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Physician Underutilization of Effective Medications for Resistant Hypertension at Office Visits in the United States: NAMCS 2006–2010

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BACKGROUND: The American Heart Association (AHA) published guidelines for treatment of resistant hypertension in 2008 recommending use of thiazide diuretics (particularly chlorthalidone), aldosterone antagonists, and fixed-dose combination medications, but it is unclear the extent to which these guidelines are being followed.

OBJECTIVE: To describe trends in physician use of recommended medications for resistant hypertension and assess variations in medication use based on geography, physician specialty and patient characteristics.

DESIGN: Cross-sectional analysis using the National Ambulatory Medical Care Survey from 2006 to 2010.

STUDY SAMPLE: We analyzed visits of hypertension patients to family physicians, general internists, and cardiologists. Resistant hypertension was defined as concurrent use of ≥ 4 classes of blood pressure (BP) medications or elevated BP despite the use of ≥ 3 medications. Pregnant patients and visits with diagnosed heart failure or end-stage renal disease were excluded.

MAIN OUTCOME: Use of AHA-recommended medications for management of resistant hypertension.

RESULTS: Of 19,500 patient visits with hypertension, 1,567 or 7.1 % CI (6.6–7.7 %) met criteria for resistant hypertension. Thiazide diuretic use was reported in 58.9 % of visits pre-guidelines vs. 54.8 % post-guidelines (p=0.37). Use of aldosterone antagonists was low and also did not change significantly after guideline publication (3.1 % vs. 4.5 %, p=0.27). Fixed-dose combinations use was 42.0 % before and 37 % after guideline publication (p=0.29). Each 10-year increase in patient age was associated with lower thiazide use (OR 0.87, CI 0.77–0.97), as was presence of comorbid ischemic heart disease (OR 0.62, CI 0.41–0.94). Medication use did not vary by geography or physician specialty.

CONCLUSION: Use of AHA-recommended medications for resistant hypertension remains low after publication of guidelines. Healthcare systems should encourage more frequent prescribing of these medications to improve care in this high-risk population.

KEY WORDS: resistant hypertension; guidelines adherence; hypertension management; medication use; spironolactone; chlorthalidone; fixed-dose combination.
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INTRODUCTION

According to recent observational studies of national data, an estimated 8.9 % to 11.4 % of US hypertensive adults have resistant hypertension,[1,2] defined by blood pressure (BP) that remains above goal despite concomitant use of ≥ 3 distinct classes of antihypertensive medications or requiring ≥ 4 medications to achieve BP control with the medication regimen ideally including a thiazide diuretic.[3] Data from clinical trials suggest that the prevalence may be substantially higher and the incidence rate among all hypertensive adults has been reported at 1.9 % per year.[4] In 2008, the American Heart Association (AHA) published guidelines for treatment of resistant hypertension that included recommendations for optimal diuretic use (chlorthalidone as the preferred thiazide diuretic), adding an aldosterone antagonist as a fourth medication for uncontrolled BP, and using fixed-dose combination drugs.[3] According to these guidelines, most resistant hypertension patients should be treated with an appropriately dosed thiazide diuretic, calcium channel blocker (CCB), and an ACE inhibitor (ACE-I) or angiotensin receptor blocker (ARB) with aldosterone antagonists as the first choice for patients whose BP remains uncontrolled on optimal doses of ≥ 3 distinct classes of antihypertensive medications. Beta blockers are indicated in the setting of ischemic heart disease (IHD) or congestive heart failure (CHF).

These therapeutic maneuvers have been shown to achieve greater rates of BP control among patients with hypertension, but it is unclear how often they are used in practice.[5–10] The National Ambulatory Medical Care Survey

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(NAMCS), an annual nationally representative sample of office visits in the US, collects blood pressure measurements, diagnoses and medications. We sought to assess the prevalence of resistant hypertension among office visits to physicians who typically manage hypertension, describe trends in physicians' use of recommended medications 2 years after publication of the AHA guidelines, and determine whether use of recommended medications varied by regional-level, physician-level, or patient-level characteristics.[11] Although European Guidelines on Hypertension discuss use of aldosterone antagonist for resistant hypertension,[12] other major guidelines in Canada, Australia, and US (the Joint National Commission JNC VII) do not include explicit recommendations for resistant hypertension.

METHODS

Data and Study Design

NAMCS is an annual, nationally representative cross-sectional survey of ambulatory office visits to physicians in the US that uses a multi-stage probability sampling design to represent all visits to non-federally employed office-based physicians engaged in direct patient care. The sampling design includes probability sampling of defined geographic areas, physician practices within those areas, and patient visits within each practice. Individuals are not followed longitudinally and are extremely unlikely to contribute multiple visits across different survey years. A more detailed description of NAMCS methodology is available from the National Center for Health Statistics (NCHS).[13–17]

Study Sample

We used NAMCS survey data from 2006–2010 and included all patient visits in which the patient was at least 18 years old, had a history of hypertension, was seen by a physician who can reasonably be expected to routinely manage hypertension (general/family practitioners, internists, and cardiologists), and had a recorded BP for the visit. NAMCS was not designed to sample visits to nephrologists systematically, so these visits were not included in this analysis. We excluded visits in which the patient was specified as pregnant, or had a positive pregnancy test that visit.

To avoid misclassification of resistant hypertension, we also excluded patients with CHF (defined by a "yes" answer to "Does the patient now have a history of heart failure?") and end-stage renal disease (ESRD) defined by ICD-9 5859, or being on dialysis (identified by procedure code V4511 or dialysis listed as the reason for visit) . Patients with CHF are often on multiple antihypertensive medications for reasons other than BP management. ESRD is associated with dialysis-related fluctuations in BP and electrolyte disturbances that impact therapeutic decisions for BP management.

Patient and Visit Characteristics

Patient demographic and visit characteristics were abstracted from the medical record by the physician, physician staff, or census bureau staff.[15] Age, race, and gender, as well as the number of medications added or continued by the physician at the visit were recorded. Office BP was ascertained by routine measurements without specifications for BP cuff size or number of repeated measurements. We also identified visits associated with diagnoses of comorbid conditions such as IHD and diabetes (DM). Practice setting characteristics are also recorded, including type of practice (private, community health center, other) and geographic region. Finally, we also included physician specialty (general/family physician, internal medicine, and cardiology).

To identify BP medications, we reviewed the Multum Lexicon database used by NAMCS for coding medications.[18] We identified antihypertensive drug classes and then reviewed specific medication names to ensure that they are medications likely used for the purpose of BP management. See the Appendix Online for the list, by class, of medications we defined as antihypertensive medications. NAMCS reported medications as either continued or newly prescribed during the visit. Medications reported as continued were considered to be the patient's medication regimen prior to the visit.

In order to identify visits that met criteria for resistant hypertension at presentation to the office, we defined resistant hypertension as visits reporting ≥ 4 distinct classes of continued BP medications, or an elevated BP ($\geq$ 140/90 mmHg) despite ≥ 3 continued medications with at least one first-line medication (thiazide, ACE-I, ARB, or CCB) included in the medication list. When describing prevalent use of medications, we considered those medications that were continued or that were newly added at the visit.

Statistical Analysis

We first described the prevalence of resistant hypertension and then used chi-square tests to compare physician use of recommended BP medications before and after 2008. Since the use of recommended medications may be different among those patients who present with uncontrolled BP, we also assessed trends in medication use among resistant hypertension visits with uncontrolled BP. We used linear regressions with visit year as a continuous predictor variable to test for linear trends. Finally, we conducted

bivariate and multivariate logistic regressions to examine characteristics associated with use of recommended medications. We compared the use of thiazide diuretics by physician-level and patient-level characteristics. The multivariate model included all covariates with P values ≤ 0.10 from bivariate analyses in addition to sex and race. NCHS considers an estimate to be reliable if it has a relative standard error (RSE) of 30 %, and estimates based on fewer than 30 records are considered unreliable.[19] Variables with sample observations of < 30 or RSE > 0.3 were excluded from the model. Analyses to assess variations in use of aldosterone antagonist and chlorthalidone were not feasible because the sample sizes of observed visits reporting their use were too small. NAMCS records a maximum of eight medications; we performed a sub-analysis excluding visits reporting eight continued medications, to account for possible differential omission of BP medications and the inability to assess additional (i.e., ninth) medications prescribed at these visits.

We conducted all analyses using Stata 12 (StataCorp, College Station, Texas) applying survey weights to account for NAMCS' complex sampling design and obtain population estimates.

RESULTS

NAMCS 2006–2010 included 154,421 observed visits representing 4.9 billion outpatient visits. A total of 19,500 observed visits of hypertensive adult patients met our criteria for inclusion, while 1,567 visits met our definition for resistant hypertension, comprising 7.1 % (95 % CI 6.5–7.7) of patient visits with hypertension (Fig. 1). Patients with resistant hypertension were elderly (mean age 68 years) and had a high prevalence of comorbid conditions like DM (35.2 % CI 31.7–38.9) and IHD (17.7 %). Over three-quarters of the visits with resistant hypertension (78.3 % CI 75.4–80.9) had recorded BPs that were uncontrolled (Table 1).

Medication Use

On average, patients were taking 6.1 total medications (SD 2.0) and 3.5 distinct classes of antihypertensive medications (SD 0.6), with no significant change in total numbers of medication used over the observation period from 2006 to 2010 (p for trend 0.32). The two most commonly used classes of antihypertensive medications in resistant hypertension were

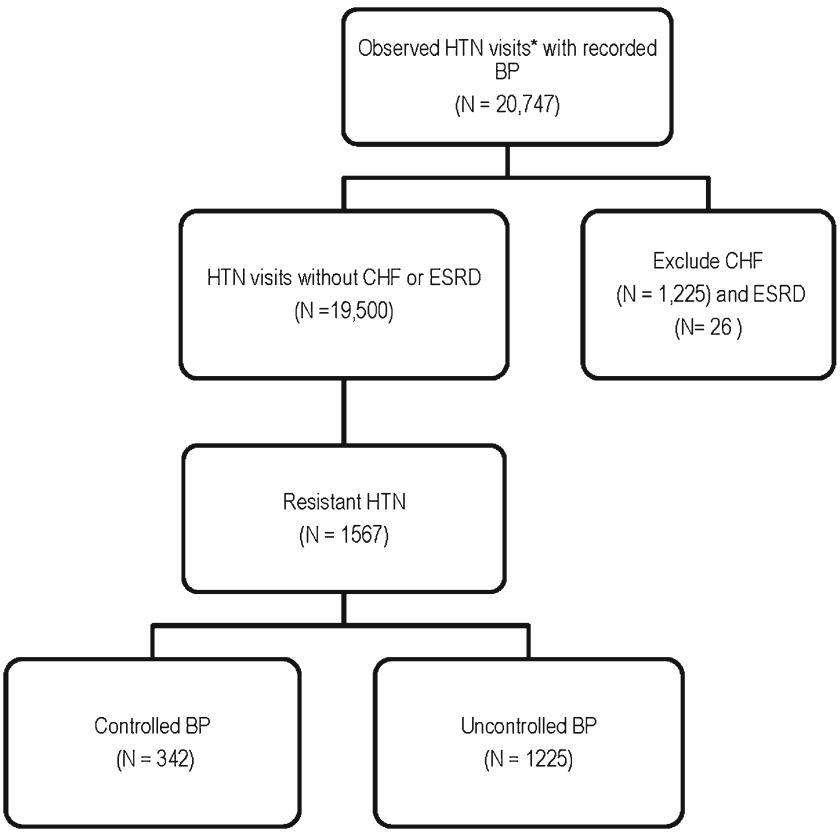

Figure 1. Selection process and study design: NAMCS 2006–2010. *Includes only visits to family physicians/general practitioners, internists, or cardiologists. HTN (hypertension) identified as a yes response to the survey question of whether the patient has HTN, ICD-9 coding of HTN listed as a diagnosis for the visit, or visits with elevated BP (≥ 140/90 mmHg) and ≥ 2 BP medications listed. CHF: congestive heart failure identified by physician survey response to whether the patient has CHF. ESRD: end-stage renal disease identified by ICD-9 coding for ESRD, or dialysis. Resistant HTN: visits reporting ≥ 4 BP medications at presentation or elevated BP ((≥ 140/90 mmHg) with ≥ 3 BP medications at presentation. BP medications at presentation refer to medications listed as continued. Uncontrolled BP: systolic BP≥140 mmHg or diastolic BP≥90 mmHg. Ace-arb: use of either an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

Table 1. Characteristics of Patient Visits with Resistant Hypertension: NAMCS 2006–2010

Characteristics	Observed visits, N (Weighted %)
Total	1,567
Classification of resistant hypertension	
Uncontrolled on 3 BP medications	901 (56.2)
Controlled on ≥ 4 BP medications	342 (23.4)
Uncontrolled on ≥ 4 BP medications	324 (20.6)
Demographic characteristics	
Age in years, mean (SD)	68 (13.8)
Female	814 (51.9)
Race	
White	1,178 (78.4)
Black	313 (18.7)
Other	76 (2.9)
Comorbid conditions	
Diabetes	533 (30.9)
Ischemic heart disease	353 (17.7)
Chronic kidney disease	29 (2.3)
BP-related characteristics	
Systolic blood pressure in mmHg, mean (SD)	146 (20)
Diastolic blood pressure in mmHg, mean (SD)	80 (12)
Blood pressure control (< 140/90 mmHg)	355 (23.4)
Number of BP medications at presentation, mean (SD)	3.5 ((0.6)
Medication use	
Number of medications of all types, mean (SD)	6.1 (2.0)
Mean number of BP medications continued (SD)	3.5 (0.6)
Source of payment	
Private	787 (56.6)
Medicare*	494 (32.3)
Medicaid only	110 (3.7)
Other (self-pay, worker's comp, family planning, unknown)	176 (7.4)
Physician-level characteristics	
Physician specialty	
General practitioner/family physician	591 (38.2)
Internal medicine	363 (24.7)
Cardiology	613 (37.1)
Visit type	
Initial visit	93 (4.4)
Return visit	1,474 (95.6)
HTN listed as a reason for the visit	206 (23.0)
Practice setting	
Region	
Northeast	314 (16.6)
Midwest	391 (25.4)
South	601 (42.8)
West	261 (15.2)
Type of clinic	
Private practice (solo or group)	1,183 (88.8)
Community health center	313 (4.8)
Other	71 (6.4)

**Includes Medicare patients also covered by Medicaid, but excludes those who also have private insurance*
HTN hypertension

diuretics and beta blockers. Thiazide diuretic use was reported at 56.4 % (CI 52.9–59.8) of visits and 1.2 % of visits recorded use of chlorthalidone (CI 0.3–2.0). Aldosterone antagonist therapy was used at only 3.6 % (CI 2.4–4.5) of visits. We did not observe any statistically significant change in use of thiazides (54.8 % vs. 58.9 %), chlorthalidone (1.4 % vs. 1.6 %), aldosterone antagonists (4.5 % vs. 3.1 %), or fixed-dose combination (37.2 % vs. 42.0 %) in the period following publication of the AHA guidelines as compared with the period prior to publication (Table 2).

Among visits with uncontrolled BP (N=1,225), medication use following the AHA guidelines was similarly unchanged (Table 2). Chlorthalidone and aldosterone antagonist use remained low throughout the 5-year period (<3 % and <4 % of visits surveyed, respectively) among these visits with uncontrolled hypertension. No significant change in use of thiazide diuretics or fixed-dose combinations was observed,[Fig. 2] but use of ACE inhibitors decreased by an absolute difference of 4.7 % after 2008 while calcium channel blocker (58.6 % vs. 64.3 %) and beta blocker use (70.9 % vs. 77.1 %) trended upward without reaching statistical significance (Table 2).

Predictors of Thiazide Use

In bivariate analyses, use of thiazide diuretics was associated with older age, absence of comorbid ischemic heart disease, use of fixed-dose combinations, and visits to a non-cardiologist. In multivariate regression, every 10-year increase in age was associated with 13 % lower odds of thiazide use (OR 0.87, CI 0.77–0.97). Use of fixed-dose combinations was associated with higher thiazide use (OR 5.04, CI 3.51–7.25). Comorbid IHD was associated with lower use of thiazides (OR 0.62, CI 0.41–0.94). Medicaid was associated with lower use of thiazide diuretics (OR 0.36, CI 0.16–0.78) as compared to private insurance, although interpretation is limited due to small sample size of Medicaid visits. Use of thiazide diuretics did not vary significantly by geographic region, clinic type, physician specialty, race or gender (Table 3). Because thiazides are commonly used in combination medications, we repeated the analysis excluding fixed-dose combinations from the model. The magnitude and direction of our results for the other significant predictors did not change.

DISCUSSION

In our analysis of a nationally representative sample of office-based visits in the United States, we found that US physicians' treatment of resistant hypertension during office visits was not consistent with recommended guidelines. While overall diuretic use was common, thiazides were used in under 60 % of these visits, fixed dose combination in only 40 %, and use of aldosterone antagonists and chlorthalidone was extremely uncommon. These low usage patterns persisted through 2010, two years after the publication of AHA guidelines for the management of resistant hypertension and unchanged from the period prior to publication of these guidelines.

Few prior studies describe how physicians manage resistant hypertension in the United States. Our finding of 7.1 % prevalence of resistant hypertension among visits

Table 2. Comparing Prevalent Use of Antihypertensive Medications Among Resistant Hypertension Office Visits 2 Years Before and After Publication of AHA Recommendations in 2008

Medication Use	Prevalent use, weighted percentage (se)			
	2006–2010	2006–2007	2009–2010	P
All visits with resistant HTN, N(weighted %*)	1,567 (7.1 %)	605 (6.9 %)	645 (6.7 %)	0.85
Total number of medications, mean (SD)	6.1 (2.0)	6.0 (1.9)	6.3 (1.9)	0.55
Number of distinct classes of BP medications, mean (SD)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)	–
Diuretics, any	78.9 % (1.5)	81.2 % (2.3)	76.7 % (2.5)	0.2
Thiazide, any	56.4 % (1.8)	58.9 % (3.2)	54.8 % (2.9)	0.37
Hydrochlorothiazide	54.3 % (1.7)	56.6 % (2.9)	54.3 % (2.0)	0.36
Chlorthalidone	1.2 % (0.4)	1.6 % (0.8)	1.4 % (0.5)	NR
Other thiazides	0.9 % (0.4)	0.7 % (0.4)	1.0 % (0.7)	NR
Loop	24.4 % (1.5)	25.7 % (2.5)	23.0 % (2.6)	0.47
Potassium sparing				
Other	5.9 % (1.1)	7.3 % (1.7)	4.7 % (1.9)	NR
Aldosterone antagonist	3.6 % (0.6)	3.1 % (0.8)	4.5 % (1.1)	0.27
Fixed-dose combination	39.7 % (2.1)	42.0 % (3.3)	37.2 % (3.4)	0.29
ACE or ARB	90.9 % (1.0)	92.8 % (1.3)	89.5 % (1.6)	0.09
ACE inhibitor	58.7 % (2.0)	62.6 % (2.6)	57.4 % (2.9)	0.12
ARB	39.5 % (1.7)	39.4 % (2.6)	38.9 % (2.9)	0.89
Calcium channel blocker	66.8 % (1.9)	63.1 % (3.2)	68.5 % (2.8)	0.2
Beta blockers	75.5 % (1.5)	73.9 % (2.3)	79.6 % (2.5)	0.11
Vasodilators	4.0 % (0.8)	3.3 % (0.9)	3.5 % (1.0)	0.9
Anti-adrenergic	24.6 % (1.6)	25.1 % (2.5)	24.7 % (2.4)	0.88
Visits with uncontrolled BP, N (%†)	1,225 (78.3 %)	474 (79.8 %)	493 (75.8 %)	2.38
Total number of medications, mean (SD)	6.0 (2.0)	5.9 (2.0)	6.2 (1.9)	0.55
Number of distinct classes of BP medications, mean (SD)	3.3 (0.6)	3.3 (0.6)	3.3 (0.6)	–
Diuretics, any	76.9 % (1.7)	79.0 % (2.6)	73.7 % (2.0)	0.2
Thiazide, any	55.0 % (2.1)	56.4 % (3.4)	52.0 % (3.5)	0.36
Hydrochlorothiazide	53.4 % (1.7)	54.8 % (3.3)	50.4 % (3.6)	0.37
Chlorthalidone	1.0 % (0.4)	1.2 % (0.7)	1.2 % (0.3 %	NR
Other thiazides	1.3 % (0.6)	0.4 % (0.3)	0.4 % (0.3)	NR
Loop	23.2 % (1.6)	24.9 % (2.9)	22.6 % (3.1)	0.59
Potassium sparing				
Other	6.0 % (1.1)	7.8 % (2.0)	3.9 % (1.6)	NR
Aldosterone antagonist	2.4 % (0.6)	2.1 % (0.6)	3.3 % (1.1)	NR
Fixed-dose combination	38.1 % (2.1)	40.7 % (3.6)	35.0 % (3.7)	2.8
ACE or ARB	89.5 % (1.2)	92.1 % (1.6)	87.4 % (2.1)	0.05
ACE inhibitor	56.6 % (2.4)	61.5 % (3.1)	54.0 % (3.4)	0.05
Angiotensin receptor blocker	38.5 % (2.1)	37.7 % (2.9)	37.9 % (3.6)	0.98
Calcium channel blocker	62.6 % (2.3)	58.6 % (3.8)	64.3 % (3.4)	0.26
Beta blockers	72.4 % (1.8)	70.9 % (3.0)	77.1 % (2.9)	0.15
Vasodilators	3.7 % (0.8)	3.4 % (1.2)	3.1 % (0.8)	0.83
Anti-adrenergic	20.7 % (1.7)	22.8 % (2.7)	21.0 % (2.6)	0.6

ACE or ARB: angiotensin converting enzyme inhibitor or angiotensin receptor blocker; P values from survey-weighted logistic regression comparing years 2006–207 vs. 2009–2010
NR – P values not reported for observations fewer than 30 or relative SE > 0.3
– outcome does not vary
**Prevalence of resistant hypertension among visits of patients with known hypertension*
†Proportion of visits with uncontrolled BP (≥140/90 mmHg) among visits of patients with resistant hypertension
HTN hypertension

with hypertension reported in this analysis is consistent with the 8.9 % reported by Persell's analysis of the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2008.[2] The small difference could be explained by the differing study periods, differences in population-based versus clinic based samples, as well as differences in self-reported medication use in NHANES versus clinically recorded medication use in NAMCS. While resistant hypertension accounts for a modest proportion of all ambulatory visits in the US, our analyses demonstrate that these visits with resistant hypertension are not rare occurrences and the low adherence with guidelines suggests existing opportunities for physicians to improve BP control.

NAMCS offers the advantage of assessing the number of concurrent medications used and describes physician prescribing behavior at the point of care. Our data suggest that physicians underutilized effective medications even when facing uncontrolled hypertension refractory to multiple medications. This underutilization is also consistent with previous findings. The NHANES analysis reported low use of aldosterone antagonists (3 %).[2] A study of pharmaceutical and claims data reported a 5.9 % use of aldosterone antagonists and 3 % use of chlorthalidone among resistant hypertension patients taking ≥ 4 medications.[20] Our study extends the current literature in a few additional ways. We examined trends in treatment of

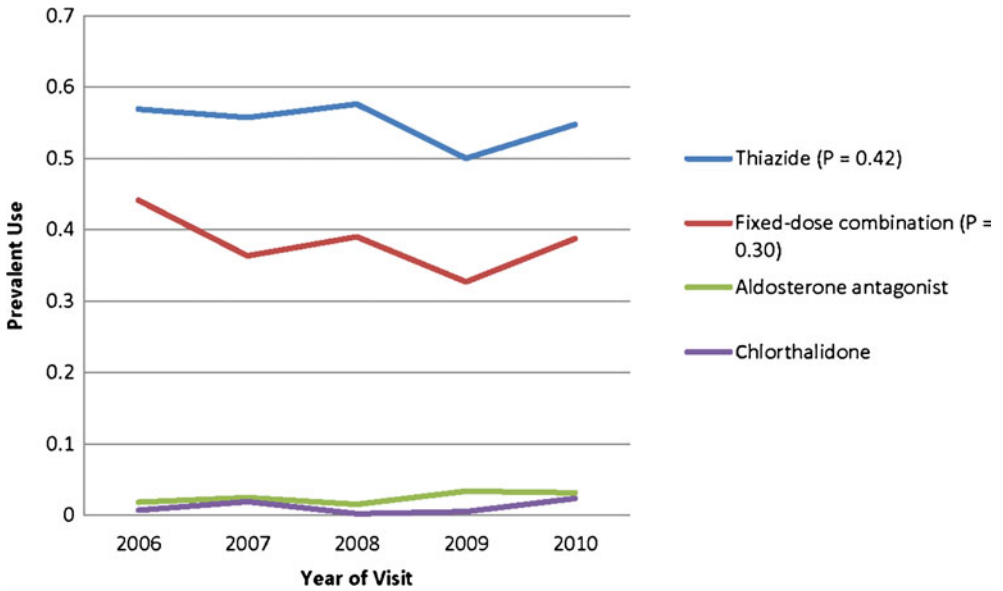

Figure 2. Trend in prevalent use of selected medications at resistant hypertension visits with uncontrolled BP. Unadjusted trends in prevalent medication use. P values were obtained using survey weighted linear regression. P values for aldosterone antagonist and chlorthalidone use are not reported because the sample sizes were less than 30.

resistant hypertension after publication of the AHA recommendations, showing no increase in physician prescribing of recommended medications for resistant hypertension. Also, the nationally representative data on physicians' practice in NAMCS allows us to examine potential systemic variations in physicians' use of evidence-based treatment at the national level based on patient factors such as age, insurance status, and presence of comorbid conditions.

Thiazide diuretic use was reported at less than 60 % of visits. Current guidelines recommend use of thiazide in resistant hypertension whenever possible.[3] This current level of thiazide use in resistant hypertension may be inappropriately low, but appropriate use is difficult to assess conclusively. Clinically appropriate reasons to avoid use of thiazides exist, including electrolyte abnormalities, orthostatic hypotension, and patient preference or non-adherence.[21,22] In fact, the higher likelihood of adverse effects and contraindications (e.g. orthostatic hypertension) seen with older age plausibly explains the age association with lower thiazide use reported here.[23,24] On the other hand, previous reports have suggested that physicians often fail to implement effective antihypertensive agents when warranted.[25–29] While NAMCS data cannot reliably help us distinguish between these explanations, systems that provide care for similarly older populations, such as the Veterans Health Administration (VHA), have been able to successfully increase thiazide use in their overall hypertensive patient population.[30] This suggests that there may be room for increased thiazide use among resistant hypertension patients in the U.S population. Longitudinal observational studies are needed to better assess appropriate use and identify potential strategies for safe increase of thiazide use in resistant hypertension. We observed a trend toward lower use of ACE-I and higher use of beta blockers, potentially suggestive of a departure from more effective therapies in management of resistant hypertension, although data about appropriateness is limited in this analysis. Ongoing monitoring of national data is warranted to assess for changes in practice patterns.

Physician use of aldosterone antagonists and chlorthalidone continues to be very uncommon, despite evidence of substantial improvement in BP control achieved by using these medications in resistant hypertension patients with uncontrolled BP.[6,7,31,32] This considerable underutilization is not likely explained by patient factors or physician practice preferences because their use is too low to be subjected to significant variations. Low awareness of the efficacy of these medications is likely a contributory factor, but may also not fully explain the low utilization rate. The AHA recommendations for aldosterone antagonist use were only recently published, but the evidence for chlorthalidone has been known for quite some time.[10,33] Why increasing the use of these medications has proven difficult is not well understood, although behavioral norms and entrenched practice patterns biased against their use may contribute to the challenges in increasing their use.

Implementation of clinical guidelines has historically been slow and uneven.[34,35] Indeed, the use of thiazide diuretics did not increase from 1992 to 1995 after publication of JNC V guidelines recommending thiazides as a first choice antihypertensive treatment.[36] However, system-level and clinic-level interventions, such as providing feedback to physicians regarding their patterns

Table 3. Prevalent Use of Thiazide Diuretics in Ambulatory Visits of Resistant Hypertension Patients by Characteristics: 2006–2010

Observed visits (*N*=1,567)	Use of thiazide diuretic, % (se)			
	Thiazide *N*=870	No thiazide *N*=697	Adjusted OR	Adjusted P Value
Demographic characteristics				
Age in years, mean (SD)*	66.6 (13.6)	70.0 (13.7)	N/A	N/A
Age (in 10 years)*			0.87 (0.77–0.97)	0.01
Female	56.0 (2.3)	55.2 (2.7)	0.97 (0.68–1.42)	0.93
Race				
White	78.0 (2.5)	79.4 (2.6)	Ref	
Black	18.4 (2.2)	17.8 (2.6)	0.91 (0.59–1.38)	0.64
Other	3.6 (1.3)	2.9 (0.7)	1.31 (0.62–2.76)	0.48
Source of payment*				0.02
Private	57.9 (2.9)	51.2 (3.1)	Ref	
Medicare	30.3 (2.5)	36.2 (3.0)	0.89 (0.67–1.29)	0.50
Medicaid□	3.3 (0.8)	6.5 (1.5)	0.36 (0.16–0.78)	0.01
Other	8.6 (1.6)	6.4 (1.3)	1.03 (0.51–2.08)	0.94
Comorbid conditions				
Diabetes	34.4 (2.2)	36.2 (3.0)		0.61
Ischemic heart disease*	13.7 (1.5)	22.6 (2.4)	0.62 (0.41–0.94)	0.02
Chronic kidney disease†	2.0 (0.8)	3.7 (1.3)	N/A	N/A
BP-related characteristics				
Systolic blood pressure, mean (SD)	145.8 (19.7)	147.7 (20.3)	N/A	
Diastolic blood pressure, mean (SD)	80.4 (12.6)	79.3 (13.1)	N/A	
Blood pressure control*				
Yes	23.7 (2.0)	19.1 (1.9)	Ref	
No	76.3 (2.0)	80.1 (1.9)	0.80 (0.57–1.13)	0.21
Fixed-dose combination	55.6 (2.8)	19.1 (2.2)	5.04 (3.51–7.25)	<0.01
Physician-level characteristics				
Physician specialty *				
Gen/FP	37.0 (3.0)	32.9 (2.8)	Ref	
Internal Medicine	41.3 (3.1)	41.1 (3.4)	0.91 (0.65–1.28)	0.60
Cardiology	21.7 (2.1)	26.0 (2.3)	0.83 (0.60–1.15)	0.26
Visit type				
Initial visit	4.7 (0.8)	3.6 (0.9)	N/A	N/A
Return visit	95.3 (0.8)	96.4 (0.9)		
HTN listed as a reason for the visit	23.0 (2.4)	18.4 (2.0)		
Practice setting				
Region			N/A	N/A
Northeast	19.1 (2.4)	17.2 (2.2)		
Midwest	24.8 (3.3)	25.5 (3.3)		
South	40.5 (3.2)	42.1 (3.6)		
West	15.7 (2.3)	15.2 (2.5)		
Type of clinic			N/A	N/A
Private practice	88.9 (1.9)	88.1 (2.3)		
Community health center	5.1 (0.9)	4.5 (1.2)		
Other	6.1 (1.6)	7.5 (1.9)		

Values are reported as mean (SD) or column weighted % (se)
**P value for bivariate linear regression or Pearson's Chi-square analysis ≤ 0.1*
Multivariable model adjusted for race and gender in addition to variables with P values≤0.1 in bivariate analysis
†Estimates may be unreliable due to small sample size: CKD (N= 29); Medicaid (N< 30 in each thiazide group)
N/A not applicable(not included in the multivariable model); HTN hypertension

of medication use, have successfully promoted more rapid adoption of guideline-recommended therapies.[34] Furthermore, clinical trials and integrated healthcare systems have achieved high BP control rates (60–80 %)[37,38] through use of stepped-care hypertension management protocols with treatment algorithms implemented by nurses or pharmacists.[39] However, while these protocols have utilized accepted therapies for stage 1 and stage 2 hypertension, guidance for resistant hypertension has been more restricted and at times not consistent with those recommended by guidelines.[40,41] Adding treatment recommendations specific to resistant hypertension in management protocols could lead to increased use of more effective medications. In fact, clinics specializing in treatment of resistant hypertension have achieved greater BP control through the use of guideline-recommended medications.[42,43]

A focus on use of combination drugs could be especially effective in improving BP control in resistant hypertension patients. In addition to their efficacy in BP lowering and improving medication adherence, fixed-dose combinations may lead to increased use of the more effective medication classes for resistant hypertension. First, more frequent use of fixed-dose combinations would likely correspond with greater thiazide use, given that they often contain a thiazide diuretic. Only 5 % of aldosterone use noted in this analysis

was as a component of the hydrochlorothiazide/spironolactone pill (see Online Appendix), a combination that may maximize BP-lowering efficacy.[32] A new fixed-dose combination that includes chlorthalidone is currently being investigated and may lead to greater use of chlorthalidone.[44]

Some limitations should be considered in interpreting these results. First, the cross-sectional nature of the data precludes us from knowing whether a medication had been discontinued in the past because of patient preference or intolerance. The degree of underutilization reported here, however, is unlikely explained primarily by patient preference or intolerance. Second, our analysis relies on routine office-based BP readings. Although there is concern in the literature regarding the reliability of office BP thresholds and white coat hypertension leading to over-diagnosis and over-treatment of hypertension, office-based BP is still the current standard used for treatment.[19,45,46] Thirdly, NAMCS does not provide information on medication adherence dosage, or indications for medication use possibly leading to some misclassification of resistant hypertension as with prior observational analyses.[2] Knowledge of patient non-adherence may impact a physician's decision in prescribing or continuing that medication, but describing patient adherence is not the primary intent in this analysis, which is focused largely on physician behavior in the management of resistant hypertension. Lastly, since NAMCS abstractors could only list up to eight medications per visit, an antihypertensive medication may have not been listed; however, patients taking eight or more medications comprised less than 7 % of our study population. Furthermore a sub-analysis excluding these patients did not significantly change our estimates of medication use.

CONCLUSION

Our study documents continued widespread underutilization of effective medications for resistant hypertension that remains unchanged 2 years after publication of AHA guidelines. Increasing the use aldosterone antagonists and fixed-dose combination medications could significantly improve BP control in resistant hypertension. Employing treatment algorithms that encourage prescription of these medications could help achieve significantly greater BP control in this high-risk population.

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REFERENCES

1. **Pimenta E, Calhoun DA.** Resistant hypertension: incidence, prevalence, and prognosis. Circulation. 2012;125(13):1594–6.
2. **Persell SD.** Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension. 2011;57(6):1076–80.
3. **Calhoun DA, Jones D, Textor S, et al.** Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510–26.
4. **Daugherty SL, Powers JD, Magid DJ, et al.** Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635–42.
5. **Nishizaka MK, Zaman MA, Calhoun DA.** Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens. 2003;16(11 Pt 1):925–30.
6. **Ouzan J, Perault C, Lincoff AM, Carre E, Mertes M.** The role of spironolactone in the treatment of patients with refractory hypertension. Am J Hypertens. 2002;15(4 Pt 1):333–9.
7. **Vaclavik J, Sedlak R, Plachy M, et al.** Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension. 2011;57(6):1069–75.
8. **Vlase HL, Panagopoulos G, Michelis MF.** Effectiveness of furosemide in uncontrolled hypertension in the elderly: role of renin profiling. Am J Hypertens. 2003;16(3):187–93.
9. **Sica DA.** Chlorthalidone: has it always been the best thiazide-type diuretic? Hypertension. 2006;47(3):321–2.
10. **Ernst ME, Carter BL, Goerdt CJ, et al.** Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension. 2006;47(3):352–8.
11. National Ambulatory Medical Care Survey. *Ambulatory Health Care Data.* Available at: http://www.cdc.gov/nchs/ahcd/about_ahcd.htm. Accessed October 08, 2013.
12. **Mancia G, Fagard R, Narkiewicz K, et al.** 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219.
13. NAMCS Survey Instruments. *Ambulatory Health Care Data.* Available at: http://www.cdc.gov/nchs/ahcd/ahcd_survey_instruments.htm#namcs. Accessed October 08, 2013.
14. NAMCS Scope and Sample Design. *Ambulatory Health Care Data* Available at: http://www.cdc.gov/nchs/ahcd/ahcd_scope.htm#namcs_scope. Accessed October 08, 2013.
15. NAMCS Data Collection and Processing. *Ambulatory Health Care Data.* Available at: http://www.cdc.gov/nchs/ahcd/ahcd_data_collection.htm#namcs_collection Accessed October 08, 2013.
16. NAMCS Estimation Procedures. *Ambulatory Health Care Data.* Available at: http://www.cdc.gov/nchs/ahcd/ahcd_estimation_procedures.htm#namcs_procedures. Accessed October 08, 2013.
17. Reliability of Estimates. *Ambulatory Health Care Data.* Available at: http://www.cdc.gov/nchs/ahcd/ahcd_estimation_reliability.htm. Accessed October 08, 2013.
18. National Drug Code Directory. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm Accessed October 08, 2013.

19. **Mancia G, Bombelli M, Seravalle G, Grassi G.** Diagnosis and management of patients with white-coat and masked hypertension. Nat Rev Cardiol. 2011;8(12):686–93.
20. **Hanselin MR, Saseen JJ, Allen RR, Marrs JC, Nair KV.** Description of antihypertensive use in patients with resistant hypertension prescribed four or more agents. Hypertension. 2011;58(6):1008–13.
21. **Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD.** Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ. 1999;160(1):41–6.
22. **Patel BV, Remigio-Baker RA, Mehta D, Thiebaud P, Frech-Tamas F, Preblick R.** Effects of initial antihypertensive drug class on patient persistence and compliance in a usual-care setting in the United States. J Clin Hypertens (Greenwich). 2007;9(9):692–700.
23. **Chobanian AV, Bakris GL, Black HR, et al.** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560–72.
24. **Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC.** Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011;124(9):1046–58.
25. **Phillips LS, Branch WT, Cook CB, et al.** Clinical inertia. Ann Intern Med. 2001;135(9):825–34.
26. **Basile J, Neutel J.** Overcoming clinical inertia to achieve blood pressure goals: the role of fixed-dose combination therapy. Ther Adv Cardiovasc Dis. 2010;4(2):119–27.
27. **Basile J, Black HR, Flack JM, Izzo JL Jr.** The role of therapeutic inertia and the use of fixed-dose combination therapy in the management of hypertension. J Clin Hypertens (Greenwich). 2007;9(8):636–45.
28. **Cushman WC, Basile J.** Achieving blood pressure goals: why aren't we? J Clin Hypertens (Greenwich). 2006;8(12):865–72.
29. **Andrade SE, Gurwitz JH, Field TS, et al.** Hypertension management: the care gap between clinical guidelines and clinical practice. Am J Manag Care. 2004;10(7 Pt 2):481–6.
30. **Ashton CM, Khan MM, Johnson ML, et al.** A quasi-experimental test of an intervention to increase the use of thiazide-based treatment regimens for people with hypertension. Implement Sci. 2007;2:5.
31. **Clark D 3rd, Ahmed MI, Calhoun DA.** Resistant hypertension and aldosterone: an update. Can J Cardiol. 2012;28(3):318–25.
32. **Epstein M, Calhoun DA.** Aldosterone blockers (mineralocorticoid receptor antagonism) and potassium-sparing diuretics. J Clin Hypertens (Greenwich). 2011;13(9):644–8.
33. **Carter BL, Ernst ME, Cohen JD.** Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension. 2004;43(1):4–9.
34. **Grimshaw J, Eccles M, Thomas R, et al.** Toward evidence-based quality improvement. Evidence (and its limitations) of the effectiveness of guideline dissemination and implementation strategies 1966–1998. J Gen Intern Med. 2006;21(Suppl 2):S14–20.
35. **Stafford RS, Radley DC.** The underutilization of cardiac medications of proven benefit, 1990 to 2002. J Am Coll Cardiol. 2003;41(1):56–61.
36. **Siegel D.** The influence of national guidelines on antihypertensive prescribing patterns. Curr Hypertens Rep. 2000;2(3):247–52.
37. **Jaffe MG, Lee GA, Young JD, Sidney S, Go AS.** Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013;310(7):699–705.
38. **Stewart S, Carrington MJ, Swemmer CH, et al.** Effect of intensive structured care on individual blood pressure targets in primary care: multicentre randomised controlled trial. BMJ. 2012;345:e7156.
39. **Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T.** Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev. 2010;3, CD005182.
40. Guidelines for the Management of Hypertension. 2005; Available at: http://www.permanente.net/healthyheart/resources/tools/KP%20CPG%20Hypertension.pdf. Accessed October 08, 2013.
41. Hypertension Clinical Practice Guidelines. *KAISER PERMANENTE NATIONAL CLINICAL PRACTICE GUIDELINES*. 2009; Available at: http://www.delfini.org/KP%20BP/2009_Hypertension_Guidelines_Public.pdf Accessed October 08, 2013.
42. **Garg JP, Elliott WJ, Folker A, Izhar M, Black HR, Service RUH.** Resistant hypertension revisited: a comparison of two university-based cohorts. Am J Hypertens. 2005;18(5 Pt 1):619–26.
43. **Yakovlevitch M, Black HR.** Resistant hypertension in a tertiary care clinic. Arch Intern Med. 1991;151(9):1786–92.
44. **Paulis L, Steckelings UM, Unger T.** Key advances in antihypertensive treatment. Nat Rev Cardiol. 2012;9(5):276–85.
45. Better technology shows that too many people are treated for high blood pressure. 2013; Available at: http://articles.washingtonpost.com/2013-06-03/national/39709940_1_have-hypertension-67-million-americans. Accessed October 08, 2013.
46. **Ruilope LM.** Current challenges in the clinical management of hypertension. Nat Rev Cardiol. 2012;9(5):267–75.