

## RESEARCH LETTER

## Anti-Hypertensive Medication Combinations in the United States

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**Background:** Examining the anti-hypertensive regimens of individuals with different comorbidities may offer insights into how we can improve hypertension management.

**Methods:** The Medical Expenditure Panel Survey (2013–2015) was used to describe the most common single-, two-, three-, and four-drug hypertension regimens among hypertensive adults in four different comorbidity groups: 1. Hypertension only; 2. Hypertension and diabetes; 3. Hypertension and cardiovascular disease (coronary heart disease or stroke history); and 4. Hypertension, diabetes, and cardiovascular disease.

**Results:** 15,901 adults with hypertension taking anti-hypertensive medications were included in the study. 58.6% (95% CI: 57.3–59.8) took multiple anti-hypertensive medications, but the proportion of adults taking multiple anti-hypertensives varied by comorbidity group. Regimens including an ACE-inhibitor/ARB were the most prevalent regimens among individuals taking  $\geq 2$  anti-hypertensive medications. The most common two-drug regimen for both the hypertension-only and hypertension-diabetes groups was an ACE-inhibitor/ARB with thiazide. The most prevalent regimen for the two cardiovascular disease groups was an ACE-inhibitor/ARB with beta-blocker.

**Conclusions:** Most individuals with hypertension use between 2–5 medications and the medications comprising these regimens vary by comorbidity. The ACCOMPLISH trial suggested that certain combinations may lead to superior cardiovascular outcomes. Research comparing the efficacy of different hypertension medication combinations among individuals with different comorbidities could lead to better patient hypertension-related outcomes. (J Am Board Fam Med 2020;33:143–146.)

**Keywords:** Angiotensin-Converting Enzyme Inhibitors, Antihypertensive Agents, Chronic Disease, Comorbidity, Coronary Artery Disease, Disease Management, Guideline Adherence, Hypertension, Outcomes Assessment, Surveys and Questionnaires, Thiazides

Most adults taking antihypertensives in the United States take multiple agents.<sup>1</sup> In addition,

the Eighth Joint National Committee recommends providers initiate 2-drug regimens for patients newly diagnosed with stage 2 hypertension.<sup>2</sup> Studies of hypertension drug regimens in the United States have investigated 2-drug regimens for adults<sup>1</sup> and Medicare recipients<sup>4</sup> but haven't compared multi-drug regimens for individuals with different comorbidities. Analyzing

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MEJ had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Table 1. Proportion of Adult 2013 to 2017 Medical Expenditure Panel Survey Respondents Taking Each Medication Regimen by Comorbidity Group**

	HTN Only	HTN-DM	HTN-CVD	HTN-DM-CVD
Number of individuals	8016	3480	2533	1872
Proportion of sample	52.8 (51.5, 54.2)	19.0 (18.0, 20.1)	17.2 (16.1, 18.3)	10.9 (10.2, 11.7)
Number of HTN medications				
1	48.9 (47.0, 50.8)	37.8 (34.9, 40.7)	33.9 (31.3, 36.6)	23.7 (20.8, 26.8)
2	35.7 (33.9, 37.5)	33.9 (31.3, 36.5)	37.2 (34.4, 40.1)	37.2 (33.8, 40.7)
3	12.7 (11.7, 13.8)	20.8 (18.5, 23.3)	20.1 (17.7, 22.6)	26.2 (23.1, 29.5)
4	2.3 (1.9, 2.8)	6.2 (5.0, 7.7)	7.3 (5.9, 9.1)	10.3 (8.5, 12.6)
≥5	0.4 (0.2, 0.6)	1.4 (0.9, 2.1)	1.5 (1.0, 2.4)	2.6 (1.9, 3.7)
1 Medication				
ACE/ARB	25.2 (23.8, 26.8)	28.3 (25.6, 31.1)	12.6 (10.8, 14.6)	13.2 (10.8, 16.0)
Thiazide	6.2 (5.4, 7.1)	2.4 (1.8, 3.4)	2.4 (1.6, 3.6)	0.9 (0.4, 2.0)
Beta-blocker	9.2 (8.2, 10.3)	3.0 (2.3, 4.0)	13.1 (11.2, 15.2)	5.2 (4.1, 6.5)
CCB	7.0 (6.3, 7.8)	3.2 (2.4, 4.3)	4.7 (3.7, 5.9)	2.6 (1.7, 4.1)
Clonidine/hydralazine/loop/spironolactone	1.3 (1.0 to 1.7)	0.9 (0.5, 1.5)	1.1 (0.7, 1.7)	1.8 (1.2, 2.9)
2 Medications				
ACE/ARB & CCB	6.0 (5.2, 6.9)	6.6 (5.4, 8.0)	4.8 (3.6, 6.3)	3.9 (2.8, 5.3)
ACE/ARB & Beta-Blocker	4.5 (3.9, 5.2)	6.6 (5.3, 8.2)	12.4 (10.6, 14.5)	15.9 (13.5, 18.8)
ACE/ARB & Thiazide	15.5 (14.0, 17.1)	12.9 (11.1, 14.9)	5.7 (4.3, 7.4)	6.3 (4.5, 8.5)
ACE/ARB & Clonidine/Hydralazine/Loop/ Spironolactone	0.8 (0.6, 1.2)	2.3 (1.5, 3.5)	1.7 (1.1, 2.7)	2.7 (1.8, 3.9)
CCB & Thiazide	1.6 (1.2, 2.0)	0.7 (0.4, 1.2)	1.0 (0.5, 1.7)	0.3 (0.1, 0.7)
CCB & beta-blocker	1.8 (1.4, 2.3)	1.0 (0.7, 1.5)	4.0 (3.0, 5.3)	2.1 (1.3, 3.1)
CCB & Clonidine/hydralazine/loop/ spironolactone	0.4 (0.3, 0.7)	0.4 (0.2, 0.7)	0.7 (0.4, 1.3)	1.3 (0.7, 2.5)
Thiazide & Beta-blocker	4.4 (3.6, 5.2)	2.3 (1.7, 3.1)	3.5 (2.6, 4.6)	1.7 (1.0, 2.8)
Thiazide & clonidine/hydralazine/loop/ spironolactone	0.2 (0.1, 0.4)	0.1 (0.0, 0.3)	0.3 (0.2, 0.7)	0.1 (0.0, 0.5)
Beta-blocker & clonidine/hydralazine/loop/ spironolactone	0.6 (0.4, 0.9)	0.8 (0.5, 1.4)	3.1 (2.2, 4.2)	2.8 (1.9, 4.2)
Clonidine/hydralazine/loop/spironolactone combination	0.0 (0.0, 0.1)	0.1 (0.0, 0.6)	0.0 (0.0, 0.2)	0.1 (0.0, 0.3)
3 Medications				
ACE/ARB & CCB & beta-blocker	1.8 (1.4, 2.3)	2.8 (2.1, 3.9)	3.9 (3.0, 5.2)	5.5 (4.1, 7.4)
ACE/ARB & CCB & thiazide	4.2 (3.6, 5.0)	6.7 (5.3, 8.5)	2.0 (1.3, 3.0)	3.1 (2.1, 4.4)
ACE/ARB & beta-blocker & thiazide	3.6 (3.0, 4.2)	6.0 (4.6, 7.6)	6.4 (5.1, 8.0)	7.3 (5.7, 9.3)
ACE/ARB & clonidine/hydralazine/diuretic/spiro & 1 other	1.6 (1.3, 2.0)	3.3 (2.6, 4.3)	4.9 (3.9, 6.3)	7.6 (5.9, 9.6)
CCB & beta-blocker & thiazide	0.8 (0.6, 1.2)	0.9 (0.4, 2.0)	1.0 (0.6, 1.8)	0.6 (0.3, 1.1)
Remaining 3 medication combinations without ACE/ARB	0.6 (0.4, 0.9)	0.9 (0.5, 1.7)	1.7 (1.1, 2.7)	2.2 (1.4, 3.4)
4 or More Medications				
ACE/ARB included combinations	2.5 (2.1, 3.1)	7.1 (5.7, 8.8)	8.1 (6.6, 9.9)	11.9 (9.8, 14.34)
4 or more medication classes without ACE/ ARB	0.2 (0.1, 0.3)	0.5 (0.3, 0.9)	0.8 (0.4, 1.4)	1.1 (0.5, 2.2)

ACE, angiotensin converting-enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension.

There were 15,901 hypertensive adults without heart failure taking hypertension medication in the Medical Expenditure Panel Survey from 2013 through 2015. We divided our sample into four different comorbidity groups based on hypertension, diabetes, and cardiovascular disease (coronary heart disease or stroke) diagnoses. We then calculated the proportion of adults taking different single-drug and multi-drug hypertension medications regimens in each comorbidity group. Numbers in parentheses represent upper and lower limits of 95% CIs.

multi-drug regimens for individuals by comorbidity is worthwhile because certain drugs and drug combinations may offer differential benefits by comorbidity.

## Methods

Using data from the 2013 through 2015 Medical Expenditure Panel Survey (MEPS), we describe the most common single-, 2-, 3-, and 4-drug hypertension regimens among hypertensive adults with 1) hypertension only (HTN-only); 2) hypertension and diabetes (HTN-DM); 3) hypertension and cardiovascular disease (ie, coronary heart disease or history of stroke) (HTN-CVD); and 4) hypertension, diabetes, and CVD (HTN-DM-CVD) (Table 1).

MEPS is a nationally representative survey of the noninstitutionalized US civilian population. Every year, MEPS collects sociodemographic, self-reported medical conditions, and medication information from 2 overlapping panels of respondents, following each panel for 2 years. Self-reported chronic prescriptions from MEPS have been validated using claims data.<sup>3</sup>

Our sample included hypertensive adults without heart failure who took any antihypertensives during the year. We categorized antihypertension medications into 5 classes: 1) angiotensin converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB); 2) thiazide diuretics; 3) calcium-channel blockers (CCB); 4)  $\beta$ -blockers; and 5) other agents (loop diuretics, spironolactone, clonidine, hydralazine). Individuals with  $\geq 3$  prescriptions or  $\geq 90$  tablets/capsules during each year were considered medication users.

We used STATA (version 13, StataCorp LLC, College Station, TX) and applied complex survey weights to all analyses. The OhioHealth Institutional Review Board ruled this study exempt.

## Results

Of the 76,792 adults included in the survey, 15,901 adults, or a survey adjusted 22.6% (95% CI, 21.9 to 23.3), had hypertension and took antihypertensive(s). Seventy percent (95% CI, 68.4 to 70.9) took an ACEI/ARB, 39.2% (95% CI, 37.9 to 40.5) took a  $\beta$ -blocker, 36.1% (95% CI, 34.7 to 37.5) took a thiazide, and 28.7% (95% CI, 27.6 to 29.9) took a CCB. Most (58.6% [95% CI, 57.3 to 59.8]) of our

sample took multiple antihypertensives, but this varied by comorbidity group. The HTN-only group had the smallest proportion taking multiple antihypertensives; followed by the HTN-DM, HTN-CVD, and HTN-DM-CVD groups. Regimens including an ACEI/ARB were the most prevalent regimens among individuals taking  $\geq 2$  antihypertensives. The most common 2-drug regimen for both the HTN-only and HTN-DM groups was an ACEI/ARB with thiazide. The most prevalent regimen for the 2 CVD (HTN-CVD and HTN-DM-CVD) groups was an ACEI/ARB with  $\beta$ -blocker. Among individuals with CVD, 61.2% (95% CI, 58.7 to 63.4) took a  $\beta$ -blocker.

## Discussion

Most individuals in our sample took multi-drug regimens, a finding compatible with previous studies.<sup>1,4</sup> Notably, the ACEI/ARB-CCB combination was used less often than the ACEI/ARB-thiazide combination. One large randomized control trial applicable to the United States population, ACCOMPLISH, tested these combinations among individuals at high-risk of cardiovascular events and showed an ACEI-CCB may prevent more cardiovascular events than ACE-thiazide. However, ACCOMPLISH was stopped early for benefit and has not been replicated or adopted into guidelines.

Our study has several limitations. Self-reported medical conditions may not accurately represent important conditions used to select antihypertensives (eg, chronic renal failure). The lack of exact medication-usage dates may overestimate the number of medications taken at 1 time.

Most individuals with hypertension use between 2 and 5 medications, which vary by comorbidity, but nearly all randomized clinical trials examine outcomes for single agents. A better understanding of the outcomes associated with different antihypertensive combinations among individuals with different comorbidities could improve hypertension management.

*To see this article online, please go to: <http://jabfm.org/content/33/1/143.full>.*

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