Cigarette Smoking Attenuates Kidney Protection by Angiotensin-Converting Enzyme Inhibition in Nondiabetic Chronic Kidney Disease

Bethany Roehm^a Jan Simoni^b Jessica Pruszynski^c Donald E. Wesson^{d, e}

^aDepartment of Internal Medicine, Tufts University School of Medicine, Boston, MA, ^bDepartment of Surgery, Texas Tech University Health Sciences Center, Lubbock, TX, and ^cDepartment of Cardiovascular and Thoracic Surgery, University of Texas Southwestern, ^dBaylor Scott and White Health and Wellness Center, and ^eDepartment of Internal Medicine, Texas A&M Health Sciences Center College of Medicine, Dallas, TX, USA

Keywords

Chronic kidney disease · Smoking cessation · Cigarette smoking · Angiotensin II · Isoprostane 8-isoprostaglandin F_{2α}

Abstract

Background: Cigarette smoking exacerbates the estimated glomerular filtration rate (eGFR) decline in nondiabetic chronic kidney disease (CKD) despite the kidney protection that is achieved by angiotensin converting enzyme inhibition (ACEI). Whether smoking cessation restores ACEI-related kidney protection is not known. **Methods:** This 5-year, prospective, prevention trial recruited 108 smokers and 108 nonsmokers with stage-2 nondiabetic CKD with primary hypertension and urine albumin-to-creatinine ratio (Ualb) >200 mg/g. All smokers underwent smoking cessation intervention programs. Blood pressure was reduced in all participants toward achieving a goal of <130 mm Hg with regimens including ACEI. The primary outcome was eGFR change, and secondary outcomes included Ualb and urine levels of angiotensinogen (UATG), a surrogate for kidney angiotensin II (All) levels, and isoprostane 8-isoprostaglandin F_{2α} (U8-iso), an indicator of oxidative stress. **Results:** One-year Ualb was

lower than baseline in nonsmokers but not in either smoking group, supporting greater ACEI-related kidney protection in nonsmokers than smokers. Higher Ualb at 1 year in continued smokers was associated with higher UATG and higher U8-iso, consistent with smoking-induced All and increased oxidative stress contributing to less ACEI-related kidney protection in smokers. Baseline eGFR was not different among groups ($p = 0.92$), but 5-year eGFR was higher in quitters than in continued smokers (62.0 ± 5.4 vs. 52.9 ± 5.6 mL/min/1.73 m², $p < 0.001$); this value was lower in quitters than in nonsmokers (64.7 ± 5.6 mL/min/1.73 m², $p = 0.02$). **Conclusions:** Smoking cessation compared with continued smoking ameliorates eGFR decline in nondiabetic CKD treated with ACEI, possibly by restoring kidney-protective effects of ACEI through reductions in kidney All and oxidative stress.

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Introduction

Cigarette smoking is a risk factor causing kidney failure in many among the general population [1], appears to enhance the estimated glomerular filtration rate (eGFR) decline in patients with nondiabetic chronic

kidney disease (CKD) associated with primary hypertension despite angiotensin converting enzyme inhibition (ACEI) [2, 3], and is associated with rapid kidney function decline [4]. Nevertheless, mechanisms by which cigarette smoking reduces kidney function, and possibly attenuates kidney-protective benefits of ACEI, are largely unknown. Kidney effects of smoking and its cessation have been the topics most studied in CKD due to diabetes where it appears to be a modifiable risk factor for eGFR decline [5, 6], but fewer studies have examined effects of cigarette smoking and its cessation in nondiabetic CKD. Because faster nephropathy progression contributes proportionately more to end-stage renal disease (ESRD) incidence than de novo CKD occurrence in at least in some US population groups [7], identifying modifiable risk factors for nephropathy progression remains an important objective to reduce ESRD incidence.

Despite conventional kidney protective interventions including blood pressure control with kidney-protective anti-hypertensive agents, US CKD prevalence has not decreased and the prevalence of more severe CKD categories has increased [8]. ACEI appears to be kidney protective in nondiabetic CKD [9]; yet many have progressive GFR decline in spite of ACEI [10]. Unrecognized factors in patients whose CKD progresses despite ACEI might reduce the kidney-protective effects of pharmacologic interventions like ACEI and their removal might help slow or stop CKD progression to ESRD.

Cigarette smoking promotes oxidative stress [11], a phenomenon associated with reduced GFR [12] and progressive GFR decline [13] in patients with nondiabetic CKD associated with primary hypertension. Furthermore, cigarette smoke increases tissue angiotensin II (AII) levels, possibly through increased chymase activity [14], and AII increases kidney oxidative stress [15]. These data suggest that at least part of the kidney protection associated with ACEI is mediated by ACEI-induced reduction in kidney oxidative stress. Consequently, cigarette smoking might inhibit the kidney-protective effect of ACEI through increasing oxidative stress.

We tested the hypothesis that smoking cessation, compared to continued cigarette smoking, restores the kidney-protective benefits of ACEI and thereby leads to better eGFR preservation in stage 2 nondiabetic CKD. We further explored to understand whether the hypothesized effect of cigarette smoking to attenuate ACEI-related kidney protection was mediated through AII-mediated increased oxidative stress.

Methods

This study sought to determine whether smoking cessation, compared to continued smoking, restores ACEI-related kidney protection in patients with stage 2 nondiabetic CKD associated with primary hypertension treated toward recommended blood pressure targets with regimens including ACEI. The primary outcome was eGFR (CKD-EPI equation using cystatin C) after 5 years. Secondary outcomes included changes in urine albumin excretion as a marker for kidney damage [16], urine isoprostane 8-isoprostaglandin $F_{2\alpha}$ (U8-iso) excretion as a surrogate for oxidative stress [11], and urine angiotensinogen (UATG) as a surrogate for kidney levels of AII [17].

Study Design

This study was approved by a local Institutional Review Board (IRB#00123) and conducted in accordance with the Declaration of Helsinki. Inclusion criteria for this 5-year prospective study were: diagnosis of primary hypertension, eGFR of 60–89 mL/min/1.73 m², and spot urine albumin-to-creatinine ratio >200 mg/g. Smokers were labeled as such if they consumed ≥ 10 cigarettes/day for ≥ 1 year. Most recruited participants (209 of 216) were not on ACEI upon study entry and were started on this therapy and enrolled 4 weeks later. The remaining participants already on ACEI were also enrolled 4 weeks later. At the time the protocol was started, published studies showed comparable efficacy of angiotensin receptor blockade (ARB) and ACEI to slow progression of nondiabetic CKD associated with primary hypertension [18]. Additionally, no ARB was approved for use on our County Medically Indigent formulary and enalapril was the only approved ACEI on this formulary. Consequently, enalapril was used in these albuminuric patients with reduced eGFR as recommended by extant guidelines [19] and no study subject was prescribed an ARB. Exclusion criteria were fasting blood sugar >105 mg/dL, systolic blood pressure (SBP) >200 mm Hg, smokers who consumed <10 cigarettes/day or who had discontinued smoking <1 year, non-smokers who last smoked 1 year before recruitment, inability to tolerate ACEI, pregnancy (because of ACEI use), history of malignancy or kidney transplant, and history of seizure. Smokers used only cigarettes and none admitted to chewing tobacco. We chose CKD participants with GFR 60–89 mL/min/1.73 m² (stage 2) and Ualb >200 mg/g creatinine (Ualb category A3) associated with primary hypertension because such patients had a greater risk for subsequent GFR decline than those with lower levels of albuminuria [2]. Goal blood pressure was <130/80 mm Hg as recommended by extant guidelines [19]. One hundred and eight nonsmokers and 108 smokers were enrolled in this nonrandomized, interventional prospective study. All smokers participated in smoking cessation intervention, which consisted of 4 weeks of daily transdermal nicotine (14–21 mg as needed/tolerated for cessation), bupropion 150 mg twice daily, and 12 weekly outpatient sessions of substance abuse counseling [6].

All participants submitted 3 spot morning urine samples, 1 week apart, for Ualb, cotinine, U8-iso, and UATG, each factored per gram creatinine. Serum was obtained for cotinine and creatinine at study entry, 12 weeks (i.e., after completing the smoking cessation protocol), and 24 weeks when it was determined if smokers successfully quit. Successful smoking cessation was defined biochemically as urine and plasma cotinine values at 12 and 24 weeks $\leq 10\%$ of the respective 1-week value for subsequent de-

Table 1. Baseline characteristics of the 3 groups

Variable	Nonsmokers (n = 108)	Quitters (n = 25)	Continued-smokers (n = 83)	p value
Age, years	50.3±7.1	49.4±6.1	50±7.1	0.843
Male, n (%)	52 (48.1)	11 (44.0)	41 (49.4)	0.894
Ethnicity, n (%)				
B	76 (70.4)	21 (84.0)	55 (66.3)	0.353
H	19 (17.6)	4 (16.0)	18 (21.7)	
W	13 (12)	0 (0)	10 (12)	
Ualb, mg/g Cr	420.2±148.2	367.4±159.9	426.3±138.3	0.196
LDL-C, mg/dL	117.05±16.06	127.24±16.62	124.51±20.09	<0.001
HDL-C, mg/dL	50.75±6.36	49.72±6.87	51.35±5.90	0.398
Blood pressure meds	2.0±0.7	2.4±0.7	2.4±0.7	<0.001
Enalapril, mg/day	12.6±4.2	13.8±4.2	13.7±3.9	0.115
U8-iso, µg/g Cr	1.6±0.3	4.1±10	4.2±1.2	<0.001
Urine cotinine, µg/g Cr	29.3±11.5	3,002.1±51.4	3,688.4±934.0	<0.001
Brinkman index (cigarettes/day × years smoked)	Not applicable	485.4±136.2	585.7±124.9	0.0008

For ethnicity, B, Black; H, Hispanic; W, White; U8-iso, urine isoprostane 8-isoprostaglandin F_{2α}.

terminations. We chose to biochemically assess smoking cessation using urine cotinine levels rather than personal attestation of smoking cessation in order to objectively determine successful smoking cessation. Of the 108 smokers, 25 met “quit” criteria and all quitters fulfilled “quit” criteria during the remaining follow-up intervention. All other smokers were labeled continued smokers. Thereafter, each participant provided urine and serum specimens at years 1, 2, 3, 4, and 5 at which time blood pressure was also measured. Yearly serum low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were obtained as part of routine care.

Analytical Methods

Serum and urine creatinine were measured with the Sigma Diagnostics Creatinine Kit (Procedure No. 555, Sigma Diagnostics) and urine albumin (mg/g creatinine) as previously [5]. Urine cotinine was measured with the double antibody Nicotine Metabolite radioimmunoassay kit (Diagnostic Products, Los Angeles, CA, USA) after C18 column solid phase extraction [20] as previously [6] and expressed as µg/g creatinine. Urine 8-iso was measured using direct ELISA after NaOH hydrolysis and ethyl acetate phase extraction with a kit (Cayman Chemical, 8-iso-prostane EIA kit Cat. No. 516351, Cayman Chemical, Ann Arbor, MI, USA) [21] as was done previously [6] and expressed as µg/g creatinine. Urine ATG was measured using RIA quantitation of angiotensin I (Ang I) generation [17] after addition of excess exogenous porcine renin (R 2761; Sigma, St. Louis, MO, USA) with a commercially available kit (Incstar, Stillwater, MI, USA). Urine samples were incubated with renin at 37°C, removed at 0, 10, 30, 60, and 120 min, and diluted with reagent blank such that RIA results were on the linear part of a previously determined standard curve. The amount of Ang I generated at each time point was determined by comparison to the standard curve. The amount of Ang I produced was plotted against time. Saturation kinetics due to conversion of all angiotensinogen to Ang I was obtained by the 60-min point.

Statistical Methods

Values were expressed as mean ± SD. A power analysis calculated using previously published data from our laboratory [2, 3] determined the need to enroll 98 nonsmokers and 98 smokers to detect an effect of smoking cessation on eGFR decline in this patient population. Allowing for 10% attrition, we recruited 108 smoking and non-smoking subjects. Continuous variables were first examined for normality and then compared using a one-way Analysis of variance or the Kruskal-Willis test, as appropriate. Comparison of changes in clinical characteristics over the 5-year period among the 3 groups (nonsmokers, continued smokers, and quitters) was done using Analysis of variance, followed by Tukey’s multiple comparisons. We considered a mixed model analysis to incorporate the correlations within the same participants, given that the relatively small number of study subjects and that not all of these subjects completed the study. Data management and statistical analysis were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) and graphs were created using R 3.0 (R Core Development Team, 2013). A *p* value of <0.05 indicates a statistical significance.

Results

Baseline characteristics of nonsmokers, quitters, and continued smokers are shown in Table 1. Although age and gender distribution were not different among groups, each group had a significantly smaller proportion of Whites compared to Blacks and Hispanics, and there were no Whites among the quitters. Baseline low density lipoprotein cholesterol was lower in nonsmokers than both smoking groups at study entry, was lower in nonsmokers than continued smokers (*p* < 0.004) but not quit-

ters at year 1, and there was no difference among the 3 groups at year 2 ($p = 0.06$) or subsequent follow-up years ($p > 0.20$). Baseline high-density lipoprotein cholesterol was not different among the groups and was not different in subsequent follow-up years ($p > 0.25$). The Brinkman index (cigarette number smoked/day times number of years smoked) was lower in smokers who eventually quit than in those who continued smoking. A higher Brinkman index in continued smokers was due to a greater number of cigarettes smoked per day (20.4 ± 5.7 vs. 16.7 ± 5.5 cigarettes/day, $p = 0.005$) and not due to a greater number of years smoked (30.0 ± 7.1 vs. 30.3 ± 6.7 years, $p = 0.87$).

Table 1 shows that the 3 groups were taking a similar dose of enalapril at enrollment, but nonsmokers were on fewer blood pressure medications than continued smokers and quitters. At year 1 follow-up, the dose of enalapril was lower than baseline in quitters (11.8 ± 2.5 vs. 13.8 ± 4.2 , $p = 0.002$) and nonsmokers (11.9 ± 3.7 vs. 12.6 ± 4.2 , $p = 0.01$) but not in continued smokers (13.8 ± 3.3 vs. 13.7 ± 3.9 , $p = 0.9$). Quitters had a lower number of blood pressure medications at 1 year follow-up (2.1 ± 0.7 vs. 2.4 ± 0.7 , $p = 0.03$), but this number was not different at 1 year for nonsmokers (2.0 ± 0.6 vs. 2.0 ± 0.7 , $p = 0.3$) or continued smokers (2.4 ± 0.7 vs. 2.4 ± 0.7 , $p = 0.3$, respectively). The lower enalapril dose and lower number of blood pressure medications were sustained in quitters at year 5 and were similar to that of nonsmokers.

There was no difference in SBP among nonsmokers, continued smokers, and quitters at baseline (155.7 ± 12.4 , 153.8 ± 15.3 , and 151.3 ± 12.7 mm Hg, respectively, $p = 0.06$) or year 5 (133.3 ± 8.0 , 131.8 ± 5.7 , and 134.5 ± 8.3 mm Hg, respectively, $p = 0.45$). There was also no difference in diastolic blood pressure (DBP) among the 3 groups at baseline (98.1 ± 10.1 , 97.8 ± 10.6 , and 96.8 ± 10.9 , respectively, $p = 0.38$) or year 5 (79.3 ± 4.6 , 80.6 ± 5.6 , and 80.8 ± 4.0 , respectively, $p = 0.25$). At year 1, both SBP and DBP were lower than their respective baseline values for all 3 groups, corresponding with the initiation of ACEI and overall medication adjustment in an effort to achieve goal blood pressure. There was no difference among the 3 groups with respect to SBP and DBP when averaged across follow-up.

Figure 1 shows that baseline Ualb was not different among groups ($p = 0.30$). One-year value compared to baseline Ualb was lower in nonsmokers (394.7 ± 142.7 vs. 420.2 ± 148.2 mg/g Cr, $p < 0.001$), higher in continued smokers (453.2 ± 152.0 vs. 426.3 ± 138.3 mg/g Cr, $p < 0.001$), and no different in quitters (356.0 ± 178.0 vs. 367.4 ± 159.9 mg/g Cr, $p = 0.10$). At 5 years, Ualb was

Fig. 1. Urine albumin-to-creatinine ratio of patients at baseline and yearly for 5 years follow-up. * $p < 0.05$ vs. NS; + $p < 0.05$ vs. quitters (Quit); # $p < 0.05$ vs. respective baseline value at 1 year of follow-up. NS, nonsmokers; Smokers, smokers who continued smoking despite smoking cessation intervention; Quit, patients who successfully quit smoking.

higher than baseline for all groups ($p < 0.01$). Five-year Ualb was higher in continued smokers than nonsmokers and quitters ($p < 0.001$).

Baseline urine cotinine (Fig. 2a) was higher in continued smokers ($3,688.4 \pm 934$ $\mu\text{g/g Cr}$) and quitters ($3,002.1 \pm 751.4$ $\mu\text{g/g Cr}$) than nonsmokers (29.3 ± 11.5 $\mu\text{g/g Cr}$, $p < 0.001$ vs. continued smokers and quitters). Smokers who eventually became quitters had lower baseline urine cotinine than continued smokers ($p < 0.001$), consistent with less baseline smoking in quitters. Urine cotinine value at 1 year was lower than baseline in both quitters ($p < 0.001$) and in continued smokers ($p < 0.001$), but the 1-year urine cotinine value was lower in quitters than in continued smokers (110.5 ± 67.9 vs. $3,216.1 \pm 227.1$, $\mu\text{g/g Cr}$ $p < 0.001$). Nevertheless, urine cotinine value at 1 year was higher in quitters than in nonsmokers (110.5 ± 67.9 vs. 29.7 ± 10.0 , $p = 0.03$), although all quitters continued to meet “quit” criteria of urine cotinine reduction to $<10\%$ of baseline value. There was no difference in urine cotinine between quitters and nonsmokers at follow-up years 2 through 5. Urine cotinine remained higher in continued smokers than nonsmokers and quitters for the study duration.

Figure 2b shows higher urine 8-iso excretion (U8-iso) in continued smokers than quitters at baseline ($4.23 \pm$

Fig. 2. Urine levels of cotinine level (a), a nicotine metabolite, and of isoprostane 8-isoprostaglandin $F_{2\alpha}$ (8-iso), a measure of oxidative stress (b), at baseline (time zero) and yearly for 5 years. * $p < 0.05$ vs. nonsmokers (NS); + $p < 0.05$ vs. quitters (Quit).

1.17 vs. 4.10 ± 1.0 µg/g Cr, $p < 0.01$), but each was higher than that in nonsmokers (1.56 ± 0.29 µg/g Cr, $p < 0.001$). At 1 year follow-up, U8-iso was not different between quitters and nonsmokers (1.65 ± 0.28 vs. 1.55 ± 0.32 µg/g Cr, respectively, $p = 0.07$) and was not different between these 2 groups for the remaining follow-up duration. By contrast, U8-iso was higher in continued smokers than nonsmokers at 1 year (3.63 ± 0.80 µg/g Cr, $p < 0.001$) and remained higher for the remaining follow-up duration.

Figure 3 shows that baseline UATG was not different among nonsmokers, continued smokers, and quitters ($p = 0.61$). One-year value compared to baseline UATG was lower in nonsmokers (21.2 ± 3.0 vs. 24.4 ± 3.4 µg/g Cr, $p < 0.001$), higher in continued smokers (27.3 ± 3.6 vs. 24.8 ± 3.2 µg/g Cr, $p < 0.01$), and no different in quitters (23.9 ± 3.0 vs. 24.8 ± 3 µg/g Cr, $p = 0.07$). Five-year UATG was higher for both continued smokers (33.0 ± 3.0 , $p < 0.001$) and quitters (28.9 ± 2.7 µg/g Cr, $p = 0.02$) than nonsmokers (25.9 ± 2.5 µg/g Cr), but 5-year UATG was higher in continued smokers than quitters ($p < 0.001$).

Baseline eGFR was not different among nonsmokers, continued smokers, and quitters (74.3 ± 5.6 , 74.4 ± 5.4 , and 73.9 ± 7.0 mL/min/1.73 m², respectively, $p = 0.92$) as shown in Figure 4. For all 3 groups, eGFR significantly decreased over time ($p < 0.01$). Five-year eGFR was higher in quitters than continued smokers (62.0 ± 5.4 vs. 52.9 ± 5.6 mL/min/1.73 m², $p < 0.001$), but eGFR for nonsmokers (64.7 ± 5.6 mL/min/1.73 m²) was higher than that for both

Fig. 3. Urine angiotensinogen (UATG)-to-creatinine ratio of patients at baseline and yearly for 5 years follow-up. * $p < 0.05$ vs. nonsmokers (NS); + $p < 0.05$ vs. quitters (Quit); # $p < 0.05$ vs. respective baseline value at 1 year of follow-up.

continued smokers ($p < 0.001$) and quitters ($p = 0.02$). The average yearly eGFR decline rate (net decrease/5 years) was slower in quitters than continued smokers (-1.7 ± 1.5 vs. -3.4 ± 1.8 mL/min/1.73 m²/year, $p < 0.001$) and that for nonsmokers (-1.3 ± 1.5 mL/min/1.73 m²/year) was slower than continued smokers ($p < 0.0001$) but was not different from that of quitters ($p = 0.06$).

Fig. 4. Cystatin C-calculated eGFR at baseline and yearly for 5 years follow-up. * $p < 0.05$ vs. nonsmokers (NS); + $p < 0.05$ vs. quitters (Quit).

Discussion

These studies show expected ACEI-related kidney protection in these nondiabetic participants with CKD associated with primary hypertension as manifest by lower-than-baseline Ualb [18] at 1 year in nonsmoking participants but not in either initially smoking participant groups. Concomitant with higher Ualb at 1 year, continued smokers had higher U8-iso and higher UATG than nonsmokers and quitters, supporting the concept that increased oxidative stress and higher kidney AII levels contributed to less ACEI-related kidney protection in continued smokers. These data support that smoking cessation compared with continued smoking at least partially restores the kidney-protection benefits of ACEI observed in nonsmokers. In support of this conclusion, quitters had higher 5-year eGFR than continued smokers. On the other hand, 5-year eGFR was lower in quitters than nonsmokers, supporting that restoration of ACEI-related kidney protection due to smoking cessation was incomplete and/or that quitters had residual kidney injury related to smoking, which did not ameliorate upon smoking cessation. Nevertheless, these studies support that smoking is a modifiable risk factor for eGFR decline in this population of patients with nondiabetic CKD treated with ACEI.

We chose participants with nondiabetic CKD associated with primary hypertension who were at high risk of subsequent eGFR decline to enhance our ability to observe an effect of smoking and its cessation on eGFR. Be-

cause only a small proportion of patients with primary hypertension and initially normal GFR experience GFR decline [22], we selected patients whose GFR had already declined from normal without other apparent causes of kidney injury. In addition, we chose patients with Ualb >200 mg/g Cr because such patients are at higher risk for subsequent eGFR decline than those with lower Ualb in an effort to observe a greater difference in our intervention [2]. Therefore, it is not unexpected that all 3 groups in the study experienced a decline in GFR over time. However, this decline was the greatest in patients who continued to smoke. Consequently, the present studies show the benefit of smoking cessation on this high-risk group but further studies will be needed to determine if continued smoking increases the risk for GFR decline and/or if its cessation preserves GFR in primary hypertension patients who are at lower risk for GFR decline.

Of note, patients who quit smoking had lower baseline albuminuria compared to continued smokers and nonsmokers, although this did not reach statistical significance. While the reason is not clear, it may be that smokers who became quitters had less underlying kidney injury in the absence of smoking such that smoking increased their urine albumin excretion to the level that made them eligible for study inclusion. In other words, it might be that had they never smoked, they would not have been eligible for study inclusion, given their lower degree of underlying kidney injury. There could also be some other unknown factors that make the quitter group inherently different from the continued smokers.

All patients received ACEI throughout the study. There was no control group to observe changes in kidney function over time in the absence of ACEI. Extant guidelines at the time of initiation of this study recommended ACEI for albuminuric hypertensive patients [19] and studies published after the study commenced supported that ACEI provided better kidney protection in such patients than other antihypertensives [23]. Accordingly, we feel that it would not have been ethical to include a group of such patients not given ACEI to examine changes in kidney function in this group of patients in the absence of ACEI.

Because participants had similar blood pressure control among the 3 groups, the observed changes in eGFR and albuminuria are not likely attributable to differences in blood pressure control or ACEI. However, the data showed that while blood pressure reduction and ACEI initiation decreased albuminuria in nonsmokers at 1 year, it was unchanged in quitters although not higher than baseline as in continued smokers. These data suggest that continued smoking lessens ACEI-related kidney protec-

tion in nondiabetic CKD and that its cessation somewhat restores, but incompletely, ACEI-related kidney protection. The latter hypothesis is supported by the data showing that although UATG was lower at 5 years in quitters than continued smokers, it was higher in quitters than nonsmokers, consistent with higher kidney AII levels. These apparently higher kidney AII levels in quitters than nonsmokers possibly contributed to the lower 5-year eGFR in quitters than nonsmokers.

The present studies suggest a mechanism by which cigarette smoking potentially attenuates kidney protection provided by ACEI. Cigarette smoking increases tissue AII levels, possibly through the increasing activity of the enzyme chymase [14], which can convert Ang I to AII without converting enzyme activity [24]. Consequently, cigarette smoking might increase kidney AII despite ACEI, possibly contributing to the higher UATG in continued smokers than nonsmokers at 5 years, while smoking cessation leads to lower UATG after the initiation of ACEI in quitters than in continued smokers at this time point. In turn, AII increases kidney oxidative stress [15], possibly contributing to higher oxidative stress as measured by higher U8-iso in continued smokers. Whether ARB might be a more effective kidney-protective intervention by inhibiting the effect of AII rather than its production awaits further study.

As a counterpoint to our hypothesis, a retrospective study published by Orth et al. [25] examining if smoking increases the risk of ESRD in patients with IgA nephropathy or autosomal dominant polycystic kidney disease found that the risk of ESRD was higher in smokers who had never been on an ACEI compared to smokers who had. However, the population included in this study had a different CKD cause than the patients who participated in our study. Additionally, while the data reported support that smoking attenuates some of the kidney-protective effects of ACEI, the data do not exclude the fact that patients who smoke derive no ACEI-related kidney pro-

tection. Specifically, it is possible that ACEI still slows progression of CKD in smokers but to a lesser degree than in nonsmokers and quitters.

Quitters had lower baseline urine cotinine than continued smokers, consistent with less intense cigarette smoking that possibly enhanced their chances to quit. Other studies show that participants consuming fewer cigarettes have greater success at smoking cessation [26, 27]. Furthermore, if quitters had less intense smoking at baseline, they might have had less initial smoking-induced kidney injury, as suggested earlier, that contributed to their having higher eGFR at 5 years than continued smokers.

In summary, this study shows that smoking cessation compared with continued smoking at least partially restores ACEI-related kidney protection and better preserves eGFR at 5 years in nondiabetic patients with CKD associated with primary hypertension. Therefore, smoking cessation appears to be a kidney-protective intervention in patients with nondiabetic CKD associated with primary hypertension treated with ACEI but may also be helpful for other CKD causes for which ACEI provides kidney protection.

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Disclosure Statement

None of the authors have conflicts relevant to these studies to disclose.

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