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Research Article

Treatment adherence, clinical outcomes, and economics of triple-drug therapy in hypertensive patients

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Abstract

Poor antihypertensive treatment adherence adversely affects blood pressure control. We analyzed US health plan data to assess the impact of fixed- versus loose-dose triple-combination therapy on adherence, clinical, and economic outcomes. Patients initiating triple therapy with an angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, or beta blocker plus amlodipine and hydrochlorothiazide comprised three cohorts. Within-cohort comparisons were made between fixed-dose combinations of two antihypertensives plus a second pill (two pills) or three separate pills. Outcomes included adherence, cardiovascular events, health care resource use, and costs for patients with ≥12 months follow-up. A total of 16,290 patients were matched. Patients receiving two pills were more likely to be adherent ($P < .001$) and less likely to discontinue treatment ($P < .001$) across all cohorts. Therapy with two versus three pills resulted in significantly lower adjusted risk of cardiovascular events (hazard ratio = 0.76, $P = .005$) in the beta blocker cohort only. Total adjusted health care costs were significantly lower for two- versus three-pill therapy in the beta blocker cohort only (cost ratio = 0.74 overall, $P < .01$; 0.71 hypertension-attributable, $P < .01$). In patients with hypertension requiring triple therapy, fixed-dose combinations that lower pill burden may improve adherence (seen across all cohorts) and clinical outcomes (seen in the beta blocker cohort) without increasing health care costs. J Am Soc Hypertens 2013;7(1):46–60.

Keywords: Adherence; adrenergic receptor blockers; angiotensin antagonist; beta blockers; calcium channel blockers; cost-benefit analysis; diuretics; drug therapy.

Introduction

The prevalence of hypertension in the United States in adults aged ≥18 years between 2003 and 2010 was estimated to be 30.4% (66.9 million adults).[1] Hypertension is a major risk factor for cardiovascular disease and the fifth most costly medical condition in the United States.[2,3] In a recent analysis, the economic cost of hypertension was approximately $16,940/person/year in 2007.[3] Annual direct and indirect costs attributable to hypertension in the United States were estimated to be $69.9 and $23.6 billion, respectively, in 2010 (2008 US$).[4]

Despite the availability of numerous antihypertensive agents, approximately 50% of individuals with hypertension do not have their blood pressure adequately controlled according to the goals recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7; <140/90 mm Hg or <130/80 mm Hg in patients with diabetes or renal disease).[5,6] A major factor that contributes to this poor control is nonadherence to the therapeutic regimen.[7–9] Approximately 40% of patients with hypertension stop taking their medications within 2 years of initiating therapy, and only 39% continue their medications for 10 years.[10]

Available data (including data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]) suggest that at least 25% of individuals with hypertension will require a triple-combination

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regimen to achieve currently recommended blood pressure goals.[11,12] Because adherence and persistence correlate inversely with the number of medications used,[13–15] patients on multiple pills for hypertension are less likely to adhere to and persist with therapy and are thereby at greater risk for uncontrolled hypertension and hypertension-associated cardiovascular disease.[16] Simplifying the therapeutic regimen with single-pill, fixed-dose combination (FDC) therapies versus free-drug or loose-dose combination (LDC) therapies has been shown to enhance adherence, improve clinical outcomes, and lower total medical costs.[17–20] The objectives of this claims-based analysis was to assess the impact of antihypertensive treatment pill burden on regimen adherence and clinical and economic outcomes in patients with hypertension receiving triple-combination therapy with amlodipine besylate (AML), hydrochlorothiazide (HCTZ), and an angiotensin receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACEi), or beta blocker (BB).

Methods

Study Design

A retrospective, observational analysis was performed using medical and pharmacy claims, linked sociodemographic information, and enrollment data from a large US health plan associated with OptumInsight. Data for commercial and Medicare enrollees (Managed Medicare Advantage health plan members, Medicare Part D, before and after 2006) between July 1, 2002, and September 30, 2009, were identified. Membership in this plan was geographically diverse, with coverage across the United States. Institutional review board approval was not required for this analysis, because identities and medical records were not disclosed; the database was evaluated using methods consistent with the Health Insurance Portability and Accountability Act.

Patients

Enrollees who initiated triple-drug antihypertensive therapy using AML, HCTZ, and either an ARB, ACEi, or BB between January 1, 2003, and September 30, 2008, were identified. Enrollees who satisfied the following criteria were identified as triple-drug antihypertensive therapy users: 1) overlapping claims for each of the three (2) components for the three-pill (2-pill) therapy users, with an overlapping claim defined as a pharmacy claim for one of the drugs before or on the run-out date (prescription fill date plus 1-day supply) of the other drug(s); and 2) continuation of the first component of the triple-drug therapy as indicated by a second fill within 30 days of running out of drug supply. For example, a subject had a pharmacy claim for medication A and a pharmacy claim for medication B within the run-out of medication A. If a pharmacy claim for medication C occurred after the fill date for medication B, but within the run-outs for both medication A and medication B, the triple-therapy date was defined as the date of the pharmacy claim for medication C. To qualify as a triple-antihypertensive therapy, subsequent fills were required for medication A (within 30 days of run-out for prior fill for medication A), medication B (30 days of run-out for prior fill for medication B), and medication C (30 days of run-out for prior fill for medication C).

Patients had a 6-month baseline period before the triple treatment date and were followed for at least 12 months after the triple treatment date until disenrollment or September 30, 2009. Patients were included in the final study sample if they had evidence of triple-drug antihypertensive therapy as defined previously, were $\geq$18 years of age on the index date, had a primary or secondary International Classification of Diseases (ICD)-9 Clinical Modification (CM) diagnosis code for hypertension (401.x, 402.xx, 403.xx, 404.xx) during the baseline period, had continuous enrollment with pharmacy and medical benefits during baseline and follow-up periods, did not receive non-study medication belonging to four or more subclasses during the baseline period, did not have evidence of hospital admission in the 30 days before the index date, and did not have a primary or secondary ICD-9-CM diagnosis, ICD-9-CM Health care Common Procedure Coding System (HCPCS), or ICD-9-CM procedure codes for pregnancy, labor, or delivery at any time during the study period.

Patients satisfying the selection criteria were assigned to one of three treatment cohorts, with each cohort further stratified into FDC (two-pill) or LDC (three-pill) groups: ARB cohort (two pill: AML/ARB plus HCTZ, ARB/HCTZ plus AML; three pill: AML plus HCTZ plus ARB), ACEi cohort (two pill: AML/ACEi plus HCTZ, ACEi/HCTZ plus AML; three pill: AML plus HCTZ plus ACEi), and BB cohort (two pill: BB/HCTZ plus AML; three pill: AML plus HCTZ plus BB).

Outcome Measures

The length of follow-up in days, inclusive of the index date, was calculated for each patient. Indices of adherence and persistence with triple therapy, treatment modification, health care cost and resource utilization, and clinically important cardiovascular and renal outcomes were assessed for the entire follow-up period. The proportion of days covered (PDC) with triple therapy was defined as the ratio of the number of days on therapy for which enrollees had access to all three agents in their antihypertensive regimen over the follow-up duration.[21] PDC was assessed for the follow-up as a continuous variable and as an ordinal categorical measure (PDC $<$50%, $\geq$50% and $<$80%, and $\geq$80%). The categories are indicative of poor adherence,