Trends in Antihypertensive Medication Monotherapy and Combination Use Among US Adults, National Health and Nutrition Examination Survey 2005–2016

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Abstract—Blood pressure (BP) control rates among US adults taking antihypertensive medication have not increased over the past decade. Many adults require 2 or more classes of antihypertensive medication to achieve guideline-recommended BP goals, but the proportion of US adults taking antihypertensive medication monotherapy, versus combination therapy, has not been quantified using contemporary data. We analyzed data from 2005 to 2008, 2009 to 2012, and 2013 to 2016 National Health and Nutrition Examination Surveys to determine trends in monotherapy and combinations of antihypertensive medication classes among US adults age ≥20 years with hypertension taking antihypertensive medication (n=7837). The proportion of US adults taking antihypertensive medication with uncontrolled BP (ie, systolic BP ≥140 or diastolic BP ≥90 mm Hg) was 32.3%, 30.2%, and 31.0% in 2005 to 2008, 2009 to 2012, and 2013 to 2016, respectively (P_{trend}=0.37). Between 2005 to 2008 and 2013 to 2016, there was no evidence of changes in the proportions of US adults taking antihypertensive monotherapy (39.5%–40.4%, P_{trend}=0.67), dual-therapy (37.9%–38.3%, P_{trend}=0.75), triple-therapy (17.6%–16.5%, P_{trend}=0.36), or quadruple-therapy (4.4%–4.3%, P_{trend}=0.93). Between 2005 to 2008 and 2013 to 2016, there was no evidence of changes in the proportions of US adults with uncontrolled BP taking antihypertensive monotherapy (39.3%–40.6%, P_{trend}=0.78). A high proportion of US adults with hypertension, including those with uncontrolled BP, are taking one antihypertensive medication class. Increasing the use of dual- and triple-therapy antihypertensive medication regimens may restore the upward trend in BP control rates among US adults. **(*Hypertension*. 2020;75:973-981. DOI: 10.1161/HYPERTENSIONAHA.119.14360.)** ● **Online Data Supplement**

Key Words: antihypertensive agents ■ blood pressure ■ cardiovascular agents ■ cardiovascular diseases ■ hypertension

Between 1988 to 1994 and 2007 to 2008, the proportion of US adults with hypertension taking antihypertensive medication that had controlled blood pressure (BP) increased from 27.3% to 50.1%.[1] However, the proportion of US adults with hypertension taking antihypertensive medication that had controlled BP has not increased over the past decade despite the increasing availability of safe, effective, and low-cost antihypertensive medications.[2,3] Combining 2 or more classes of antihypertensive medication is more efficacious to control BP than monotherapy.[4–7] The 2017 American College of Cardiology/American Heart Association BP guideline recommends initiating antihypertensive medication with dual-therapy, either with separate products or in a fixed-dose combination (FDC) product, in adults with a systolic BP (SBP)/diastolic BP (DBP) ≥140/90 mm Hg and an average BP >20/10 mm Hg above their BP goal.[8] Also, the 2018 European Society of Cardiology/European Society of Hypertension BP guideline recommends initiating dual-therapy with an FDC in all patients with hypertension except in the frail elderly and those with SBP/DBP of 140 to 160/90 to 99 mm Hg who have a low risk for cardiovascular disease (CVD).[9] The American Society of Hypertension recommended FDC antihypertensive medication for most adults initiating antihypertensive medication in 2010.[10]

Previous studies have assessed trends in the use of individual antihypertensive medication classes among US adults.[11–15] However, there are few data on the trends of antihypertensive medication regimens, including the frequency of monotherapy and combination therapy among US adults with hypertension. Determining the proportion of US adults with hypertension taking antihypertensive monotherapy could guide interventions to optimize combination medication use and restore the upward trend in BP control rates among US adults with hypertension.

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Table 1. Characteristics of NHANES Participants Taking Antihypertensive Medication Regimens in 2005–2008, 2009–2012, and 2013–2016

Characteristics	Calendar Period			
	2005–2008 (n=2157)	2009–2012 (n=2840)	2013–2016 (n=2840)	*P* Trend
Age, y				
<40	5.0 (3.7–6.8)	4.9 (4.0–6.0)	5.8 (4.6–7.3)	0.38
40–49	15.3 (13.2–17.7)	12.9 (11.0–15.1)	11.8 (10.3–13.5)	0.01
50–59	24.5 (21.8–27.4)	25.1 (22.6–27.8)	22.2 (19.6–25.0)	0.20
60–74	36.9 (33.7–40.3)	37.1 (34.9–39.3)	41.4 (38.4–44.5)	0.04
≥75	18.3 (16.2–20.6)	20.1 (18.4–21.8)	18.8 (16.5–21.4)	0.83
Female sex	55.5 (53.0–58.0)	54.9 (52.6–57.2)	54.9 (52.3–57.5)	0.67
Race/ethnicity				
Non-Hispanic white	76.6 (71.4–81.0)	72.3 (66.5–77.5)	69.9 (65.0–74.4)	0.04
Non-Hispanic black	14.0 (10.4–18.4)	14.7 (11.3–19.0)	14.3 (11.1–18.2)	0.84
Hispanic	5.6 (4.1–7.7)	8.0 (5.3–11.8)	9.2 (6.5–12.7)	0.05
Household income <$20,000	18.6 (16.3–21.1)	18.3 (15.8–21.2)	17.7 (14.8–21.0)	0.55
High school graduate	78.9 (75.7–81.8)	78.6 (75.4–81.4)	83.2 (80.4–85.6)	0.02
Health insurance				
Private	66.4 (63.7–69.0)	63.2 (60.0–66.3)	60.0 (56.9–63.0)	0.004
Government	26.9 (24.5–29.5)	29.2 (26.7–31.9)	33.5 (31.0–36.2)	0.001
None	6.7 (5.3–8.5)	7.6 (6.3–9.3)	6.5 (5.3–7.8)	0.93
Current smoker	15.8 (13.6–18.2)	13.1 (11.5–14.8)	17.8 (16.0–19.9)	0.06
Body mass index, kg/m^2				
Underweight	0.5 (0.3–0.8)	0.9 (0.5–1.7)	0.8 (0.5–1.3)	0.30
Normal weight	17.6 (15.6–19.9)	13.9 (12.1–15.9)	15.1 (13.5–16.8)	0.05
Overweight	32.4 (29.8–35.1)	32.7 (30.5–35.0)	30.6 (28.0–33.5)	0.25
Obese	49.5 (46.8–52.2)	52.5 (49.8–55.1)	53.5 (50.6–56.4)	0.02
Comorbidities				
Diabetes mellitus	21.2 (18.5–24.2)	27.7 (25.8–29.6)	29.0 (26.8–31.3)	<.001
Coronary heart disease	9.4 (8.2–10.9)	9.0 (7.8–10.3)	10.5 (9.0–12.1)	0.40
Chronic kidney disease	46.3 (42.7–49.8)	43.2 (40.2–46.2)	43.0 (40.4–45.6)	0.04
Stroke	8.2 (6.8–9.8)	7.4 (6.2–8.8)	7.6 (6.5–8.9)	0.41
Heart failure	6.6 (5.7–7.6)	6.9 (5.5–8.5)	7.1 (6.1–8.1)	0.71
Mean 10-year CVD risk, %*	7.8 (7.2–8.5)	8.8 (8.1–9.5)	9.1 (8.3–9.9)	0.09
Mean systolic blood pressure, mm Hg	131.7 (130.7–132.8)	130.8 (129.8–131.8)	131.8 (130.5–133.0)	0.91
Systolic blood pressure, mm Hg				
<130	49.7 (46.8–52.6)	52.9 (50.5–55.2)	49.1 (46.0–52.1)	0.86
130–139	20.9 (18.6–23.4)	18.9 (17.6–20.3)	21.6 (19.0–24.5)	0.60
140–159	20.9 (19.2–22.8)	21.1 (19.2–23.2)	21.8 (19.9–23.8)	0.65
≥160	8.5 (7.2–10.0)	7.1 (5.8–8.7)	7.5 (6.5–8.6)	0.20
Mean diastolic blood pressure, mm Hg	71.4 (70.5–72.2)	69.9 (68.9–70.9)	69.8 (69.0–70.6)	0.03
Diastolic blood pressure, mm Hg				
<80	73.4 (70.2–76.4)	78.7 (75.8–81.4)	79.5 (76.9–81.8)	0.005
80–89	18.7 (16.1–21.5)	14.9 (13.0–17.1)	15.0 (13.1–17.1)	0.07
90–99	6.5 (5.1–8.1)	5.2 (3.9–6.7)	4.5 (3.7–5.5)	0.03

(*Continued*)

Table 1. Continued

Characteristics	Calendar Period 2005–2008 (n=2157)	2009–2012 (n=2840)	2013–2016 (n=2840)	*P* Trend
≥100	1.5 (1.0–2.0)	1.2 (0.7–1.9)	1.0 (0.6–1.8)	0.31
Uncontrolled blood pressure				
SBP ≥140 or DBP ≥90 mm Hg	32.4 (30.4–34.5)	30.3 (28.3–32.4)	31.1 (28.6–33.7)	0.35
SBP ≥130 or DBP ≥80 mm Hg	58.6 (55.1–62.1)	54.3 (52.0–56.7)	55.6 (52.4–58.8)	0.22

Numbers in table are column percents (95% CI) or means (95% CI). CVD indicates cardiovascular disease; DBP, diastolic blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

*Cardiovascular disease risk calculated using the Pooled Cohort Risk Equation.

Therefore, we determined trends in antihypertensive monotherapy and combinations of antihypertensive medication classes being taken among US adults ≥20 years of age with hypertension between 2005 and 2016 using data from the National Health and Nutrition Examination Survey (NHANES).

Methods

Study Design and Population

Detailed methods and protocols for NHANES are provided elsewhere.[16] All data used in the current analysis are publicly available through the National Center for Health Statistics and can be accessed at https://wwwn.cdc.gov/nchs/nhanes/default.aspx. NHANES consists of a series of cross-sectional surveys conducted in 2-year cycles. Participants are selected using a multi-stage probabilistic sampling approach such that the results can be weighted to produce estimates for the non-institutionalized civilian US adult population.[17] All participants provided written informed consent, and the survey protocol for each NHANES cycle was approved by the National Center for Health Statistics ethics review board. We analyzed 6 consecutive 2-year cycles (2005–2006 through 2015–2016), and data were grouped into 3 separate, 4-year calendar periods: 2005 to 2008, 2009 to 2012, and 2013 to 2016 to provide more stable estimates.[18]

Of the 34 180 NHANES participants ≥20 years old who were interviewed and examined, we excluded 3906 participants who did not have 3 SBP and DBP measurements taken during their medical evaluation (Figure S1 in the online-only Supplement). Of the 30 274 participants with complete SBP and DBP data, we excluded another 19 576 participants who did not self-report a prior diagnosis of hypertension and 2813 participants who were not taking antihypertensive medication or were missing information about antihypertensive medication use in the NHANES BP questionnaire or during the study's pill bottle review. Finally, we excluded 48 pregnant women. The final analysis included 7837 participants with complete BP data, self-reported hypertension and who were taking at least one class of antihypertensive medication.

Data Collection

Trained interviewers administered standardized questionnaires in participants' homes. Age, sex, race-ethnicity, household income, education, health insurance, smoking status, and history of coronary heart disease, diabetes mellitus, stroke, or heart failure were self-reported. Participants were invited to attend a study visit at a mobile examination center following the interview. During this visit, BP, height, and weight were measured, and blood and urine samples were collected. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Participants were categorized as underweight, normal weight, overweight, and obese based on BMI <18.5 kg/m^2, 18.5 to <25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/m^2, respectively. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation[19] or a urinary albumin-to-creatinine ratio >30 mg/g. Estimated 10-year CVD risk was calculated among participants without a self-reported history of coronary heart disease, myocardial infarction, or stroke using the Pooled Cohort Risk Equations.[20]

BP measurements were performed by trained physicians following a standardized protocol. After resting for 5 minutes, 3 consecutive, seated readings were obtained using a mercury sphygmomanometer and appropriately sized cuff with 30-second intervals between measurements. The 3 SBP and DBP measurements were averaged.

Antihypertensive medication use was determined from participant self-report during the in-home questionnaire as an affirmative answer to the questions, "Have you ever been told by a doctor that you had hypertension, also called high BP?" and "Are you now taking prescribed medicine for high BP?"[21] The interviewer reviewed participants' pill bottles for prescription and nonprescription medications and supplements reported to have been taken in the previous 30 days.[22] For the main analysis, FDC products were classified into individual generic compounds (eg, lisinopril/hydrochlorothiazide was classified as 2 distinct compounds, lisinopril and hydrochlorothiazide). Antihypertensive medications were categorized into classes: aldosterone receptor antagonists, α-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, calcium channel blocker (CCB), centrally acting agents (eg, clonidine), direct vasodilators, diuretics, and renin inhibitors. For ease of presentation, ACEI and ARB were grouped together, and diuretics (ie, thiazide, loop, and potassium-sparing) were grouped together. In a separate analysis, FDC products were categorized by their unique antihypertensive class components (eg, ACEI or ARB and diuretic).

Statistical Analyses

Characteristics of the US adult population taking antihypertensive medication were reported for each 4-year calendar period: 2005 to 2008, 2009 to 2012, and 2013 to 2016. Trends in participant characteristics across calendar periods were assessed by linear regression for continuous variables and logistic regression for binary variables. The proportions of US adults taking each antihypertensive medication class, distinct combinations of classes, and number of classes used in a regimen (eg, monotherapy, dual-therapy) were calculated for each 4-year calendar period. Trends in the proportion of US adults taking each antihypertensive medication regimen across calendar periods were assessed by modeling each medication regimen as a dependent variable and the 4-year calendar periods as a continuous independent variable.

The distribution and combinations of the antihypertensive medication classes being taken may differ by age, sex, race-ethnicity, and for those with and without controlled BP or comorbid conditions. Therefore, we calculated the proportions of US adults taking each antihypertensive medication class and combinations of classes within subgroups defined by (1) uncontrolled BP at 2 thresholds: SBP/DBP ≥140/90 mm Hg and ≥130/80 mm Hg, separately, given the use of JNC7 for defining controlled BP during the study period and the recent lowering of BP treatment targets in the 2017 American College of Cardiology/American Heart Association BP guidelines[8]; (2) age less than or greater than/equal to 75 years; (3) sex; (4) race/ethnicity (ie, non-Hispanic white, non-Hispanic blacks, and Hispanics); and (5) presence or absence of 5 compelling indications for specific antihypertensive medication classes (ie, diabetes mellitus, coronary heart

disease, chronic kidney disease, stroke, or heart failure), separately, because the JNC7 clinical practice guidelines[23] recommended specific classes based on the presence of these comorbidities (Table S1). We also calculated the proportion of the population taking each antihypertensive medication class (ie, ACEI or ARB, diuretic, β-blocker, and CCB), independent of whether the medication was taken as monotherapy or combination therapy. Finally, the proportion of US adults taking FDC products were calculated for each 4-year calendar period.

The NHANES sampling weights and the complex sampling design were applied in all calculations to obtain US nationally representative prevalence estimates. All analyses were performed using Stata v.13.1 (StataCorp, College Station, TX).

Results

Characteristics of the Study Population

In each calendar period, the majority of US adults taking antihypertensive medication were female, non-Hispanic white, and had private health insurance (Table 1). The proportion of US adults taking antihypertensive medication who were high school graduates, obese, had government insurance, or had diabetes mellitus increased, and the proportion with private insurance decreased (P_{trend}<0.05). The proportion of US adults with uncontrolled BP as defined by SBP ≥140 mm Hg or DBP ≥90 mm Hg was 32.4%, 30.3%, and 31.1% in 2005 to 2008, 2009 to 2012, and 2013 to 2016, respectively (P_{trend}=0.35).

Antihypertensive Medication Use

There was no evidence that the proportion of US adults taking 1, 2, 3, 4, or 5 or more classes of antihypertensive medication changed from 2005 to 2008 to 2013 to 2016 (Table 2; see Tables S2 and S3 for regimens with <1% prevalence and ACEI categorized separately from ARB). ACEI or ARB monotherapy was the most common antihypertensive medication class being taken as monotherapy in each calendar period and increased from 18.9% to 24.2% between 2005 to 2008 and 2013 to 2016 (P_{trend}=0.004). Between 2005 and 2008 to 2013 and 2016, the proportion of US adults taking a β-blocker as monotherapy decreased from 9.0% to 5.9% (P_{trend}=0.003), and the proportion taking a diuretic as monotherapy decreased from 6.6% to 4.9% (P_{trend}=0.06).

Use of an ACEI or ARB with a diuretic was the most common dual-therapy combination in each calendar period. Dual therapy with a β-blocker and a diuretic decreased from 5.9% to 3.9% between 2005 to 2008 to 2013 and 2016 (P_{trend}=0.003). Dual-therapy with an ACEI or ARB and β-blocker increased from 5.0% to 7.2% between 2005 to 2008 to 2013 and 2016 (P_{trend}=0.04). The combination of an ACEI or ARB, a β-blocker, and a diuretic was the most common triple-therapy regimen in each calendar period but decreased from 7.7% to 5.8% between 2005 and 2008 and 2013 and 2016 (P_{trend}=0.03).

As a group, ACEI or ARB were the most common medication classes taken within each calendar period, followed by diuretics, β-blockers, then CCBs (Table S4). From 2005 to 2008 to 2013 to 2016, the proportion of US adults with hypertension taking antihypertensive medication who were on an ACEI or ARB, alone or as part of combination therapy, increased from 66.0% to 74.1% (P_{trend}<0.001). Diuretic use, as monotherapy or combination therapy, decreased from 48.4% to 43.3% (P_{trend}=0.015) and β-blocker use decreased from 39.4% to 35.1% (P_{trend}=0.021) over this time period.

Antihypertensive Medication Use Among US Adults With Uncontrolled BP

There was no evidence that the number of antihypertensive medication classes being taken changed between 2005 and 2008 and 2013 and 2016 among US adults taking antihypertensive medication with uncontrolled BP defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg (Table 3) or SBP ≥130 mm Hg or DBP ≥80 mm Hg (Table 4). Among those with SBP ≥140 mm Hg or DBP ≥90 mm Hg, 40.2% and 35.1% were taking 1 and 2 classes of antihypertensive medication, respectively, in 2013 to 2016.

Age, Race, and Ethnicity Subgroups

There was no evidence that, among US adults taking antihypertensive medication, the number of antihypertensive medication classes being taken changed between 2005 and 2008 and 2013 and 2016 for any age, sex, or race-ethnicity subgroup investigated (Tables S5 through S11), except for non-Hispanic blacks, in whom monotherapy with an ACEI or ARB increased and dual-therapy with a β-blocker and a CCB increased (Table S10, each P_{trend}<0.05). Among Hispanics, the use of 5 or more antihypertensive medication classes decreased (Table S11, P_{trend}=0.03).

US Adults With and Without Compelling Indications

Among US adults without compelling indications, there were no trends in the number of antihypertensive medication classes being taken between 2005 and 2008 and 2013 and 2016 (Table S12). Between 2005 and 2008 and 2013 and 2016, ACEI or ARB monotherapy increased from 22.4% to 30.0% (P_{trend}=0.006) and β-blocker monotherapy decreased from 12.1% to 6.4% (P_{trend}=0.003).

There was no evidence that the number of antihypertensive medication classes being taken changed between 2005 and 2008 and 2013 and 2016 for US adults with compelling indications (ie, diabetes mellitus, coronary heart disease, chronic kidney disease, stroke history, or heart failure history; Tables S13 through S17), except there was a decrease in US adults with diabetes mellitus taking 5 or more antihypertensive classes from 1.3% to 0.4% (Table S13, P_{trend}=0.03).

FDC Use

There was no evidence that the proportion of US adults taking FDC antihypertensive products changed from 2005 to 2008 to 2013 to 2016 (Tables S18 and S19).

Discussion

In the current study, a high proportion of US adults with hypertension taking antihypertensive medication had uncontrolled BP, which was unchanged between 2005 and 2008 and 2013 and 2016. Over the same time period, the proportion of US adults with hypertension taking antihypertensive medication who were taking one antihypertensive medication class was unchanged. Also, a high proportion of US adults with uncontrolled BP were taking only one class of antihypertensive medication. Although national efforts to increase the proportion of

Table 2. Proportion of US Adults Taking Antihypertensive Medication Regimens in 2005–2008, 2009–2012, and 2013–2016

Number and Specific Antihypertensive Combinations	Calendar Year			
	2005–2008 (n=2157)	2009–2012 (n=2840)	2013–2016 (n=2840)	*P* Trend
One medication class	39.5 (36.4–42.7)	40.4 (37.7–43.1)	40.1 (37.6–42.7)	0.78
ACEI or ARB	18.9 (16.4–21.8)	21.0 (18.8–23.3)	24.2 (21.7–26.9)	0.004
BB	9.0 (7.3–11.1)	8.2 (6.8–9.7)	5.9 (4.9–7.1)	0.003
Diuretic	6.6 (5.3–8.1)	5.8 (4.4–7.6)	4.9 (4.0–6.0)	0.06
CCB	4.3 (3.1–5.9)	4.6 (3.5–6.2)	4.4 (3.4–5.7)	0.93
Two medication classes, any combination	37.9 (35.5–40.4)	36.8 (34.7–39.1)	38.4 (35.8–41.1)	0.70
ACEI or ARB+diuretic	14.3 (12.3–16.5)	14.2 (12.4–16.3)	15.9 (13.3–18.9)	0.30
ACEI or ARB+BB	6.2 (4.8–8.1)	5.5 (4.6–6.6)	6.5 (5.3–8.0)	0.72
ACEI or ARB+CCB	5.0 (4.0–6.3)	6.0 (5.0–7.3)	7.2 (5.7–9.0)	0.04
BB+diuretic	5.9 (4.9–7.1)	5.8 (4.6–7.1)	3.9 (3.0–4.9)	0.003
CCB+diuretic	2.0 (1.4–2.8)	1.9 (1.3–2.8)	1.7 (1.2–2.5)	0.55
BB+CCB	2.1 (1.5–3.1)	1.4 (0.9–2.1)	2.2 (1.5–3.0)	0.87
Three medication classes, any combination	17.6 (15.7–19.8)	17.9 (16.1–19.9)	16.6 (14.9–18.5)	0.43
ACEI or ARB+BB+diuretic	7.7 (6.2–9.5)	7.9 (6.7–9.4)	5.8 (4.8–7.1)	0.03
ACEI or ARB+CCB+diuretic	4.8 (3.8–6.0)	3.9 (2.9–5.2)	4.3 (3.5–5.4)	0.57
ACEI or ARB+BB+CCB	2.5 (1.8–3.5)	2.9 (2.0–4.2)	3.8 (2.9–5.0)	0.07
BB+CCB+diuretic	1.4 (1.0–2.0)	1.3 (0.9–1.9)	1.0 (0.7–1.4)	0.19
Four medication classes, any combination	4.4 (3.4–5.6)	4.4 (3.3–5.7)	4.3 (3.4–5.5)	0.93
ACEI or ARB+BB+CCB+diuretic	3.1 (2.3–4.1)	3.0 (2.1–4.1)	2.9 (2.1–4.0)	0.72
Five or more medication classes, any combination	0.6 (0.3–1.2)	0.5 (0.2–1.0)	0.5 (0.2–1.1)	0.69

Numbers in table are column percentage (95% CI). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, β-blocker; and CCB, calcium channel blocker.

US adults diagnosed hypertension who take antihypertensive medication likely contributed to the dramatic improvements in BP control observed between 1988 and 2008,[1] achieving population-wide BP control in the future will be difficult if the high prevalence of monotherapy persists.

A substantial proportion of US adults taking antihypertensive medication, including those with uncontrolled BP, were taking antihypertensive monotherapy, which has repeatedly been shown to have less BP-lowering efficacy compared to dual- and triple-therapy regimens.[4,24] It is well-established that achieving and maintaining intensive BP control often requires combining 2 or more antihypertensive medication classes.[4–6] Based on the cross-sectional design of the current analysis, we could not determine if the high prevalence of monotherapy was due to patient or prescriber factors. The persistently high proportion of US adults with uncontrolled BP who are only taking one antihypertensive medication class represents a missed opportunity to lower BP and CVD risk. In conjunction with previous evidence,[4–6] the current analysis suggests that to restore an upward trend in BP control rates, initiatives should focus on increasing the use of dual- and triple-therapy regimens.

Patient preferences, cost, and pill-taking disutility may be barriers to combination medication use.[25] The patient's perception of medication burden, in which the patient does not want to take more medications, should be distinguished clinically from pill burden, in which the patient does not want to take more pills. FDC products represent an attractive option to reduce pill burden, increase patient acceptance, achieve BP goals, improve adherence, and prevent CVD events with a more favorable adverse event profile than individually formulated products at standard doses.[24,26–28] The World Health Organization recently added FDC antihypertensive medications to their Essential Medicines List, further underscoring the international and national support for combination antihypertensive therapy.[29] Beyond initial management with lifestyle modifications, a paradigm shift may be needed in how medical educators promote initial pharmacological hypertension management from a monotherapy-dependent strategy (ie, starting with one medication and increasing the dose as tolerated before adding another medication) to a lower-dose combination-dependent strategy (ie, starting with low doses of multiple medications and increasing the dose of the total combination in a stepwise fashion as needed). Guideline recommendations may further influence the use of FDCs when initiating or intensifying antihypertensive treatment.

The current analysis revealed several trends in antihypertensive medication use that may reflect changes in practice

Table 3. Proportion of US Adults With Uncontrolled Blood Pressure (SBP ≥140 mm Hg or DBP ≥90 mm Hg) Taking Antihypertensive Medication Regimens in 2005–2008, 2009–2012, and 2013–2016

Number and Specific Antihypertensive Combinations	Calendar Year			
	2005–2008 (n=759)	2009–2012 (n=964)	2013–2016 (n=976)	*P* Trend
One medication class	39.3 (34.0–45.0)	42.6 (37.7–47.7)	40.2 (36.3–44.2)	0.87
ACEI or ARB	18.2 (14.3–22.8)	19.7 (15.7–24.4)	20.9 (17.9–24.2)	0.28
BB	8.0 (6.1–10.4)	10.7 (8.0–14.2)	7.1 (5.4–9.2)	0.38
Diuretic	6.5 (4.5–9.4)	4.7 (2.9–7.6)	4.9 (3.4–7.0)	0.35
CCB	5.2 (3.2–8.3)	6.1 (4.4–8.4)	6.2 (4.6–8.2)	0.52
Two medication classes, any combination	34.4 (30.8–38.3)	32.2 (28.6–36.1)	35.1 (32.3–38.0)	0.69
ACEI or ARB+diuretic	9.9 (7.7–12.6)	8.8 (6.8–11.2)	12.8 (10.0–16.3)	0.11
ACEI or ARB+BB	6.3 (4.3–9.1)	5.9 (4.2–8.2)	5.9 (4.0–8.7)	0.87
ACEI or ARB+CCB	5.6 (3.5–8.8)	5.8 (4.4–7.6)	6.9 (5.0–9.6)	0.48
BB+diuretic	6.3 (4.3–9.2)	6.0 (4.1–8.7)	3.8 (2.4,6.0)	0.07
CCB+diuretic	2.1 (1.2–3.5)	1.6 (0.9–2.8)	2.0 (1.3–3.2)	1.00
BB+CCB	1.9 (1.1–3.3)	1.2 (0.6–2.3)	2.8 (1.7–4.5)	0.26
Three medication classes, any combination	20.0 (16.3–24.4)	19.7 (16.3–23.5)	19.4 (16.0–23.2)	0.80
ACEI or ARB+BB+diuretic	7.9 (5.9–10.4)	9.0 (6.5–12.2)	5.6 (4.1–7.5)	0.05
ACEI or ARB+CCB+diuretic	5.4 (3.6–8.0)	2.6 (1.8–3.8)	5.1 (3.0–8.5)	0.97
ACEI or ARB+BB+CCB	3.0 (1.9–4.9)	4.4 (2.8–6.8)	5.3 (3.7–7.4)	0.09
BB+CCB+diuretic	1.4 (0.7–2.7)	1.0 (0.5–2.1)	0.8 (0.4–1.5)	0.18
Four medication classes, any combination	4.9 (3.3–7.1)	4.5 (2.8–7.0)	5.1 (3.5–7.4)	0.84
ACEI or ARB+BB+CCB+diuretic	3.1 (0.1–1.2)	3.3 (0.0–0.5)	3.2 (0.0–0.6)	1.00
Five or more medication classes, any combination	1.4 (0.7–2.7)	1.1 (0.5–2.5)	0.3 (0.1–1.3)	0.04

Numbers in table are column percentage (95% CI). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

patterns after publication of landmark trials and clinical practice guideline recommendations. For example, the current analysis observed a 53% decrease in the proportion of US adults with hypertension but without compelling indications taking β-blocker monotherapy from 12.1% in 2005 to 2008 to 6.4% in 2013 to 2016. This may reflect the results of several trials which suggested superior BP reduction and CVD risk reduction with an ACEI and CCB combination compared with a β-blocker and diuretic combination.[30–32] Consequently, the Eighth Panel Report of the Joint National Committee recommended that β-blockers not be used as initial therapy for essential hypertension,[33] which may have influenced the decrease in β-blocker mono- and combination therapy observed during the study period. Additionally, a high proportion of US adults taking antihypertensive medication were taking medication classes that were preferred in a 2011 American Society of Hypertension position article (ie, an ACEI or ARB plus either a CCB or a diuretic).[10] Efforts should be made to reduce the proportion of adults taking less effective, harmful, or nonpreferential regimens, such as β-blocker use in patients without compelling indications (20% prevalence overall in most recent year of analysis).

In the current analysis, the most common dual-therapy was an ACEI or ARB combined with a diuretic. In 2009, The ACCOMPLISH trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) showed that dual-therapy with an ACEI and a CCB had superior CVD risk reduction compared with dual-therapy with an ACEI and a diuretic despite similar achieved SBP between the groups.[34] These results should be interpreted within the context that the daily dose of hydrochlorothiazide studied may have been suboptimal at 12.5 mg. Over the past decade, more combination products have become available that contain an ACEI or ARB and a thiazide diuretic than products containing an ACEI or ARB and a CCB (16 products versus 6 products, respectively).[35] Additionally, most ACEI/thiazide combination products became generically available by 2005.[36] In contrast, the first ACEI/CCB combination product did not become generically available until 2010. The higher prevalence of dual-therapy with an ACEI or ARB and a diuretic instead of an ACEI or ARB and a CCB in the current analysis may represent the overall availability and generic cost of available combination products rather than implementation of evidence-based recommendations. These data highlight that prescribers choose to use specific combinations of antihypertensive medication classes commensurate with

Table 4. Proportion of US Adults With Uncontrolled Blood Pressure Defined as SBP ≥130 mm Hg or DBP ≥80 mm Hg Taking Antihypertensive Medication Regimens in 2005–2008, 2009–2012, and 2013–2016

Number and Specific Antihypertensive Combinations	Calendar Year			
	2005–2008 (n=1284)	2009–2012 (n=1658)	2013–2016 (n=1669)	*P* Trend
One drug class, any combination	40.6 (37.1–44.1)	44.1 (41.0–47.2)	41.6 (38.5–44.7)	0.77
ACEI or ARB	19.3 (16.4–22.7)	21.0 (18.2–24.1)	23.3 (20.6–26.2)	0.04
BB	8.6 (6.7–11.0)	11.0 (8.9–13.7)	6.2 (4.9–7.9)	0.03
Diuretic	6.6 (5.1–8.4)	5.4 (4.0–7.4)	5.7 (4.5–7.3)	0.55
CCB	4.9 (3.2–7.4)	5.6 (4.1–7.6)	5.5 (4.3–7.1)	0.60
Two drug classes, any combination	35.6 (32.8–38.6)	33.4 (30.2–36.6)	36.0 (33.2–39.0)	0.76
ACEI or ARB+diuretic	13.4 (11.6–15.4)	10.5 (8.9–12.4)	14.0 (11.8–16.6)	0.50
ACEI or ARB+CCB	5.9 (4.3–7.9)	5.7 (4.6–7.1)	6.5 (4.8–8.7)	0.62
ACEI or ARB+BB	4.1 (2.8–5.9)	5.9 (4.5–7.7)	6.7 (5.4–8.4)	0.03
BB+diuretic	5.7 (4.2–7.6)	5.6 (4.3–7.3)	3.6 (2.5–5.1)	0.03
CCB+diuretic	2.5 (1.6–3.8)	2.2 (1.3–3.6)	2.2 (1.6–3.1)	0.67
BB+CCB	1.8 (1.1–2.8)	1.4 (0.9–2.2)	2.1 (1.4–3.1)	0.61
Three drug classes, any combination	18.1 (15.6–21.0)	17.5 (14.8–20.6)	17.1 (14.9–19.5)	0.56
ACEI or ARB+BB+diuretic	7.2 (5.8–8.9)	7.5 (5.9–9.5)	4.7 (3.7–5.9)	0.01
ACEI or ARB+CCB+diuretic	5.3 (3.8–7.4)	3.5 (2.6–4.5)	4.7 (3.3–6.6)	0.67
ACEI or ARB+BB+CCB	2.5 (1.6–3.8)	3.2 (2.2–4.7)	4.5 (3.2–6.3)	0.05
BB+CCB+diuretic	1.7 (1.1–2.6)	1.2 (0.6–2.1)	0.9 (0.6–1.4)	0.05
Four drug classes, any combination	4.9 (3.6–6.5)	4.3 (3.0–6.2)	4.8 (3.5–6.5)	1.00
ACEI or ARB+BB+CCB+diuretic	3.3 (2.4–4.5)	2.9 (1.8–4.5)	3.3 (2.3–4.6)	0.89
Five or more drug classes, any combination	0.8 (0.4–1.6)	0.7 (0.3–1.6)	0.5 (0.2–1.4)	0.47

Numbers in table are column percentage (95% CI). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

evidence and practical considerations (eg, availability and cost of combination products). Providers must balance the demonstrated safety and efficacy of combination use within the context of patient-specific drivers of benefit and risk of harm with combinations.[37]

The current study has several strengths. The sampling design used by NHANES allows for prevalence estimates representative of the US population. NHANES collected detailed medication data to allow in-depth analyses of antihypertensive medication monotherapy and combination use. One limitation of the current study is that medication doses are not available in NHANES, which could distinguish the intensity of regimens. Although combining 2-year study periods led to more stable estimates with small sample sizes, this may have led to dilution of any effects. Finally, although validated with pill bottle review, medication use was based on self-report and may not reflect actual use.

Perspectives

In conclusion, between 2005 and 2008 and 2013 and 2016, a high proportion of US adults with hypertension were taking only one class of antihypertensive medication, even among those with uncontrolled BP. Use of ACEI or ARB monotherapy increased while the use of β-blocker monotherapy decreased. The current analysis suggests that a high proportion of uncontrolled BP among US adults with hypertension taking antihypertensive medication may be the result of an inadequate antihypertensive medication regimen. Therefore, initiatives to increase the use of dual- and triple-therapy antihypertensive medication regimens may present an opportunity to restore the upward trend in BP control rates in US adults.

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Novelty and Significance

What Is New?

- In a nationally representative survey from 2005 to 2016, a large proportion of adults with hypertension taking antihypertensive medication were using one antihypertensive medication class.
- Monotherapy and combinations with angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker were most prevalent; monotherapy and combinations with β-blockers decreased.

What Is Relevant?

- Over the past 2 decades, new evidence has significantly impacted the guideline-directed management of adults with hypertension.
- Uncontrolled blood pressure rates may be due to inadequate prevalence of combination therapy.
- Characterizing trends in antihypertensive medication use may be 1 way to examine how evidence-based literature and guidelines are being implemented in clinical practice, informing targeted public health initiative to improve blood pressure control and patient outcomes.

Summary

With the more intensive SBP goals recommended in current guidelines, more research is needed to investigate (1) use of effective medication combinations to control hypertension in real-world settings; (2) barriers to use of more antihypertensive medications for blood pressure control (eg, clinical inertia); and (3) patient preferences for antihypertensive regimens.