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Original Article

Prevalence of Concomitant Use of Angiotensin Converting Enzymes Inhibitors and Angiotensin Receptors Blockers: A Retrospective Study

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ABSTRACT

Background: A retrospective study was conducted using Electronic Health Records (EHRs) from several hospitals in Saudi Arabia. **Materials and Methods:** All hypertensive patients who visited the hospitals between 2016 and 2022 and received at least one drug from the ACE inhibitor or angiotensin receptor blocker category were included in the study. Demographic variables and treatment regimens were collected from the real-world evidence research network available at the SFDA. **Results:** The study found that of the total number of medical prescriptions during the study period (2016-2022), was 55.1% of ACEIs and 44.9% of ARBs. The most commonly used medications in the ACEI group were captopril, enalapril, fosinopril, perindopril, lisinopril, ramipril, and quinapril. In the ARB group, the most commonly used medications were olmesartan, candesartan, irbesartan, eprosartan, losartan, and telmisartan. The analysis of the data also revealed the frequency of prescription use for ACEIs and ARBs in each year. The most frequent use of ACEI prescriptions was in 2019, while for ARBs, it was in 2018. The study also identified 2,706 patients who concurrently used ACEIs and ARBs, with a higher percentage in females. The median age of these patients was 61 years. Regarding the number of exposure times and episodes, the year 2019 had the highest frequency, followed by 2018 and 2017. The incidence rate per 10,000 patient years was highest in 2016. **Conclusion:** The prevalence of concomitant use is still detected but at a low rate. This reflects adherence to the implementation of risk reduction measures by the Saudi Food and Drug Authority.

Keywords: Angiotensin Converting Enzymes Inhibitors, Angiotensin Receptors Blockers, Acute Kidney Injury, Hypertension, Combination Therapy.

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INTRODUCTION

Diabetic Nephropathy (DN) is a significant consequence resulting from diabetes and a major contributor to end-stage renal failure. The patient with diabetic nephropathy exhibits persistent albuminuria, lower limb edemas, hypertension, and increasing renal failure, as documented by Umanath *et al.*, 2018. These symptoms significantly impact the patient's quality of life. Therefore, it is crucial to address this problem with appropriate treatment choices. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are commonly used to treat diabetic nephropathy (Figure 1) (Du *et al.*, 2022).

Angiotensin-Converting Enzyme (ACE) inhibitors decrease mortality and cardiovascular events in patients with cardiovascular disease or high-risk diabetes and slow the progression of Chronic Kidney disease (CKD) in patients with proteinuria (Jessup *et al.*, 2009; National Kidney Foundation, 2004). ACEIs do not block the vasoconstrictor response to angiotensin II fully. According to that Blocking of the renin-angiotensin pathway with Angiotensin Converting Enzyme Inhibitors (ACE) concomitantly with Angiotensin Receptor Blockers (ARBs) has some physiological bases. Also, some increase in angiotensin II levels may occur in long term treatment with ACEIs leading to decrees in treatment efficacy of inducing vasoconstriction (Farquharson and Struthers, 2002). Two indications have been cited for the use of ACEIs and ARBs concomitantly: CKD with proteinuria and heart failure (Kuenzli *et al.*, 2010). Many randomized controlled trials on patients with heart failure compared the combination therapy with ACE-inhibitor monotherapy showed that the combination therapy decreases cardiovascular morbidity. In contrast, ONTARGET (Ongoing Telmisartan Alone and in Combination

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with Ramipril Global Endpoint Trial) that was done on patients diagnosed with diabetes with end-organ damage or vascular disease, indicated that death and cardiovascular events did not decrease when using combination therapy with ACEIs and ARBs. It was associated with higher rates of adverse events, including Acute Kidney Failure (AKF) requiring dialysis and hyperkalemia. Moreover, there were 208 acute kidney failure events in 2690 patients on ACEi + ARB versus 170 in 4264 patients with ACEi or ARB monotherapy Also, 304 hyperkalemia events in 2818 patients on ACEi + ARB versus 208 in 4396 patients with ACEi or ARB monotherapy. Combination therapy in patients with proteinuria, although it has no definitive evidence that it is effective in improving clinically meaningful outcomes, it is suggested to be beneficial based on a meta-analysis of small trials (Kunz *et al*., 2008).

Antihypertensive medication use for hypertension patients not only lowers BP but also reduces the risk of CVD, cerebrovascular events, and death. Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) are both first-choice groups of medications for treating high blood pressure, Calcium channel blockers and Thiazide diuretics are other treatment options. According to the American Heart Association, patients can start hypertension treatment with only one single agent, but for patients with persistent elevated blood pressure, the option of giving two drugs of different classes should be considered. Based on the recommendations, drug combinations that have similar mechanisms of action or clinical effects should be avoided due to less effectiveness and potential harm when used together (e.g., ACE inhibitors, ARBs) (Whelton *et al*., 2018). In 2015, The Saudi Food and Drug Authority approved a letter issued to healthcare professionals to inform them about the avoidance of using medicines that act on the renin-angiotensin-aldosterone system concomitantly, such as ARBs, ACEI, or direct renin inhibitors. The safety concerns of combining ACEI and ARBs together are related to increased risk of hyperkalemia, worsening of kidney function and hypotension (Elfawal, 2015). The SFDA advised healthcare professionals that concomitant use of ARBs and ACEIs should be avoided unless medically justified. If their use was necessary, it should only be under supervision and with monitoring of renal function electrolytes and blood pressure. Data regarding the prevalence of ACEIs and ARBs concomitant use among the Saudi population are limited therefore, the purpose of this study is to evaluate the spread of using both ACEIs and ARBS together in Saudi hospitals. The present study is to estimate the adherence to risk minimization measures implemented by Saudi Food and Drug Authority (SFDA). This research use measures taken by SFDA targeting to reduce the concomitant administration of ACE and ARBs. The main Objective of this study to estimate the prevalence of ACEIs and ARBs in concomitant use for hypertensive patients over years.

MATERIALS AND METHODS

Study design, data source and patient population

A retrospective study using the Electronic Health Records (EHRs) imported and mapped from a several hospitals in Saudi Arabia. All the patients who visited the hospital in the period between 2016 till the end of 2022 and received at least one drug from the category ACE inhibitors or angiotensin receptor blockers will be included for the study.

Inclusion criteria

a. Patients with minimum one oral antihypertensive medication from the category of ACE inhibitors or AR blockers.

b. Patients 18 years or older.

Exclusion criteria

Patients received ACE inhibitors and AR blockers other than hypertension were not included in the study.

Method of data collection

The data were collected from the Real-world Evidence Research Network available at Saudi Food and Drug Authority. The recorded data were included like demographic variables and treatment regimens.

Variables of the study

Patient characteristics, including socio-demographic factors (Age, sex), concomitant use of medication and treatment episodes for individual and concomitant therapy, were included in the study. The prevalence of concomitant use of ACE inhibitors and AR blockers were calculated as number of patients in the sample with the characteristic of interest, divided by the total number of patients in the sample. Incidence rate per 10000-patient years were calculated as number of episodes of each category of drugs in a year divided by exposures in years multiple with 10000.

Statistical analysis

Patient characteristics were summarized using descriptive statistics for categorical variables. The age of the participants was calculated by the median interquartile range. The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 24. Statistical significance was set at $p<0.05$.

Ethical approval

The research proposal was approved by Institutional Review Board, Research Center, Riyadh ELM University with the IRB approval number "FPGRP/2023/771/1034/935" and Saudi Food and Drug Authority, KSA with the approval number 2023_8.

RESULTS

Prevalence of ACE inhibitors and ARBs use

The total number of patients included in the study is 106034. 54071 patients were male (50.9%) and 51963 patients were female (49.1%) with median age of the patients is 61 and IQR 18. 1631419 prescriptions were given to these patients from 2016 to 2022. The percentage of prescriptions used for ACEI was 55.1% (899302) and 44.9% (732117) for ARBs of the total number of medical prescriptions during this period (1631419).

The average duration of use for the group ACEIs was approximately 101932 times and for ARBs Group about 90643 times overall years, (Table 1) (Figure 1).

Name of the drug for ACEIs and ARBs

Table 2 illustrated the most common drug for ACEIs and ARBs from 2016 to 2022. Through the aforementioned period, it was found that the most common medications used in ACEIs group were Captopril, Enalapril, Fosinopril, Perindopril, Lisinopril, Ramipril and Quinapril with different doses, while the most common medications used from ARBs group were Olmesartan, Candesartan, Irbesartan, Eprosartan, Losartan, Telmisartan, Valsartan, (Table 2).

Number of prescriptions in each year

Table 3 showed the number of prescriptions for ACEI Group and ARBs Group were used during each year. For ACEIs group, the survey illustrated that the most frequent use of prescriptions was in 2019 with 18.9%, followed by 2018 (16.7%), year 2020 with 15.1%, 2017 year with 14.6% and 2022 with14.3% while we find that the least number of times used was in 2016, with 8.6%. On the other hand, for ARBs groups, we find that the most frequent years in which prescriptions were used was 2018 with a ratio of 18.7%, followed by 2019 with 17.9%, 2017 with ratio 16.6% while the lowest years were recorded in year 2016 (Figure 2).

The Concomitant Use ACEIs & ARBs during 2016 to 2022

Table 4 shows Concurrent Use of ACEIs and ARBs from 2016 to 2022. The study showed that the total number of patients Concurrent Use of ACEIs and ARBs during these periods was 2706 patients (2.6% of total number of patients). The highest percentage of Concurrent Used was recorded in the females with 56.7%, while in the males was 43.3% and the median age of the patients was 61 years and IQR (18) (Figure 3).

The number of exposure times during the 2016 to 2022

Table 5 illustrated the number of exposure times during the 2016 to 2022, The results of the inventory process showed that the year 2019 was the most frequent for the number of exposure time with 19.4% from the total number of exposure times, followed by 2018 (17.6%), year 2017 (15.5%), year 2020 (14.2%) and year 2022 (13.7%), while the years 2016 and 2021 were the least years for

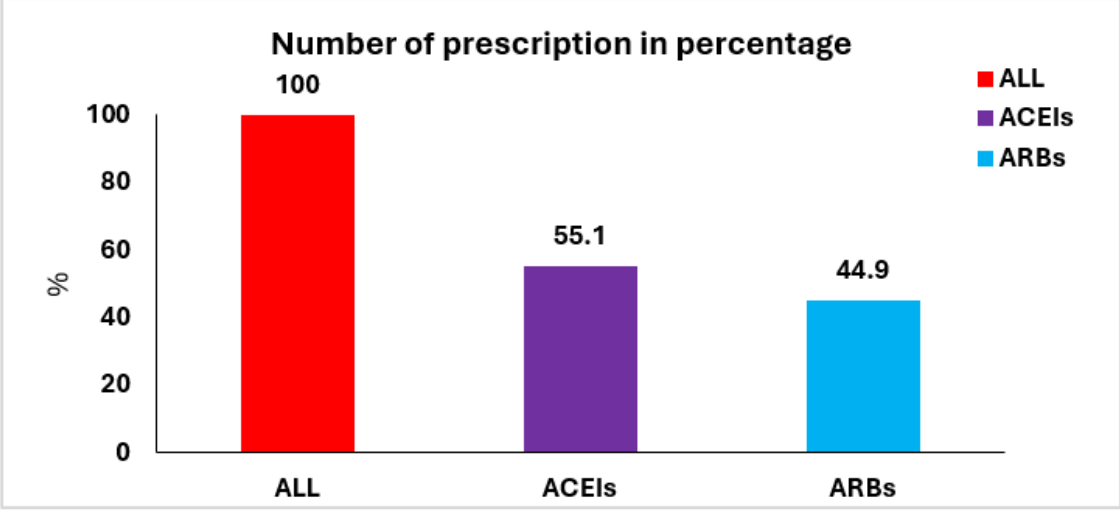

Figure 1: Descriptive statistic for prescriptions.

Table 1: Prescriptions details of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blocker (ARBs).

	All		ACEIs		ARBs	
	N	%	N	%	N	%
Number of prescriptions	1631419	100%	899302	55.1	732117	44.9
Total number of patients	106034					
Total exposure time (years)	192575		101932		90643	

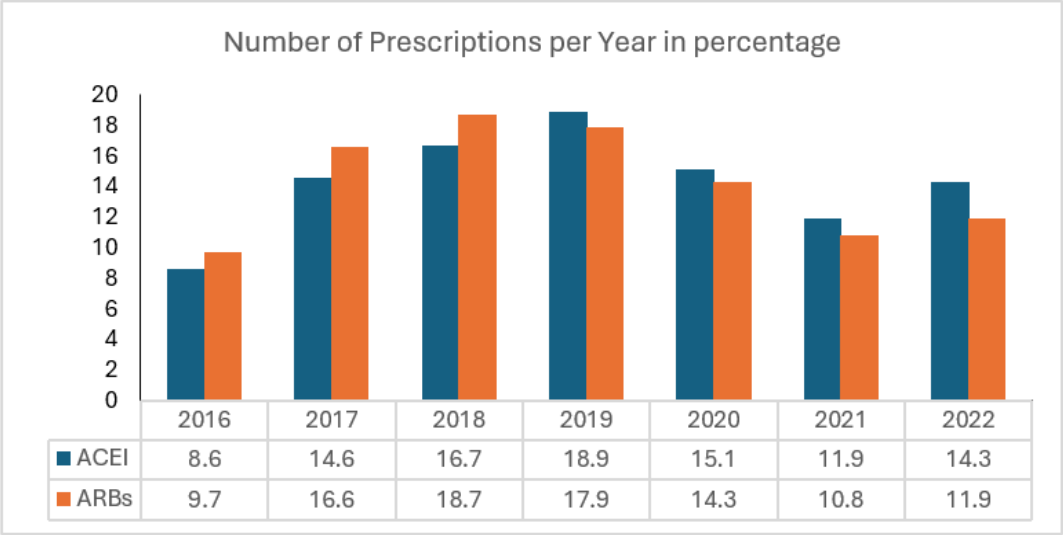

Figure 2: Number of prescriptions in each year in percentage.

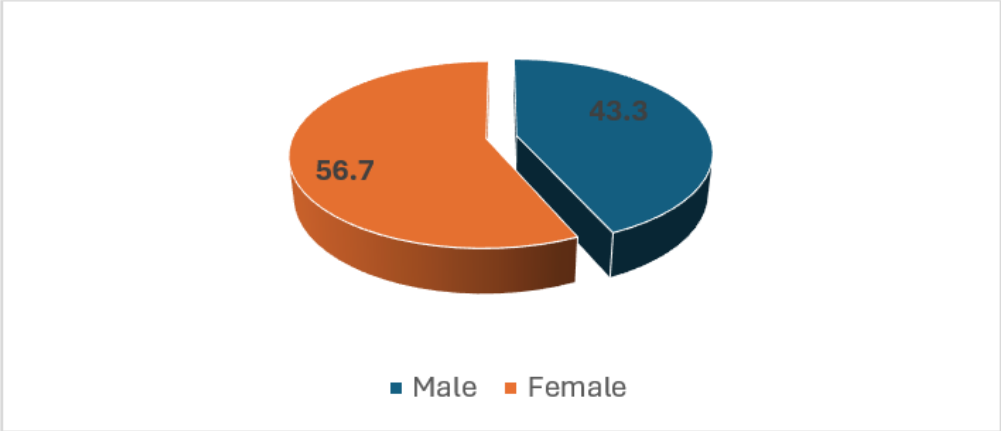

Figure 3: The Concomitant Use of ACEIs & ARBs during 2016 to 2022 according to gender in percentage.

the number of exposure times, with 9.3% and 10.3%, respectively (Figure 4).

Number of Episodes and Incidence rate per 10000-patient years

Table 6 showed the Number of episodes and incidence rate from 2016 to 2022. Regarding the number of episodes, we found the year 2019 was the most (604), followed by the year 2018 (563), then the year 2017 (543), the year 2022, but the least years for the Number of episodes were the year 2020, 2016 and 2021. As for the Incidence rate per 10000-patient years, the year 2016 was the most year for the Incidence rate, followed by the year 2017, then the year 2022, 2018 and 2019, and finally the least years were the year 2021 and 2020 (Figure 5).

DISCUSSION

The current retrospective has identified a notable prevalence of concomitant use of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs). This

Table 2: **Name of the drugs for ACE and ARBs.**

ACEIs	ARBs
Captopril	Olmesartan
Enalapril	Candesartan
Fosinopril	Irbesartan
Perindopril	Eprosartan
Lisinopril	Losartan
Ramipril	Telmisartan
Quinapril	Valsartan

percentage reflects a similar trend in the utilization of these drugs as has been reported in other studies.

However, it is imperative to consider the implications of our findings against the backdrop of existing literature. Previous research has raised concerns about the risk of adverse events such as kidney dysfunction and hyperkalemia with the concurrent use of ACEIs and ARBs.

Table 3: Number of prescriptions in each year.

	Years	ACEI		ARBs	
		N	%	N	%
Number of Prescriptions per Year	2016	139891	8.6	87181	9.7
	2017	237494	14.6	149602	16.6
	2018	272261	16.7	168030	18.7
	2019	308407	18.9	160755	17.9
	2020	246380	15.1	128966	14.3
	2021	194466	11.9	97549	10.8
	2022	232520	14.3	107219	11.9
	Total	1631419	100%	899302	100%

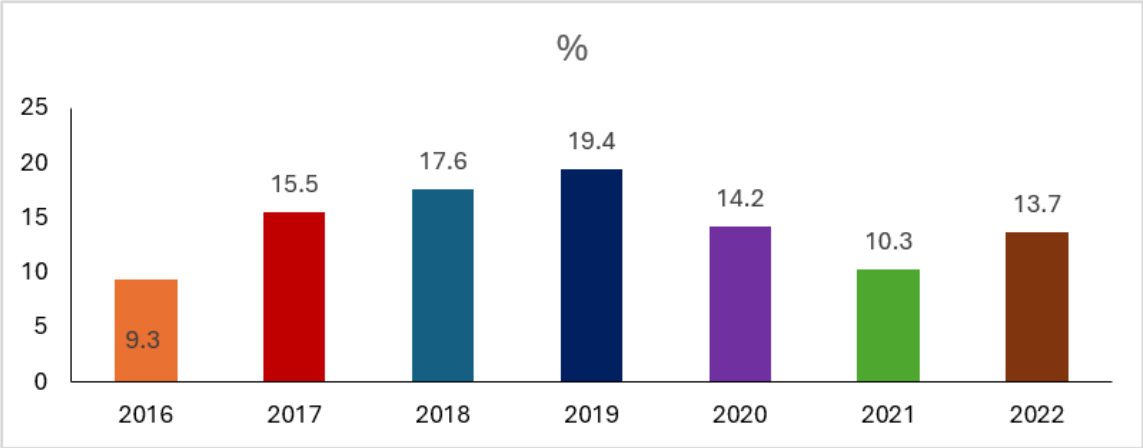

Figure 4: The number of exposure times during the 2016 to 2022 in percentage.

This study's primary objective was to ascertain the prevalence of concomitant ACE inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB) use and its clinical implications. We analyzed data from 106,034 patients, revealing that 55.1% of the 1,631,419 prescriptions issued between 2016 and 2022 were for ACEIs and 44.9% for ARBs. A substantial finding was the proportion of concomitant usage among these prescriptions, which stood at a notable prevalence, highlighting a prevalent prescribing pattern that differs from the cautionary stance observed in earlier studies.

Notably, the concomitant use of ACEIs and ARBs was 2.6% the patients, with a higher prevalence in females (56.7%) compared to males (43.3%). This figure sheds light on the persistence of combined therapy despite known risks. Our results indicate a distinct contrast to studies like those by Philips *et al*, 2011, which suggested limited benefits and heightened risks associated with such combination therapies.

Furthermore, our study's findings on the distribution of concomitant therapy across different years with the highest usage in 2019 provide new insights into prescribing trends, which have not been extensively covered in previous literature. This temporal analysis is particularly relevant given the ongoing debates about the safety and efficacy of ACEIs and ARBs in combination therapy (Almutlaq *et al*., 2021).

Table 4: The Concomitant Use ACEIs & ARBs during 2016 to 2022.

	Concomitant Use ACEIs & ARBs	No Concomitant Use
Number of patients	2706 (2.6%)	103328 (97.4%)
Gender		
Male	1172 (43.3%)	52899
Female	1534 (56.7%)	50429
Median Age (IQR)	61 (18)	60 (19)

In comparison with previous research, our study offers updated insights into prescribing behaviors and prevalence rates, adding a contemporary layer to the understanding of ACEI and ARB use in a large patient population. It underscores the need for further prospective studies to understand the full clinical impact of concomitant ACEI and ARB therapy, especially in light of the diverse findings from past studies that range from highlighting potential benefits to indicating severe risks" (Herman *et al*., 2023).

The limitation of our study lies in its observational nature and the potential for underreporting or misclassification of medication use, which could lead to an underestimation or overestimation of the true rate of concomitant use. Furthermore, our study does

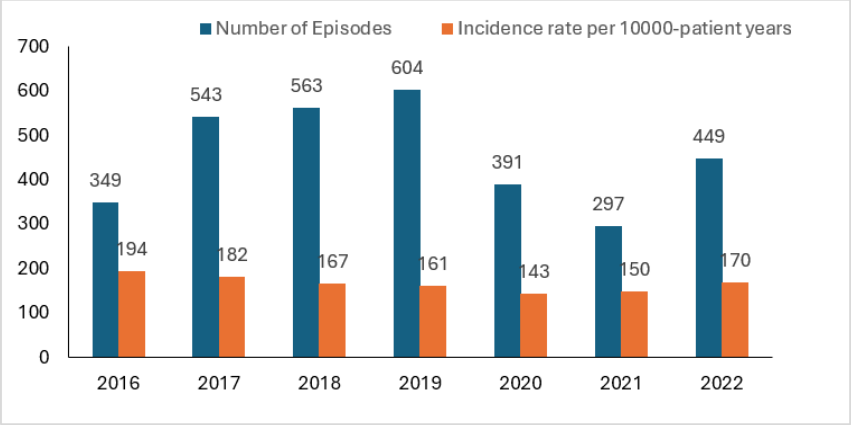

Figure 5: Number of Episodes and Incidence rate per 10000-patient years.

Table 5: The number (N) of exposure times during the 2016 to 2022.

	Exposure time (N)	%
Overall	**193054**	**100%**
2016	18000	9.3%
2017	30000	15.5%
2018	34000	17.6%
2019	37500	19.4%
2020	27342	14.2%
2021	19800	10.3%
2022	26412	13.7%

Table 6: Number of Episodes and Incidence rate per 10000-patient years.

Years	Number of Episodes	Incidence rate per 10000-patient years
Overall	3196	166
2016	349	194
2017	543	182
2018	563	167
2019	604	161
2020	391	143
2021	297	150
2022	449	170

not account for potential confounders such as the severity of disease, the duration of treatment, or the presence of comorbid conditions, which may influence the outcomes of interest.

Despite these limitations, our findings contribute valuable insights into the current practices surrounding the use of ACEIs and ARBs and highlight the need for rigorous monitoring when these medications are used together. Future research should aim to quantify the risks and benefits of this treatment approach more precisely, guiding clinicians in optimizing therapy for patients with chronic kidney disease and cardiovascular condition (Parikh *et al.*, 2020).

CONCLUSION

In the present study, the findings concluded that the prevalence of concomitant use is still detected but at a low rate reflecting that the implementation of risk reduction measures by the Saudi Food and Drug Authority has been adhered to by most doctors during practice. However, the adherence rate still needs to be increased to reach a zero percentage of concomitant use of ACEIs and ARBs among hypertension patients.

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ABBREVIATIONS

ACEI: Angiotensin converting enzyme inhibitors; **ARBs:** Angiotensin receptor blockers; **SFDA:** Saudi Food and Drug Authority; **CVD:** Cardiovascular disease; **CKD:** Chronic kidney disease.

CONFLICT OF INTEREST

We have no conflict of interest related to this work.

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