACEI/ARB following the ADR using stabilised inverse probability of treatment weighting (IPTW) with the propensity score estimated from all covariates as in the main analysis. The follow-up commenced from 12 months following the ADR until whichever occurred first;the outcome of interest, patient transferred out,death or study end date. Competing risk analysis were performed using Fine-Gray's subdistribution hazard model.[37] Subgroup analyses were performed separately based on different indications for ACEI/ARB, i.e., hypertension, CKD, and

HF. Sensitivity analysis using stabilised IPTW was conducted for the primary analysis. We adjusted time window period to examine treatment changes from 12 months to 6 months period in the secondary analysis to evaluate robustness.[26] As UK clinical guideline considers ethnic differences for the selection of antihypertensive drugs including ACEI/ARB, for patients with ethnicity data available, separate sensitivity analysis was conducted. Additional analysis among those who continued ACEI/ARB in the ADRs group versus control group was conducted to examine whether the continuation of ACEI/ARB affect the outcomes.

### Statistical analyses

Baseline characteristics were expressed as frequencies (percentages) for categorical variables and as means (±SDs) for continuous variables. Cox proportional hazard regression model and Kaplan Meier were used to estimate the risk of CVD events and all-cause mortality. The results were presented as adjusted hazard ratios (HRs) with 95% CIs. A two-sided *p*-value of less than 0.05 was considered statistically significant. Analysis was performed using SAS 9.4.

## Results

### Baseline characteristics

During the study period of 2004-2019, there were 1,513,241 ACEI/ARB users identified. After exclusion, 1,471,906 patients were eligible to be included in the analysis. We found that 13,652 patients (0.93%) had an ACEI/ARB-related ADRs consultation in primary care. The flowchart of the selection of participants can be found in the Supplementary Figure 2. The mean ages ± SD were 68.11 ± 13.28 and 74.58 ± 10.91 for the CVD primary and secondary prevention cohorts, respectively

(Table 1). After matching, the standardised mean difference of all covariates was < 0.2, indicating comparability between ADRs consultation and non-ADRs consultation group in both primary and secondary prevention cohort. The baseline characteristics before and after propensity score matching can be found in the Supplementary Table 2.

**Table 1. Baseline characteristics of the participants**

| Characteristics | CVD Primary Prevention Matched Cohort | | | CVD Secondary Prevention Matched Cohort | | |
|---|---|---|---|---|---|---|
| | With ACEI/ARB-related ADR consultation (n=3,098) | Without ACEI/ARB-related ADR consultation (n=3,098) | SMD* | With ACEI/ARB-related ADR consultation (n=7,119) | Without ACEI/ARB-related ADR consultation (n=7,119) | SMD |
| Age, mean ± SD | 68.11 (13.38) | 68.11 (13.18) | -0.0006 | 74.58 (10.96) | 74.59 (10.86) | -0.0008 |
| Sex (male), n (%) | 1,210 (39.06) | 1,177 (37.99) | 0.0219 | 3,712 (52.14) | 3,741 (52.5) | -0.0082 |
| Interval between commencement of ACEI/ARB therapy and index date, mean (year) ± SD | 3.60 (3.80) | 3.60 (2.98) | -0.0003 | 5.04 (4.41) | 4.98 (3.74) | 0.0161 |
| Comorbidities, n (%) | | | | | | |
| Hypertension | 2,728 (88.06) | 2,739 (88.41) | -0.0110 | 5,038 (70.77) | 5,019 (70.50) | 0.0059 |
| Dyslipidaemia | 528 (17.04) | 508 (16.40) | 0.0173 | 1,809 (25.41) | 1,796 (25.23) | 0.0042 |
| Diabetes | 1,367 (44.13) | 1,393 (44.96) | -0.0169 | 2,462 (34.58) | 2,444 (34.33) | 0.0053 |
| CKD | 1,333 (43.03) | 1,301 (41.99) | 0.0209 | 2,826 (39.70) | 2,808 (39.44) | 0.0052 |
| Liver Disease | 44 (1.42) | 49 (1.58) | -0.0133 | 74 (1.04) | 77 (1.08) | -0.0041 |
| COPD | 287 (9.26) | 287 (9.26) | 0.0000 | 1,280 (17.98) | 1,26 (17.78) | 0.0051 |
| Rheumatic Disease | 360 (11.62) | 348 (11.23) | 0.0122 | 1,263 (17.74) | 1,272 (17.87) | -0.0033 |
| Concomitant medications, n (%) | | | | | | |
| CCBs | 1,268 (40.93) | 1,254 (40.48) | 0.0092 | 2,432 (34.16) | 2,453 (34.46) | -0.0062 |
| Diuretics | 1,534 (49.52) | 1,517 (48.97) | 0.0110 | 4,221 (59.29) | 4,166 (58.52) | 0.0157 |
| Beta-blockers | 790 (25.50) | 814 (26.28) | -0.0177 | 3,533 (49.63) | 3,588 (50.40) | -0.0155 |
| Statins | 1,342 (43.32) | 1,298 (41.90) | 0.0287 | 5,145 (72.27) | 5,199 (73.03) | -0.0170 |
| Antiplatelets/anticoagulants | 974 (31.44) | 971 (31.34) | 0.0021 | 5,425 (76.20) | 5,464 (76.75) | -0.0129 |
| Antidiabetics | 1,002 (32.34) | 1,036 (33.44) | -0.0234 | 1,691 (23.75) | 1,685 (23.67) | 0.0020 |
| Nitrates | 47 (1.52) | 39 (1.26) | 0.0221 | 2,402 (33.74) | 2,420 (33.99) | -0.0053 |
| NSAIDs | 427 (13.78) | 432 (13.94) | -0.0047 | 747 (10.49) | 730 (10.25) | 0.0078 |
| Electronic Frailty Index (eFI) | | | 0.0509 | | | 0.1089 |
| Fit | 2,090 (67.46) | 2,075 (66.98) | | 2,438 (34.25) | 2,304 (32.36) | |
| Mild | 843 (27.21) | 882 (28.47) | | 2,928 (41.13) | 3,263 (45.84) | |
| Moderate | 146 (4.71) | 133 (4.29) | | 1,403 (19.71) | 1,245 (17.49) | |
| Severe | 19 (0.61) | 8 (0.26) | | 350 (4.92) | 307 (4.31) | |
| Polypharmacy | | | 0.0241 | | | 0.0360 |
| No polypharmacy | 814 (26.28) | 816 (26.34) | | 715 (10.04) | 664 (9.33) | |
| Polypharmacy (5-9 medications) | 1,453 (46.90) | 1,421 (45.87) | | 2,908 (40.85) | 2,996 (42.08) | |
| Excessive polypharmacy (≥ 10 medications) | 831 (26.82) | 861 (27.79) | | 3,496 (49.11) | 3,459 (48.59) | |

*SMD indicates difference in mean or proportion of covariates in the exposed vs control group divided by the pooled standard deviation. SMD of less than 0.2 indicates a negligible difference in covariates between both groups. CVD: Cardiovascular Disease. ADR: Adverse Drug Reaction. SMD: Standardised Mean Difference. SD: Standard Deviation; ACEI: Angiotensin Converting Enzyme Inhibitor. ARB: Angiotensin Receptor Blocker. CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; CCBs: Calcium Channel Blockers; NSAIDs: Non-steroidal anti-inflammatory drugs.

## ACEI/ARB-related ADRs and the Risk of CVD Event and All-Cause Mortality

*CVD Primary Prevention Cohort*

During the mean (±SD) follow-up time of 6.57 (±3.96) years, 648 patients had CVD events, with 366 (11.81%) and 282 (9.10%) were in the ADR consultation and control group, respectively. Cox regression analysis showed that patients with an ACEI/ARB-related ADR had an increased risk of subsequent CVD event compared to ACEI/ARB users without an ADR, with an adjusted HR of 1.22 (95% CI,1.05,1.43).

Similar results were observed for the secondary outcome, all-cause mortality. During the mean (± SD) follow-up time of 6.93 (±3.96) years, there were 1,196 deaths (659 (21.27%) and 537 (17.33%) in the ADR consultation and control group, respectively). ACEI/ARB-related ADR increased the risk of all-cause mortality (adjusted HR 1.14, 95% CI 1.01,1.27).

*CVD Secondary Prevention Cohort*

During the mean follow-up time of 4.84±3.84 years, 3,005 patients had recurrent CVD events in secondary prevention cohort, with 1,574 (22.11%) and 1,431 (20.10%) occurred among ADR and control groups, respectively. ACEI/ARB-related ADR were associated with an increased risk of recurrent CVD events (adjusted HR 1.13,95% CI.1.05, 1.21).

Similarly, for the mortality outcome, during the mean (±SD) follow-up of 5.63 (±3.95) years, there were 5,208 deaths (2,792 (39.22%) and 2,416 (33.94%) in the ADR and control groups, respectively). ACEI/ARB-related ADR increased the risk of all-cause

mortality, with adjusted HR of 1.15 (95% CI,1.09, 1.21) (Table 2, Supplementary Figure 3).

**Table 2. Adjusted hazard ratio and incidence rate per 1000 person-years (95%) CI for CVD events and all-cause mortality in CVD primary and secondary prevention cohorts**

| Outcome | CVD Primary Prevention Cohort | | | | | CVD Secondary Prevention Cohort | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ADR group | | Control group | | Adjusted HR (95% CI) | ADR group | | Control group | | Adjusted HR (95% CI) |
| | Event (%) | Incidence Rate (95% CI) | Event (%) | Incidence Rate (95% CI) | | Event (%) | Incidence Rate (95% CI) | Event (%) | Incidence Rate (95% CI) | |
| **Primary Outcome** | | | | | | | | | | |
| Composite CVD events | 366 (11.81) | 17.46 (15.76, 19.34) | 282 (9.10) | 14.27 (12.70, 16.04) | 1.22 (1.05, 1.43) | 1,574 (22.11) | 46.07 (43.85, 48.41) | 1,431 (20.10) | 41.12 (39.05, 43.31) | 1.13 (1.05, 1.21) |
| Myocardial infarction | 140 (4.52) | 6.43 (5.44, 7.58) | 98 (3.16) | 4.81 (3.95, 5.86) | 1.33 (1.03, 1.72) | 667 (9.37) | 17.78 (16.42, 19.26) | 510 (7.16) | 12.62 (11.49, 13.86) | 1.32 (1.18, 1.48) |
| Stroke/TIA | 250 (8.07) | 11.71 (10.34, 13.26) | 198 (6.39) | 9.85 (8.57, 11.32) | 1.19 (0.98, 1.43) | 1,041 (14.62) | 28.87 (27.17, 30.68) | 1,016 (14.27) | 28.13 (26.45, 29.91) | 1.04 (0.95, 1.13) |
| **Secondary Outcome** | | | | | | | | | | |
| All-cause mortality | 659 (21.27) | 29.65 (27.47, 32.00) | 537 (17.33) | 25.90 (23.80, 28.19) | 1.14 (1.01, 1.27) | 2,792 (39.22) | 69.53 (67.00, 72.16) | 2,416 (33.94) | 60.38 (58.02, 62.84) | 1.15 (1.09, 1.21) |

CVD: Cardiovascular Disease; ADR: Adverse Drug Reaction; HR: Hazard Ratio; TIA: Transient Ischaemic Attack.

*Subgroup Analysis among Patients with Hypertension, CKD, and HF*

Patients with hypertension who had ACEI/ARB-related ADR had an increased risk of subsequent CVD event (adjusted HR. 1.13, 95% CI 1.05,1.21) and all-cause mortality (adjusted HR. 1.16, 95% CI 1.09,1.22). Consistent finding observed among patients with CKD; ACEI/ARB-related ADR were associated with CVD events and all-cause mortality, with adjusted HR of 1.35 (95% CI 1.22,1.50) and 1.24 (95% CI 1.16,1.33), respectively. In patients with HF, the highest incidence rates of CVD events and mortality were observed compared to hypertension and CKD population. However, HF patients with ACEI/ARB-related ADR had similar risk of CVD events (HR. 1.12, 95% CI 0.98,1.28), but increased risk of all-cause mortality (HR. 1.16, 95% CI 1.07,1.25) (Table 3, Figure 1).

**Table 3. Subgroup analysis across different indications for ACEI/ARB**

| Outcomes | ADR group | | Control group | | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| | Event (%) | Incidence Rate (95% CI) | Event (%) | Incidence Rate (95% CI) | |
| | **Patients with hypertension (total, n=141,151)** | | | | |
| | *Before PS matching:* Patients with ADR n=7,801, Control group n=132,683<br>*After PS matching:* Patients with ADR n=7,750, Control group n=7,750 | | | | |
| Composite CVD events | 1,494 (19.28) | 35.44 (33.69, 37.29) | 1,334 (17.21) | 31.67 (30.01, 33.41) | 1.13 (1.05, 1.21) |
| All-cause mortality | 2,629 (33.92) | 55.18 (53.11, 57.33) | 2,217 (28.61) | 47.48 (45.54, 49.50) | 1.16 (1.09, 1.22) |
| | **Patients with CKD (total, n=30,028)** | | | | |
| | *Before PS matching:* Patients with ADR n=4,223, Control group n=26,609<br>*After PS matching:* Patients with ADR n=4,168, Control group n=4,168 | | | | |
| Composite CVD events | 826 (19.82) | 47.49 (44.36, 50.84) | 645 (15.48) | 35.03 (32.43, 37.84) | 1.35 (1.22, 1.50) |
| All-cause mortality | 1,712 (41.07) | 85.65 (81.69, 89.80) | 1,404 (33.69) | 68.95 (65.44, 72.65) | 1.24 (1.16, 1.33) |
| | **Patients with heart failure (total, n=12, 646)** | | | | |
| | *Before PS matching:* ADR group n=2,544, Control group n=10,102<br>*After PS matching:* ADR group n=2,485, Control group n=2,485 | | | | |
| Composite CVD events | 438 (17.63) | 49.86 (45.41, 54.76) | 420 (16.90) | 44.37 (40.32, 48.82) | 1.12 (0.98, 1.28) |
| All-cause mortality | 1,327 (53.40) | 132.05 (125.13, 139.35) | 1,222 (49.18) | 113.91 (107.69, 120.48) | 1.16, (1.07, 1.25) |

RAAS: Renin-angiotensin-aldosterone system ADR: Adverse Drug Reaction IR: Incidence Rate HR: Hazard Ratio

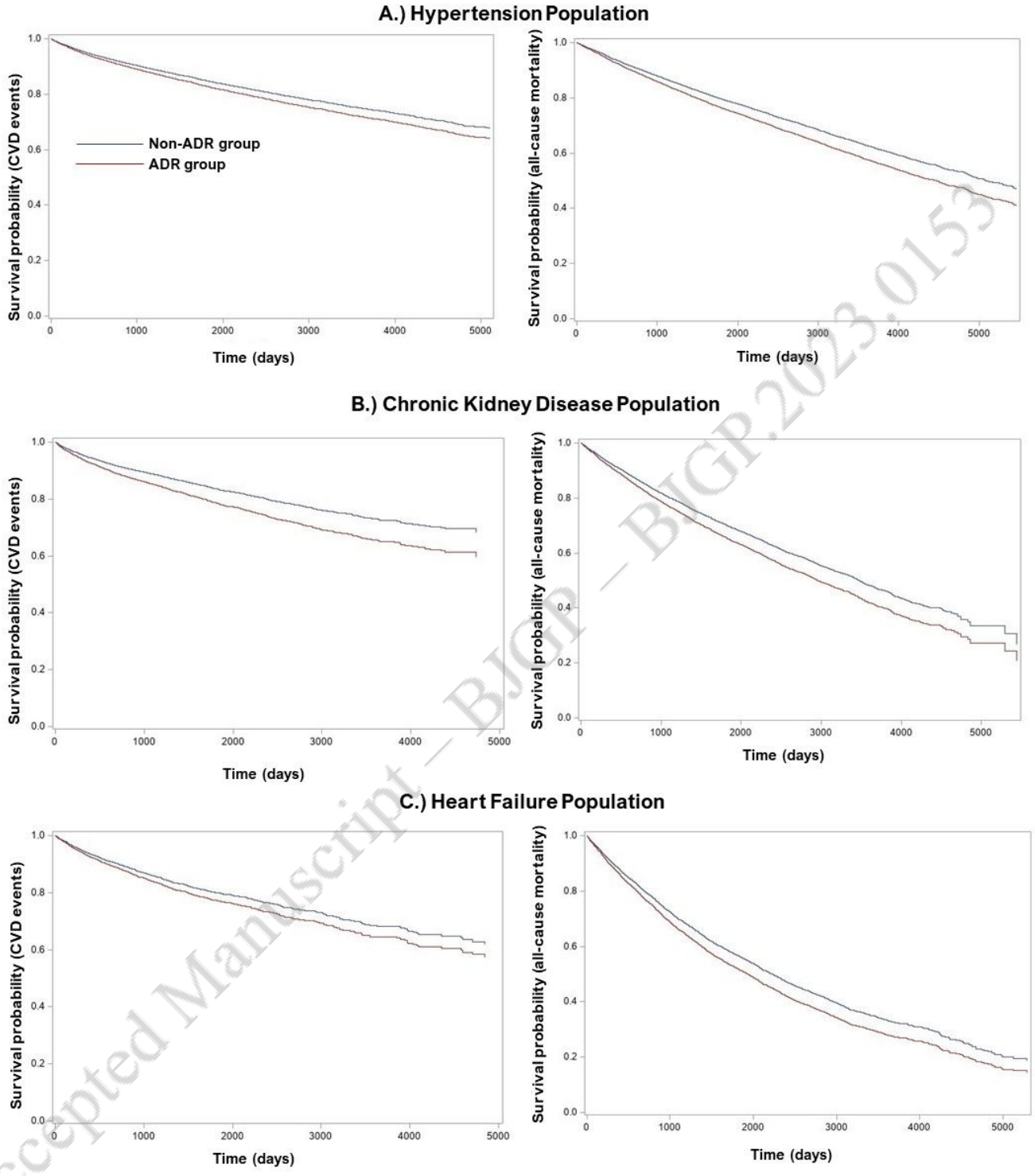




**Figure 1. Kaplan-Meier survival curves comparing CVD outcomes and all-cause mortality between ADR and non-ADR group across different indications for ACEI/ARB**

**Treatment Pattern Changes following ACEI/ARB-related ADR**

Treatment pattern changes in the year following the ADR are summarised in Table 4. Half (n=4,333, 50.19%) of the patients continued using ACEI/ARB, including switching from ACEI to ARB (n=2,228, 51.42%), continuing ACEI (n=921, 21.26%), continuing ARB, (n=204, 4.71%), and switching from ACEI and ARB combination to single ACEI/ARB drug (n=980, 22.62%). The remaining half of the patients (n=4,301, 49.81%) discontinued ACEI/ARB, with the majority (n=3,695, 85.91%) were prescribed other anti-hypertensive drugs only and few patients (n=606, 14.09%) discontinued all anti-hypertensive drugs altogether. Cox regression analysis showed that continued prescription of ACEI/ARB following ADR consultations did not lower the risk of CVD events (adjusted HR 0.95, 95% CI 0.85, 1.05), but reduced the risk of mortality (adjusted HR 0.88, 95% CI 0.82, 0.95) compared to those who discontinued ACEI/ARB (Supplementary Table 3).

**Table 4. Treatment pattern changes following ACEI/ARB-related ADR**

| Treatment changes following ACEI/ARB-related ADR | Total, n=8,634 (%) | CVD Primary Prevention n=2,889 (%) | CVD Secondary Prevention n=5,745 (%) |
|---|---|---|---|
| **Continued RAASI therapy** | 4,333 (50.19) | 1,679 (58.12) | 2,654 (46.20) |
| ⇨ Switching from ACEI to ARB. | 2,228 (51.42) | 864 (51.46) | 1,364 (51.39) |
| ⇨ Continuing on ACEI. | 921 (21.26) | 232 (13.82) | 689 (25.96) |
| ⇨ Continuing on ARB. | 204 (4.71) | 81 (4.82) | 123 (4.63) |
| ⇨ Switching from dual RAASI combination to single RAASI drug. | 980 (22.62) | 502 (29.90) | 478 (18.01) |
| **Cessation of RAASI therapy** | 4,301 (49.81) | 1,210 (41.88) | 3,091 (53.80) |
| ⇨ Using other types of anti-hypertensive drugs only | 3,695 (85.91) | 989 (81.74) | 2,706 (87.54) |
| ⇨ Cessation of all antihypertensive drugs | 606 (14.09) | 221 (18.26) | 385 (12.46) |

RAASI: Renin-Angiotensin-Aldosterone System Inhibitor. ADR: Adverse Drug Reaction. CVD: Cardiovascular Disease. ACEI: Angiotensin converting enzyme inhibitors. ARB: Angiotensin receptor blocker.

## Sensitivity Analysis

Similar findings were observed using IPTW method, with ACEI/ARB-related ADR were associated with an increased risk of subsequent CVD events and all-cause mortality in both primary and secondary prevention cohorts (Supplementary Table 4). In the secondary analysis, consistent results were observed when the window period was adjusted from 12 months to 6 months period; continued RAASI therapy was associated with reduced risk of all-cause mortality (adjusted HR, 0.88, 95% CI 0.82, 0.95) (Supplementary Table 5). Among patients with complete ethnicity data (n=68,591, 41.60%), consistent finding was observed (Supplementary Table 6). We found that

patients with ADRs who continued ACEI/ARB had an increased risk of CVD events compared to those who continued ACEI/ARB without ADRs (Supplementary Table 7).

## Discussion

*Summary*

Using longitudinal primary care medical records from 2004 to 2019, we found that patients with ACEI/ARB-related ADRs consultation had an increased risk of subsequent CVD events and all-cause mortality. The finding was relatively consistent across CVD history and different indications for ACEI/ARB. In addition, we found that the discontinuation of ACEI/ARB following the ADR was associated with an increased risk of mortality.

*Comparison with existing literature*

Our findings showed that the burden of ADRs for patients and the healthcare system were considerable. Previous studies have reported that ADRs related to other cardiovascular drugs increased the risk of adverse cardiovascular outcomes.[20, 26] Another study by Albani et al which focused on patients with history of acute coronary syndrome, showed that the intolerance to medications used for secondary CVD prevention, including ACEI/ARB, were independently associated with recurrent CVD event.[38] This is consistent with our findings. Another study by Schmidt et al showed that elevated creatinine levels of ≥ 30% following ACEI/ARB use were associated with CVD events, mortality, and end-stage renal diseases.[39] This echoes the finding of our study which indicate closer monitoring for patients with potential ADRs is needed.

Clinical guidelines recommend scheduled monitoring of renal function and serum potassium among ACEI/ARB users.[7, 9, 22] However, previous study showed that only 10% of ACEI/ARB users in the UK received guideline-recommended clinical monitoring. [40] A study by Raebel et al which focused on patients with diabetes and CKD further showed that ACEI/ARB users who received potassium monitoring are less likely to experience severe ADRs.[41] Early identification of ADRs through guideline-recommended laboratory monitoring may help to mitigate the subsequent burden of the ADRs.

Our findings showed that half of the patients with ADR continued ACEI/ARB use and these patients had a reduced risk of mortality. Several studies have examined the impact of ACEI/ARB discontinuation following a specific ADR.[42-45] A study by Leon et al showed that discontinuation of ACEI/ARB after hyperkalaemia was associated with an increased risk of mortality.[44] Using target trial emulation, Xu et al also found that hyperkalaemia-related discontinuation was associated with an increased risk of adverse clinical outcomes, with the absolute risk difference for mortality was two times higher than that of CVD events.[45,46] The decision to continue or discontinue ACEI/ARB following ADRs should be considered based on each patient's circumstances. Additional treatment strategies are of importance to facilitate continued ACEI/ARB following hyperkalaemia. This may include adequate monitoring, careful dosing, and the use of novel potassium binders such as sodium zirconium cyclosilicate, that was found to be effective and well-tolerated in patients with CKD, diabetes, and HF.[47, 48] Recently, National Institute for Health and Care Excellence (NICE) UK guideline has recommended this agent for patients with advanced CKD and HF who cannot achieve an optimal dose of ACEI/ARB due to hyperkalaemia.[49]

In our study, more than half of patients switched to ARB following ACEI-related ADRs. This is in line with current clinical guidelines.[5, 23] When ACEI-related ADR is confirmed or other causes have been ruled out, ACEI rechallenge, e.g., using the same or other types of ACEI, is generally not recommended due to high risk of recurrent reactions.[50] Although a marginal risk of subsequent ADRs may still occur with the use of ARB due to generally similar pathway, several studies have reported that tolerability of ARB is excellent in patients with previous ACEI-related ADRs, with lower rate of discontinuation, cough, and angioedema.[51-54] A Cochrane systematic review showed that the effectiveness of ARB was found to be non-inferior compared to ACEI.[55]

Since 2013, the use of dual ACEI and ARB combination has not been endorsed due to increased risk of ADRs, with no cardiovascular and mortality benefit.[56, 57] In our study, 13.17% of patients with ADRs used dual ACEI and ARB combination, as compared to only 1.22% of patients without ADRs on dual ACEI and ARB combination. Majority (n=980, 86.19%) of them switched to single ACEI/ARB, with or without other antihypertensive drugs. Existing evidence recommend ACEI/ARB with CCB or combination of two first-line drugs for high-risk patients, including patients with establised CVD, renal disease, and those with markedly high baseline blood pressure.[8, 58, 59] This combination showed superior efficacy with minimal ADRs for high-risk patients.[60]

*Strengths and limitations*

To our knowledge, this is the first study examining the impact of ACEI/ARB-related ADRs consultation on patients' outcomes in UK primary care. We conducted a thorough analysis with stratification based on CVD history and accross different

indications for ACEI/ARB. In addition, we examined treatment pattern changes following the ADRs which might help to improve understanding of how ADRs were managed in a real-world setting and whether current practice complied with the treatment guidelines.

However, our study has several limitations. Firstly, we used ADRs-related consultation in primary care as a proxy of the ADRs, identified using standardised designated codes. In our study, ACEI/ARB-related ADR were observed in about 1 % ACEI/ARB users, which was lower than in previous studies (up to 3.9%),[13,14] which may be due to variability in ADRs assessment and/or recording.[26, 27] Secondly, the severity of ADRs consultation could not be identified, which might affect the decision to continue/discontinue the medication. However, previous systematic review estimated that majority of ADRs in primary care setting were of mild-moderate severity, as compared to those requiring urgent medical care/hospitalization.[61] Thirdly, we found relatively long interval between ACEI/ARB initiation date and ADRs date in our study. It is possible that these ADRs occurred after the increase in dose of ACEI/ARB. Nevertheless, we are unable to capture the dose relationship data in our study.

*Implications for Practice and Research*

As this study showed that ACEI/ARB-related ADRs increased the risk of subsequent CVD event and all-cause mortality, in clinical practice, the monitoring of patients affected with ADRs should be performed more closely to mitigate the risk of adverse clinical outcomes. The monitoring should not only include laboratory monitoring, but also medication adherence as previous studies have reported that ADRs negatively affected medication adherence.[62, 63] In our subgroup analysis among patients who

continued ACEI/ARB, patients with ADRs had an increased risk of CVD events compared to those without ADRs, indicating the importance of additional monitoring for the affected patients as their medication adherence might be compromised even after the treatment has been switched and/or modified, resulting in suboptimal treatment outcomes. In chronic diseases such as hypertension, CKD, and HF, medication adherence is of utmost importance for disease control.[64-66] Thus, both medication safety and adherence should be monitored vigilantly by healthcare professionals for patients with ADRs, particularly when the evidence is apparent that those affected by ADRs may have an increased risk of untoward clinical outcomes. This additional monitoring may be incorporated in a medication review/structured medication review (SMR) for patients with chronic disease by primary care providers.

## Conclusions

Patients with ACEI/ARB-related ADRs had an increased risk of subsequent CVD events and all-cause mortality, indicating more careful monitoring and additional treatment strategies are needed for the affected patients to mitigate the risks of adverse clinical outcomes.

## Additional Information


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### Ethical approval

Data in IQVIA medical research data are anonymised and generated during routine care. The study protocol was approved by IMRD Scientific Review Committee (reference number: 21SRC008).

### Data

All relevant data are within the manuscript and its supplementary files.

### Competing Interest

The authors have declared no competing interests.

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