ORIGINAL RESEARCH

Comparative Effectiveness of Antihypertensive Therapeutic Classes and Treatment Strategies in the Initiation of Therapy in Primary Care Patients: A Distributed Ambulatory Research in Therapeutics Network (DARTNet) Study

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Background: **Few comparative effectiveness studies of treatment strategies using antihypertensive therapeutic classes in hypertension control have been assessed in a primary care environment. The objectives are to compare the effectiveness of common antihypertensive therapeutic classes initiated as monotherapy and of fixed-dose combinations (FDCs), free-equivalent combinations (FECs), and monotherapy on hypertension control.**

Methods: **This article reports observational comparative effectiveness analyses of data electronically extracted from electronic health records. The study population consisted of 8,676 patients with an incident prescription for an antihypertensive agent of a total of 79,176 patients receiving antihypertensive therapy in 33 geographically diverse primary care clinics. The main measures were reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and rates of attaining goals per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).**

Results: **There were small, clinically insignificant differences in blood pressure reductions between the monotherapy classes. Higher rates of blood pressure control were obtained when patients were initiated on an angiotensin-converting enzyme inhibitor than a thiazide or thiazide-like diuretic (47.8% vs 39.9%) or a β-blocker versus a thiazide (45.9% vs 39.9%). Patients initiated on FDCs had significantly larger reductions in blood pressure than patients initiated on FECs (−17.3 vs −12.0 mm Hg SBP; −10.1 vs −6.0 mm Hg DBP) or monotherapy (−17.3 vs −13.6 mm Hg SBP; −10.1 vs −7.9 mm Hg DBP). Rates of attaining JNC7 goals also were better for FDCs than FECs (57.2% vs 42.5%) and for FDCs versus monotherapy (57.2% vs 44.9%).**

Conclusions: **Patients initiated on angiotensin-converting enzyme inhibitors and β-blockers had slightly higher rates of blood pressure control. The use of FDCs as initial therapy is more effective in the control of hypertension than monotherapy or FECs.(J Am Board Fam Med 2013;26:529–538.)**

Keywords: **Antihypertensives, Comparative Effectiveness Research, Drug Therapy, Hypertension, Practice-based Research, Primary Health Care**

About one third of US adults (76.4 million)[1] have hypertension, which is strongly associated with an increased risk of major adverse cardiovascular events (MACEs); treatment of hypertension has been shown to reduce that risk.[2–4] However, only

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about half of hypertensive patients have control of their blood pressure,[1] which leaves a substantial proportion of the population at an increased, but modifiable, risk of MACEs.

Monotherapy is the recommended initial approach for reducing blood pressure, except for stage II hypertension (blood pressure ≥160/100 mmHg).[5] While some individuals can achieve control of their blood pressure and bring it to guideline-recommended levels using a single medication, 63% of 12,210 patients with a 5-year visit in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) required ≥2 agents.[6] Another strategy for treating hypertension is the use of combination therapy: either a fixed-dose combination (FDC), which combines 2 active agents into a single pill, or a free-equivalent combination (FEC), which is the separate use of the corresponding single-agent pills. Several efficacy trials have previously shown combination therapy to be more effective than monotherapy in achieving blood pressure control, but we have found no randomized control trials that explicitly evaluated differences in efficacy between the 2 combination strategies.[7–9] Other studies, however, have shown that patients using an FDC have greater adherence to and persistence with medication regimens compared with patients using an FEC.[10,11]

The objectives of the present study were to (1) assess the comparative effectiveness of several antihypertensive therapeutic classes initiated as monotherapy, and (2) compare the effectiveness of the initial use of 3 treatment strategies (monotherapy, FDC, and FEC) in hypertensive patients receiving care in a diverse primary care setting.

Methods

Data Source

This study was conducted using data from primary care clinics participating in the Distributed Ambulatory Research in Therapeutics Network (DARTNet) collaborative, a federated network of electronic health record (EHR) data that has as one of its objectives the facilitation of observational comparative effectiveness research.[12–14] DARTNet, in collaboration with QED Clinical, Inc. (doing business as CINA; http://www.cina-us.com/), has developed data extraction, transformation, and loading (ETL) processes that allow aggregation of data from disparate EHRs into a limited database. All data were imported nightly from the organization EHR to a relational clinical data repository (CDR) located behind the firewall of each organization. The CINA software used for ETL was already in place and being used by each organization to produce reports of clinical decision support and population management at the point of care.

Data validation was largely the responsibility of CINA, as the ETL vendor in place at each organization before the initiation of this project. Because CINA provides software tools that utilize data from the CDR in the course of clinical care and decision making, CINA has several processes in place to ensure the reliability and validity of the data that is contained within the CDR. Data reliability testing by CINA includes the following: (1) patient-level sampling comparing the data imported into the CDR with the source data as it is represented in the EHR; (2) daily use of the data in the CDR in clinical practice through the point-of-care clinical decision support tool and population management tools provided by CINA; and (3) data reliability testing with data extraction for research analysis.

The DARNet Cardiovascular Risk Reduction Learning Community was designed to provide patient-specific clinical decision support at the point of care and an audit with feedback on national guidelines (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC7]) for the control of blood pressure (unpublished data). The Cardiovascular Risk Reduction Learning Community limited data set obtained from the DARTNet collaborative also was used for the current study, which includes 33 primary care clinics from 10 health organizations and approximately 154 clinicians providing care to more than 250,000 patients.

Data use agreements for access to the limited data set were obtained from each organization, and a waiver of informed consent and Health Insurance Portability and Accountability Act authorization were approved by the American Academy of Family Physicians' institutional review board and the Colorado Multiple Institutional Review Board of the University of Colorado Denver.

Data Collection and Cleaning

The data used in the present analyses included patient demographics, height, weight, blood pressure, comorbidities (International Classifica-

tion of Diseases, 9th revision, codes from the problem lists and reasons for visit), medications, laboratory data, and dates of encounters between August 2001 and August 2011. Data on patient race/ethnicity and frequency of medication dosing were sparsely populated and were not included in our analyses.

For continuous variables, physiologically implausible values were identified by clinicians examining the distributions of the variables. These consensus-derived, physiologically implausible values were systolic blood pressure <50 or >260 mm Hg, diastolic blood pressure <0 or >200 mm Hg, height <45 or >90 inches, weight <50 or >500 lb, and serum creatinine <0.2 or >20 mg/dL and were excluded in the current study. The proportion of values deleted varied from 0.005% for systolic blood pressure to 0.5% for serum creatinine. In addition, height and weight were missing for 4.2% and 0.3% of patients, respectively, and were replaced with sex-specific mean values for height (women, 63.9 inches; men, 69.8 inches) and weight (women, 178.9 lb; men, 212.9 lb).

Definitions

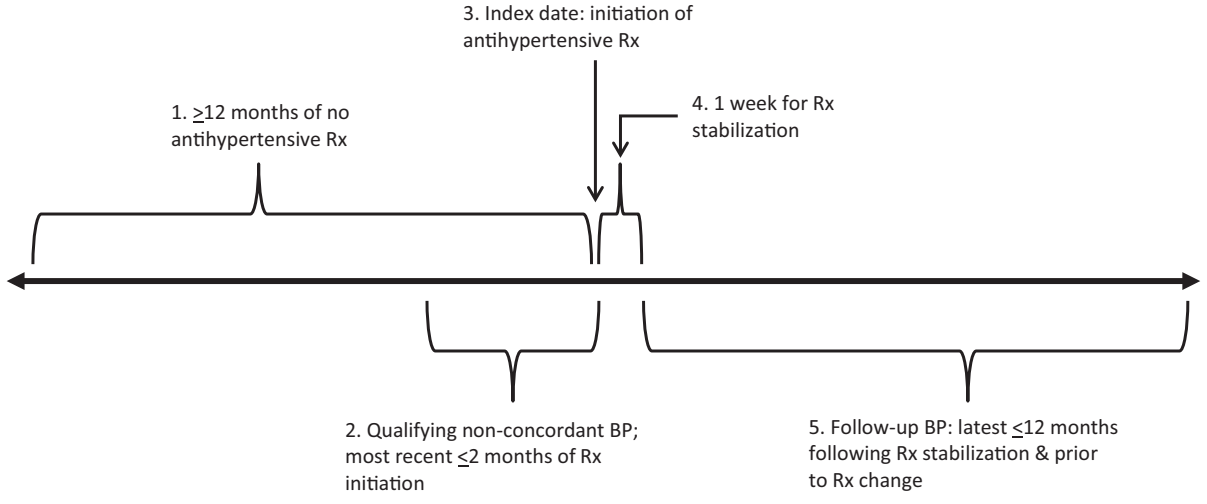
A diagnosis of hyperlipidemia was defined as an active International Classification of Diseases, 9th revision, code from 272.xx during at least one visit, hypertension as a code from 401 to 405.xx or 437.2 during at least one visit, diabetes mellitus as codes from 250.xx during at least 2 visits or ≥1 antidiabetic medication, and chronic kidney disease (CKD) as a code from 403 to 404.xx, 581 to 582.x, 585 to 586.x, V45.11, V45.12, or V56.x during at least one visit or a calculated glomerular filtration rate[15] of >60 mL/min/1.73 m^2. Patients were assumed to be white for purposes of calculating glomerular filtration rate. Finally, therapeutic goals were defined per the JNC7 (<130/80 mm Hg for patients with CKD or diabetes mellitus and <140/90 for all others).[5]

Antihypertensive agents were categorized into the following therapeutic classes: angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARB), cardioselective β-blockers, calcium channel blockers (CCBs), and thiazides and thiazide-like diuretics (thiazide) using the Medi-Span Master Drug Data Base version 2.5 (Medi-Span/Wolters Kluwer Health, Indianapolis, IN). FDCs and FECs were defined as being composed of 2 of the 5 monotherapy therapeutic classes. All other antihypertensive therapeutic classes were excluded because of numbers insufficient for adequate analyses.

Patient Inclusion

Figure 1 defines the inclusion criteria for this study. The index date was defined as the date of the first prescription of an antihypertensive agent, before which the patient had been followed with no antihypertensive prescriptions for ≥12 months. The index blood pressure was the value closest to and falling within the 2-month

Figure 1. Timeline defining key events in the study for patients initially using antihypertensive agents. BP, blood pressure; Rx, prescription.



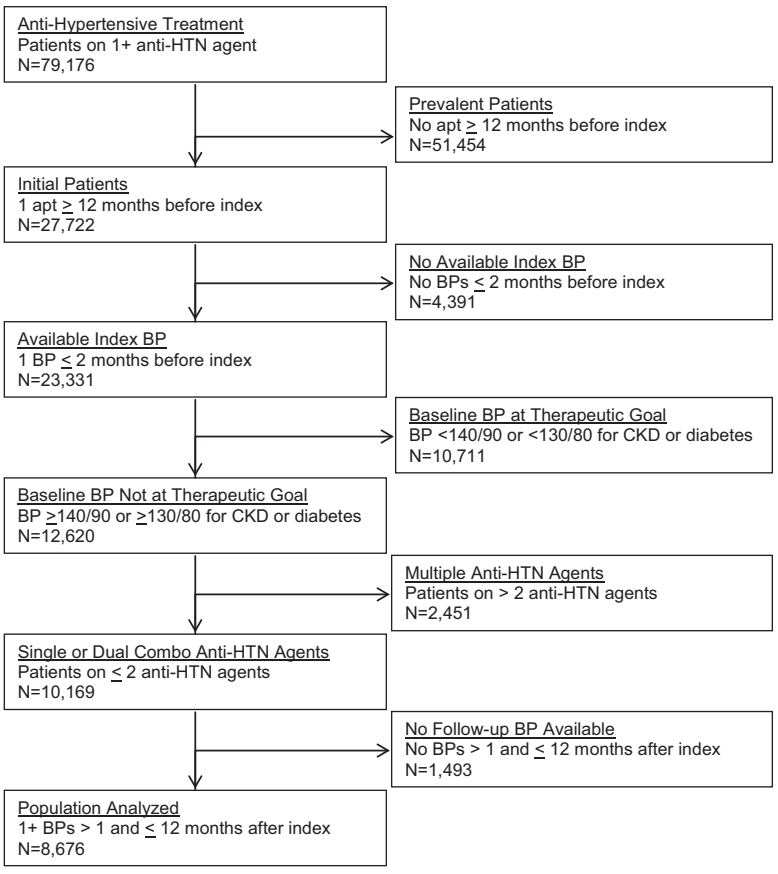
interval before the initiation of antihypertensive therapy. If the patient's treatment was classified as FEC, the second drug must have been started within 3 days of the first. The blood pressure value used to assess reduction and goal attainment from the index pressure was the one with the latest date/time stamp within the time period of 1 week to 1 year following the index time point during which no change had been made in the antihypertensive drug regime.

Figure 2 shows the STROBE diagram for inclusion of patients in our analyses. There were 79,176 patients ≥18 years old who were receiving at least one antihypertensive agent. Exclusions were as follows: (1) 51,454 patients classified as prevalent users of antihypertensive agents because there was no period ≥12 months in duration when they received no antihypertensive agents; (2) 4,391 patients who had no blood pressure measured in the 2 months before initiation of antihypertensive therapy; (3) 10,711 patients whose blood pressure was at goal in the 2 months before initiating antihypertensive therapy; (4) 2,451 patients taking ≥3 antihypertensive agents; and (5) 1,493 patients with no blood pressure measurements available following the initiation of antihypertensive therapy. The final analytic subset consists of 8,676 patients (11.0%) of the 79,176 patients ≥18 years old who had received at least one prescription for an antihypertensive agent and had elevated blood pressures (as defined by the JNC7) before or on the index date. The outcomes evaluated in this study were changes in follow-up systolic and diastolic blood pressures from index blood pressures and JNC7 therapeutic goal attainment rates at follow-up.

Statistical Analyses

To characterize the study population, we calculated descriptive statistics using means and standard deviations for continuous variables and compared the different antihypertensive therapeutic classes using analyses of variance. For categorical variables, frequencies and percentages were calculated and lo-

Figure 2. STROBE diagram of included patients with initial use of antihypertensive agents (anti-HTN). Apt, appointment; BP, blood pressure; CKD, chronic kidney disease.



gistic regression was used to compare patient characteristics between the groups.

We used analysis of covariance to model mean reductions in blood pressures and logistic regression to compare the proportion of patients achieving blood pressure control in each group. To account for patient differences, we constructed multivariable prediction models using the covariates listed in Table 1, which were chosen using clinical judgment and prior research. All covariates were included in each risk-adjusted model, except in the case of mean reductions in blood pressures, for which baseline diastolic blood pressure was not included in the model of mean reductions in systolic blood pressure and vice versa. Hierarchical linear models including clinic and organization also were evaluated and gave similar results (data not shown).

Risk-adjusted outcomes for each antihypertensive therapeutic class were calculated from predicted values obtained from models fitted with covariates only. Means and standard deviations of the predicted values were calculated to obtain risk-adjusted average reductions in blood pressures. For risk-adjusted control rates, expected rates of control for each antihypertensive therapeutic class were compared with the observed rates of control as an observed-to-expected ratio, which was converted to standardized rates by multiplying each observed-to-expected ratio by the observed rate of control for all patients across all antihypertensive therapeutic classes.

For all outcomes, *P* values were adjusted for multiple tests using the Bonferroni method. All statistical tests were considered to be significant at a 2-sided $P < .05$. All analyses were performed using SAS software version 9.3 (SAS Inc., Cary, NC).

Table 1. Population Characteristics

Selected Risk-Adjustment Variables	Study Cohort (n = 8676)
Female sex	4693 (54.1)
Age at index (years), mean (SD)	54.4 (13.4)
Body mass index (kg/m^2), mean (SD)	30.7 (6.9)
Index SBP (mm Hg), mean (SD)	148.7 (15.1)
Index DBP (mm Hg), mean (SD)	90.4 (10.9)
Chronic kidney disease	854 (9.8)
Diabetes mellitus	1325 (15.3)
Hyperlipidemia diagnosis	2841 (32.8)
Hypertension diagnosis	5330 (61.4)
Follow-up duration (months)	
Mean (SD)	6.3 (3.9)
Median (IQR)	6.5 (2.5–10.5)
Clinic visits within 1 year before index	
Mean (SD)	3.9 (3.4)
Median (IQR)	3.0 (2.0–5.0)

Data are n (%) unless otherwise indicated.
DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

Results

Population Characteristics

The population characteristics for all 8676 patients initially using antihypertensives in primary care are shown in Table 1. They tended to be middle-aged and overweight, and slightly less than a quarter of the patient had either diabetes or CKD requiring lower blood pressure goals. Only 61% had a diagnosis of hypertension. The median follow-up duration was a little more than 6 months and, in general, the patients had approximately 3 clinic visits in the year before index date.

Population characteristics stratified by therapeutic class are presented in Table 2 and by treatment strategy in Table 3. The proportions and mean values for essentially all risk factors differed significantly across therapeutic classes and treatment strategies. The prevalence of CKD was greater in those initiated on a β-blocker (11.5%), ARB (9.8%), and CCB (17.8%) compared with an ACEI (7.1%) or a thiazide (6.5%), and patients with diabetes and hyperlipidemia tended to receive an ACEI (25.2% and 37.6%, respectively) or an ARB (20.5% and 36.8%) more than the other therapeutic classes. For the groups defined by treatment strategy, women, older patients, and patients with CKD or diabetes were initiated on an FEC more often than an FDC or monotherapy, and patients with a diagnosis of hypertension were initiated on an FDC or an FEC more often than monotherapy. Also of note is that the index systolic and diastolic blood pressures were substantially higher in those initiated on an FDC (154 and 94 mm Hg, respectively) compared with those initiated on an FEC (148 and 86 mm Hg, respectively) or monotherapy (148 and 90 mm Hg, respectively).

Table 4 presents the frequencies and proportions of patients initiated on FDC or FEC treatment strategies by different therapeutic class combinations. Although similar numbers of patients

Table 2. Unadjusted Population Characteristics for Primary Care Patients With Initial Use of Monotherapy Antihypertensive Agents by Therapeutic Class

Characteristics	ACEI (n = 3131)	Thiazide (n = 1947)	Cardioselective β-blocker (n = 1029)	ARB (n = 533)	CCB (n = 529)	*P**
Female sex, n (%)	1442 (46.1)	1248 (64.1)	601 (58.4)	275 (51.6)	312 (59.0)	<.001
Age at index (years)	53.6 (13.0)	52.6 (13.0)	54.1 (14.4)	55.2 (12.4)	57.8 (14.7)	<.001
BMI (kg/m^2)	30.9 (6.8)	31.1 (7.3)	28.9 (6.2)	30.4 (6.1)	29.7 (6.7)	<.001
Index systolic BP (mm Hg)	147.6 (15.0)	149.3 (13.4)	147.7 (15.4)	147.8 (14.9)	149.5 (15.7)	<0.001
Index diastolic BP (mm Hg)	90.1 (10.7)	91.5 (10.1)	90.1 (10.9)	89.7 (10.4)	89.4 (11.4)	<.001
CKD, n (%)	221 (7.1)	127 (6.5)	118 (11.5)	52 (9.8)	94 (17.8)	<.001
Diabetes, n (%)	789 (25.2)	89 (4.6)	75 (7.3)	109 (20.5)	29 (5.5)	<.001
Hyperlipidemia, n (%)	1177 (37.6)	557 (28.6)	296 (28.8)	196 (36.8)	155 (29.3)	<.001
Hypertension, n (%)	1902 (60.8)	1335 (68.6)	506 (49.2)	258 (48.4)	279 (52.7)	<.001
Follow-up duration (months)	6.5 (3.8)	5.9 (3.9)	6.3 (3.9)	6.2 (3.8)	6.4 (4.0)	<.001
Number of clinic visits	3.8 (3.2)	3.9 (3.2)	4.2 (4.0)	3.6 (3.4)	4.3 (3.8)	<.001

Data are mean (standard deviation) unless otherwise indicated.
**P* values were from analysis of variance (ANOVA) or logistic regression and test the overall effect across the five therapeutic classes.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; thiazide, thiazide and thiazide-like diuretics.

were initiated on an FDC (n = 795) as an FEC (n = 712), some combination of an ACEI plus a thiazide or ARB plus a thiazide accounted for 81% of those initiated on an FDC, whereas the distribution among 2-drug combinations was much more heterogeneous for those started on an FEC.

Antihypertensive Therapeutic Class Outcomes

Table 5 presents the unadjusted and risk-adjusted changes in blood pressure and goal attainment rates for patients initiated on a monotherapy. All 5 therapeutic classes were efficacious in reducing blood pressure with remarkably similar average reductions. There were no significant differences in the unadjusted average systolic blood pressure reductions and only 2 statistically significant (albeit questionably clinically significant) differences after risk adjustment (both <1.0 mm Hg). The unadjusted average diastolic blood pressure reductions also were similar, with only a single significant differ-

Table 3. Unadjusted Population Characteristics for Primary Care Patients with Initial Use of Antihypertensive Agents by Treatment Strategy

Characteristics	FDC (n = 795)	FEC (n = 712)	Monotherapy (n = 7169)	*P**
Female sex, n (%)	373 (46.9)	442 (62.1)	3878 (44.7)	<.001
Age at index (years)	52.9 (12.6)	61.9 (12.9)	53.8 (13.4)	<.001
BMI (kg/m^2)	31.9 (7.2)	30.4 (6.9)	30.6 (6.8)	<.001
Index systolic BP (mm Hg)	153.8 (16.5)	147.8 (16.4)	148.2 (14.7)	<.001
Index diastolic BP (mm Hg)	94.3 (11.1)	85.9 (12.2)	90.4 (10.6)	<.001
CKD, n (%)	54 (6.8)	188 (26.4)	612 (7.1)	<.001
Diabetes, n (%)	66 (8.3)	168 (23.6)	1091 (12.6)	<.001
Hyperlipidemia, n (%)	251 (31.6)	209 (29.4)	2381 (27.4)	.09
Hypertension, n (%)	594 (74.7)	456 (64.0)	4280 (49.3)	<.001
Follow-up duration (months)	6.2 (3.8)	6.7 (3.9)	6.3 (3.9)	.02
Number of clinic visits	3.0 (2.8)	4.2 (3.8)	3.9 (3.4)	<.001

Data are mean (standard deviation) unless otherwise indicated.
**P* values were from analysis of variance (ANOVA) or logistic regression and test the overall effect across the three treatment strategies.
BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; FDC, fixed-dose combination; FEC, free-equivalent combination.

Table 4. Therapeutic Classes for Initial Use Patients Initiated on a Fixed-Dose Combination (FDC) or Free-Equivalent Combination (FEC)

Therapeutic class	FDC (n = 795)	FEC (n = 712)
ACEI and thiazide	397 (49.9)	187 (26.3)
ARB and thiazide	250 (31.5)	39 (5.5)
ACEI and CCB	83 (10.4)	80 (11.2)
ACEI and β-blocker	0 (0)	140 (19.7)
β-Blocker and thiazide	34 (4.3)	81 (11.4)
CCB and thiazide	0 (0)	73 (10.3)
ARB and CCB	31 (3.9)	28 (3.9)
β-Blocker and CCB	0 (0)	38 (5.3)
ARB and β-blocker	0 (0)	34 (4.8)
ACEI and ARB	0 (0)	12 (1.7)

Data are number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; β-blocker, cardioselective β-blocker; CCB, calcium channel blocker; thiazide, thiazide and thiazide-like diuretics.

ence (between ACEI and thiazide), albeit in reverse, after risk adjustment. However, although statistically significant, these differences were small (unadjusted 1.5 mm Hg; risk-adjusted 0.3 mm Hg). Patients initiated on either an ACEI or β-blocker had significantly higher rates of unadjusted and adjusted goal attainment than patients initiated on a thiazide.

Antihypertensive Treatment Strategy Outcomes

Table 6 presents the unadjusted and risk-adjusted change in blood pressures and goal attainment rates for patients initiated on FDC, FEC, or monotherapy treatment strategies. Patients initiated on an FDC had significantly larger average reductions in systolic and diastolic blood pressures and goal attainment rates than patients initiated on an FEC or monotherapy for both the unadjusted and risk-adjusted outcomes. Patients receiving FEC therapy had significantly smaller unadjusted reductions in systolic and diastolic blood pressures and unadjusted goal attainment rates when compared with patients initiated on monotherapy. After risk adjustment, patients initiated on monotherapy demonstrated a significantly larger average reduction in only systolic blood pressure over patients initiated on an FEC, although this difference was <2 mm Hg.

Table 5. Unadjusted and Risk-Adjusted Change* in Blood Pressure (BP) and Goal Attainment Rates by Antihypertensive Therapeutic Classes Initiated as Monotherapy

Outcomes	ACEI (n = 3131)	Thiazide (n = 1947)	Cardioselective β-blocker (n = 1029)	ARB (n = 533)	CCB (n = 529)
Systolic BP (mm Hg)					
At index	147.6 (15.0)	149.3 (13.4)	147.7 (15.4)	147.8 (14.9)	149.5 (15.7)
At follow-up	133.6 (16.2)	136.6 (14.9)	134.9 (16.9)	135.1 (15.8)	136.7 (17.1)
Unadjusted change	−14.0 (18.1)	−12.7 (17.1)	−12.8 (18.2)	−12.7 (17.7)	−12.8 (19.5)
Risk-adjusted change	−13.4 (10.3)	−14.1 (9.3)†	−13.4 (10.8)	−13.3 (10.4)	−14.0 (10.9)‡
Diastolic BP (mm Hg)					
At index	90.1 (10.7)	91.5 (10.1)	90.1 (10.9)	89.7 (10.4)	89.4 (11.4)
At follow-up	81.8 (10.1)	84.6 (10.5)	82.8 (10.8)	82.5 (10.5)	82.0 (11.1)
Unadjusted change	−8.3 (11.4)†	−6.8 (11.3)	−7.4 (11.3)	−7.1 (11.3)	−7.3 (11.9)
Risk-adjusted change	−7.9 (6.6)	−8.2 (6.3)†	−7.7 (6.8)	−7.6 (6.4)	−7.5 (7.0)
Goal attainment, n (%)					
Unadjusted at goal	1465 (46.8)§	826 (42.4)	508 (49.4)‖	229 (43.0)	239 (45.2)
Risk-adjusted at goal	1495 (47.8)†	776 (39.9)	472 (45.9)¶	230 (43.1)	234 (44.2)

Data are mean (standard deviation) unless otherwise indicated.
*Unadjusted *P* values were from analysis of variance or logistic regression, whereas risk-adjusted *P* values were from analysis of covariance or logistic regression.
†ACEI vs thiazide, $P < .001$.
‡ACEI vs CCB, $P = .04$.
§ACEI vs thiazide, $P = .02$.
‖β-blocker vs thiazide, $P = .003$.
¶β-blocker vs thiazide, $P = .01$.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; thiazide, thiazide and thiazide-like diuretics.

Table 6. Unadjusted and Risk-Adjusted Change in Blood Pressure (BP) and Goal Attainment Rates by Initial Antihypertensive Treatment Strategy

Outcomes	FDC (n = 795)	FEC (n = 712)	Monotherapy (n = 7169)	*P* Values*		
				FDC vs FEC	FDC vs Mono	FEC vs Mono
Systolic BP (mm Hg)						
At index	153.8 (16.5)	147.8 (16.4)	148.2 (14.7)	<.001	<.001	.47
At follow-up	132.3 (16.1)	137.5 (18.6)	134.9 (16.1)	<.001	<.001	<.001
Unadjusted change	−21.5 (20.5)	−10.3 (20.7)	−13.3 (17.9)	<.001	<.001	<.001
Risk-adjusted change	−17.3 (11.6)	−12.0 (11.5)	−13.6 (10.2)	<.001	<.001	.04
Diastolic BP (mm Hg)						
At index	94.3 (11.1)	85.9 (12.2)	90.4 (10.6)	<.001	<.001	<.001
At follow-up	82.0 (10.6)	79.8 (11.7)	82.8 (10.5)	<.001	.06	<.001
Unadjusted change	−12.3 (12.3)	−6.1 (12.5)	−7.6 (11.4)	<.001	<.001	.003
Risk-adjusted change	−10.1 (6.8)	−6.0 (7.5)	−7.9 (6.6)	<.001	<.001	.34
Goal attainment, n (%)						
Unadjusted at goal	440 (55.4)	226 (37.4)	3267 (45.6)	<.001	<.001	<.001
Risk-adjusted at goal	455 (57.2)	303 (42.5)	3216 (44.9)	<.001	<.001	.69

Data are mean (standard deviation) unless otherwise indicated.
*Unadjusted *P* values were calculated using analysis of variance or logistic regression, whereas risk-adjusted *P* values were from analysis of covariance or logistic regression.
FDC, fixed-dose combination; FEC, free-equivalent combination.

Discussion

This study found that patients receiving care from 33 primary care clinics and who were initiated on 1 of 5 antihypertensive therapeutic classes as monotherapy had remarkably similar average reductions in blood pressure at follow-up (Table 5). These results are consistent with those found in a meta-analysis of 354 randomized, double-blind trials, which reported little difference in mean placebo-corrected reduction in blood pressure across the same 5 therapeutic classes.[16] Our results extend this meta-analysis of efficacy studies done under strictly controlled conditions to the real world of effectiveness in daily practice.

Despite similar reductions in blood pressure across therapeutic classes, patients initiated on ACEIs and β-blockers had higher rates of JNC7 goal attainment than patients initiated on thiazide, even after adjusting for patient risk factors. The results of our study cannot be directly compared with those of the Treatment of Mild Hypertension Study,[17] ALLHAT,[18] or Materson et al;[19] these evaluated efficacy by individual agents, whereas we evaluated effectiveness by therapeutic class. In addition, response to therapeutic classes has been shown to vary by race,[19] and racial distributions are likely to be different between studies. Unfortunately, we did not have adequate racial data to adjust for this factor.

We also observed that primary care patients initiated on an FDC had considerably larger reductions in blood pressure and higher goal attainment rates at follow-up than patients initiated on monotherapy (Table 6). These results confirm those observed in short-term, randomized clinical efficacy studies and 2 recent observational studies, all of which showed that patients initiated on an FDC obtain better control of their blood pressure than patients initiated on monotherapy alone.[7–9,20,21] However, both of the observational studies also demonstrated superior effectiveness in blood pressure control in patients initiated on an FEC when compared with patients on monotherapy, whereas there was little difference between these 2 treatment strategies observed in the present study. The lack of improved blood pressure control in patients initiated on an FEC could be due to the inclusion of combinations that have been identified by the American Society of Hypertension as being less effective (eg, ACEI and β-blocker, ARB and β-blocker, and ACEI and ARB).[22] Another difference between the present study and the 2 observational studies is that the latter allowed for therapeutic classes to be added and dosages to be changed, while the present study did not. In addition, several studies have shown that patients taking an FDC have improved adherence over patients taking an FEC, which might further explain the

differences seen in our study.[10,11] Finally, the current study found that patients initiated on an FDC had larger reductions in blood pressure and superior rates of blood pressure control when compared with patients initiated on an FEC, which is similar to a report by Egan et al.[21]

Effective treatment of high blood pressure is the key therapeutic strategy shown to reduce hypertension-related MACEs. However, hypertension frequently remains uncontrolled in the general population, and most patients require the combination of ≥2 drugs to reach recommended blood pressure goals.[6] The American Society of Hypertension recently published a position paper recommending the routine use of combination therapy to achieve blood pressure targets and classifying combinations as preferred, acceptable, or less effective.[22] The use of a combination of drugs from complementary classes at low doses has been shown to be more effective at lowering blood pressure than increasing the dose of a single agent.[23] The use of low-dose combinations could potentially improve overall tolerability since most side effects of antihypertensive agents are dose-dependent and often drug-specific. While these benefits should apply regardless of whether they were initiated as an FDC or FEC, several studies have shown that patients taking an FDC have improved adherence over patients receiving an FEC since patient adherence is inversely related to the number of pills prescribed.[10,11] The oft-stated disadvantage of FDCs has been their inability to independently titrate the doses of the component drugs along with higher cost because of the limited availability of generic FDCs. However, if goal attainment is better, the need for titration is lessened.

The strengths of this study include the use of patients from clinical practices, which allows for comparisons of initial hypertension treatment strategies and therapeutic classes outside of a research-intensive setting such as is seen in clinical trials; a geographically diverse sample of primary care clinics; a relatively large sample size; and the ability to adjust for differences in patient characteristics. However, there were several limitations to the study: (1) the observational nature of the study compared with a randomized clinical trial, which could lead to selection biases in the choice of treatments for the patients and residual confounding even after statistical adjustment for some important variables; (2) the inability to adjust for patient race/ethnicity, which had been shown to be associated with hypertension treatment; (3) the lack of prescription fulfillment data and pill counts or use of other techniques to monitor pills consumed by the patient; and (4) the lack of data on dose and dosing frequency.

Conclusions

Patients initiated on any of the 5 antihypertensive therapeutic classes as a monotherapy had similar reductions in blood pressure, while patients initiated on ACEIs and β-blockers had slightly higher rates of blood pressure control than patients initiated on a thiazide. The use of FDCs as initial therapy is more effective in the control of hypertension than monotherapy or FECs.

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