Single-Pill Versus Loose-Dose Combination Triple Therapy for Hypertension: Formulary Impact

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ABSTRACT

Objectives: To estimate the managed care budget impact of greater use of triple-agent single-pill combination (SPC) versus comparable 2- and 3-pill loose-dose combination (LDC) regimens (angiotensin II receptor blockers [ARB] + amlodipine + hydrochlorothiazide [HCTZ]) for hypertensive patients uncontrolled on dual therapy.

Study Design: Budget impact model.

Methods: An estimated 11,308 patients in a hypothetical plan of 5 million are eligible for triple antihypertensive therapy as a 1-, 2- or 3-pill daily regimen of ARB + amlodipine + HCTZ. Price, market share, and tier/co-pay for each aforementioned agent were obtained from published sources, as were percentages of patients with 30- versus 90-day refill schedules. Adherence to and persistence with therapy vary by regimen type; these factors influence pharmacy costs, cardiovascular outcomes, and medical care costs.

Results: Among hypertensive patients not controlled on dual therapy, we estimate that a doubling of SPC triple-therapy use (from 16% to 31%) within a formulary of 1-, 2-, and 3-pill alternative regimens would result in 2 fewer cardiovascular events (335 vs 333), lower all-cause medical care costs ($47.64 million vs $47.45 million), and higher pharmacy costs ($2.99 million vs $3.58 million) over the course of 1 year. Taken together, the model projects an approximately net-neutral economic impact from the health plan perspective ($0.006 per member per month with 31% use of SPC therapy).

Conclusions: In this model, gains in adherence realized as a result of SPC triple antihypertensive therapy translated into improvements in health outcomes and lower downstream medical care costs with an approximately net-neutral overall budget impact to health systems.

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Chronic hypertension is a major risk factor for cardiovascular disease (CVD). Systemic hypertension is a pervasive public health concern in the United States, affecting more than 78 million adults.[1] It is also the fifth-most costly medical condition in the United States[2]; direct and indirect medical care costs attributable to hypertension were recently estimated to be $51 billion annually (2009 dollars).[1] A strong causal relationship between untreated hypertension and cardiovascular (CV) events has been established.[1] Uncontrolled hypertension can lead to cerebrovascular disease, ischemic heart disease, and death.[3] By the same token, blood pressure (BP) control is strongly associated with reduced CVD risk and, in turn, lower medical care costs.[4] Indeed, the primary goal of treating hypertension is the reduction of CVD morbidity and mortality.[5] Sustained antihypertensive therapy is necessary to achieve this goal. However, despite the availability of numerous, highly effective antihypertensive agents, BP remains inadequately controlled in more than half (53.5%) of the individuals with hypertension in the United States.[6]

Current evidence suggests that the majority of patients treated for hypertension—roughly two-thirds of the diagnosed population—will require combination therapy to achieve targeted BP goals.[7-9] Of these, many will require a triple-combination regimen.[10] A major obstacle to BP goal attainment is poor regimen adherence and persistence, both of which are exacerbated by regimen complexity.[11,12]

Ample evidence suggests that simplifying a therapeutic regimen with the use of fixed-dose, single-pill combination (SPC) antihypertensive therapy in place of loose-dose combination (LDC) alternatives can improve regimen adherence and lead to fewer cardiovascular events and lower all-cause medical care costs. For instance, increasing adherence to a once-daily antihypertensive regimen by as little as 1 pill per week has been shown to reduce multivariate-adjusted mortality risk by 7% (HR 0.93; 95% CI, 0.90-0.096).[13] A recent retrospective analysis by Brixner and colleagues used a nationally representative claims database to show that patients receiving SPC

PRACTICAL IMPLICATIONS

The objective of this cost analysis was to facilitate productive discussions about the use of single-pill fixed dose versus loose-dose combination therapies for hypertension. The potential benefits of single-pill fixed dose combinations are:

- Regimen complexity is reduced.
- Patient adherence to therapy is increased.

These factors can influence the incidence and costs of suboptimal clinical outcomes associated with hypertension.

regimens had 6.6% greater adherence (P <.001) compared with patients given LDC regimens.[14] Similarly, a study by Zeng and colleagues found that patients on SPC regimens were significantly more likely to be adherent (OR 2.915; P <.001) and less likely to discontinue therapy (HR 0.537; P <.001) compared with those on LDC regimens.[15] Two recent meta-analyses have reported that, in patients with chronic conditions such as hypertension, SPC regimens significantly improved therapeutic adherence compared with separate LDC regimens of the same drug components.[16,17] A third meta-analysis found that hypertensive patients prescribed SPC therapies had higher treatment adherence and lower all-cause healthcare costs compared with patients given comparable LDC regimens.[18] In addition, both greater adherence and greater persistence with hypertensive therapy have been associated with significantly lower risk of CV events, healthcare resource use, and hospitalization compared with nonadherent and/or nonpersistent patients.[13,15,19-23]

The objective of this analysis is to estimate the budget impact, from the perspective of a commercial health plan, of regimen simplification via greater use of SPC regimens (valsartan/amlodipine/hydrochlorothiazide [HCTZ] or olmesartan/amlodipine/HCTZ) within a formulary of comparable 2- and 3-pill alternative LDC regimens (angiotensin II receptor blockers [ARB] + amlodipine + HCTZ) prescribed for hypertensive patients not controlled on dual therapy. Specifically, our goal is to evaluate the potential of lower medical care costs due to greater adherence (and, thus, reduced risk of CV events) to offset the incrementally higher acquisition costs of SPC therapies versus comparable LDC alternatives.

METHODS

We developed a Microsoft Excel–based, 1-year budget impact model to consider the effect to a health plan of increasing the use of triple-therapy SPC regimens for hypertensive patients not controlled on dual therapy. In the model, therapeutic adherence and persistence vary by regimen type (daily pill burden) which, in turn, can influence hypertension drug costs, cardiovascular outcomes, and related medical care costs (**Figure 1**).

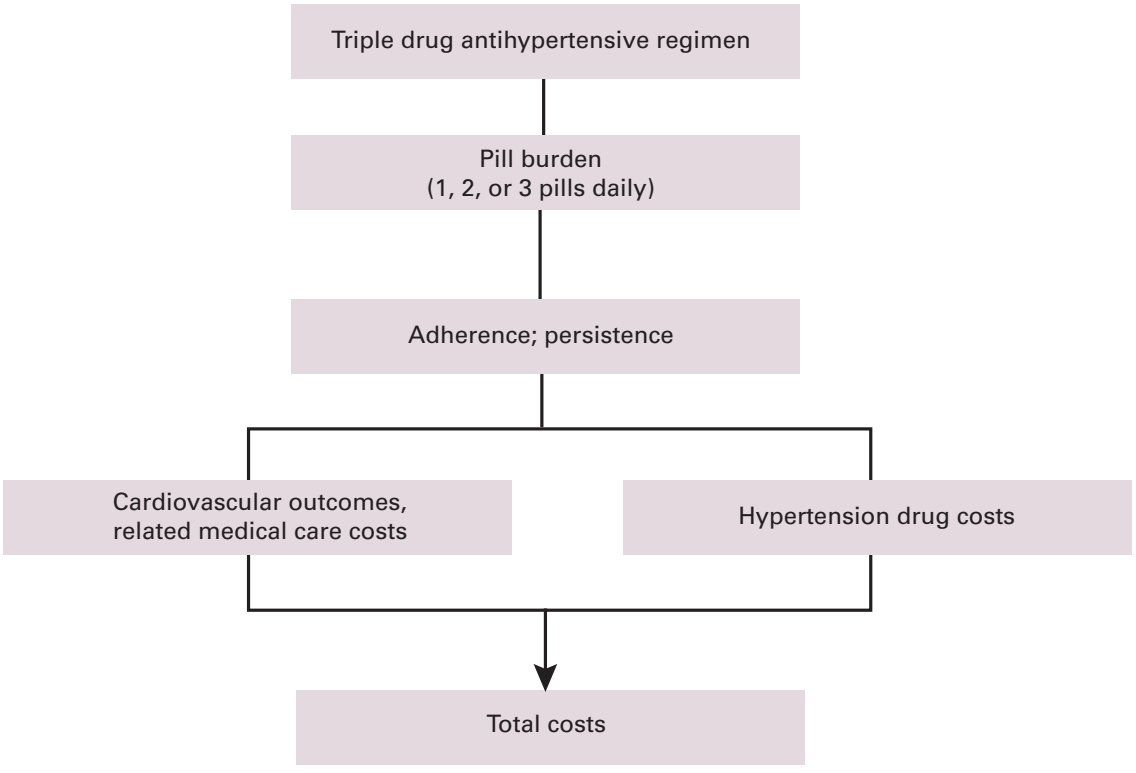
Based on the analysis, we estimated that 11,308 patients in a hypothetical plan size of 5 million would be eligible for triple antihypertensive therapy as a 1-, 2- or 3-pill daily regimen of ARB + amlodipine + HCTZ (**Table 1**[1,24]).

The model considered adherence in terms of patients' medication possession ratio (MPR), defined as the percentage of time a patient has access to all components of the triple regimen (according to prescription refill patterns). Following Pittman and colleagues,[4] patients with low, moderate, and high adherence were assumed to have MPR of 0% to 59%; 60% to 79%; and 80% to 100%, respectively, in a 360-day year. Estimates of high adherence by pill burden were obtained directly from Ferrario and colleagues[25] (1 pill) and Panjabi and colleagues[26] (2 and 3 pills); sub-analyses of the same data informed assumptions about the distribution of low and moderate adherence for patients on 2- and 3-pill daily regimens[27] (**Table 2**).

Following Yang and colleagues,[28] our model assumed that a lower daily pill burden is associated with higher patient persistence with therapy (60% persistence with SPC regimens and 40% persistence with 2-pill daily LDC regimens). In addition, our model assumed that patient persistence with 3-pill daily LDC regimens was incrementally lower (30%) than that reported by Yang and colleagues for 2-pill daily LDC therapies.[28]

Formulary options for antihypertensive triple therapy in the model included 2- and 3-pill LDC regimens containing ARB + amlodipine + HCTZ as well as SPC regimens with valsartan/amlodipine/HCTZ or olmesartan/amlodipine/HCTZ. Baseline average wholesale acquisition costs (WACs) were obtained from Medi-Span Price Rx.[29] Formulary tier assignments/co-pay for each of these agents were consistent with published sources,[30,31] as were percentages of patients with 30- versus 90-day refill schedules[32] (**Table 3**). In the case of valsartan, with planned generic entry following the expiration of its patent, the branded version was assumed to be placed on tier 3 while the generic version was placed on tier 1. Baseline market share for each drug combination in the ARB + amlodipine + HCTZ triple-therapy market was obtained from an analysis of IMS Health Plan Claims Database.[24] Market shares unavailable from this source were calculated using actual market volume

Figure 1. Model Flow



from IMS Health's National Prescription Audit (NPA) database.[33] Market share for molecules with recent or planned generic entry in 2013 (eg, candesartan, eprosartan, irbesartan, and valsartan) were adjusted so that the total market share assigned to a molecule is split between the generic entry (95%) and its branded counterpart (5%). In addition, the prices of molecules with recent generic entry were calculated to be 10% of the price of the corresponding branded ARB product. These assumptions were intended to reflect the market share and pricing characteristics that generics achieve once they reach a steady state in the marketplace.

A manufacturer rebate was applied to all ARB products assigned tier 2 status (20% for branded olmesartan; 30% for branded telmisartan); no rebate was applied to the generic (tier 1) or tier 3 agents. Our base case scenario assumed a higher rebate for branded telmisartan due to its higher acquisition cost relative to other branded tier 2 alternatives. These rebate levels were assumptions and not reflective of the actual rebate levels that olmesartan and telmisartan manufacturers offer.

One-year risk-adjusted utilization (CV-related hospitalizations and emergency department [ED] visits) and medical care costs based on therapeutic adherence levels were

Table 1. Patients Eligible for Triple Antihypertensive Therapy[1,24]

Input	Value
Plan size	5,000,000
% patients with hypertension[1]	33.0%
Of those, % treated with antihypertensive agents[1]	74.9%
% hypertension patients eligible for triple therapy[24]	15.0%
% triple-therapy patients eligible for (ARB + amlo + HCTZ) regimen[24]	6.1%
No. patients eligible for (ARB + amlo + HCTZ) regimen	11,308

ARB indicates angiotensin II receptor blocker; amlo, amlodipine; HCTZ, hydrochlorothiazide.

Table 2. Impact of Daily Pill Burden on Adherence

Treatment Cohort Adherence Level	1 Pill Daily, %	2 Pills Daily, %	3 Pills Daily,%
Low (0%-59% MPR)	40.98	53.29	67.95
Moderate (60%-79% MPR)	14.91	21.35	18.36
High (80%-100% MPR)	44.11	25.36	13.69

MPR indicates medication possession ratio.

Table 3. Formulary Assumptions for ARB in Triple Combination Prescriptions

Type of Regimen	ARB in Triple Combination (brand name; pill burden)	Formulary Allocation			
		Unit Cost[a]	Baseline, %	Increased SPC Use, %	Tier Assignment[b]
Loose-dose combination (LDC)					
	azilsartan (Edarbi; 3 pills daily)	$2.70	0.14	0.13	tier 3
	azilsartan/CTZ (Edarbychlor; 2 pills daily)	$2.77	0.07	0.06	tier 3
	candesartan (generic; 3 pills daily)	$0.34	0.94	0.86	tier 1
	candesartan (Atacand; 3 pills daily)	$3.39	0.05	0.04	tier 3
	candesartan/HCTZ (generic; 2 pills daily)	$0.41	0.36	0.33	tier 1
	candesartan/HCTZ (Atacand HCTZ; 2 pills daily)	$4.06	0.02	0.02	tier 3
	eprosartan (generic; 3 pills daily)	$0.39	0.04	0.04	tier 1
	eprosartan (Teveten; 3 pills daily)	$3.95	0.00	0.00	tier 3
	eprosartan/HCTZ (Teveten HCTZ; 2 pills daily)	$4.07	0.02	0.02	tier 3
	irbesartan (generic; 3 pills daily)	$0.31	3.41	3.14	tier 1
	irbesartan (Avapro; 3 pills daily)	$3.14	0.18	0.17	tier 3
	irbesartan/HCTZ (generic; 2 pills daily)	$0.36	0.97	0.88	tier 1
	irbesartan/HCTZ (Avalide; 2 pills daily)	$3.57	0.05	0.05	tier 3
	losartan (generic; 3 pills daily)	$0.28	26.04	23.91	tier 1
	losartan (Cozaar; 3 pills daily)	$2.78	1.37	1.26	tier 3
	losartan/HCTZ (generic; 2 pills daily)	$0.30	13.39	12.30	tier 1
	losartan/HCTZ (Hyzaar; 2 pills daily)	$3.00	0.70	0.65	tier 3
	olmesartan (Benicar; 3 pills daily)	$3.91	2.71	1.24	tier 2
	olmesartan/HCTZ (Benicar HCTZ; 2 pills daily)	$4.21	11.06	5.06	tier 2
	olmesartan/amlo (Azor; 2 pills daily)	$4.89	1.63	0.75	tier 2
	telmisartan (Micardis; 3 pills daily)	$4.47	2.10	1.93	tier 2
	telmisartan/HCTZ (Micardis HCTZ; 2 pills daily)	$4.47	1.70	1.56	tier 2
	telmisartan/amlo (Twynsta; 2 pills daily)	$4.80	0.05	0.05	tier 2
	valsartan (generic; 3 pills daily)	$0.42	3.57	3.28	tier 1
	valsartan (Diovan; 3 pills daily)	$4.16	0.19	0.17	tier 3
	valsartan/HCTZ (generic; 2 pills daily)	$0.50	10.44	9.59	tier 1
	valsartan/HCTZ (Diovan HCTZ; 2 pills daily)	$4.98	0.55	0.50	tier 3
	valsartan/amlo (generic; 2 pills daily)	$0.48	2.13	1.38	tier 1
	valsartan/amlo (Exforge; 2 pills daily)	$4.85	0.11	0.07	tier 3
Single-pill combination (SPC)					
	olmesartan/amlo/HCTZ (Tribenzor; 1 pill daily)	$5.10	0.00	15.00	tier 2
	valsartan/amlo/HCTZ (generic; 1 pill daily)	$0.57	15.21	14.78	tier 1
	valsartan/amlo/HCTZ (Exforge HCTZ; 1 pill daily)	$5.71	0.80	0.78	tier 3

ARB indicates angiotensin II receptor blocker; amlo, amlodipine; CTZ, cyclothiazide; HCTZ, hydrochlorothiazide.
[a]2- and 3-pill regimens include the cost of generic amlo (unit cost $0.35) and/or HCTZ (unit cost $0.10). Unit cost was standardized across all ARBs by calculating average wholesale acquisition cost price/day of therapy, and then price for a particular molecule was calculated according to the market share of each dose and price per dose. Generic prices are assumed to be 10% of the price of the corresponding brand product.
[b]Co-pay amount for 30-day regimen are $10.00 (tier 1), $28.00 (tier 2), and $49.00 (tier 3); 90-day regimen co-pays were assumed to be twice the 30-day amount (2012 dollars). Distribution of scripts assumed is 85% (30-day) and 15% (90-day) for all products.

drawn from published estimates (**Table 4**)[4]; costs were inflated to 2012 dollars using the medical care component of the Consumer Price Index.[34]

Two model scenarios were evaluated. In the first scenario (baseline), patients were allocated to a mix of branded and generic LDC (84%) and SPC (16%) triple-therapy daily regimens. The second scenario (increased SPC use) evaluated the budget impact of a 15% shift in the mix of daily regimens, to LDC (69%) and SPC (31%) therapies, with the increased SPC share assigned to olmesartan/amlodipine/HCTZ (Table 3). Model results compared the estimated number of CV-related events, all-cause healthcare costs, hypertension drug costs, total healthcare costs, health plan impact (net of co-pays, rebates), and the net

Table 4. One-Year CV-Related Resource Utilization and All-Cause Healthcare Costs[4]

	1-Year, CV-Related Utilization		1-Year, All-Cause Costs[a]		
Treatment Cohort Adherence Level	Hospitalizations	ED Visits	Outpatient Care	Hospitalizations	ED Visits
Low (0%-59% MPR)	2.10%	1.00%	$4353	$2304	$193
Moderate (60%-79% MPR)	2.10%	0.90%	$4071	$1970	$147
High (80%-100% MPR)	1.80%	0.80%	$3803	$1530	$114

CV indicates cardiovascular; ED, emergency department; MPR, medication possession ratio.
[a]All costs reflect 2012 dollars.

Table 5. Base Case Results: Budget Impact of Increased SPC Use

	Annual Cost		PMPM	
Cost	Baseline	Increased SPC Use	Baseline	Increased SPC Use
Outpatient care	$47,146,495	$46,969,175	$0.786	$0.783
Hospitalizations (CV-related)	$472,385	$465,062	$0.008	$0.008
ED visits (CV-related)	$17,498	$17,166	$0.000	$0.000
Pharmacy (HTN drugs)	$2,990,902	$3,583,480	$0.050	$0.060
Total Healthcare Costs	$50,627,280	$51,034,883	$0.844	$0.851
Co-pay collected	$1,919,703	$1,818,069	$0.032	$0.030
Rebate applied	$425,168	$556,134	$0.007	$0.009
Net to Plan	$48,282,409	$48,660,680	$0.805	$0.811

CV indicates cardiovascular; ED, emergency department; HTN, hypertension; PMPM, per member per month; SPC, single-pill combination.
A 20% rebate was applied to all olmesartan products assigned tier 2 status and a 30% rebate was applied to all telmisartan products assigned tier 2 status; no rebate was applied to tier 1 or tier 3 products in this scenario. These rebate levels are assumptions and not are reflective of the actual rebate levels that olmesartan and telmisartan manufacturers offer.
Assumes that 11,308 patients in a hypothetical commercial health plan size of 5 million would be eligible for triple antihypertensive therapy as a 1-, 2-, or 3-pill daily regimen of ARB + amlodipine + hydrochlorothiazide.

per member per month (PMPM) impact associated with each modeled scenario.

RESULTS

Among hypertensive patients not controlled on dual therapy, our model estimated that a 15% increase in SPC triple-therapy use (from 16% to 31%) within a formulary of 1-, 2-, and 3-pill alternative regimens would result in 2 fewer cardiovascular events (335 vs 333), modestly lower all-cause medical care costs ($47.64 million vs $47.45 million), and higher pharmacy costs ($2.99 million vs $3.58 million) over the course of 1 year (**Table 5**). Taken together, the model projects that this 15% increase in the use of SPC therapies would result in an approximately net-neutral economic impact ($0.006 PMPM) from a health plan perspective (**Figure 2**).

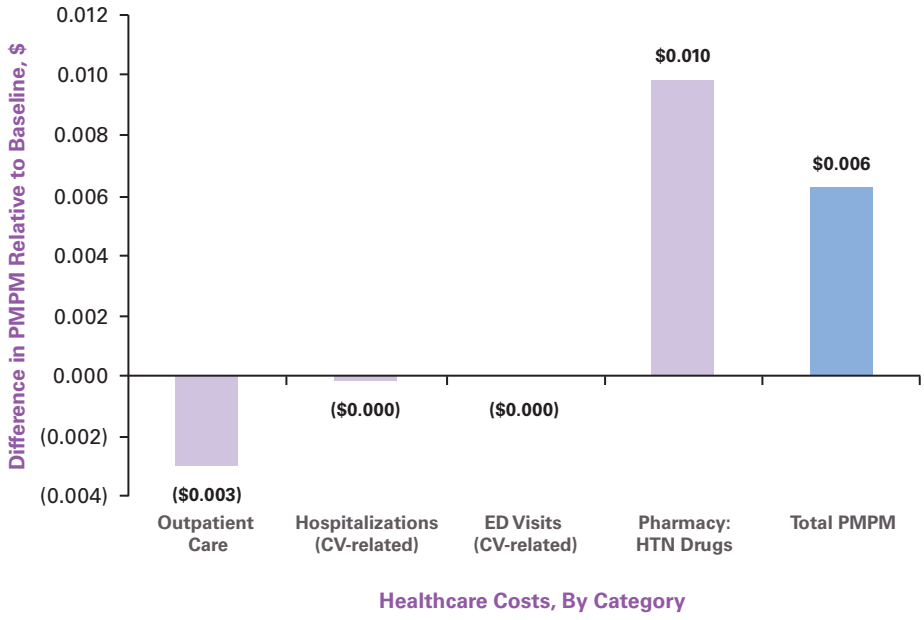
Sensitivity Analysis

Sensitivity analyses verified that, as anticipated, the model results are linear; that is, a doubling of the proportion of patients eligible for triple antihypertensive therapy (from 6.1% to 12.2%) results in a doubling of the PMPM associated with each scenario (baseline [from $0.805 to $1.609], increased SPC use [from $0.811 to $1.622]) and that the magnitude of the difference between scenarios would remain constant. The sensitivity of the model to pricing was explored by varying the formulary tier assignment for branded products without a corresponding generic entrant (ie, olmesartan, telmisartan, and azilsartan) while keeping all other assumptions constant (**Table 6**). Broadly speaking, our model was not sensitive to formulary tier assignment. For instance, reclassifying all telmisartan and azilsartan products as tier 3 agents having no rebate (pricing analysis 1) instead of tier 2 agents having 20% to 30% rebates (pricing analysis 2) produced no meaningful change in model results (**Table 7**).

DISCUSSION

The objective of this study was to estimate the managed care budget impact of regimen simplification via greater use of triple-agent SPC regimens (valsartan/amlodipine/HCTZ or olmesartan/amlodipine/HCTZ) within a formulary of comparable 2- and 3-pill LDC regimens (ARB + amlodipine + HCTZ) for hypertensive patients not controlled on dual therapy. In particular, we focused on the potential of lower medical care costs to offset the incrementally higher acquisition costs of SPC therapies versus comparable LDC alternatives. Indeed, we found that,

Figure 2. Impact to Per Member Per Month (increased single-pill combination use vs baseline)



CV indicates cardiovascular; ED, emergency department; HTN, hypertension; PMPM, per member per month; SPC, single-pill combination.
Assumes that 11,308 patients in a hypothetical health plan size of 5 million would be eligible for triple antihypertensive therapy as a 1-, 2-, or 3-pill daily regimen of ARB + amlodipine + hydrochlorothiazide. The Total PMPM was calculated based on the total healthcare costs to the plan, less rebates and co-pays collected.

Table 6. Formulary Tier Assignments for Pricing Analyses

Scenario	olmesartan	telmisartan	azilsartan
Base case	tier 2	tier 2	tier 3
Pricing analysis 1	tier 2	tier 3	tier 3
Pricing analysis 2	tier 2	tier 2	tier 2

A 20% rebate was applied to olmesartan and azilsartan products when assigned tier 2 status; a 30% rebate was applied to telmisartan products when assigned tier 2 status. No rebate was applied to products assigned tier 3 status in these scenarios.

among hypertensive patients not controlled on dual therapy, increased use of SPC triple therapy within a formulary of 1-, 2-, and 3-pill alternative daily regimens resulted in slightly better clinical outcomes (fewer CV events) and reductions in all-cause medical care costs sufficient to offset increases in pharmacy costs associated with the use of SPC products. Taken together, the model projects an approximately net-neutral economic impact ($0.006 PMPM) from the health plan perspective of a 15% increase in use of SPC therapies.

From a payer perspective, increased adherence to any pharmaceutical therapy leads to increased drug utilization and higher pharmacy costs. This concern is naturally magnified in the case of combination drug regimens used to treat chronic conditions. In addition, payers may be initially wary of the incrementally higher acquisition cost of branded SPC products relative to that of comparable LDC products available as separate, multisource pills. Nevertheless, especially in the case of triple-combination therapy for chronic hypertension, there may be subgroups of high-risk, high-cost patients for whom gains in adherence realized as a result of an SPC regimen translate into meaningful improvements in health outcomes and lower downstream medical care costs, resulting in an approximately net-neutral overall budget impact to the health system. Gains in medication adherence with antihypertensive therapy (including ARBs) can also positively impact Medicare Star Quality Ratings, which are directly tied to bonus payments as mandated by the Patient Protection and Affordable Care Act (PPACA).[35] For Medicare plans operating in highly competitive environments, a small increase in revenue would potentially enable better performers to offer a more attractive package to retain or attract new beneficiaries.[36] Such focus on medication adherence is starting to impact commercial health plans, which may also ultimately impact their reimbursement schemes.

From the perspective of a prescribing provider, LDC therapies offer the flexibility of titrating doses for individual patients to optimal levels. This may have unintended consequences if patients do not use all of the prescribed agents as intended due to regimen complexity, misunderstanding the importance of taking all medications, lack of access to 1 or more regimen components, and/or multiple co-pays. In many of these cases, the opportunity to achieve optimal, or even good, BP control may be lost.

Table 7. Comparison of Results From the Pricing Analyses

	Base Case		Pricing Analysis 1		Pricing Analysis 2	
Cost	**Increased SPC Use**	**Baseline**	**Increased SPC Use**	**Baseline**	**Baseline**	**Increased SPC Use**
Total healthcare costs [PMPM]	$50,627,280 [$0.844]	$51,034,883 [$0.851]	$50,627,280 [$0.844]	$51,034,883 [$0.851]	$50,627,280 [$0.844]	$51,034,883 [$0.851]
Co-pay collected	$1,919,703	$1,818,069	$1,978,062	$1,871,721	$1,916,798	$1,815,448
Rebate applied	$425,168	$556,134	$306,131	$446,690	$427,578	$558,308
Net to Plan [PMPM]	$48,282,409 [$0.805]	$48,660,680 [$0.811]	$48,343,087 [$0.806]	$48,716,472 [$0.812]	$48,282,904 [$0.805]	$48,661,127 [$0.811]

All the scenarios above assume that 11,308 patients in a hypothetical health plan size of 5 million would be eligible for triple antihypertensive therapy as a 1-, 2-, or 3-pill daily regimen of ARB + amlodipine + hydrochlorothiazide.
Pricing analysis 1 reclassified all telmisartan and azilsartan products as tier 3 agents; pricing analysis 2 categorized all olmesartan, telmisartan and azilsartan products as tier 2 agents. A 20% rebate was applied to olmesartan and azilsartan products when assigned tier 2 status; a 30% rebate was applied to telmisartan products when assigned tier 2 status. No rebate was applied to products assigned tier 3 status in these scenarios.

From a patient's perspective, the use of a once-daily SPC therapy with an effective and well-tolerated agent greatly simplifies the treatment regimen and may improve treatment adherence. This, in turn, can help patients reach their BP goals and reduce their short- and long-term CV risks.

The baseline formulary in our model is intended as an example of a formulary containing triple agent SPC versus 2- and 3-pill LDC antihypertensive regimens. Given the rapidly changing market for antihypertensive agents, it does not represent, and it cannot be claimed to represent, the current formulary of any individual health plan. Nevertheless, the aim of our analysis was to transparently model a broad mix of available antihypertensive products, at different tier allocations, at different market prices, and with different hypothetical rebate agreements. To the extent that we succeeded, we believe that the model results represent the relative, if not the absolute, approximately net-neutral budget impact of including SPC therapy on a health plan's formulary.

CONCLUSION

Gains in adherence realized as a result of SPC triple antihypertensive therapy may translate into improvements in health outcomes and lower downstream medical care costs, with an approximately net-neutral overall budget impact to health systems.

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