IMPACT OF NON-ADHERENCE ON RENAL AND CARDIOVASCULAR OUTCOMES IN US VETERANS

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Abstract

Background—Adherence is paramount in treating hypertension; still, no gold standard method is available for non-adherence screening delineating high-risk patients. An *ICD-9-CM* non-adherence diagnostic code (V15.81) has been available for decades; however, its utility is poorly studied. We examined the association between V15.81 code assigned prior to initiation of antihypertensive drugs (AHD) and renal and cardiovascular outcomes.

Methods—This was a historical prospective cohort study involving 312,489 newly treated hypertensive individuals (mean age 53.8years, 90.9% males, 20.3% black, median follow-up 8.0 years). We used crude and Cox models adjusted for baseline socio, demographic characteristics, estimated glomerular filtration rate (eGFR), BMI, blood pressure, co-morbidities, and prospective AHD adherence (measured as proportion of days covered,PDC).

Results—In unadjusted analysis, V15.81 code was associated with higher risks for faster eGFR decline (HR1.22, [95% CI] 1.11-1.33), incident CKD (HR1.17 [1.09-1.27]), ESRD (HR2.53 [1.72-3.72]), incident coronary artery disease (CAD) (HR1.26 [1.15-1.38], and stroke (HR1.55 [1.38-1.73]). In adjusted model, V15.81 code remained predictive of increased risk of CKD (HR1.33 [1.22-1.45]), ESRD (HR1.81 [1.18-2.78]), incident CAD (HR1.26 [1.14-1.40]), and

stroke (HR1.46 [1.29-1.65]). Additional adjustment for PDC did not alter adverse associations between V15.81 code and studied outcomes.

Conclusions—Assignment of V15.81 code prior to AHD therapy was associated with higher risks of renal and cardiovascular outcomes in incident hypertensive US veterans. Previous history of non-adherence is a poor prognostic marker in hypertensive individuals; therefore, patients with V15.81 code may require close monitoring. The observational nature of this study limits our ability to make firm recommendations for clinical practice.

Keywords

non-adherence; V15.81 code; chronic kidney disease; end-stage renal disease; coronary artery disease; stroke

Introduction

Hypertension (HTN) is the most common chronic medical condition, and one of leading causes of cardiovascular disease, and end-stage renal disease (ESRD). Oral anti-hypertensive drugs (AHD) have unequivocally shown to improve outcomes in hypertensive individuals [1,2]. Nevertheless, the rates of BP control remain in need for improvement despite the availability of numerous AHD [3]. It has been increasingly recognized that adherence to AHD is an important mediator of achieving desirable BP control [4,5]. Unfortunately, rates of adherence to AHD remain suboptimal and at least 40% of patients with HTN are reported to be poor adherers [6,7].

There are several direct and indirect methods for adherence evaluation [8]. A common feature of these methods is that they can be applied after initiation of AHD therapy. In the mid-1970s, the International Classification of Diseases 9th Edition (*ICD-9-CM*) introduced a diagnostic code for medical treatment non-adherence –V15.81. We have recently shown, that patients who had the V15.81 code established prior to the diagnosis of HTN had subsequently higher all-cause mortality, independent of BP control and adherence to AHD therapy following the diagnosis of HTN [8]. Nonetheless, it is unknown whether the presence of the V15.81 code may also confer heightened risk for renal and cardiovascular outcomes. We investigated the association of the V15.81 assigned prior to the initiation of AHD with renal and cardiovascular outcomes in a large cohort on incident hypertensive US veterans.

Methods

Cohort Definition

The institutional review committees at the Memphis and Long Beach Veterans Affairs Medical Centers approved the study. The data was obtained from the Racial and Cardiovascular Risk Anomalies in CKD (RCAV) study examining risk factors of incident CKD in US veterans, and which was previously described in detail [9]. Inclusion criteria for the study were: (1) patients with diagnosis of incident hypertension, (2) and baseline eGFR 60 ml/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation, (3) and who initiated one or more major AHD classes (α, or β-blockers,

calcium channel blockers, thiazide, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers) in the outpatient setting after October 1, 2006, preceded by no prescription of any AHDs during October 1, 2004-September 30, 2006, based on information obtained from VA Pharmacy dispensation records [10]. Exclusion criteria were: (1) the combined use of all other AHD (peripheral vasodilators, other diuretics, and direct renin inhibitors (0.26%), (2) patients on α-blocker monotherapy as we could not ascertain the presence of alternative indications for their use, such as benign prostate hypertrophy (2.0%), and (3) patients diagnosed with congestive heart failure (*ICD-9-CM* codes 428.x) or with tachyarrhytmias (*ICD-9-CM* codes 427.x) (0.4%). The final cohort comprised 312,489 patients, including 10,401 patients with a V15.81 code assigned prior to initiation of AHDs and 302,088 patients without a V15.81 code.

Socio-demographic and laboratory characteristics, and comorbid conditions were obtained as previously described [11-18]. Information about age, gender, race, marital status, mean per capita income, and blood pressure (BP) were obtained through the VA Corporate Data Warehouse (CDW) and from Medicare through the VA-Medicare data merge project [14]. Baseline systolic BP (SBP) and diastolic BP (DBP) values were obtained on the date of the first AHD prescription. Information about comorbidities was collected from the VA Inpatient and Outpatient Medical SAS Datasets using *ICD-9-CM* diagnostic and procedure codes and C*urrent Procedural Terminology* (CPT) codes (Supplement Table 1) [13]. non-adherence was defined as the presence of *ICD-9-CM* code V15.81 during any inpatient or outpatient encounter preceding the initiation of AHD therapy. In addition we included selected socioeconomic indicators using 2004 county typology codes (housing stress, low education, low employment and persistent poverty) based on the patients' residential address, obtained from the Area Health Resources Files (AHRF) system issued by the US National Center for Health Workforce Analysis, Bureau of Health Workforce, Health Resources and Services Administration (http://ahrf.hrsa.gov/).

Adherence to AHD was estimated as the percentage of days a subject had medication available (proportion of days covered, PDC) [8], based on medication dispensation records from any VA pharmacy. PDC was calculated as the ratio of the total number of days with medication available on-hand and the number of days between the first fill of the medication and the end of the 12-month evaluation period. In patients prescribed several AHDs, PDC was calculated as the mean PDC of individual AHDs. Patients were grouped into the following adherence levels: inadequate (PDC<80%), and adequate (PDC 80%) [19-21].

Outcomes

A median follow-up period for the renal and cardiovascular outcomes was 8.0 years. We had 3 pre-specified renal outcomes: (1) faster rate of eGFR decline, defined by slope of eGFR reduction of more than 5 ml/min/1.73m^2/year [22], (2) incident CKD, defined as the development of persistent eGFR<60ml/min/1.73m^2 (2 consecutive measurements separated by 90 days), and a 25% decrease of eGFR from baseline [22], and (3) incident ESRD, defined as the initiation of renal replacement therapy (dialysis or preemptive kidney transplantation. The median (interquartile range (IQR)) number of serum creatinine

measurements used to calculate eGFR slopes was 10 (5-17). Data on ESRD was obtained from the United States Renal Data System (USRDS).

Incident coronary artery disease (CAD) was defined as the composite outcome of a first occurrence of an *ICD-9-CM* or Current procedural terminology (CPT) codes for acute myocardial infarction, coronary artery bypass grafting, or percutaneous angioplasty, and incident stroke was defines as the first occurrence of ICD-9-CM codes for ischemic stroke following October 1, 2006 in patients without such diagnoses prior to this date. Supplemental Table 2 and 3 list the aforementioned *ICD-9-CM* and CPT codes for incident CAD and stroke.

Statistical Analysis

Descriptive analyses were performed and skewed variables were log- transformed. The start of the follow-up period was the date of initial AHD prescription. Patients were followed until the date of last healthcare or administrative visit, or until July 26, 2013.

The association of the V15.81 code with cardiovascular and renal outcomes was assessed using the Kaplan-Meier method and Cox regression models after adjusting for the following confounders: age, gender, race-ethnicity, marital status, mean income level, service-connectedness (a measure indicating whether one or more of a patient's comorbidities were caused by their military service, and resulting in certain privileges such as preferential access to care and lower co-payments), baseline eGFR, body mass index (BMI), SBP and DBP, and comorbid conditions (diabetes, CAD, peripheral artery disease, chronic lung disease, dementia, liver disease, malignancies, HIV/AIDS, and depression). We hypothesized that medication non-adherence could be in the path of V15.81's effects on all-cause mortality; therefore, we did not include PDC in our main multivariable model, but rather adjusted for this variable in sensitivity analyses.

Analyses were repeated in subgroups of patients categorized by relevant demographic and clinical characteristics.

Statistical analyses were performed using STATA MP Version 12 (STATA Corporation, College Station, TX).

Results

Baseline Characteristics

The mean (SD) age of the total cohort) was 53.8 (12.6) years, 90.9% were males, 20.3% were black, and 48.7% were married. Baseline characteristics of the overall cohort and of patients categorized by the presence or absence of V15.81 code are shown in Table 1. Patients with V15.81 code were younger, more likely to be black and to be unmarried, and had lower mean income. Additionally, patients with V15.81 code had a higher eGFR, a lower BMI and SBP, and a higher prevalence of co-morbidities such as diabetes, chronic lung and liver disease, and depression, and a lower prevalence of malignancies.

Renal Outcomes: Faster Slope of eGFR decline, incident CKD, and ESRD

All renal outcomes were significantly higher in incident hypertensive patients with V15.81 code (Table 2). Overall, faster slope of eGFR decline was seen in 14,974 (4.9%) patients. Faster eGFR decline was seen in 605 (5.9%) and 14,369 (4.9%) patients with and without V15.81 code and it corresponded to a 22% higher risk of faster eGFR decline in the V15.81+ group (unadjusted OR 1.22, 95%CI 1.12-1.32). Adjustment for baseline demographic characteristics and eGFR did not alter this association; however, addition to the adjusted model of baseline BP, BMI, and co-morbidities lead to the attenuation of increased risk of faster eGFR decline in the V15.81"+" cohort (adjusted HR 1.07, 95%CI 0.98-1.17).

Incident CKD developed in 16,359 (5.2%) patients (event rate 7.1 [7.0-7.2]/1000 patient-years). Incident CKD occurred in 634 (6.1%, event rate 8.1 [7.5-8.8]/1000 patient-years, and 15,725 (5.2%, event rate 7.0 [6.9-7.1]/1000 patient-years) patients with and without the V15.81 code, respectively. The presence of the V15.81 code was associated with a 17% higher risk of incidence CKD in unadjusted analysis (unadjusted HR 1.17, 95%CI 1.08-1.27), and a 33% higher risk in fully adjusted analysis (adjusted HR 1.33, 95%CI 1.22-1.45).

The development of ESRD was an infrequent event and occurred in 390 (0.12%) patients in the total cohort (event rate 0.15 [0.13,0.16]/1000 patient-years). Nevertheless, patients with the V15.81 code were 2.5 times more likely to develop ESRD as compared with patients without the V15.81 code: event rate 0.35 [0.24-0.50]/1000 patient-years and 0.14 [0.13-0.16]/1000 patient-years in the V15.81"+" and V15.81"−" groups, respectively (unadjusted HR 2.53, 95%CI 1.72-3.72, p<0.001). Adjustments for confounders only marginally diminished the increased risk of ESRD in patients with the V15.81 code (Table 2).

The risks of incident CKD and ESRD were increased in patients with the V15.81 code and higher baseline eGFR (Supplemental Figure 1).

Incident Coronary Artery Disease and Incident Stroke

Similarly to renal outcomes, incident CAD and stroke were adversely associated with the presence V15.81 code in newly treated hypertensive individuals (Table 3). A total of 10,749 patients (3.5%, event rate 4.6 [4.5-4.7]/1000 patient-years) developed incident CAD. There were 457 incident CAD events in the group with the V15.81 (4.4%, event rate 5.7 [5.2-6.3]/ 1000 patient-years) and 10,292 incident CAD events in the group without V15.81 (3.4%, event rate 4.5 [4.4-4.6]/1000 patient-years). The presence of V15.81 was associated with 26% higher risk of incident CAD (HR 1.26, 95% CI 1.15-1.38, p<0.001) in unadjusted analysis. Incident stroke occurred in 6,111 patients (2.0%, event rate 2.6 [2.5-2.7/1000 patient-years). The event rates of incident stroke were 4.0 [3.6-4.5]/1000 patient years (3.1%) and 2.5 [2.4-2.6]/1000 patient-years (2.0%) in patients with and without the V15.81 code, respectively. In unadjusted analysis, patients in the V15.81"+" group had 55% higher risk of incident stroke (unadjusted HR 1.55, 95%CI 1.38-1.74, p<0.001), as compared with

the V15.81"–" group. The higher risks of incident CAD and stroke remained unchanged in patients with the V15.81 code after adjustment for confounders (Table 3).

The presence of the V15.81 code was associated with increased risk for CAD and stroke in the majority of studied subgroups (Supplemental Figure 2).

Effect of follow up adherence to AHD on the association between the V15.81 code and CV and renal outcomes

The mean (SD) adherence to AHD as defined by PDC was 83.3% (17.5%) in the whole cohort. Adequate adherence (PDC 80%) was present in 63.2% and 61.2% of patients with and without the V15.81 code. The inclusion of PDC into Cox model did not alter the original associations between the V15.81 code and renal and cardiovascular outcomes (Table 2 and 3).

Discussion

We examined the effects of the *ICD-9-CM* code for medical treatment non-adherence (V15.81) that was assigned prior to the initiation of AHD therapy on renal and cardiovascular outcomes in a large cohort of US veterans with newly treated hypertension. Patients with past history of non-adherence had a higher likelihood of incident CKD and ESRD, and a marginally faster decline of eGFR over time, as well as an increased risk of incident CAD and stroke.

The V15.81 code has been introduced into *ICD-9-CM* in the mid1970s [8-23]. Its original definition included "personal history presenting hazard to health and noncompliance with medical treatment" and the V15.81 code was intended to describe diverse behaviors influencing treatment outcomes (e.g. non-adherent medication,taking behavior, non-adherence with diet, appointments, unwillingness to stop hazardous health habits, and noncompliance with preventive measures). Therefore, the V15.81 code cannot delineate which non-adherent behavioral component lead to the assignment of this diagnosis. The International Classification of Diseases 10th revision (*ICD-10)* acknowledged the complex nature of non-adherence and incorporated 8 non-adherence codes in (Z91.11-Z91.19) including diagnoses such as voluntary and involuntary non-adherence with medications, diet, dialysis, and other (unspecified) non-adherence. Hopefully, the future use of *ICD-10* non-adherence-related codes may allow better understanding of what effects the different aspects of adherence may have on health outcomes.

It is unlikely, that patients themselves would report medical diagnosis of non-adherence the same way as they would report a history of a disease such as diabetes. However, once recorded in the electronic medical record, a previous history is generally easily accessible. Therefore, the presence of the V15.81 code in a patient initiating AHD can allow providers to identify high-risk patients for a wide variety of adverse outcomes and alert for a need of closer attention to these individuals. Patients with the V15.81 code assigned prior to the initiation of AHD were not at higher risk for subsequent inadequate adherence to AHD. Nevertheless, the V15.81 code conferred increased risk of adverse renal and cardiovascular outcomes after the adjustment to AHD adherence. Similarly, we recently reported that newly

treated hypertensive individuals with the V15.81 code had augmented all-cause mortality independent from follow up levels of blood pressure or adherence to AHD [9]. The V15.81 code was present prior to the initiation of AHD therapy; hence, its assignment might have been induced by behavioral patterns that have independent from subsequent adherence to AHD effects. This further underscores the complex nature of adherence and emphasizes that its assessment and any interventions need to have a broad scope and focus on patient behaviors beyond medication adherence. The present study reinforces the usefulness of routine addition of the medical non-adherence code to patients' histories where inadequate adherence is suspected.

To our knowledge, no previous studies evaluated predictive utility of non-adherence diagnostic code on cardiovascular and renal outcomes. However, nonadherence, established via analysis of pharmacy databases, a widely used method for the evaluation of outcomes related to medication,taking behavior in hypertension, was previously linked to adverse cardiovascular and renal outcomes [4,21]. Good adherence was linked to a 22% reduction in rates of cerebrovascular disease during a median of 3.3 years of follow up in a cohort of 83,267 hypertensive individuals (RR 0.78, 95% CI 0.70-0.87) [24]; while, poor adherence with AHD was associated with a 15% higher risk of acute myocardial infarction (RR 1.15, 955 CI 1.00-1.33) and a 28% increase in risk of stroke (RR 1.28, 95% CI 1.15-1.45) among 77,193 newly treated hypertensive patients during 4 years of follow up [25]. Similarly, 2- and 10-year stroke-related mortality was 3.8 and 3.0 fold higher (OR [95%CI] 3.8 [2.85-5.10] and 3.01 [2.27-3.83], respectively) in incident AHD users with adherence to AHD of <80% [26]. A single study examining the association between adherence to AHD assessed via pharmacy database and incidence of ESRD, found a 33% higher risk of ESRD in patients with compliance of <80%, as compared with   80% during a median of 5.1 years of follow up [21]. The findings of the present study complement findings by Roy et al, demonstrating an elevated risk of incident CKD and ESRD in the presence of non-adherence in newly treated hypertensive veterans. Pharmacy databases allow assessment of only medication-taking aspect of adherence. In contrast, the V15.81 code could be a more global descriptor of non-adherent behavior, and the use of a diagnostic non-adherence code requires only a review of previous medical history.

Strength and Limitations

This is the first study to investigate the association between *ICD-9* code for medical treatment non-adherence (V15.81) and renal and cardiovascular outcomes in newly treated hypertensive patients. The current study has several limitations. We report an association between the V15.81 code and renal and cardiovascular outcomes, but no causal conclusions can be made. Additionally, given the complex nature of non-adherence and the lack of information about the reasons behind the assignment of V15.81 code, we cannot conclude as to which aspect of nonadhrence was responsible for the adverse association between the V15.81 code and health-related outcome. We did not evaluate follow up level of BP as possible mediators of worse cardiovascular and kidney outcomes. Nonetheless, we have recently shown that the presence of the V15.81 code before initiation of AHD was associated with 38% higher risk of all-cause mortality in incident hypertensive individuals, and follow-up blood pressure levels did not explain the differences in mortality in patients

with the V15.81 code [9]. Not all variables influencing cardiovascular and renal outcomes such as smoking and alcohol use were assessed due to inability to ascertain this information from our database. The assignment of the V15.81 code is not standardized; however, the overall use of V15.81 code among providers between different geographic regions was not clinically different and varied between 3-11.3% (median 6.3%, interquartile range 5.8-7.7%). We did not collect information about albuminuria and, therefore, could not assess the development of earlier stages of CKD. The information about incident ESRD events was obtained from the USRDS; however, a potential survival bias was reported with this database due to fact that patients who die soon after initiating dialysis might not be enrolled into the USRDS [27]. Nevertheless, this study strengthens the importance of using medical coding of non-adherence in routine clinical practice and is based on data from a large cohort representative of veterans from the entire geographic US.

Conclusions

The V15.81 diagnostic code for medical treatment non-adherence from *ICD-9-CM* assigned prior to AHD therapy was independently associated with increased risk of renal outcomes such as the development of incident CKD and ESRD, as well we higher risk of cardiovascular disease as defined by incident CAD and stroke in a large cohort of 312,489 incident hypertensive individuals. non-adherence assessed via a medical diagnostic coding can be useful "marker" of increased cardiovascular and renal risks among newly treated hypertensive individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of individuals stratified by ICD-9-CM code for medical treatment non-adherence

Baseline Variables	Total Cohort (N=312, 489)	Presence of V15.81 code[*] (N=10,401)	Absence of V15.81 code[*] (N= 302,088)	P-value
Age, mean (SD), year	53.8 (12.6)	50.1 (11.0)	54.0 (12.7)	<0.001
Gender, males, n (%)	284,105 (90.9)	9,415 (90.5)	274,690 (90.9)	0.1
Race, n (%)				
African-American	9,389 (20.3)	3,370 (33.3)	56,019 (19.9)	<0.001
Non-African American	303,100 (79.7)	6,764 (66.7)	225,831 (80.1)	<0.001
Marital Status, n (%)				
Married	146,441 (48.7)	3,044 (30.7)	143,397(49.4)	<0.001
Non-married	166,048 (51.3)	6,861 (69.3)	147,132 (50.6)	<0.001
Income, median, $	19,851	15,489	20,009	<0.001
Living in area with high housing stress, n (%)	110,373 (36.8)	3,790 (38.7)	106,583 (36.7)	<0.001
Living in area with low education, n (%)	32,313 (10.8)	1,010 (10.3)	31,303 (10.8)	0.1
Living in area with low employment, n (%)	28,152 (9.4)	849 (8.9)	27,303 (9.4)	0.013
Living in area of persistent poverty, n (%)	15,142 (5.1)	474 (4.8)	14,668 (5.1)	0.3
eGFR, mean (SD), ml/min/1.73m^2	88.5 (15.8)	93.4 (16.9)	88.3 (15.8)	<0.001
BMI, mean (SD) (kg/m^2)	28.6 (5.4)	28.0 (5.6)	28.6 (5.4)	<0.001
SBP, mean (SD), mmHg	139.4 (18.7)	136.6 (19.4)	139.5 (18.7)	<0.001
DBP, mean (SD), mmHg	83.4 (12.8)	83.5 (13.2)	83.4 (12.8)	0.9
Diabetes, n (%)	34,383 (11.0)	2,124 (20.4)	32,259 (10.7)	<0.001
CAD, n (%)	6,678 (2.1)	209 (2.0)	6,469 (2.1)	0.4
Cerebrovascular disease, n (%)	6,465 (2.1)	245 (2.4)	6,220 (2.1)	0.04
PVD, n (%)	6,457 (2.1)	230 (2.2)	6,227 (2.1)	0.3
Chronic lung disease, n (%)	47,462 (15.2)	1,964 (18.9)	45,498 (15.1)	<0.001
Dementia, n (%)	599 (0.2)	32 (0.3)	567 (0.2)	0.006
Chronic liver disease, n (%)	2,655 (0.9)	150 (1.4)	2,505 (0.8)	<0.001
Malignancies, n (%)	18,895 (6.1)	455 (4.4)	18,440 (6.1)	<0.001
HIV, n (%)	3,256 (1.0)	361 (3.5)	2,895 (1.0)	<0.001
Depression, n (%)	37,711 (12.1)	2,971 (28.6)	34,740 (11.5)	<0.001

Footnotes: SD, standard deviation

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all p values between groups were significant; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; PVD, peripheral vascular disease; HIV, human immunodeficiency virus.

Table 2

Hazard ratios of renal outcomes in patients with V15.81 code using unadjusted analysis and various adjusted models

Analysis	Faster slope of eGFR decline HR with 95% CI*, p-value	Incident CKD HR with 95% CI*, p-value	ESRD HR with 95% CI*, p-value
Unadjusted analysis	1.22 (1.12-1.32), <0.001	1.17 (1.08-1.27), <0.001	2.53 (1.72-3.72), <0.001
Adjusted analysis #1	1.20 (1.10-1.32), <0.001	1.50 (1.38-1.63), <0.001	2.19 (1.44-3.34), <0.001
Adjusted analysis #2	1.14 (1.04-1.25), 0.006	1.53 (1.41-1.67), <0.001	2.22 (1.46-3.39), <0.001
Adjusted analysis #3	1.07 (0.98-1.17), 0.1	1.33 (1.22-1.45), <0.001	1.81 (1.18-2.78), 0.006
Adjusted analysis #4	1.07 (0.97-1.17), 0.2	1.33 (1.22-1.45), <0.001	1.81 (1.18-2.78), 0.007
Adjusted analysis #5	1.11 (0.98-1.26), 0.09	1.21 (1.08-1.36), 0.002	1.91 (1.13-3.23), 0.015

Footnotes: V15.81 "-" group served as a reference group for all analyzes; HR, hazard ratio; CI, confidence interval; ESRD, end stage kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Adjusted analysis 1, adjusted analysis for age, gender, race, mean income, marital status, area-level housing stress, low education, low employment and persistent poverty; Adjusted analysis 2, adjusted analysis 1 plus estimated glomerular filtration rate (eGFR); Adjusted analysis 3, adjusted analysis 2 plus baseline comorbidities; Adjusted analysis 4, adjusted analysis 3 plus baseline systolic and diastolic blood pressure and body mass index. Adjusted analysis 5, adjusted analysis 4 plus adherence to antihypertensive drugs.

Table 3

Hazard ratios of incident coronary artery disease and stroke in patients with V15.81 code using unadjusted analysis and various adjusted models

Analysis	Incident CAD	Incident stoke
	HR with 95% CI*, p-value	HR with 95% CI*, p-value
Unadjusted analysis	1.26 (1.15-1.38), <0.001	1.55 (1.38-1.73), <0.001
Adjusted analysis #1	1.38 (1.25-1.52), <0.001	1.56 (1.38-1.76), <0.001
Adjusted analysis #2	1.38 (1.25-1.52), <0.001	1.54 (1.36-1.74), <0.001
Adjusted analysis #3	1.33 (1.20-1.47), <0.001	1.49 (1.32-1.69), <0.001
Adjusted analysis #4	1.26 (1.14-1.40), <0.001	1.46 (1.29-1.65), <0.001
Adjusted analysis #5	1.35 (1.17-1.57), <0.001	1.55 (1.30-1.85), <0.001

Footnotes:

*V15.81"-" group served as a reference group for all analyzes; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; Adjusted analysis 1, adjusted analysis for age, gender, race, mean income, marital status, area-level housing stress, low education, low employment and persistent poverty; Adjusted analysis 2, adjusted analysis 1 plus estimated glomerular filtration rate (eGFR); Adjusted analysis 3, adjusted analysis 2 plus baseline comorbidities; Adjusted analysis 4, adjusted analysis 3 plus baseline systolic and diastolic blood pressure and body mass index. Adjusted analysis 5, adjusted analysis 4 plus adherence to antihypertensive drugs.