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Restoring the upward trend in blood pressure control rates in the United States: a focus on fixed-dose combinations

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Barriers to optimal blood pressure (BP) control in the United States (US)

Between 1988 and 2008, BP control rates (defined as systolic/diastolic BP <140/90 mm Hg) steadily increased from 47% to 69% among US adults with hypertension taking antihypertensive medication.^{1,2} However, this upward trend has since stagnated at around 70%.^{3,4} The reasons for this plateau are complex, multifactorial, and likely interrelated. For example, therapeutic inertia, rising obesity rates, high healthcare costs, inequities in access to healthcare, poor dietary choices, and declining rates of physical activity likely all contribute. Despite these pressures, several integrated healthcare systems have successfully increased their BP control rates to >80% with multimodal interventions including patient registries, simplified treatment algorithms, and team-based care.^{5,6} One part of the success of these programs may be the increased use of fixed-dose combination (FDC) antihypertensive medication products, which reduce daily pill burden and improve adherence.⁷ Herein, we review the current landscape and potential for FDCs in the management of hypertension in the US.

Underutilization of combination antihypertensive therapy

Most patients require two or more antihypertensive medication classes to achieve adequate BP control. Monotherapy may only be successful in 10–33% of patients, perhaps even less with the more intensive BP goals recommended by the 2017 American College of Cardiology/American Heart Association guidelines.⁸ Accordingly, data from the Systolic Blood Pressure Intervention Trial (SPRINT) suggest that nearly all patients (87%) require at least two antihypertensive classes to achieve more intensive systolic BP goals (systolic BP <120 mm Hg).⁹ This is consistent with data from a meta-analysis of randomized trials

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showing the superior BP-lowering effect of combination therapy over monotherapy, with an equivalent safety profile.¹⁰

Both the US and European BP guidelines currently recommend initial combination antihypertensive therapy for most patients with systolic/diastolic BP $\geq 140/90$ mm Hg, either as an FDC regimen or free-equivalent products.^{11,12} However, monotherapy has long occupied a precedent in hypertension management. Historically, US guidelines recommended (and clinicians practiced) a stepped-care approach to initial therapy for most patients.¹¹ The stepped-care approach involves initiation of a single agent, with up-titration of the dose or conversion to a different monotherapy prior to the addition of another antihypertensive class. Consistent with this practice, recent data from the National Health and Nutrition Examination Surveys (NHANES) show that 40% of US adults with uncontrolled BP ($\geq 140/90$ mm Hg) take only one antihypertensive medication class.³ The findings suggests that a suboptimal antihypertensive medication regimen may contribute, in large part, to uncontrolled BP rates.

Underutilization of FDC antihypertensive therapy

FDC antihypertensive products represent one strategy to increase the use of combination therapy. Kaiser Permanente Northern California increased use of the FDC lisinopril/hydrochlorothiazide (HCTZ) from $<1\%$ to $>27\%$ as part of a multi-modal intervention that increased BP control rates from 44% to $>80\%$.⁵ However, FDC antihypertensive products are perhaps not commonly used outside of integrated health systems. In NHANES 2005–2016, only 23% of US adults taking antihypertensive medication were using at least one FDC product.³ National prescription sales data also show low and declining FDC use from 17% to 14% between 2009 and 2014.¹³ Only 16% of commercial claims for initial hypertension management between 2009 and 2013 were for FDC products.¹⁴ A shift in the hypertension treatment paradigm is needed to promote earlier use of combination therapy and FDCs in the treatment sequence for most patients.

Barriers to broader use of FDC antihypertensive therapy

One potential barrier to FDC use is insufficient availability of FDC products that contain the number of medication classes often needed to successfully meet BP goals. At the time of this editorial, there are 33 Food and Drug Administration-approved FDC products for hypertension available in the US (Table 1). The majority contain two medication classes in one pill (31/33, 94%). Only two products contain three medication classes in one pill, both of which are composed of an angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and HCTZ. No products are commercially available that contain four medications in one pill. The lack of a four-medication FDC product may represent an important unmet need, as there is a growing body of evidence showing that low-dose triple and quadruple antihypertensive medication therapy provides superior or equivalent BP lowering with a reduced risk of adverse effects compared with fewer medications at standard doses.^{15–18} To achieve an intensive systolic BP goal of <120 mm Hg, data from SPRINT indicate that 32% and 24% of patients will need at least three and four antihypertensive medication classes, respectively.⁹

Another barrier to FDC use is the limited selection of specific medications available within each medication class and the doses available. Notably, of 26 FDCs containing a thiazide diuretic, 23 (88%) contain HCTZ, two contain chlorthalidone, and one contains bendroflumethiazide. Also, there are no thiazide diuretic/CCB dual-therapy FDCs. Such a product would be a significant addition for treating women who are or wish to become pregnant,¹⁹ and/or to provide evidence-based combination therapy for African Americans, who generally respond better to CCBs and thiazides compared to ACEIs, ARBs, and beta-blockers.^{20,21} Only one dual-therapy FDC product contains spironolactone, an important medication for the management of resistant hypertension. Lisinopril 40mg, a commonly used dose in practice, is not available in any FDC product. Additionally, HCTZ doses <25mg are ubiquitous in FDC products, which are not sufficiently potent to elicit a substantial BP-lowering effect.

Generic availability, cost, and insurance coverage of FDC products are also important considerations for clinicians. At the time of this editorial, the majority (29/33, 88%) of FDC products are generically available, but there is a wide variation in average monthly cost to patients and insurers between and within class combinations. Only four FDCs are brand-only products (azilsartan/chlorthalidone [Edarbyclor], perindopril/amlodipine [Prestalia], metoprolol succinate/HCTZ [Dutoprol®], and aliskiren/HCTZ [Tekturna HCT]). However, generic products are not necessarily affordable or accessible to all patients. Generic FDC products may still be expensive for patients because 1) the insurer requires a prior authorization or step therapy and may still deny the prescription; 2) the patient has a high prescription deductible or medication copay; or 3) the patient has no prescription insurance coverage. The frequency and reasons that prescription insurers reject claims for FDC products in favor free-equivalent combinations is unclear. One potential reason may be that significant price differences exist between an FDC pill and free-equivalent combinations, even if the FDC product is generically available (Table 2). For example, for a benazepril/amlodipine regimen, the average Medicare Part D total monthly cost is \$16.80 for one FDC pill, compared to \$7.50 if prescribed with two pills. Of 32 regimens with FDC and free-equivalent product availability, only 10 (31%) are cheaper as FDC products compared to free-equivalent counterparts (Figure 1). Some lower-cost FDC products are available on low-cost pharmacy lists and are frequently prescribed for patients. For example, lisinopril/HCTZ and losartan/HCTZ are the two most frequently prescribed ACEI/thiazide and ARB/thiazide FDC products, respectively, with the greatest annual Medicare dispenses for their respective classes (Table 3).

Several logistical concerns may limit FDC use in clinical practice. One challenge is that separate medication components within FDCs cannot be tailored individually. This limits a clinician's flexibility to easily titrate medications according to patient needs or discriminate which medication may be causing a nonspecific side effect (e.g., dizziness). Non-adherence may be more impactful to a patient taking FDCs compared to those taking free-equivalent combinations. For example, if a patient stops taking their one, triple-therapy FDC pill, they have no antihypertensive coverage, compared with at least partial coverage if they stop taking one of three individual pills. Clinicians also may have varied perceptions about FDC costs, formulary availability, effectiveness, safety, and role in hypertension treatment.²² Qualitative data exploring these clinical perceptions are needed to inform interventions

around FDC use. Finally, implementation studies are needed to develop effective interventions for increasing FDC use and evaluate impact on BP control. Team-based care strategies, such as pharmacist-delivered medication therapy management, should be tested.

Future directions

Options for FDC products containing an ACEI or ARB and HCTZ therapy are quite robust. However, several important gaps in the armamentarium of FDC antihypertensive products need to be addressed. First, a wider array of FDC options containing triple- or quadruple-therapy is needed to translate emerging evidence, such as the benefits of low-dose combination therapy, into clinical practice. This is especially important given that patients will likely require more medications to achieve the more intensive BP goals recommended in recent guidelines. Second, more FDC products should incorporate chlorthalidone and/or spironolactone. Among the thiazide diuretics, chlorthalidone provides the most consistent and robust data supporting a reduction in cardiovascular outcomes.^{9,23,24} Spironolactone is the preferred agent for most patients with resistant hypertension, as supported by recent data from the PATHWAY-2 study.²⁵ However, spironolactone is not available in any triple- or quadruple-therapy FDCs. Products incorporating spironolactone may assist with adherence for patients with resistant hypertension, who require at least three medication classes to achieve BP control. Additional FDC products are needed which incorporate doses commonly used in clinical practice (e.g., lisinopril 40 mg) or other medications used to treat comorbid cardiovascular diseases (i.e., anti-anginal, anti-platelet, and anti-hyperlipidemic agents). Additional research is needed to: 1) explore clinician perspectives of antihypertensive FDC use; 2) describe the frequency and reasons for insurer denials of antihypertensive FDC prescriptions; 3) ensure access to FDC products is equitable for all patients; and 4) develop and evaluate effective interventions to increase FDC products.

Summary and conclusions

Increasing use of combination therapy is crucial to achieve more intensive BP goals recommended in clinical practice guidelines. By providing combination therapy in one pill, FDCs are promising agents for the treatment of hypertension, but these products are underutilized. More aggressive use of the available safe, effective, and generic FDC products may help to restore the upward trend in BP control rates in the US.

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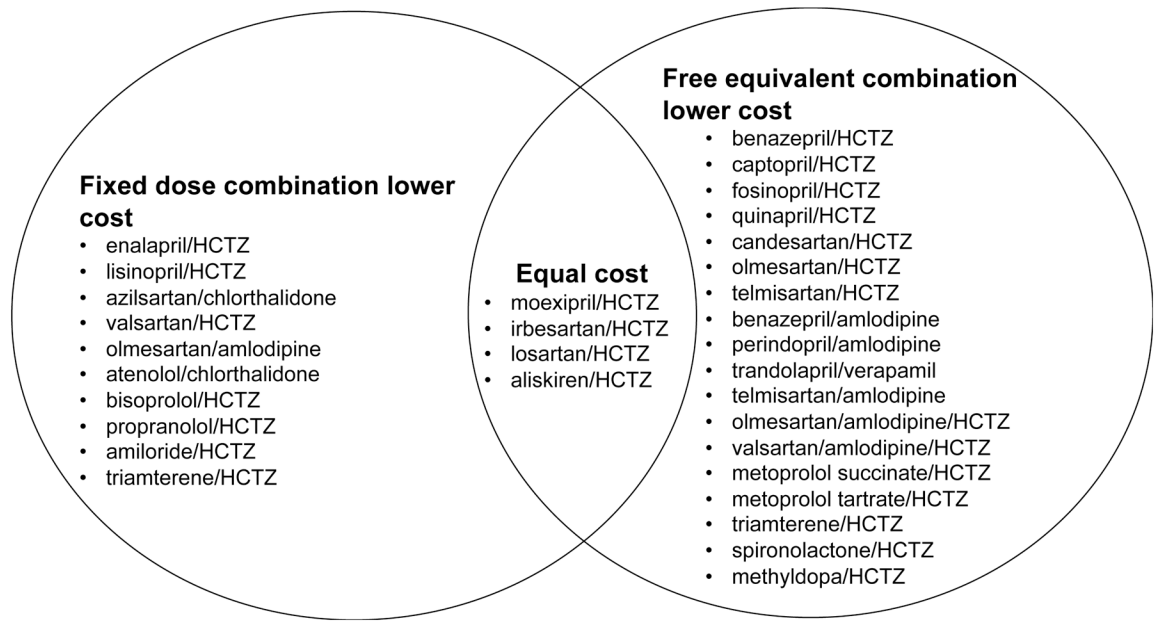


Figure 1. Antihypertensive regimens that are lower cost when prescribed as a fixed dose combination pill or free equivalent products.
 HCTZ: hydrochlorothiazide

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Table 1.

Commercially available antihypertensive fixed-dose combination products in the United States, as of February 2020.

Antihypertensive medication class combination	Generic name	Brand name	Generic available	Doses available
ACEI/thiazide diuretic	Benazepril/HCTZ	Lotensin HCT®	Yes	5/6.25mg, 10/12.5mg, 20/12.5mg, 20/25mg
	Captopril/HCTZ	(none)	Yes	25/15mg, 25/25mg, 50/15mg, 50/25mg
	Enalapril/HCTZ	Vaseretic®	Yes	5/12.5mg, 10/25mg
	Fosinopril/HCTZ	Monopril HCT	Yes	10/12.5mg, 20/12.5mg
	Lisinopril/HCTZ	Zestoretic®	Yes	10/12.5mg, 20/12.5mg, 20/25mg
	Moexipril/HCTZ	Uniretic®	Yes	7.5/12.5mg, 15/12.5mg, 15/25mg
	Quinapril/HCTZ	Accuretic™	Yes	10/12.5mg, 20/12.5mg, 20/25mg
	Azilsartan/chlorthalidone	Edarbyclor	No	40/12.5mg, 40/25mg
	Candesartan/HCTZ	Atacand HCT®	Yes	16/12.5mg, 32/12.5mg, 32/25mg
	Irbesartan/HCTZ	Avalide®	Yes	150/12.5mg, 300/12.5mg
ARB/thiazide diuretic	Losartan/HCTZ	Hyzaar®	Yes	50/12.5mg, 100/12.5mg, 100/25mg
	Olmesartan/HCTZ	Benicar HCT®	Yes	20/12.5mg, 40/12.5mg, 40/25mg
	Telmisartan/HCTZ	Micardis HCT	Yes	40/12.5mg, 80/12.5mg, 80/25mg
	Valsartan/HCTZ	Diovan HCT®	Yes	80/12.5mg, 160/12.5mg, 320/12.5mg, 160/25mg, 320/25mg
	Benazepril/amlodipine	Lotel	Yes	10/2.5mg, 10/5mg, 20/5mg, 20/10mg, 40/5mg, 40/10mg
	Perindopril/amlodipine	Prestalia	No	3.5/2.5mg, 7/5mg, 14/10mg
	Trandolapril/verapamil	Tarka	Yes	1/240mg, 2/180mg, 2/240mg, 4/240mg
	Olmesartan/amlodipine	Azor®	Yes	5/20mg, 5/40mg, 10/20mg, 10/40mg
	Telmisartan/amlodipine	Twynsta®	Yes	40/5mg, 80/5mg, 40/10mg, 80/10mg
	Valsartan/amlodipine	Exforge	Yes	160/5mg, 320/5mg, 160/10mg, 320/10mg
ARB/CCB/thiazide diuretic	Olmesartan/amlodipine/HCTZ	Tribenzor®	Yes	20/5/12.5mg, 40/5/12.5mg, 40/5/25mg, 40/10/12.5mg, 40/10/25mg
	Valsartan/amlodipine/HCTZ	Exforge HCT®	Yes	5/160/12.5mg, 5/160/25mg, 10/160/12.5mg, 10/160/25mg, 10/320/25mg
Beta-blocker/thiazide diuretic	Atenolol/chlorthalidone	Tenoretic	Yes	50/25mg, 100/25mg
	Bisoprolol/HCTZ	Ziac®	Yes	2.5/6.25mg, 5/6.25mg, 10/6.25mg
	Metoprolol succinate/HCTZ	Dutoprol®	No	25/12.5mg, 50/12.5mg, and 100/12.5mg
	Metoprolol tartrate/HCTZ	Lopressor HCT®	Yes	50/25mg, 100/25mg, 100/50mg

Antihypertensive medication class combination	Generic name	Brand name	Generic available	Doses available
	Nadolol/ Bendroflumethiazide	Corzide®	Yes	40/5mg
	Propranolol/HCTZ	(none)	Yes	40/25mg, 80/25mg
Potassium-sparing diuretic/thiazide diuretic	Amloride/HCTZ	(none)	Yes	5/50mg
	Triamterene/HCTZ	Dyazide®, Maxzide®	Yes	25/37.5mg, 50/75mg
Aldosterone antagonist/thiazide diuretic	Spironolactone/HCTZ	Aldactazide®	Yes	25/25mg, 50/50mg [†]
Alpha-2-agonist/thiazide diuretic	Methyldopa/HCTZ	(none)	Yes	250/15mg, 250/25mg
Direct renin inhibitor/thiazide diuretic	Aliskiren/HCTZ	Tekturma HCT	No	150/12.5mg, 150/25mg, 300/12.5mg, 300/25mg

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel antagonist; HCTZ: hydrochlorothiazide; rx: prescription

* Available in 1/240mg formulation in branded Tarka® product only.

[†] Available in 50/50mg formulation in branded Aldactazide® product only.

Table 2. Total monthly cost differences between free equivalent and fixed-dose combination regimens.

Class combination	Medication combination	Free equivalent combination		Sum of individual costs	Fixed-dose combination		Cost Difference (FDC – Free equivalent)	Less expensive regimen
		Individual cost	Cost		Cost			
ACEI/thiazide diuretic	Benazepril	\$3.90	\$6.75	\$33.30	\$26.55	Free equivalent		
	HCTZ	\$2.85						
	Captopril	\$36.00	\$38.85	\$62.40	\$23.55	Free equivalent		
	HCTZ	\$2.85						
	Enalapril	\$12.60	\$15.45	\$7.50	\$-7.95	FDC		
	HCTZ	\$2.85						
	Fosinopril	\$7.20	\$10.05	\$28.50	\$18.45	Free equivalent		
	HCTZ	\$2.85						
	Lisinopril	\$3.30	\$6.15	\$3.00	\$-3.15	FDC		
	HCTZ	\$2.85						
	Moexipril	\$27.00	\$29.85	\$27.90	\$-1.95	Equal		
	HCTZ	\$2.85						
Quinapril	\$8.10	\$10.95	\$19.20	\$8.25	Free equivalent			
HCTZ	\$2.85							
ARB/thiazide diuretic	Azilsartan	\$185.10	\$209.40	\$178.20	\$-31.20	FDC		
	Chlorthalidone	\$24.30						
	Candesartan	\$68.40	\$71.25	\$83.70	\$12.45	Free equivalent		
	HCTZ	\$2.85						
	Irbesartan	\$11.40	\$14.25	\$15.90	\$1.65	Equal		
	HCTZ	\$2.85						
	Losartan	\$4.80	\$7.65	\$6.00	\$-1.65	Equal		
	HCTZ	\$2.85						
	Olmesartan	\$104.70	\$107.55	\$116.40	\$8.85	Free equivalent		
	HCTZ	\$2.85						
	Telmisartan	\$31.20	\$34.05	\$81.60	\$47.55	Free equivalent		

Class combination	Medication combination	Free equivalent combination		Fixed-dose combination	Cost Difference (FDC – Free equivalent)	Less expensive regimen
		Individual cost	Sum of individual costs			
	HCTZ	\$2.85				
	Valsartan	\$18.00	\$20.85	\$14.40	\$-6.45	FDC
	HCTZ	\$2.85				
ACEI/CCB	Benazepril	\$3.90	\$7.50	\$16.80	\$9.30	Free equivalent
	Amlodipine	\$3.60				
	Perindopril	\$23.40	\$27.00	\$153.90	\$126.90	Free equivalent
	Amlodipine	\$3.60				
	Trandolapril	\$12.00	\$45.90	\$94.80	\$48.90	Free equivalent
	Verapamil	\$33.90				
ARB/CCB	Olmesartan	\$104.70	\$108.30	\$84.60	\$-23.70	FDC
	Amlodipine	\$3.60				
	Telmisartan	\$31.20	\$33.80	\$100.80	\$67.00	Free equivalent
	Amlodipine	\$3.60				
	Valsartan	\$18.00	\$21.60	\$34.80	\$13.20	Free equivalent
	Amlodipine	\$3.60				
ARB/CCB/ thiazide diuretic	Olmesartan	\$104.70	\$111.15	\$131.40	\$20.25	Free equivalent
	Amlodipine	\$3.60				
	HCTZ	\$2.85				
	Valsartan	\$18.00	\$24.45	\$96.60	\$72.15	Free equivalent
	Amlodipine	\$3.60				
	HCTZ	\$2.85				
Beta-blocker/thiazide diuretic	Atenolol	\$3.00	\$27.30	\$16.50	\$-10.80	FDC
	Chlorthalidone	\$24.30				
	Bisoprolol	\$14.70	\$17.55	\$5.10	\$-12.45	FDC
	HCTZ	\$2.85				
	Metoprolol succinate	\$15.00	\$17.85	\$196.80	\$178.95	Free equivalent
	HCTZ	\$2.85				

Class combination	Medication combination	Free equivalent combination		Fixed-dose combination	Cost Difference (FDC – Free equivalent)	Less expensive regimen
		Individual cost	Sum of individual costs			
	Metoprolol tartrate	\$2.10	\$4.95	\$29.40	\$24.45	Free equivalent
	HCTZ	\$2.85				
	Nadolol	\$68.10	n/a	\$91.20	n/a	n/a
	Bendroflumethiazide	n/a				
Potassium-sparing diuretic/thiazide diuretic	Propranolol	\$30.00	\$32.85	\$29.40	\$–3.45	FDC
	HCTZ	\$2.85				
	Amloride	\$17.10	\$19.95	\$13.50	\$–6.45	FDC
	HCTZ	\$2.85				
Aldosterone antagonist/thiazide diuretic	Triamterene	\$289.80	\$292.65	\$6.30	\$–286.35	FDC
	HCTZ	\$2.85				
	Spirinolactone	\$6.00	\$8.85	\$29.40	\$20.55	Free equivalent
	HCTZ	\$2.85				
Alpha-2-agonist/thiazide diuretic	Methyldopa	\$6.90	\$9.75	\$44.10	\$34.35	Free equivalent
	HCTZ	\$2.85				
	Aliskiren	\$190.20	\$193.05	\$194.10	\$1.05	Equal
Direct renin inhibitor/thiazide diuretic	HCTZ	\$2.85				

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel antagonist; FDC: fixed-dose combination; HCTZ: hydrochlorothiazide.

Cost data were generated from the 2014–2018 Medicare Part D Drug Spending Data available from the Centers for Medicaid and Medicare Services (<https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD>). The medication costs represent ingredient costs, dispensing fees, taxes, and patient out-of-pocket costs, inflated to 2019 US Dollars and averaged over the one-year calendar year; however, they do not reflect manufacturer rebates. The cost represents per 30 tablets of the generic product, if available. Costs are averaged across manufacturers.

Table 3.

Number of Medicare prescriptions dispensed for each antihypertensive fixed-dose combination product in the United States in 2018.

Antihypertensive medication class combination	Generic name Brand name	Generic dispenses	Brand dispenses
ACEI/thiazide diuretic	Lisinopril/HCTZ Zestoretic®	6,794,908	2,021
	Benazepril/HCTZ Lotensin HCT®	384,946	68
	Enalapril/HCTZ Vasercite®	199,297	18
	Quinapril/HCTZ Accuretic™	105,208	932
	Fosinopril/HCTZ Monopril HCT	19,972	0
	Captopril/HCTZ (none)	13,149	0
	Moexipril/HCTZ Uniretic®	10,290	0
	Losartan/HCTZ Hyzaar®	7,212,362	9,891
	Valsartan/HCTZ Diovan HCT®	2,347,400	21,627
	Irbesartan/HCTZ Avalide®	555,805	3,793
ARB/thiazide diuretic	Olmesartan/HCTZ Benicar HCT®	700,911	35,271
	Telmisartan/HCTZ Micardis HCT	167,794	7,668
	Candesartan/HCTZ Atacand HCT®	56,500	3,072
	Azilsartan/chlorthalidone Edarbyclor	0	67,752
	Benazepril/amlodipine Lotrel	1,892,257	8,572
	Trandolapril/verapamil [controlled release] Tarka	8,173	3,344
	Perindopril/amlodipine Prestalia	0	14

Antihypertensive medication class combination	Generic name Brand name	Generic dispenses	Brand dispenses
ARB/CCB	Valsartan/amlodipine Exforge	360,471	10,289
	Olmesartan/amlodipine Azor®	212,891	14,114
ARB/CCB/thiazide diuretic	Telmisartan/amlodipine Twynta®	686,682	279
	Olmesartan/amlodipine/HCTZ Tribenzor®	138,913	8,297
ARB/CCB/thiazide diuretic	Valsartan/amlodipine/ HCTZ Exforge HCT®	87,652	2,499
	Bisoprolol/HCTZ Ziac®	756,170	1,052
Beta-blocker/thiazide diuretic	Atenolol/chlorthalidone Tenoretic	546,542	507
	Metoprolol tartrate/HCTZ Lopressor HCT®	57,550	0
Beta-blocker/thiazide diuretic	Propranolol/HCTZ (none)	5,968	0
	Nadolol/ Bendroflumethazide Corzide®	1,713	115
Potassium-sparing diuretic/thiazide diuretic	Metoprolol succinate/HCTZ Dutoprol®	0	1,237
	Triamterene/HCTZ Dyazide®, Maxzide®	3,880,450	9,300
Aldosterone antagonist/thiazide diuretic	Amiloride/HCTZ (none)	71,435	0
	Spirolactone/HCTZ Aldactazide®	265,366	1,064
Alpha-2-agonist/thiazide diuretic	Methyldopa/HCTZ (none)	812	0
Direct renin inhibitor/thiazide diuretic	Aliskiren/HCTZ Tekturna HCT	0	13,210

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel antagonist; HCTZ: hydrochlorothiazide; rx: prescription Utilization data were generated from the 2014–2018 Medicare Part D Drug Spending Data available from the Centers for Medicaid and Medicare Services (<https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD>).