Association of Medical Treatment Nonadherence With All-Cause Mortality in Newly Treated Hypertensive US Veterans

Elvira O. Gosmanova, Jun L. Lu, Elani Streja, William C. Cushman, Kamyar Kalantar-Zadeh, Csaba P. Kovesdy

Abstract—Nonadherence to antihypertensive drugs is associated with adverse outcomes; however, mediators of this relationship are poorly understood. We examined the association between the International Classification of Diseases-Ninth Revision code for medical treatment nonadherence (V15.81) assigned before initiation of antihypertensive drug therapy and all-cause mortality in a large cohort of incident hypertensive US veterans. A propensity score–matched cohort of 18,822 patients (9,411 patients with and without a V15.81 code) was generated based on variables predictive of the presence of the V15.81 code to assess its independent association with all-cause mortality during 3.8 years of follow-up. We used Cox models before and after adjustment for antihypertensive drug adherence (measured as the proportion of days covered) and for measures of blood pressure to determine whether the association of nonadherence with mortality was mediated through consequences of not following prescribed antihypertensive drugs. At baseline, the mean age of patients was 50.0 years, 91.4% were men, and 33.2% were blacks. The V15.81 code presence was associated with higher all-cause mortality (hazard ratio, 1.38; 95% confidence interval, 1.26–1.52; P<0.001). Adjustment for medication adherence, blood pressure levels, and blood pressure variability during follow-up did not alter the association between the V15.81 code and all-cause mortality (hazard ratio, 1.35; 95% confidence interval, 1.20–1.52; P<0.001). In conclusion, assignment of a V15.81 code before antihypertensive drug therapy was associated with higher all-cause mortality in incident hypertensive US veterans and can be useful to identify high-risk patients in administrative databases. This association was not mediated by worse adherence to antihypertensive drugs or differences in follow-up blood pressure. (Hypertension. 2014;64:00-00.)

Key Words: antihypertensive agents • medication nonadherence • mortality
and all-cause mortality after adjusting for actual medication adherence to AHDs, and follow-up blood pressure (BP) as higher BP might be expected in nonadherent patients.

Methods

Cohort Definition
The institutional review committees at the Memphis and Long Beach Veterans Affairs Medical Centers approved the study. Our study used data from a cohort study examining risk factors in patients with incident chronic kidney disease (Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease [RCAV] study). We used the national Veterans Affairs (VA) Decision Support System National Data Extracts Laboratory Results file to extract data about serum creatinine and identify veterans with normal kidney function on the basis of estimated glomerular filtration rate (eGFR) of ≥60 mL/min per 1.73 m².14 eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation.15 We identified 3,582,478 patients with eGFR ≥60 mL/min per 1.73 m² among a total of 4,444,699 patients with any available eGFR between October 1, 2004, and September 30, 2006. The algorithm for cohort definition is shown in Figure 1. Incident hypertension was defined as the prescription of ≥1 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, to September 30, 2006, based on the information obtained from VA Pharmacy dispensation records.16 The combined use of all other antihypertensive classes (peripheral vasodilators, other diuretics, carboanhydrase inhibitors, and direct renin inhibitors) amounted to only 0.26% of all AHD prescriptions, and hence these were excluded from analyses. We excluded patients on α-blocker monotherapy as we could not ascertain the presence of alternative indications for their use, such as benign prostate hypertrophy. We also excluded patients diagnosed with congestive heart failure (ICD-9-CM codes 428.x) or with tachyarrhythmias (ICD-9-CM codes 427.x). The final cohort included 312,489 patients, among whom we identified 10,401 patients with a V15.81 code before initiation of AHDs and 302,088 patients without a V15.81 code. To minimize the effect of baseline differences between groups with and without V15.81 on outcomes, we generated a propensity score–matched cohort of 18,822 patients (9411 with and 9411 without V15.81) for our analysis. In addition, a second propensity score–matched cohort of 40,346 patients was created for a sensitivity analysis, comparing 20,173 patients who were assigned a V15.81 code at baseline or during follow-up after the initiation of AHD and 20,173 patients without a V15.81 code.

Sociodemographic characteristics, comorbid conditions, and laboratory characteristics were obtained as previously described.17–20 Briefly, information about age, sex, race, and BP were obtained through the VA Corporate Data Warehouse and from Medicare through the VA-Medicare data merge project.21 Baseline systolic BP (SBP) and diastolic BP (DBP) values were obtained on the date of the first AHD prescription. Longitudinal BP recorded after the date of the first AHD prescription was analyzed as the mean value of all outpatient recordings. The median number of encounters with BP measurements was 17 (interquartile range, 8–34) overall, with 17 (interquartile range, 8–39) and 13 (interquartile range, 6–24) encounters in patients with and without V15.81, respectively. The median number of BP measurements at each encounter was 1 (interquartile range, 1–2). At the time of this study, the majority of the VA hospitals were using electronic BP monitors.22,23 Information about comorbidities was collected from the VA Inpatient and Outpatient Medical SAS Datasets,20 using ICD-9-CM diagnostic and procedure codes and Current Procedural Terminology codes. Nonadherence was defined as the presence of ICD-9-CM code V15.81 during any inpatient or outpatient encounter preceding the initiation of AHD therapy.

Assessment of Medication Adherence
Adherence to AHD was estimated as the percentage of days a subject had medication available (proportion of days covered [PDC]).24 Based on medication dispensation records from any VA pharmacy, PDC was calculated as the ratio of the total number of pills and the number

![Figure 1. Cohort selection flow chart. AHD indicates antihypertensive drug; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HTN, hypertension; and ICD-9, International Classification of Diseases-Ninth Revision.](http://hyper.ahajournals.org/content/118/6/862/F1.expansion.html)
of days between the first fill of the medication and the end of the evaluation period. We calculated PDC during the first year after AHD initiation and for the entire follow-up period. Results were essentially identical; therefore, for all analyses we used PDC calculated during the first 12 months of AHD therapy. In patients prescribed several AHDs, PDC was calculated as the mean PDC of individual AHDs. Patients were grouped into the following adherence levels: low (PDC, <40%), intermediate (PDC, 40%–79%), and high (PDC, ≥80%).

Outcome
Data on all-cause mortality was obtained from the VA Vital Status Files, which contain dates of death or last medical/administrative encounter from all sources in the VA system with sensitivity and specificity of 98.3% and 99.8%, respectively, as compared with the National Death Index as gold standard.

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 up until death or were censored at the date of last healthcare or administrative visit or on July 26, 2013. The propensity score method was used to account for baseline differences arising from dissimilarities in clinical and demographic characteristics of patients with the V15.81 code. This method allows for the generation of a single variable representing the likelihood of an individual patient having been assigned the V15.81 code based on the presence or absence of defined clinical characteristics in each individual. Patients with and without V15.81 can then be matched based on similar propensity scores to secure that its predictors are similar in the 2 groups and to eliminate confounding the association of V15.81 with the studied outcome attributable to baseline differences between the 2 groups. Variables associated with V15.81 were identified using logistic regression and were used to calculate propensity scores. Staåsa’s psmatch2 command suite was used to generate the propensity score–matched cohorts by a 1-to-1 nearest neighbor matching without replacement.

The association of V15.81 with mortality was assessed using the Kaplan–Meier method and Cox regression. The V15.81 code may represent a broad category of nonadherent patient behavior that could include both medication nonadherence and nonadherence with prescribed treatment plans, diets, or lifestyle. Therefore, patients with V15.81 may be more likely to have higher rates of AHD nonadherence with subsequent higher chance of differences in follow-up BP and BP variability. We hypothesized that medication nonadherence and follow-up BP could be mediators of V15.81’s effects on all-cause mortality. Hence, we adjusted our models for PDC, mean follow-up SBP and DBP, and BP variability (defined as the median absolute deviation of SBP and DBP).

Analyses were repeated in the entire cohort by examining crude and adjusted associations of V15.81 with all-cause mortality in Cox models. Models were adjusted for the following confounders based on a priori considerations: age, sex, race-ethnicity, marital status, mean income level, service-connectedness (a measure indicating or absence of defined clinical characteristics in each individual).26 Patients with and without V15.81 can then be matched based on similar propensity scores to secure that its predictors are similar in the 2 groups and to eliminate confounding the association of V15.81 with the studied outcome attributable to baseline differences between the 2 groups. Variables associated with V15.81 were identified using logistic regression and were used to calculate propensity scores. Staåsa’s psmatch2 command suite was used to generate the propensity score–matched cohorts by a 1-to-1 nearest neighbor matching without replacement.

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

Results
Baseline Characteristics
The mean (SD) age of the full cohort of 312,489 patients was 53.8 (12.6) years, 90.9% were men, and 20.3% were blacks. Baseline characteristics of the overall cohort and of patients categorized by the presence or absence of V15.81 (overall and after propensity score matching) are shown in Table 1. Groups with and without V15.81 were significantly different in all baseline characteristics; however, these differences were no longer present after propensity-score matching. Among the 312,489 patients of the full cohort, those with V15.81 were younger, more likely to be blacks, and to be unmarried. The V15.81 + group also had a higher eGFR and lower SBP, a higher prevalence of diabetes mellitus, chronic lung and liver disease and depression, and a lower prevalence of malignancies. Table 2 shows the predictors of V15.81 in a multivariable logistic regression analysis. Younger age, male sex, unmarried status, black race-ethnicity, and lower income were associated with the presence of V15.81. In addition, patients with chronic medical conditions such as diabetes mellitus, coronary artery disease, peripheral artery disease, chronic lung and liver disease, HIV, and depression were more likely to have a V15.81 code.

Follow-Up BP
Initiation of AHD led to a reduction in both SBP and DBP during follow-up. In the propensity score–matched cohort, mean (SD) SBP was lowered to 129.5 (11.3) mmHg and 130.1 (11.1) mmHg in patients with and without V15.81, respectively (P<0.001). However, the lower SBP in patients with V15.81 was associated with a higher mean (SD) SBP variability compared with the group without V15.81: 8.3 (3.9) mmHg versus 8.0 (3.7) mmHg, respectively (P<0.001). Similarly, follow-up mean (SD) DBP was lower with higher mean (SD) DBP variability in patients with V15.81. Mean follow-up (SD) DBP and DBP variability were 79.0 (8.0) mmHg and 5.5 (2.4) mmHg in patients with V15.81 and 79.3 (8.3) mmHg and 5.4 (2.4) mmHg in patients without V15.81, respectively (P values of 0.008 and 0.001, respectively).

Medication Adherence
In the overall cohort of 312,489 patients, good adherence to AHD during the first year of follow-up as defined by the proportion of patients with a mean PDC ≥80% was higher in patients without V15.81 (74.5%) compared with patients with V15.81 (67.5%) (P<0.001). Results were similar in the propensity score–matched cohort: PDC ≥80% was observed in 67.5% and 71.6% of patients with and without V15.81, respectively (P<0.001). During subsequent follow-up beyond the first year, adherence to AHD declined in both groups but remained higher in patients without V15.81: PDC ≥80% was seen in 54.2% of patients with V15.81 as compared with 61.0% of patients without V15.81 (P<0.001).

The majority of patients (95.6%) in the propensity-matched cohort were receiving ≥2 AHDs: 77.2% were on a single AHD, 18.4% on 2 AHDs, 3.7% on 3 AHDs, and <1% on ≥4 AHDs. There were no differences in percentages of patients who were receiving 1, 2, and ≥3 AHDs in the groups with and without V15.81 code (P=0.6).

All-Cause Mortality
A total of 1717 patients (9.1%; mortality rate, 24.9 [23.8–26.1]/1000 patient-years) died during a median follow-up of 3.8 years in the propensity score–matched cohort. There were 937 deaths in the group with V15.81 (10.0%; mortality rate, 29.2 [27.4–31.1]/1000 patient-years) and 780 deaths in the group without V15.81 (8.3%; mortality rate, 21.2 [19.8–22.8]/1000 patient-years). The presence of V15.81 was associated with 38% higher risk of all-cause mortality (hazard ratio
Baseline Characteristics

Table 1. Baseline Characteristics of Individuals Stratified by ICD-9 Code for Medical Treatment Nonadherence

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Total Cohort (n=312,489)</th>
<th>Presence of V15.81 Code* (n=10,401)</th>
<th>Absence of V15.81 Code* (n=302,088)</th>
<th>Presence of V15.81 Code† (n=9,411)</th>
<th>Absence of V15.81 Code† (n=9,411)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>53.8 (12.6)</td>
<td>50.1 (11.0)</td>
<td>54.0 (12.7)</td>
<td>49.9 (10.9)</td>
<td>50.1 (11.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Sex, men, n (%)</td>
<td>284 (90.9)</td>
<td>9415 (90.5)</td>
<td>274690 (90.9)</td>
<td>8561 (91.0)</td>
<td>8629 (91.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
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</tr>
<tr>
<td>Blacks</td>
<td>9389 (20.3)</td>
<td>3370 (33.3)</td>
<td>56019 (19.9)</td>
<td>3153 (33.5)</td>
<td>3096 (32.9)</td>
<td>0.4</td>
</tr>
<tr>
<td>Nonblacks</td>
<td>303100 (79.7)</td>
<td>6764 (66.7)</td>
<td>225831 (80.1)</td>
<td>6258 (66.5)</td>
<td>6315 (67.1)</td>
<td></td>
</tr>
<tr>
<td>Marital status, n (%)</td>
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</tr>
<tr>
<td>Married</td>
<td>146441 (48.7)</td>
<td>3044 (30.7)</td>
<td>143397 (49.4)</td>
<td>2800 (29.8)</td>
<td>2758 (29.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nonmarried</td>
<td>166048 (51.3)</td>
<td>6861 (69.3)</td>
<td>147132 (50.6)</td>
<td>6611 (70.3)</td>
<td>6653 (70.7)</td>
<td></td>
</tr>
<tr>
<td>Income, median, $</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, mean (SD), ml/min per 1.73 m2</td>
<td>88.5 (15.8)</td>
<td>93.4 (16.9)</td>
<td>88.3 (15.8)</td>
<td>93.6 (16.9)</td>
<td>93.3 (16.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>28.6 (5.4)</td>
<td>28.0 (5.6)</td>
<td>28.6 (5.4)</td>
<td>27.9 (5.6)</td>
<td>27.9 (5.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>138 (14.7)</td>
<td>136.6 (19.4)</td>
<td>139.5 (18.7)</td>
<td>134.5 (17.8)</td>
<td>134.2 (17.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>83.4 (12.8)</td>
<td>83.5 (13.2)</td>
<td>83.4 (12.8)</td>
<td>82.5 (12.3)</td>
<td>82.6 (12.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>34383 (11.0)</td>
<td>2124 (20.4)</td>
<td>32259 (10.7)</td>
<td>1920 (20.4)</td>
<td>1954 (20.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>6678 (2.1)</td>
<td>209 (2.0)</td>
<td>6469 (2.1)</td>
<td>193 (2.1)</td>
<td>181 (1.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>6465 (2.1)</td>
<td>245 (2.4)</td>
<td>6220 (2.1)</td>
<td>224 (2.4)</td>
<td>218 (2.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>6457 (2.1)</td>
<td>230 (2.2)</td>
<td>6227 (2.1)</td>
<td>219 (2.3)</td>
<td>444 (2.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
<td>47462 (15.2)</td>
<td>1964 (18.9)</td>
<td>45498 (15.1)</td>
<td>1785 (19.0)</td>
<td>1796 (18.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Dementia, n (%)</td>
<td>599 (0.2)</td>
<td>32 (0.3)</td>
<td>567 (0.2)</td>
<td>32 (0.3)</td>
<td>22 (0.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Chronic liver disease, n (%)</td>
<td>2655 (0.9)</td>
<td>150 (1.4)</td>
<td>2505 (0.8)</td>
<td>136 (1.5)</td>
<td>131 (1.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>Malignancies, n (%)</td>
<td>18895 (6.1)</td>
<td>455 (4.4)</td>
<td>18440 (6.1)</td>
<td>419 (4.5)</td>
<td>429 (4.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>HIV, n (%)</td>
<td>3256 (1.0)</td>
<td>361 (3.5)</td>
<td>2895 (1.0)</td>
<td>326 (3.4)</td>
<td>306 (3.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>37711 (12.1)</td>
<td>2971 (28.8)</td>
<td>34740 (11.5)</td>
<td>2731 (29.0)</td>
<td>2736 (29.1)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD-9, International Classification of Diseases-Ninth Revision; PVD, peripheral vascular disease; SBP, systolic blood pressure; and V15.81, ICD-9 code for nonadherence.

*All P values between groups were significant.
†Propensity score–matched cohort stratified by ICD-9 code for nonadherence (V15.81).
‡Value compares propensity score–matched groups with and without ICD-9 code for nonadherence.

We examined patient-related demographic and clinical characteristics associated with the presence of the ICD-9-CM code for nonadherence with medical treatment (V15.81) and its effect on all-cause mortality in a large cohort of US veterans with newly treated hypertension. Similar to previous reports about the impacts of race and age on adherence, we found that blacks and younger patients had a higher prevalence of V15.81. Although female sex has been linked to lower adherence in our study, male veterans were more likely to have the V15.81 code. Female veterans are likely to be different from females in the general population. Better life ratings were reported in female veterans as compared with male counterparts; and personal optimism, in turn, might be associated with better medical adherence. Depression is a well-described barrier to medical adherence, and we similarly observed that concomitant depression was strongly associated with the presence of V15.81 code. In addition to depression, other comorbidities strongly associated with V15.81 were diabetes mellitus, dementia, and HIV/AIDS, suggesting that patients...
Table 2. Odds Ratios (95% Confidence Intervals) of V15.81 Code Assignment in Newly Treated Hypertensive Veterans

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (each +10 y)</td>
<td>0.84</td>
<td>0.83–0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, women vs men</td>
<td>0.70</td>
<td>0.65–0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blacks (vs nonblacks)</td>
<td>1.70</td>
<td>1.62–1.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried (vs married)</td>
<td>1.65</td>
<td>1.57–1.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Income (for 1 log unit)</td>
<td>0.88</td>
<td>0.87–0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (each +10 mL/min per 1.73 m²)</td>
<td>1.05</td>
<td>1.03–1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (each +10 kg/m²)</td>
<td>0.80</td>
<td>0.77–0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (each +10 mm Hg)</td>
<td>0.93</td>
<td>0.91–0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (each +10 mm Hg)</td>
<td>1.03</td>
<td>1.00–1.05</td>
<td>0.039</td>
</tr>
<tr>
<td>Diabetes mellitus (presence vs absence)</td>
<td>2.35</td>
<td>2.25–2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.23</td>
<td>1.06–1.43</td>
<td>0.006</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.26</td>
<td>1.09–1.45</td>
<td>0.001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.17</td>
<td>1.02–1.35</td>
<td>0.025</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.32</td>
<td>1.25–1.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>2.07</td>
<td>1.43–2.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1.29</td>
<td>1.08–1.54</td>
<td>0.005</td>
</tr>
<tr>
<td>Any malignancy</td>
<td>0.93</td>
<td>0.83–1.02</td>
<td>0.13</td>
</tr>
<tr>
<td>HIV</td>
<td>2.04</td>
<td>1.81–2.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>2.64</td>
<td>2.51–2.77</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Odds ratios of presence of V15.81 code were calculated from multivariate regression model. BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; and SBP, systolic blood pressure.

Experiencing conditions predisposing to suboptimal behavior or carry poor survival are especially prone to nonadherence. The presence of V15.81 before initiation of AHD therapy was independently associated with higher all-cause mortality. Despite being an integral part of successful treatment of chronic medical conditions, measurement of adherence has no accepted gold standard method. In general, adherence includes many components such as adherence to medications, nonpharmacological aspects such as healthy lifestyle and diet, adherence to medical appointments, and receptiveness to follow medical advice to modify risky behaviors or dangerous habits. In addition, adherence to medical treatment results from a complex interaction of several elements: patient related (demographic, social, and medical condition–specific factors), provider and healthcare delivery specific (accessibility, restricted formulary, provider–patient communications, continuity of care), and treatment specific (cost, complexity of a regimen, adverse effects, lack of immediate effects of therapy). Traditionally, studies that evaluated effects of adherence and health-related outcomes in hypertensive patients involved the assessment of adherence via evaluation of AHD usage behavior through analysis of pharmacy dispensation databases or self-reported adherence. Because medication adherence is only a single component of adherent behavior, it has limited ability to assess nonpharmacological components of adherence or pharmacological components related to non-AHD type medications. Hence, the presence of V15.81 could be a more inclusive marker of nonadherence.

It is important to consider mechanisms responsible for the worse survival in patients with V15.81 to implement appropriate interventions and improve patient outcomes. Pharmacological nonadherence was demonstrated as an important barrier in achieving treatment goals in the general hypertensive population. We only included V15.81 codes assigned before the initiation of AHDs in our cohort, which was thus not affected by future adherence patterns to AHDs, but such future nonadherence to AHDs could be expected in patients displaying nonadherent behavior in other areas. Therefore, we investigated adherence to AHDs as a possible mediator of increased mortality in patients with V15.81. Indeed, lower adherence to AHDs was present in V15.81+ patients; however, it was insufficient to explain the difference in mortality among patients with V15.81 in adjusted analysis. Difference in follow-up BP control is another possible intermediate that could lead to increased mortality in patients with V15.81. Patients with and without V15.81 at baseline had good overall BP control during...
follow-up according to recent hypertension guidelines, with an absolute difference in treated SBP and DBP of <1 mm Hg between the 2 groups, but with a larger difference in BP variability. Nevertheless, the association between V15.81 and all-cause mortality was unchanged after adjustment for follow-up BP characteristics. These results suggest that newly diagnosed hypertensive individuals with V15.81 exhibit clinically important nonadherent behavior beyond AHD adherence or BP control. Contrasting these findings, once we considered V15.81 codes that were assigned after initiation of AHD therapy, the association between V15.81 and mortality was attenuated after adjustment for AHD adherence and follow-up BP levels. This highlights the complexity of the interaction between V15.81 and all-cause mortality depending on whether it was assigned before or after the initiation of AHD therapy. Consequently, it is essential to have a global approach to adherence beyond focusing on just BP targets and AHD adherence and to consider nonpharmacological components of adherence.

Strength and Limitations

The current study has a large sample size representative of veterans from the entire geographic United States. However, several limitations need to be acknowledged. No conclusion about causality can be drawn from this study. Therefore, although the presence of V15.81 was associated with 38% higher all-cause mortality, we cannot conclude that any particular aspect of nonadherence was indeed directly responsible for the worse survival in newly treated hypertensive veterans. We used the propensity score–matching method to minimize the effects of bias arising from baseline differences between cohorts with and without V15.81; however, even this method may not fully address unmeasured confounders in an observational study. The assignment of V15.81 code is not standardized, and its sensitivity and specificity are unknown. Because nonadherence is in itself a vaguely defined term that has no gold standard diagnostic test, any measure used to describe it would be inherently uncertain. The study population consisted mainly of male veterans; therefore, the results of the study may not be generalized to female patients. We did not collect information about other clinically relevant outcomes such as cardiovascular events and hospitalizations and we had no information about causes of death; thus, we could not test the association of the V15.81 code with such outcomes. Finally, we did not have information about smoking and alcohol use history that may be associated with medical treatment nonadherence and which could also influence all-cause mortality.

Perspectives

In this large cohort of 312,489 incident hypertensive individuals, the V15.81 code for medical treatment nonadherence was associated with worse survival. Given the importance of nonadherence in causing adverse health outcomes and increased medical costs, providers should closely monitor patients who bear a V15.81 code. Further research is needed to identify modifiable patient characteristics that might have led to the assignment of the V15.81 code and to determine which aspects of nonadherence are responsible for the observed adverse association to implement interventions that could improve outcomes in hypertensive individuals.

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Disclosures

Csaba P. Kovessy and William C. Cushman are employees of the Department of Veterans Affairs. The other authors report no conflicts.

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Novelty and Significance

What Is New?

• This is the first study to investigate the association between International Classification of Diseases-Ninth Revision, Clinical Modification code for medical nonadherence (V15.81) and all-cause mortality in newly treated hypertensive veterans.

What Is Relevant?

• The understanding of modifiable patient’s characteristics leading to medical nonadherence is critical for the development of strategies that could improve outcomes in individuals affected by hypertension.

Summary

Assignment of a V15.81 code before antihypertensive drug therapy was associated with higher all-cause mortality in incident hypertensive US veterans and this association was not mediated by worse adherence to antihypertensive drug or differences in follow-up blood pressure.
Association of Medical Treatment Nonadherence With All-Cause Mortality in Newly Treated Hypertensive US Veterans
Elvira O. Gosmanova, Jun L. Lu, Elani Streja, William C. Cushman, Kamyar Kalantar-Zadeh and Csaba P. Kovesdy

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