Comparison of Amlodipine/Valsartan Fixed-Dose Combination Therapy And Conventional Therapy

The use of a single-pill combination of amlodipine/valsartan resulted in higher acquisition costs but fewer clinic visits, laboratory tests, and electrocardiograms — and therefore lower gross costs — compared with the use of individual drug components

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ABSTRACT

Purpose

Single-pill-combination (SPC) antihypertensive drug products have been shown to improve compliance but are associated with higher acquisition costs. This study compared the clinical and economic outcomes associated with the use of an SPC of amlodipine/valsartan (trade name Exforge) with the outcomes from conventional combination therapy in patients failing to respond to initial monotherapy with either a dihydropyridine calcium channel blocker (DHP-CCB) or an angiotensin receptor blocker (ARB).

Design

We conducted a retrospective cohort study of hypertensive patients failing to respond to monotherapy with either a DHP-CCB or an ARB who were switched to an SPC of amlodipine/valsartan (SPC group) or to treatment that could not include any SPC (control group). The groups were matched for age, gender, race, baseline blood pressure (BP), and comorbidities. The primary outcomes of the study included the proportion of patients achieving BP targets, the absolute change in BP from baseline, the proportion of patients discontinuing drug therapy because of side effects, the proportion of patients noncompliant with drug therapy, and health care resource utilization and costs.

Principal findings

Fifty-eight SPC patients achieved BP targets compared with 47 control patients ($P = 0.119$). The absolute reduction in BP was significantly greater in the SPC group (–22.8 ± 6.9/–19.3 ± 5.2 mmHg) than in the control group (–20.6 ± 6.4/–17.8 ± 5.6 mmHg) ($P < 0.03$). Significantly fewer patients discontinued antihypertensive therapy because of side effects and noncompliance in the SPC group compared with the control group (both $P = 0.042$). SPC patients accrued fewer clinic visits, laboratory tests, and electrocardiograms but had higher drug acquisition costs. Median medical therapy costs were significantly lower in the SPC group at the end of the 6-month follow-up, primarily because of lower costs for clinic visits.

Conclusion

The use of the SPC of amlodipine/valsartan was associated with greater absolute BP reductions and fewer antihypertensive drug discontinuations because of side effects and noncompliance compared with the use of the individual drugs. Although the acquisition cost of the SPC was greater than that of the individual drugs, SPC combination therapy resulted in fewer clinic visits, laboratory tests, and electrocardiograms. As a result, the total cost of SPC therapy was significantly less than that associated with the use of the individual drug components.

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INTRODUCTION

Hypertension remains the most common cardiovascular disease in the United States, affecting approximately 73 million adults (Chobanian 2003, Lloyd-Jones 2009). It is estimated that more than 50% of patients started on a single antihypertensive drug fail to achieve their target blood pressure (BP) (Materson 1993). Furthermore, only about one-third of patients with hypertension have their BP controlled to recommended levels in the United States (Chobanian 2003). It is obvious that there is a need for more aggressive intervention in patients with hypertension.

Treatment options in hypertensive patients not responding to their initial drug treatment attempt include dose titration, the use of drug combinations, and switching patients to another class of therapy. The effectiveness of these approaches has not been directly compared (Epstein 1996, Giles 2001, Hilleman 1999, Sica

2001). Survey data indicate that of patients who present at physicians' offices with blood pressures that are not at target, nearly 75% do not have adjustments in medical therapy (Berlowitz 1998, Oliveria 2002). Often, dosage titration is not attempted because of the belief that antihypertensive drug classes have relatively flat dose-response curves and that titrated doses will produce higher rates of side effects (Berlowitz 1998, Oliveria 2002).

Most hypertensive patients require the use of a combination of drugs to achieve BP targets (Bakris 2000, O'Rourke 2001). Use of combinations, although necessary to achieve BP targets, is associated with poorer rates of compliance and potentially higher cost (Hilleman 1999). One potential solution is the use of single-pill antihypertensive combinations, which incorporate two drugs into one tablet or capsule. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure says that most hypertensive patients need two or more drugs to achieve blood pressure targets, and it recommend the use of drug combinations for the initial management of patients with stage 2 hypertension (Chobanian 2003).

This is a cohort study of short term clinical outcomes and health care resource utilization and costs in patients with hypertension who are failing to respond to treatment with either an angiotensin receptor blocker (ARB) or a dihydropyridine calcium channel blocker (DHP-CCB). Patients who were then switched to a single-pill combination of amlodipine and valsartan were compared to controls who were not switched to that SPC. The objectives of this study were to compare the study groups in relation to achievement of blood pressure targets, absolute change in BP, discontinuance of a drug because of side effects, noncompliance with drug therapy, utilization of health care resources, and costs.

METHODS

Description of the study

Our study, a retrospective chart review of patients with hypertension who have failed to respond to initial monotherapy with either an ARB or with a DHP-CCB, was approved by the Creighton University Institutional Review Board.

We identified consecutive patients who were switched to a single-pill combination (SPC) of amlodipine/valsartan after they failed to achieve BP targets on monotherapy with an ARB or a DHP-CCB by searching through the electronic medical records of outpatient clinics affiliated with universities in eastern Nebraska and western Iowa. Eligible subjects were 19 years of age or older who had not responded to an ARB or a DHP-CCB between July 1, 2007 and June 30, 2008. The comparison group (controls) included matched consecutive patients failing to achieve BP targets on an ARB or DHP-CCB who were not switched to a single-pill combination of amlodipine/valsartan.

Patients who failed to achieve BP targets because of side effects related to antihypertensive therapy were not included in either the case or control groups. Patients not responding to initial ARB or DHP-CCB therapy who were enrolled in the control group could be switched to any other antihypertensive therapy or have any other antihypertensive therapy added to the existing therapy, except that those switched to any type of single-pill-combination therapy were excluded from this analysis.

Control patients were matched on the basis of age, gender, race, baseline BP, and comorbidities. We performed matching using a propensity score, which uses logistic regression to allow matching based on multiple parameters (D'Agostino 1998). Because patients with concomitant disease states were included in this analysis, patients receiving other drugs with antihypertensive effects (e.g., beta-blockers, diuretics) were not excluded unless that concomitant therapy was modified (i.e., discontinued or dose-adjusted) during the course of the study.

Duration of follow-up was a minimum of 6 months after the failure of the ARB or DHP-CCB. For patients with no concomitant BP goal-modifying comorbidity, the BP target was defined as below 140/90 mmHg. For patients with a BP target-modifying comorbidity (diabetes mellitus, coronary heart disease, chronic renal insufficiency), the BP target was defined as below 130/80 mmHg. For patients with heart failure (left ventricular dysfunction), the BP target was defined as below 120/80.

Short-term clinical outcomes: The primary outcomes of the study included the proportion of patients achieving BP targets, the absolute change in BP from baseline compared to final during the final follow-up visit, the proportion of patients discontinuing drug therapy because of side effects, the proportion of patients noncompliant with drug therapy, and health care resource utilization and costs. Noncompliant patients were defined as those who stopped filling a prescription for an antihypertensive drug, as documented in the medical chart. Health care resources included the antihypertensive agents prescribed, clinic visits, laboratory tests, and 12-lead electrocardiograms. Hospitalizations and emergency room visits were excluded for lack of complete data.

Costs: Costs of outpatient clinic visits, 12-lead electrocardiograms, and laboratory testing were based on 2009 American Medical Association Current Procedural Terminology (CPT) Code and Medicare's Resource Based Relative Value Scale (RBRVS) payment schedule (Table 1) (American Medical Association 2009, St. Anthony Publishing 2009). The cost of antihypertensive agents was based on *2009 Red Book* (Thomson Reuters Healthcare, Montvale, N.J.) average

TABLE 1
Health care resources and medications included in the analysis

Parameter	Basis of cost	Cost
Clinic visit	CPT-4 99212 straight forward medical decision CPT-4 99213 low complexity CPT-4 99214 moderate complexity CPT-4 99215 high complexity	$26.58 $42.76 $66.10 $93.70
12-lead ECG	CPT-4 93000	$18.59
Laboratory tests	CPT-4 85022 complete blood count CPT-4 80048 basic metabolic panel CPT-4 80051 electrolytes CPT-4 80053 comprehensive metabolic panel CPT-4 80061 lipid panel CPT-4 80069 renal function panel CPT-4 80076 hepatic function panel	$ 9.08 $11.83 $ 9.80 $14.77 $18.72 $12.00 $11.42
Antihypertensive drugs	*2009 Red Book*	Average wholesale price

wholesale price. Costs accrued by the treatment groups were reported as the median and the 25th and 75th percentiles.

Statistical analysis

Data were presented as the mean and standard deviation (SD) where appropriate. A student's nonpaired two-tailed *t*-test was used to compare continuous variables, and the *chi*-square test was used to compare categorical variables. For data not normally distributed (health care resource utilization and cost data), the Mann-Whitney U test was used to compare continuous variables and the Fisher exact test was used to compare categorical variables. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patients: After failing to respond to ARB or DHP-CCB monotherapy, 100 patients were switched to amlodipine/valsartan (SPC) and 100 controls were not. Demographics and clinical characteristics of the study patients are shown in Table 2. There were no significant differences between the study groups regarding age, gender, race, past medical history, proportion of patients with uncomplicated hypertension, or baseline systolic and diastolic BP because of the matching. The identity of the initial antihypertensive agent that failed before study entry differed significantly between the groups. Control patients were significantly more likely to have

TABLE 2
Demographics and clinical characteristics of the study patients

Parameter	Single-pill combination group	Control group	*P* value
Number of patients	100	100	
Age (years)	58.6 ± 10.2	57.9 ± 10.8	0.937
Gender			1.00
Men	48	48	
Women	52	52	
Race			1.00
White	75	75	
Black	13	13	
Hispanic	12	12	
Past medical history*			0.902
Coronary artery disease	18	18	
Diabetes mellitus	43	41	
Chronic renal disease	5	5	
Heart failure	5	7	
Uncomplicated hypertension	41	41	1.00
BP at study entry			
Systolic (mmHg)	154.9 ± 8.6	155.1 ± 8.4	0.71
Diastolic (mmHg)	97.6 ± 4.1	97.6 ± 4.2	0.73
Failed drug at study entry			
ARB	49	68	0.04
DHP-CCB	51	32	0.04

*Some patients had multiple conditions.

failed to respond to an ARB (68%) compared with SPC patients (49%) ($P = 0.04$). At the time of study entry, the control group received diuretics, 15%; beta blockers, 30%; ARBs, 69%; and CCBs. 31%. At the time of entry into the study, 57 patients in the SPC group were receiving a single antihypertensive prescription, compared with 60 patients in the control group. Thirty-two SPC patients were receiving two antihypertensive prescriptions, compared with 34 control patients. Eleven SPC patients were receiving three antihypertensive prescriptions, compared with six controls.

Short-term clinical outcomes: At the end of the six-month follow-up, 58 (58%) SPC patients achieved BP targets, compared with 47 (47%) control patients ($P = 0.119$). At the end of the follow-up, the reduction in systolic BP in SPC patients was 22.8 ± 6.9 mmHg compared to 20.6 ± 6.4 mmHg in control patients ($p = 0.021$). At the end of follow-up, the reduction in diastolic BP in SPC patients was 19.3 ± 5.2 mmHg compared to 17.8 ± 5.6 mmHg ($P = 0.03$). A total of nine patients in the SPC group discontinued nine antihypertensive prescriptions (all were using SPC amlodipine/valsartan because of side effects, compared with 19 patients in the control group who discontinued 21 antihypertensive prescriptions because of side effects ($P = 0.042$) (Table 3). Also, nine patients in the SPC group were noncompliant with nine antihypertensive prescriptions (all were using SPC amlodipine/valsartan) compared with 19 controls who were noncompliant with 21 antihypertensive prescriptions ($P = 0.042$) (Table 3).

At the end of follow-up, 56 single-pill-combination patients were receiving one antihypertensive prescription (amlodipine/valsartan counted as one prescription), compared to one control patient. Thirty-three SPC patients were receiving two antihypertensive prescriptions, compared with 41 control patients. Ten SPC patients were receiving three antihypertensive prescriptions, compared with 49 control patients. And one SPC patient was receiving four antihypertensive prescriptions, compared to nine control patients.

Health care resource utilization and costs: Over the duration of follow-up, there were fewer clinic visits in the SPC group, compared with the control group (432 vs. 579, $P = 0.005$) (Table 4). SPC patients were prescribed a total of 156 antihypertensive prescriptions, compared to 267 antihypertensive prescriptions in the control patients ($P = 0.005$). The numbers of laboratory tests and 12-lead electrocardiograms ordered in SPC patients were less than in control patients (Table 4), but these differences were not statistically significant.

Costs of clinic visits were significantly lower in the SPC treatment group, compared to the individual drug treatment group ($P = 0.001$). Differences in costs of laboratory tests and electrocardiograms were not significantly different between the treatment groups.

Although drug acquisition costs were greater in the SPC group, compared with the control group, the difference was not statistically significant. The higher drug acquisition costs in the SPC treatment group were more than offset by lower costs for clinic visits, laboratory tests, and 12-lead electrocardiograms. The total median cost was significantly lower for the SPC treatment group than for the control group ($P = 0.024$).

TABLE 3
Drug discontinuation in single-pill combination and control groups

Single-pill combination group			Control group*		
Drug	**Side effect**	**No. of patients**	**Drug**	**Side effect**	**No. of patients**
Amlodipine/ valsartan	Edema	4	Metoprolol and verapamil†	Bradycardia and fatigue	1
HCTZ	Dyspepsia/diarrhea	1	DHP-CCB	Edema	5
Metoprolol	Fatigue	1	Beta-blocker	Fatigue	7
HCTZ	Headache	1	Clonidine	Drowsiness	2
HCTZ	Hypokalemia	1	HCTZ	Rash	2
HCTZ	Rash	1	Atenolol	Angioedema	1
			Hydralazine	Fever	1
			Metoprolol	Sexual dysfunction	2

*Two patients in the control group discontinued two separate drugs. †Both drugs were discontinued.

TABLE 4
Health care resource utilization in the single-pill combination and control groups

Health care resource	Case group	Control group
Clinic visits		
CPT-4 99212	259	324
CPT-4 99213	137	155
CPT-4 99214	26	58
CPT-4 99215	10	42
Total	432	579*
12-lead electrocardiograms (CPT-4 93000)	119	140
Laboratory tests		
CPT-4 85022 CBC	104	108
CPT-4 80048 BMP	78	80
CPT-4 80051 Electrolytes	24	38
CPT-4 80053 CMP	34	40
CPT-4 80061 Lipid panel	62	63
CPT-4 80069 Renal panel	59	74
CPT-4 80076 Hepatic panel	42	59
Antihypertensive drugs prescribed†	156	267*

*$P = 0.005$. † Amlodipine/valsartan fixed dose combination counted as one prescription.

DISCUSSION

The results of this study suggest that the use of an SPC of amlodipine/valsartan has several advantages compared to a treatment strategy that does not include SPC therapy. In patients initially failing to respond to monotherapy with either a DHP-CCB or an ARB, the use of an SPC product was associated with a significantly greater reduction in both systolic and diastolic BP, fewer patients discontinuing antihypertensive drug therapy because of side effects, and fewer patients who were noncompliant with antihypertensive drug therapy, compared with a treatment strategy not using an SPC product. The SPC treatment group received a significantly lower number of antihypertensive prescriptions (with the SPC counting as one prescription), compared to the control group. A greater proportion of patients receiving SPC therapy also achieved their target BP targets compared to the group not receiving SPC therapy, but this difference was not statistically significant.

The SPC treatment group had fewer clinic visits, laboratory tests, and electrocardiograms. Costs associated with clinic visits were significantly lower in the SPC treatment group, compared with the control group.

Patients in the SPC group had a higher antihypertensive drug acquisition cost, which was more than offset by the reduction in costs for clinic visits, laboratory tests, and electrocardiograms. As a result, total health care costs were significantly lower in the SPC group.

There were fewer clinic visits, probably because a greater proportion of SPC patients achieved their BP goal at an earlier point after the start of therapy.

There is clear and substantial evidence that approximately two thirds of hypertensive patients require more than one antihypertensive agent to achieve their BP targets (Bakris 2000, Chobanian 2003, O'Rourke 2001). As the number of prescribed medications increases, rates of compliance, potential for drug interactions, potential for side effects, and the cost of purchasing and monitoring drug therapy increase. A meta-analysis of nine studies in different chronic disease states compared adherence to drug therapy with single-pill combinations versus free-drug components of the regimen (Bangalore 2007). SPC products improved the relative adherence rate by 26%, compared with free-drug-component regimens. A subgroup analysis of the four studies in patients with hypertension demonstrated that SPC drugs reduced noncompliance by 24%, compared with free drug combinations.

In a separate study, hypertensive patients had significantly greater compliance using SPC amlodipine/benazepril than using the individual components (81% vs 73%; $P < 0.001$) (Taylor 2003). The cost of cardiovascular care was also significantly less in the SPC treatment group compared with the use of the individual components ($P < 0.001$).

When combination therapy is needed to treat hypertension, the *JNC-7* guidelines indicate a preference for a thiazide-like diuretic (Chobanian 2003). Diuretics produce an additive antihypertensive effect with most other classes of antihypertensive drugs, have been shown to reduce mortality in a variety of hypertensive populations, and are inexpensive (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002, Beckett 2008, Chobanian 2003). This preference is largely based on the results of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002). In ALLHAT, amlodipine-based and chlorthalidone-based treatment strategies produced similar effects on mortality, myocardial infarction, and stroke. Given the lower cost of thiazides and certain secondary out-

TABLE 5
Per patient health care resource utilization costs in case and control groups accrued over the 6-month follow-up*

Health care resource	Single-pill combination group	Control group
Clinic visits	$1,539 ($1,420–$1,645)	$2,300 ($2,195–$2,478)†
12-lead electrocardiograms (CPT-4 93000)	$221 ($190–$255)	$260 ($235–$289)
Laboratory tests	$495 ($426–$563)	$563 ($501–$608)
Antihypertensive drugs prescribed	$479 ($402–$556)	$367 ($290–$456)
Total	$2,734 ($2,438–$3,019)	$3,490 ($3,221–$3,831)‡

*Costs are reported as the median and the 25th and 75th percentiles. †$P = 0.001$. ‡$P = 0.024$

comes, the ALLHAT investigators concluded that thiazides should be the initial choice of antihypertensive agent for most patients unless they have a compelling indication for another specific type of drug. The major limitation of ALLHAT is that the three treatment arms included drug combinations that would not typically be used during the ordinary course of clinical hypertension management.

More recent studies suggest that drugs other than thiazides may be better choices for the management of hypertension. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) demonstrated that the use of amlodipine plus an angiotensin-converting enzyme (ACE) inhibitor was superior to the use of a beta-blocker (atenolol) plus a thiazide diuretic in hypertensive patients with three or more major cardiovascular risk factors (Dahlof 2005). Over a 5.7-year follow-up, the amlodipine/ACE inhibitor group had an average 2.7/1.9 mmHg greater reduction in BP than the beta-blocker/diuretic group. Compared to beta-blocker/thiazide therapy, the amlodipine/ACE inhibitor combination was also associated with a statistically greater reduction in fatal and nonfatal stroke, total cardiovascular events, and all-cause mortality.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial randomized 11,506 hypertensive patients to single-pill combinations of an ACE inhibitor plus a diuretic or an ACE inhibitor plus amlodipine (Jamerson 2008). After a mean follow-up of 36 months, the ACE inhibitor plus amlodipine group produced a statistically significant greater reduction in systolic (–0.9 mmHg) and diastolic (–1.11 mmHg) BP, compared to the single-pill combination of ACE-inhibition and thiazide. More important, the ACE inhibitor-plus-amlodipine group had a significantly lower rate of fatal and nonfatal cardiovascular events (9.6%) than the ACE inhibitor-plus-thiazide group (11.8%). The absolute risk reduction was 2.2%, with a relative risk reduction of 19.6% (hazard ratio, 0.80; 95% CI 0.72 to 0.90; $P < 0.001$).

The results of the ASCOT-BPLA and ACCOMPLISH suggest that renin-angiotensin-aldosterone system (RAAS)–modulating drugs should be the initial drug of choice for a majority of patients with hypertension (Dahlof 2005, Jamerson 2008). For patients failing to reach their BP target, the addition of amlodipine to a RAAS-modulating drug is a better choice than the selection of a thiazide-like diuretic. Recently the U.S. FDA approved two single-pill formulations of the combination of amlodipine with RAAS modulating agent: amlodipine/valsartan and amlodipine/olmesartan for use as initial therapy in the management of hypertension. The results of the present study suggest that the use of a single-pill combination of an RAAS modulator and amlodipine has specific advantages over the use of these drugs as free drug components.

STUDY LIMITATIONS

Our study has several limitations. Most important, data collection was retrospective. Although the study groups were well matched at baseline, it is never possible to adjust for all potential differences that a true prospective, randomized trial would address.

It is also possible that study participants sought medical care from providers outside of their usual health care system, which our study would not be able to identify. The initial drug failure at study entry was significantly different: More control patients, compared with case patients, failed to respond to an ARB at entry into the study. It is not known what clinical implications, if any, this had on the study findings.

Finally, a larger number of study participants might have given the study the power needed to demonstrate a difference in the number of patients achieving their BP targets.

CONCLUSION

These of the single-pill combination of amlodipine/valsartan was as-

sociated with greater absolute BP reductions, fewer antihypertensive drug discontinuations because of side effects, and fewer antihypertensive drug discontinuations because of noncompliance, compared with the use of the individual free drug components.

Although the cost of the single-pill combination was greater than the individual drugs, SPC therapy resulted in fewer clinic visits, laboratory tests, and electrocardiograms. As a result, the total cost of SPC therapy was not significantly greater than the use of the individual drug components.

DISCLOSURE

The authors report that Novartis Pharmaceuticals provided partial funding for the study but did not have input into study design, data input, or manuscript preparation. Novartis markets amlodipine/valsartan as the registered trade name product Exforge.

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