Prevalence of Optimal Treatment Regimens in Patients With Apparent Treatment-Resistant Hypertension Based on Office Blood Pressure in a Community-Based Practice Network

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Abstract—Hypertensive patients with clinical blood pressure (BP) uncontrolled on ≥3 antihypertensive medications (ie, apparent treatment-resistant hypertension [aTRH]) comprise ≥28% to 30% of all uncontrolled patients in the United States. However, the proportion receiving these medications in optimal doses is unknown; aTRH is used because treatment adherence and measurement artifacts were not available in electronic record data from our >200 community-based clinics Outpatient Quality Improvement Network. This study sought to define the proportion of uncontrolled hypertensives with aTRH on optimal regimens and clinical factors associated with optimal therapy. During 2007–2010, 468 877 hypertensive patients met inclusion criteria. BP <140/<90 mm Hg defined control. Multivariable logistic regression was used to assess variables independently associated with optimal therapy (prescription of diuretic and ≥2 other BP medications at ≥50% of maximum recommended hypertension doses). Among 468 877 hypertensives, 147 635 (31.5%) were uncontrolled; among uncontrolled hypertensives, 44 684 were prescribed ≥3 BP medications (30.3%), of whom 22 189 (15.0%) were prescribed optimal therapy. Clinical factors independently associated with optimal BP therapy included black race (odds ratio, 1.40 [95% confidence interval, 1.32–1.49]), chronic kidney disease (1.31 [1.25–1.38]), diabetes mellitus (1.30 [1.24–1.37]), and coronary heart disease risk equivalent status (1.29 [1.14–1.46]). Clinicians more often prescribe optimal therapy for aTRH when cardiovascular risk is greater and treatment goals lower. Approximately 1 in 7 of all uncontrolled hypertensives and 1 in 2 with uncontrolled aTRH are prescribed ≥3 BP medications in optimal regimens. Prescribing more optimal pharmacotherapy for uncontrolled hypertensives including aTRH, confirmed with out-of-office BP, could improve hypertension control. (Hypertension. 2013;62:00-00.)

Key Words: blood pressure || hypertension || therapy

Hypertension control in the United States nearly doubled from ≈27% in 1988–1994 to 52% in 2007–2010.1,2 The improvement in hypertension control reflected both an increase in the percentage of patients on antihypertensive medications and a rise in control among those on treatment.1–3 Among treated, uncontrolled hypertensive patients, the proportion on ≥3 medications increased from 16% in 1988–1994 to 28% in 2005–2008.3 Treatment-resistant hypertension (TRH) was defined as blood pressure (BP) above goal on ≥3 medications or controlled to goal on ≥4 BP medications prescribed at optimal doses and preferably including a diuretic.4 National Health and Nutrition Examination Survey (NHANES) data include medications reportedly taken but not the dose; thus, optimal therapy cannot be assessed.5 Furthermore, NHANES does not assess medication adherence or BP measurement artifacts, that is, the percentage of uncontrolled hypertensive patients reported taking ≥3 BP medications with pseudoresistance cannot be assessed.3,4 The term apparent TRH (aTRH) was used to encompass the 4 groups of patients in NHANES with BP ≥140/≥90 mm Hg who reported taking ≥3 BP medications, including those with (1) suboptimal adherence, (2) BP measurement artifacts, (3) suboptimal pharmacotherapeutic regimens, and (4) true TRH.3

Previous studies suggest that 30% to 50% of patients with TRH are pseudoresistant (ie, nonadherent and/or out-of-office BP nonhypertensive).4,6 However, the percentage of aTRH patients on suboptimal regimens, their clinical characteristics, and clinical factors associated with optimal therapy in primary care settings are unknown. This information could be...
useful in developing a strategic approach to improve hypertension control among the large group of uncontrolled hypertensive patients with aTRH. More specifically, for those on suboptimal regimens, improved pharmacotherapy may raise hypertension control and obviate the need for additional measures for many patients. Conversely, for patients on optimal pharmacotherapy, verifying adherence and novel therapeutic approaches may be more useful for reducing BP than adding antihypertensive medications.

Methods

This study used electronic record data of patients at 200 clinical sites in the Outpatient Quality Improvement Network. Each clinic signed a business associate agreement, authorizing use of deidentified data for research, approved by legal counsel and the Medical University of South Carolina Office of Research Protection.

Inclusion and Exclusion Criteria

Adults aged ≥18 years with a diagnosis of hypertension who had ≥2 clinical visits with a valid BP in calendar years 2007–2010 and ≥1 prescription medication for any disease state were eligible. A valid BP was defined as systolic BP in the range of 60 to 200 mm Hg, diastolic BP in the range of 40 to 120 mm Hg, and systolic BP greater than diastolic BP. To facilitate generalization of study findings, exclusion criteria were limited to estimated glomerular filtration rate <30 mL/1.73 m² per minute or International Classification of Diseases (ICD) Ninth Revision codes 403, 585, 586, active drug or alcohol abuse (ICD9 303, 303.9X, 304.XX), major psychiatric illness (ICD9 295.XX, 296.3, 297.X, 298.X), and malignancy (ICD9 140–209).

Operational Definitions

BP at the last visit was used to determine control. BP control was defined as <140/<90 mm Hg for all patients, including those with diabetes mellitus and chronic kidney disease (CKD). Although the goal BP for patients with diabetes mellitus and CKD is <130/80 mm Hg, the evidence that lower BP targets significantly reduce cardiovascular disease (CVD) is limited. TRH was defined as in the American Heart Association Consensus Statement as BP above goal, in our analysis ≥140/90 mm Hg for all patients, while prescribed ≥3 different antihypertensive medications. For this report, the term aTRH is used, because BP measurement artifact and patient adherence data are unavailable. Patients controlled to <140/<90 mm Hg on ≥4 different BP medications were also included as aTRH.

Antihypertensive treatment and optimal therapy were defined by BP medications in effect at the last visit but no changes in medications at the last visit. Optimal therapy for uncontrolled aTRH included prescription of a diuretic and ≥2 other BP medications, with each medication at ≥50% of the maximum recommended or approved dose for hypertension. For controlled aTRH patients, optimal therapy was defined as a diuretic and ≥3 other BP medications, each prescribed at ≥50% of the maximum recommended or approved dose.

Dose equivalents for each prescribed BP medication were determined by dividing the dose prescribed by the maximum recommended dose in the hypertension guidelines or the Food and Drug Administration maximum approved dose for medications approved after guideline publication. Therapeutic inertia was defined as the number of visits with elevated BP in which pharmacotherapy was not changed divided by the number of visits with BP above goal. CVD was defined by ICD9 codes 410 to 414, 428, 431 to 437, 440, and equivalent text in a discrete field problem list. CKD was defined by estimated glomerular filtration rate <60 mL/1.73 m² per minute, urine albumin excretion >300 mg/d or ≥30 mg/g creatinine, and protein detected on urine dipstick. CKD was also defined by ICD9 codes 403, 585.3 to 585.9, and 586 and equivalent text in a discrete field problem list. Alcohol dependence was defined by ICD 303.XX, excluding 303.03 and 303.93 (in remission).

Data Reporting and Analysis

Baseline descriptive data are presented as mean and 95% confidence intervals. One-way ANOVA was used to analyze continuous variables among hypertensive patients grouped by BP control, number of medications prescribed, and optimal versus suboptimal therapy for those with aTRH. Bonferroni adjustment was applied to multiple comparisons on continuous variables. For those with aTRH, Fisher’s exact test was used to adjust for multiple comparisons of categorical variables. Fisher’s exact test was used to determine whether visit frequencies were different among the groups classified by numbers of medications (Table 1) and optimal versus suboptimal therapy for those with aTRH (Table 2).

Univariable and multivariable regression analyses were used to identify factors associated with optimal antihypertensive therapy among aTRH patients with uncontrolled and controlled hypertension. Logistic regression was also used to identify covariates associated with BP control among patients with aTRH. Independent variables significant at P<0.20 in the univariable model were included in multivariable modeling. SAS version 9.2 was used for all analyses. Two-sided P<0.05 were accepted as significant.

Results

The process for deriving the study sample is summarized in Figure S1 in the online Data Supplement. The characteristics of all hypertensive patients and those with uncontrolled and controlled BP <140/<90 mm Hg are provided in Table S1. The controlled and uncontrolled groups were significantly different, given the large sample size, at P<0.0001 on all variables, except prevalence of white race. On average, controlled hypertensive patients were a year older and less obese but more likely to have diabetes mellitus, CKD, and CVD. Controlled hypertensive patients were prescribed fewer antihypertensive medications but more likely to be on a statin, and they had lower low-density-lipoprotein cholesterol (LDL-C) than uncontrolled hypertensives. Framingham 10-year coronary heart disease (CHD) risk was high in both groups but greater in those with uncontrolled than controlled hypertension and likely reflected lower BP and LDL-C in the former. Controlled hypertensive patients were more likely to be military veterans.

The characteristics of uncontrolled and controlled hypertensive patients grouped by number of antihypertensive medications prescribed are shown in Table 1. In both groups, age, the percentage of men, body mass index, visit frequency, and the percentage of patients receiving a statin and the percentage who had diabetes mellitus, CKD, CVD, CHD risk equivalent status, and military veterans were higher in those with aTRH. In uncontrolled patients, systolic BP was higher in patients with aTRH but was relatively flat in controlled hypertensive patients. Diastolic BP was lower in patients with uncontrolled and controlled aTRH than those on fewer BP medications and likely reflected older age and greater prevalence of comorbidities associated with vascular disease (eg, diabetes mellitus, CKD, and clinical CVD). Alcohol dependence was diagnosed in 3% to 4% of hypertensive patients, with a lower prevalence in uncontrolled and controlled aTRH patients than patients on fewer BP medications with the lowest prevalence in controlled aTRH patients. Missing data included race 40.6%, body mass index 20.6%, LDL-C 19.3%, 10-year CHD risk 16.4%, and estimated glomerular filtration rate 10.9%.
The characteristics of uncontrolled aTRH patients grouped by optimal characteristics of prescribed antihypertensives are provided in Table 2. The first column of both groups includes uncontrolled hypertensive patients for whom <3 medications and controlled patients for whom <4 medications were prescribed at ≥50%, that is, dose equivalents <0.5, of the maximum recommended hypertension dose. In the middle column of both groups, uncontrolled hypertensive patients were prescribed ≥3 medications and controlled patients were prescribed ≥4 BP medications at ≥50% of the maximum recommended hypertension dose. However, either a diuretic was not prescribed or prescribed at <50% of the maximum recommended dose. In the third column, the requisite number of medications including a diuretic was prescribed at ≥50% of the maximum recommended hypertension dose.

In both groups, the percentage of white patients declined, whereas the percentage of black patients increased as adequacy of antihypertensive therapy improved (first to third column). In both groups, the middle column included the fewest patients. In both groups, those on optimal therapy had higher values for body mass index, visit frequency, and number of antihypertensive medications prescribed. They were more likely to have diabetes mellitus, CKD and CVD, and statin prescriptions, and they had lower LDL-C.

Table 1. Characteristics of Uncontrolled and Controlled Hypertensive Patients by Number of BP Medications Prescribed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncontrolled (147 635, 31.5%)</th>
<th>Controlled (321 242, 68.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–2</td>
<td>≥3</td>
</tr>
<tr>
<td>n, (%)</td>
<td>102 951 (69.7)</td>
<td>44 668 (30.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.9 (55.8–56.0)*</td>
<td>60.6 (60.5–60.7)</td>
</tr>
<tr>
<td>Male, %</td>
<td>64.7*</td>
<td>66.4</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>41.3*</td>
<td>36.0</td>
</tr>
<tr>
<td>Black</td>
<td>22.6*</td>
<td>31.0</td>
</tr>
<tr>
<td>Unk/other</td>
<td>36.1*</td>
<td>33.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30.7 (30.6–30.7)*</td>
<td>31.4 (31.3–31.5)</td>
</tr>
<tr>
<td>&lt;25, %</td>
<td>19.5*</td>
<td>17.0</td>
</tr>
<tr>
<td>&gt;30, %</td>
<td>47.4*</td>
<td>51.8</td>
</tr>
<tr>
<td>Visit frequency, y</td>
<td>4.09 (4.06–4.11)*</td>
<td>5.31 (5.27–5.35)</td>
</tr>
<tr>
<td>SBP, mmHg (last visit)</td>
<td>149.0 (149.0–149.1)*</td>
<td>152.1 (152.0–152.3)</td>
</tr>
<tr>
<td>DBP, mmHg (last visit)</td>
<td>86.3 (86.2–86.4)*</td>
<td>83.7 (83.6–83.8)</td>
</tr>
<tr>
<td>SBP, mmHg (all visits)</td>
<td>142.2 (142.1–142.3)*</td>
<td>144.0 (143.9–144.2)</td>
</tr>
<tr>
<td>DBP, mmHg (all visits)</td>
<td>83.5 (83.5–83.6)*</td>
<td>81.0 (80.9–81.1)</td>
</tr>
<tr>
<td>Visits BP &lt;140/&lt;90, %</td>
<td>37.5 (37.3–37.6)*</td>
<td>38.4 (38.2–38.7)</td>
</tr>
<tr>
<td>Therapeutic inertia, %</td>
<td>77.0 (76.8–77.2)</td>
<td>59.2 (58.9–59.4)</td>
</tr>
<tr>
<td>Stage 2 (≥160/≥100), %</td>
<td>23.8*</td>
<td>28.7</td>
</tr>
<tr>
<td>BP med count, n</td>
<td>1.53 (1.53–1.54)*</td>
<td>3.76 (3.75–3.77)</td>
</tr>
<tr>
<td>BP single-pill comb, %</td>
<td>19.0*</td>
<td>39.0</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>108.7 (108.5–108.9)</td>
<td>99.9 (99.5–100.3)</td>
</tr>
<tr>
<td>Statin, %</td>
<td>43.8*</td>
<td>49.2</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>27.8*</td>
<td>49.2</td>
</tr>
<tr>
<td>CKD, %</td>
<td>12.3*</td>
<td>28.9</td>
</tr>
<tr>
<td>eGFR, mL/1.73m² per minute</td>
<td>88.1 (87.9–88.3)</td>
<td>77.6 (77.3–77.9)</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>20.6*</td>
<td>45.0</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>28.2</td>
<td>28.7</td>
</tr>
<tr>
<td>Alcohol dependence, %</td>
<td>4.19 (4.07–4.31)*</td>
<td>3.72 (3.54–3.90)</td>
</tr>
<tr>
<td>10-y CHD risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20%</td>
<td>72.5*</td>
<td>82.2</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>7.9*</td>
<td>5.4</td>
</tr>
<tr>
<td>Veterans Affairs, %</td>
<td>41.8*</td>
<td>48.2</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; SBP, systolic BP; and Unk, unknown.

*P<0.001 for comparisons within uncontrolled and controlled groups.
In uncontrolled and controlled aTRH patients, the most commonly prescribed drug classes in decreasing order were diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, and angiotensin receptor blockers (Table S2). The percentage of patients on diuretic therapy overall was not a major distinguishing feature between uncontrolled and controlled patients. Controlled hypertensives were more likely to have aldosterone antagonists and loop diuretics prescribed than their uncontrolled counterparts, whereas thiazide-type diuretic prescriptions were generally similar.

Clinical factors positively associated with optimal treatment in uncontrolled and controlled aTRH included black versus white and other versus white race, body mass index, visit frequency, diabetes mellitus, CKD, and CHD risk equivalence (Figure 1). Factors negatively associated with optimal treatment in both groups included increasing age, therapeutic inertia, and current smoker. By multivariable analysis, variables with the strongest association with optimal prescribing were black race, diabetes mellitus, CKD, and CHD risk equivalents.

Clinical variables positively associated with BP control included increasing age, body mass index, and visit frequency, as well as care at a veterans administration facility, diabetes mellitus, CKD, CVD, statin therapy, and single-pill antihypertensive combination therapy (Figure 2). Variables negatively associated with hypertension control included black race and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncontrolled aTRH</th>
<th>Controlled TRH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>18792 (42.1)</td>
<td>23789 (60.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.7 (60.5–60.9)</td>
<td>63.5 (63.3–63.7)</td>
</tr>
<tr>
<td>Male, %</td>
<td>66.6*</td>
<td>75.4</td>
</tr>
<tr>
<td>Race, %</td>
<td>40.0†</td>
<td>39.8†</td>
</tr>
<tr>
<td>White</td>
<td>34.1†</td>
<td>40.3</td>
</tr>
<tr>
<td>Black</td>
<td>3.0†</td>
<td>2.7‡</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Mean</td>
<td>30.7 (30.5–30.8)</td>
</tr>
<tr>
<td>&lt;25, %</td>
<td>19.3</td>
<td>18.0*</td>
</tr>
<tr>
<td>&gt;30, %</td>
<td>47.1</td>
<td>48.4</td>
</tr>
<tr>
<td>Visit frequency/y</td>
<td>5.03† (4.97–5.09)</td>
<td>5.65 (5.59–5.71)</td>
</tr>
<tr>
<td>SBP, mm Hg (last visit)</td>
<td>150.8† (150.6–151.0)</td>
<td>121.4† (121.3–121.6)</td>
</tr>
<tr>
<td>DBP, mm Hg (last visit)</td>
<td>83.7 (83.6–8.39)</td>
<td>70.0 (69.9–70.1)</td>
</tr>
<tr>
<td>SBP, mm Hg (all visits)</td>
<td>141.8† (141.6–142.0)</td>
<td>130.1† (130.0–130.3)</td>
</tr>
<tr>
<td>DBP, mm Hg (all visits)</td>
<td>80.6* (80.4–80.7)</td>
<td>74.3† (74.2–74.4)</td>
</tr>
<tr>
<td>Visits BP &lt;140/&lt;30, %</td>
<td>41.8‡ (41.4–42.2)</td>
<td>70.6† (70.3–70.9)</td>
</tr>
<tr>
<td>Therapeutic inertia, %</td>
<td>62.7† (62.3–63.2)</td>
<td>49.5† (49.0–50.0)</td>
</tr>
<tr>
<td>Stage 2 (≥160/≥100), %</td>
<td>25.4</td>
<td>0.0</td>
</tr>
<tr>
<td>BP med count, n</td>
<td>3.28‡ (3.27–3.29)</td>
<td>4.24‡ (4.23–4.24)</td>
</tr>
<tr>
<td>BP single pill comb, %</td>
<td>41.8‡</td>
<td>36.5‡</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>101.1‡ (100.5–101.6)</td>
<td>90.0 (89.6–90.5)</td>
</tr>
<tr>
<td>Statin, %</td>
<td>65.3</td>
<td>76.8*</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>42.1†</td>
<td>51.8†</td>
</tr>
<tr>
<td>CKD, %</td>
<td>23.9†</td>
<td>34.8‡</td>
</tr>
<tr>
<td>eGFR, mL/1.73m² per minute</td>
<td>80.8‡ (80.3–81.2)</td>
<td>73.9† (73.5–74.3)</td>
</tr>
<tr>
<td>CVD, %</td>
<td>40.6†</td>
<td>58.1</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>29.3‡</td>
<td>31.0</td>
</tr>
<tr>
<td>10-y CHD risk</td>
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<td>&lt;10%</td>
<td>6.2‡</td>
<td>8.7</td>
</tr>
</tbody>
</table>

aTRH indicates apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; D, diuretic; DBP, diastolic BP; de, dose equivalents where 1=maximum recommended/approved dose; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; med, medication; SBP, systolic BP, and Unk, unknown.

*P<0.05, †P<0.01, ‡P<0.001 for comparisons within uncontrolled and controlled groups. Column 1 compared with column 2, column 2 with 3, and column 3 with 1.
likely to have an optimal regimen prescribed but less likely to
patients with controlled and uncontrolled aTRH were more
factors associated with optimal therapy (Figure 2). Black
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risk, including black race, diabetes mellitus, CKD, and CHD
therapy in uncontrolled and controlled aTRH patients clus-
this group was prescribed an optimal regimen. Among 468,877
controlled hypertensive patients, 12.3% were prescribed
4 ≥ 3 BP medications (Table 1).

Other studies addressed measurement artifacts and adher-
ance.4–6,16–18 Adherence is an important consideration with
reports suggest high levels of adherence in patients with
hypertension, including those with aTRH. Low adherence was
identified in ≤10% of hypertensive patients with and without
aTRH.19,20 In REGARDS (REasons for Geographic And Racial
Differences in Stroke), medication adherence was higher
among patients in the stroke belt, the location of patients in
our practice network, than other regions of the United States.19
The better adherence reported in more recent studies is consist-
with reports that hypertension control increased from
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Figure 1. The independent relationship is shown between
various clinical factors and the relative probability (odds ratio,
95% confidence interval) of receiving prescriptions for optimal
pharmacotherapy for patients with controlled and uncontrolled
apparent treatment-resistant hypertension. BMI indicates body
mass index; CHD, coronary heart disease; CKD, chronic kidney
disease; CVD, cardiovascular disease; DM, diabetes mellitus;
LDL-C, low-density lipoprotein cholesterol; and TI, therapeutic
inertia (visits with uncontrolled blood pressure [BP] without
medication change/visits with uncontrolled BP).

er other race versus white, therapeutic inertia, cigarette smoker,
and higher values of LDL-C.

Discussion
This study was undertaken to define the percentage of patients
with aTRH prescribed an optimal regimen and to determine
clinical factors independently associated with optimal therapy.
Among 468,877 hypertensive patients in a community-based
practice network in 2007–2010, 31.5% had uncontrolled
hypertension (Table S1). In uncontrolled hypertensives, mean
systolic BP was ≈10 mm Hg above the control value of <140
mm Hg, whereas mean diastolic BP values were in the mid to
low 80 range. The relatively wide pulse pressures suggest vas-
cular stiffness, which, in turn, is consistent with observations
that this was an older population with a relatively high preva-
ence of diabetes mellitus and dyslipidemia.11 In this group
of uncontrolled hypertensive patients, aTRH was common
because ≈30% were prescribed ≥3 BP medications (Table 1).
Only half of the patients with aTRH were prescribed an opti-
mal regimen (Table 2). Thus, ≈15% of all uncontrolled hyper-
tensive patients were prescribed an optimal regimen. Among
controlled hypertensive patients, 12.3% were prescribed ≥4
BP medications and are considered to have aTRH4; 37.8% of
this group was prescribed an optimal regimen.

Factors most strongly related to prescription of optimal
therapy in uncontrolled and controlled aTRH patients clus-
tered around clinical variables associated with greater CVD
risk, including black race, diabetes mellitus, CKD, and CHD
risk equivalent status (Figure 1). Factors that predicted con-
trol among patients with aTRH did not overlap as clearly with
the factors associated with optimal therapy (Figure 2). Black
patients with controlled and uncontrolled aTRH were more
likely to have an optimal regimen prescribed but less likely to
be controlled than white patients. This is consistent with evi-
dence that untreated BP values are generally higher and hyper-
tension is more difficult to control in blacks than whites.4,7,11
Patients with diabetes mellitus and CKD were more likely to
be prescribed an optimal regimen and controlled to <140/<90
mm Hg than patients without these comorbidities, which may
reflect the lower treatment goal of <130/<80 mm Hg. However,
evidence does not clearly support the lower target.12,13 Excessive
alcohol intake is noted as a contributor to resistant hyperten-
sion.4 Prevalent alcohol dependence identified by ICD9 coding
in this population of hypertensive patients was low and may
reflect limited detection. Of note, alcohol dependence was
coded less frequently in uncontrolled and controlled hyperten-
sive patients with than without aTRH (Table 1).

We suggested the term aTRH for patients with uncontrolled
hypertension on ≥3 BP medications, because all information
required to define true TRH is often unavailable.4 Thus, aTRH
includes patients with pseudohypertension, that is, subopti-
mal adherence and BP measurement artifacts, predominantly
office resistance, suboptimal regimens, and true TRH. Studies
using 24-hour ambulatory BP monitoring indicate that 35% to
50% of patients with aTRH have office resistance.5,6,16 Patients
with confirmed treatment resistance are at greater risk for clinical
CVD than those with office resistance.6,16

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risk equivalent status (Figure 1). Factors that predicted con-
trol among patients with aTRH did not overlap as clearly with
the factors associated with optimal therapy (Figure 2). Black
patients with controlled and uncontrolled aTRH were more
likely to have an optimal regimen prescribed but less likely to
be controlled than white patients. This is consistent with evi-
dence that untreated BP values are generally higher and hyper-
tension is more difficult to control in blacks than whites.4,7,11
Patients with diabetes mellitus and CKD were more likely to
be prescribed an optimal regimen and controlled to <140/<90
mm Hg than patients without these comorbidities, which may
reflect the lower treatment goal of <130/<80 mm Hg. However,
evidence does not clearly support the lower target.12,13 Excessive
alcohol intake is noted as a contributor to resistant hyperten-
sion.4 Prevalent alcohol dependence identified by ICD9 coding
in this population of hypertensive patients was low and may
reflect limited detection. Of note, alcohol dependence was
coded less frequently in uncontrolled and controlled hyperten-
sive patients with than without aTRH (Table 1).

We suggested the term aTRH for patients with uncontrolled
hypertension on ≥3 BP medications, because all information
required to define true TRH is often unavailable.4 Thus, aTRH
includes patients with pseudohypertension, that is, subopti-
mal adherence and BP measurement artifacts, predominantly
office resistance, suboptimal regimens, and true TRH. Studies
using 24-hour ambulatory BP monitoring indicate that 35% to
50% of patients with aTRH have office resistance.5,6,16 Patients
with confirmed treatment resistance are at greater risk for clinical
CVD than those with office resistance.6,16

Other studies addressed measurement artifacts and adher-
ance.4–6,16–18 Adherence is an important consideration with
reported discontinuation rates during the first year after initiati-
ing antihypertensive treatment of ≈30% to 50%.16 More recent
reports suggest high levels of adherence in patients with
hypertension, including those with aTRH. Low adherence was
identified in ≤10% of hypertensive patients with and without
aTRH.19,20 In REGARDS (REasons for Geographic And Racial
Differences in Stroke), medication adherence was higher
among patients in the stroke belt, the location of patients in
our practice network, than other regions of the United States.19
The better adherence reported in more recent studies is consist-
with reports that hypertension control increased from ≈1 in 2 in 1988–1994 to 7 in 10 treated patients in 2005–2010.12

Figure 2. The independent relationship is shown between various
clinical factors and the relative probability of blood pressure
control to <140/<90 mm Hg on the last (most recent) clinical visit.
BMI indicates body mass index; CKD, chronic kidney disease;
CVD, cardiovascular disease; DM, diabetes mellitus; and LDL-C,
low-density lipoprotein cholesterol.
Yet, of uncontrolled hypertensives in the Czech Republic on multiple BP medications, partial or total nonadherence was found in ≈65% using serum drug levels.21

The second purpose of this report was to generate information that could inform strategies to improve hypertension control among patients with aTRH. Clinical factors most strongly and independently associated with BP control among patients with aTRH were CVD and prescription of single-pill antihypertensive combinations and statins (Figure 2). Our article confirms previous reports that indicate that white race, use of single-pill combinations, and prescription of statins were linked to better BP control.4,7,22–24 In contrast to previous reports,3 older age, higher body mass index, and CKD were associated with BP control among patients with aTRH in the current analysis. This study was not designed to elucidate whether these associations reflect cause-and-effect relationships. The relationship of statins to BP control23 may reflect a reduction of angiotensin receptors.26

For patients uncontrolled on optimal therapy, strategies to select more efficacious regimens represent a potentially effective option.27–29 Recent guidelines and consensus statements recommend a renin–angiotensin system blocker, calcium channel blocker, and diuretic in a 3-drug regimen.30,31 Approximately 3 of 10 patients with uncontrolled aTRH on suboptimal regimens and 2 of 3 on optimal regimens were prescribed these 3 medication classes simultaneously (Table S2). Controlled patients with aTRH were more likely to have these 3 medications prescribed concurrently, with the exception of the small group not prescribed a diuretic at ≥50% of maximum recommended dose. Additional factors, which may have contributed to BP control among patients with aTRH, included the observation that the controlled subset was more likely to receive aldosterone antagonists and loop diuretics than their uncontrolled counterparts, but they were not more likely to receive thiazide diuretics than uncontrolled aTRH patients. Aldosterone antagonist and loop diuretics are effective strategies for some patients with TRH.4,32 Because some patients with TRH are not prescribed an optimal regimen, attempts to optimize the regimen represent a logical step for those with uncontrolled hypertension outside the office. The likelihood that BP will respond to an optimal regimen may be greater with guideline-recommended evidence-based strategies, for example, concurrent prescription of a renin–angiotensin system blocker, calcium channel blocker and diuretic, intensification of diuretic therapy with an aldosterone antagonist or loop diuretic, or renin or hemodynamic-guided therapy.

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Disclosures

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References


**Novelty and Significance**

**What Is New?**

• Approximately 30% of patients with treated uncontrolled hypertension are prescribed ≥3 antihypertensive medications (apparent treatment-resistant hypertension); 50% of them have not been prescribed an optimal regimen.

**What Is Relevant?**

• For patients with apparent treatment-resistant hypertension prescribed a suboptimal regimen with uncontrolled hypertension sustained outside the office, optimization of their regimen could improve blood pressure control.

**Summary**

Apparent treatment-resistant hypertension affects ≥30% of treated uncontrolled patients, but half of them have not been prescribed an optimal regimen. For the subset with suboptimal regimens and sustained blood pressure elevation outside the office, optimization of their antihypertensive treatment could improve blood pressure control and reduce their high risk for cardiovascular events.
Prevalence of Optimal Treatment Regimens in Patients With Apparent Treatment-Resistant Hypertension Based on Office Blood Pressure in a Community-Based Practice Network
Brent M. Egan, Yumin Zhao, Jiexiang Li, W. Adam Brzezinski, Thomas M. Todoran, Robert D. Brook and David A. Calhoun

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Prevalence of Optimal Treatment Regimens in Patients with Apparent Treatment Resistant Hypertension Based on Office BP in a Community-Based Practice Network

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e-mail: eganbm@musc.edu

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subcategory</th>
<th>Uncontrolled</th>
<th>Controlled</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td></td>
<td>147,635 (31.5)</td>
<td>321,242 (68.5)</td>
<td>468,877 (100)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td></td>
<td>57.3 (57.3, 57.4)</td>
<td>58.3 (58.3, 58.4)</td>
<td>58.0 (58.0, 58.0)</td>
</tr>
<tr>
<td>Male, %</td>
<td></td>
<td>65.2</td>
<td>69.9</td>
<td>68.4</td>
</tr>
<tr>
<td>Race, %</td>
<td>White</td>
<td>39.7</td>
<td>39.7</td>
<td>39.7</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>25.1</td>
<td>17.3</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>Unknown/Other</td>
<td>35.2</td>
<td>43.1</td>
<td>40.6</td>
</tr>
<tr>
<td>BMI, kg/m², % (with value)</td>
<td>Mean/ kg/m²</td>
<td>30.9 (30.9, 30.9)</td>
<td>30.1 (30.1, 30.2)</td>
<td>30.4 (30.3, 30.4)</td>
</tr>
<tr>
<td></td>
<td>&lt;25, %</td>
<td>18.7</td>
<td>20.5</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td>25-30, %</td>
<td>32.5</td>
<td>34.7</td>
<td>34.0</td>
</tr>
<tr>
<td></td>
<td>&gt;30, %</td>
<td>48.8</td>
<td>44.8</td>
<td>46.0</td>
</tr>
<tr>
<td>Visit freq/yr</td>
<td></td>
<td>4.5 (4.4, 4.5)</td>
<td>4.6 (4.6, 4.6)</td>
<td>4.5 (4.5, 4.5)</td>
</tr>
<tr>
<td>SBP, mm Hg (last visit)</td>
<td></td>
<td>150.0 (149.9, 150.0)</td>
<td>121.9 (121.9, 121.9)</td>
<td>130.7 (130.7, 130.8)</td>
</tr>
<tr>
<td>DBP, mm Hg (last visit)</td>
<td></td>
<td>85.5 (85.4, 85.6)</td>
<td>72.6 (72.6, 72.6)</td>
<td>76.7 (76.6, 76.7)</td>
</tr>
<tr>
<td>SBP, mm Hg (all visits)</td>
<td></td>
<td>142.8 (142.7,142.8)</td>
<td>129.3 (129.3, 129.4)</td>
<td>133.6 (133.5,133.6)</td>
</tr>
<tr>
<td>DBP, mm Hg (all visits)</td>
<td></td>
<td>82.8 (82.7, 82.8)</td>
<td>76.6 (76.6, 76.7)</td>
<td>78.6 (78.5,78.6)</td>
</tr>
<tr>
<td>Stage 2 HTN (≥160/100), %</td>
<td></td>
<td>25.3</td>
<td>0.0</td>
<td>8.0</td>
</tr>
<tr>
<td>% of visits BP &lt;140/&lt;90, %</td>
<td></td>
<td>26.7 (26.6,26.9)</td>
<td>60.8 (60.7,60.9)</td>
<td>50.1 (50.0,51.2)</td>
</tr>
<tr>
<td>Therapeutic Inertia, %</td>
<td></td>
<td>60.5 (60.3, 60.6)</td>
<td>59.0 (58.9, 59.2)</td>
<td>59.5 (59.4,59.7)</td>
</tr>
<tr>
<td>Med Count, N</td>
<td></td>
<td>2.47 (2.46, 2.48)</td>
<td>2.29 (2.29, 2.30)</td>
<td>2.34 (2.34, 2.35)</td>
</tr>
<tr>
<td>Single Pill Combination, %</td>
<td></td>
<td>27.4</td>
<td>24.0</td>
<td>25.0</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td></td>
<td>105.7 (105.4,105.9)</td>
<td>98.9 (98.8, 99.0)</td>
<td>100.9 (100.8,101.0)</td>
</tr>
<tr>
<td>Statin, %</td>
<td></td>
<td>51.3</td>
<td>58.9</td>
<td>56.5</td>
</tr>
<tr>
<td>Diabetics, %</td>
<td></td>
<td>34.3</td>
<td>36.5</td>
<td>35.8</td>
</tr>
<tr>
<td>CKD, %</td>
<td></td>
<td>17.3</td>
<td>18.2</td>
<td>17.9</td>
</tr>
<tr>
<td>eGFR, ml/1.73m²/min</td>
<td></td>
<td>84.7 (84.5, 84.8)</td>
<td>84.1 (84.0, 84.2)</td>
<td>84.3 (84.2,84.4)</td>
</tr>
<tr>
<td>CVD, %</td>
<td></td>
<td>27.9</td>
<td>33.1</td>
<td>31.5</td>
</tr>
<tr>
<td>Smoke, %</td>
<td></td>
<td>28.3</td>
<td>30.6</td>
<td>29.9</td>
</tr>
<tr>
<td>Framingham 10 year Risk, %</td>
<td>&gt;20%</td>
<td>75.9</td>
<td>62.4</td>
<td>66.4</td>
</tr>
<tr>
<td></td>
<td>&lt;10%</td>
<td>7.1</td>
<td>14.2</td>
<td>12.1</td>
</tr>
<tr>
<td>VA, %</td>
<td></td>
<td>43.7</td>
<td>53.4</td>
<td>50.4</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=body mass index, S=systolic, D=diastolic, LDL-C=low-density lipoprotein cholesterol, CKD=chronic kidney disease, CVD=cardiovascular disease, VA=Veterans Affairs. Data are presented as mean and 95% confidence intervals *controlled and uncontrolled are significantly different on all the variables at p<0.0001 except for white race.
### Table S2. Antihypertensive medication classes prescribed to patients with aT"RH.

<table>
<thead>
<tr>
<th>BP Med Class</th>
<th>Patients, N(%)</th>
<th>Uncontrolled aT&quot;RH</th>
<th>Controlled aT&quot;RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 3 meds de &lt; 0.5</td>
<td>≥ 3 meds de ≥ 0.5</td>
<td>≥ 3 meds de ≥ 0.5 incl D</td>
</tr>
<tr>
<td>α₁-blocker, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18,792 (42.1)</td>
<td>3,703 (8.3)</td>
<td>22,189 (49.6)</td>
</tr>
<tr>
<td>α₁,β-blocker, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>12.4</td>
<td>9.4</td>
</tr>
<tr>
<td>≥1 RAS blocker, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI, %</td>
<td>70.9</td>
<td>84.9</td>
<td>76.9</td>
</tr>
<tr>
<td>ARB, %</td>
<td>23.1</td>
<td>49.4</td>
<td>36.2</td>
</tr>
<tr>
<td>DRI, %</td>
<td>0.6</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB, %</td>
<td>52.3</td>
<td>69.8</td>
<td>56.4</td>
</tr>
<tr>
<td>dCCB, %</td>
<td>53.3</td>
<td>92.5</td>
<td>75.3</td>
</tr>
<tr>
<td>ndCCB, %</td>
<td>39.6</td>
<td>83.6</td>
<td>64.6</td>
</tr>
<tr>
<td>≥1 Diuretic, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldo Antag, %</td>
<td>2.5</td>
<td>0.2</td>
<td>8.7</td>
</tr>
<tr>
<td>K⁺-sparing, %</td>
<td>9.9</td>
<td>0.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Loop, %</td>
<td>21.2</td>
<td>14.2</td>
<td>33.9</td>
</tr>
<tr>
<td>Thiazide type, %</td>
<td>64.6</td>
<td>22.2</td>
<td>77.6</td>
</tr>
<tr>
<td>Chlorthalidone, %</td>
<td>1.6</td>
<td>0.0</td>
<td>5.6</td>
</tr>
<tr>
<td>HCTZ, %</td>
<td>62.4</td>
<td>22.1</td>
<td>68.8</td>
</tr>
<tr>
<td>Other Thiazide, %</td>
<td>0.7</td>
<td>0.03</td>
<td>3.6</td>
</tr>
<tr>
<td>Sympatholytic, %</td>
<td>0.5</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Vasodilator, %</td>
<td>2.8</td>
<td>10.1</td>
<td>8.5</td>
</tr>
<tr>
<td>RASB+CCB+Diuertic, %</td>
<td>29.3</td>
<td>32.0</td>
<td>68.3</td>
</tr>
</tbody>
</table>

de= dose equivalents (percent of maximum recommended/approved hypertension dose); D=diuretic; incl=include(s); RAS=renin-angiotensin system blocker (B); ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; DRI=direct renin inhibitors; CCB=calcium channel blocker; d=dihydropyridine; nd=non-dihydropyridine; aldo antag=aldosterone antagonist. Given the sample sizes differences, of 1% between columns 1 and 3 and differences of 3% between columns 1 and 2 and 2 and 3 are significant.
**S1 Figure.** The process for deriving the study sample is depicted. As shown, from an initial sample of 844,533, a total of 468,877 met inclusion/exclusion criteria.

- **Having at least 3 BPs in 2007-2010:**
  - **844,533**
  - Not Hypertensive
    - **314,044**
  - Hypertensive
    - **530,489**
    - No medications
      - **22,161**
    - Medications available
      - **508,328**
      - Age < 18 or age > 85 or missing gender
        - **27,321**
      - **18 ≤ age ≤ 85**
        - **481,007**
        - Dementia or pregnant
          - **12,130**
  - **Final analytical data**
    - **468,877**