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Time trends in the use of anti-hypertensive medications: results from the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Previous research has suggested that emerging evidence from randomized controlled trials (RCTs) is often not reflected in physician selection of medication class for first-line anti-hypertensive therapy.

Objectives—To evaluate the association of RCT evidence in December 2002 from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) on use of anti-hypertensive medications over time in a multi-ethnic cohort.

Methods—The Multi-Ethnic Study of Atherosclerosis study, a prospective cohort study of 6,814 adults from 4 ethnic groups, had four separate assessments of drug use. Users of anti-hypertensive medications at baseline were excluded. We evaluated temporal changes in the medication class reported by new users of antihypertensive medications.

Results—After the exclusion of antihypertensive drug users at baseline, 32% of new users of anti-hypertensive drugs seen at exam 2 were prescribed a diuretic. The publication of ALLHAT was associated with a subsequent increase in the proportion of new users taking diuretics at exam 3 compared with exam 2 (Relative Risk (RR):1.31; 95% Confidence Interval (CI):1.09–1.59). After the report from ALLHAT, the proportion of users of diuretics seen at exam 3 rose to 44% (starting in 2004) and 39% in exam 4 (starting in 2005). This increase in the proportion of diuretic use among new users of anti-hypertensive medications declined slightly but could still be detected at exam 4 as compared to exam 2 (RR:1.28; 95% CI:1.04–1.57).

Conclusions—The randomized trial evidence from the ALLHAT study was temporally associated with a moderate increase in diuretic use.

Keywords

Multi-Ethnic Study of Atherosclerosis; antihypertensive medications; drug utilization; longitudinal

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INTRODUCTION

Uncontrolled hypertension is a potential source of increased cardiovascular mortality and morbidity. It is estimated that roughly half of deaths due to coronary heart disease can be attributed to sub-optimal blood pressure control [1]. A number of different drug classes are used to treat hypertension, and guidelines have evolved over time as to which one is the most appropriate first-line anti-hypertensive agent.

When the National Heart, Lung and Blood Institute released the 1993 recommendations from Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC V), diuretics and beta-blockers were listed as the first-line agents for the pharmacologic treatment of hypertension [2]. These guidelines were motivated by results from the Systolic Hypertension in the Elderly Program (SHEP) randomized controlled trial (RCT). This trial had demonstrated the value of low-dose diuretics in preventing cardiovascular complications in older adults with systolic hypertension [3]. When these guidelines were updated in 1997 as the JNC VI recommendations, they reiterated the importance of low-dose diuretics as first-line agents [4].

However, despite these recommendations and the clinical trial evidence about the efficacy and safety of low-dose diuretics, the use of low-dose diuretic declined in the 1990s [5]. Instead, the use of newer agents for controlling hypertension, including angiotensin-converting-enzyme inhibitors and calcium-channel blockers, increased [5].

The results of the antihypertensive and lipid-lowering treatment to prevent heart attack (ALLHAT) RCT provided important evidence about the efficacy and safety of low-dose diuretics [6,7]. In this large active-comparison trial, low-dose diuretics were superior to angiotensin-converting-enzyme inhibitors and calcium-channel blockers in preventing one or more of the various cardiovascular complications of untreated hypertension evaluated in ALLHAT.

After the release of these results, investigators evaluated their effect on the prescribing practices of the clinical centers that participated in the ALLHAT trial. The early analysis of time trends in antihypertensive drug use suggested that these recommendations may have had little effect on the use of low-dose diuretics to treat incident hypertension in these centers [8]. However, the ALLHAT results also led to the revised 2003 JNC VII guidelines [9] which were further reinforced by the release of a meta-analysis summarizing the randomized controlled trial evidence [10] in the same year. The longer term effect of these continued efforts to shift first line treatment of incident hypertension to low-dose diuretics still requires further investigation.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of the determinants and progression of subclinical cardiovascular disease. Participants receive medical care from their community providers and not at the MESA field centers. The results of the ALLHAT RCT were reported in December 2002 which was after the end of the baseline assessment period (July 2000 to April 2002) and during the first follow-up period (September 2002 to January 2004). Serial measurements on the use of anti-hypertensive medications in MESA, before and after the publication of ALLHAT in December 2002, can be used to estimate the potential association of the reporting of the results of the trial and the subsequent recommendations on the use of medications in clinical practice in a multi-ethnic population.

METHODS

The MESA study includes 6,814 participants between the ages of 45 and 84 years from four different race/ethnic groups (38% Caucasian, 28% African-American, 22% Hispanic and 12% Asian). These participants were recruited from six field centers across the United States:

Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY and St. Paul, MN. The MESA design and recruitment methods are described in detail elsewhere [11]. There have been four exams in the MESA study to date: a baseline visit and 3 follow-up visits. The baseline exam occurred between July 2000 and April 2002. The first follow up exam (visit 2) occurred between September 2002 to January 2004. The second follow-up exam (visit 3) occurred between March 2004 and July 2005. The third follow-up exam (visit 4) occurred between September 2005 and June 2007.

Participants with a self reported history of either prevalent cardiovascular disease or previous surgery for cardiovascular disease were excluded. The 845 participants who did not return for at least one follow-up visit were excluded as changes in drug utilization over time could not be assessed for these participants.

Data Collected

While the methods used in the MESA study have been reported on more extensively elsewhere [11], we will quickly summarize the key details. Study participants were asked to come to a morning clinic examination after an overnight fast for each visit. Participants were given standard questionnaires to assess a variety of risk factors which included demographic information, smoking, and any medical history of either hypertension or diabetes. Participants were asked to bring their medications to the clinic and antihypertensive drug use was assessed using a medication inventory approach [12,13]. Anthropometric measures were also taken on all study participants and used to calculate body mass index. Resting seated blood pressure was measured three times at the baseline visit and the average of the last two measurements taken was used to establish baseline blood pressure, as in previous MESA studies [14]. Blood samples taken from fasting participants were analyzed for both glucose and cholesterol levels.

Primary Outcome

The primary study outcome was the use of one or more of the following commonly defined classes of anti-hypertensive medications: diuretics, beta-blockers, angiotensin-converting-enzyme inhibitor/angiotensin receptor blockers (ACE-I), calcium channel blockers (CCB) or alpha-blockers. We used the distribution of prescriptions among new users at exam 2 as a sample of the pre-ALLHAT prescribing patterns. This distribution was then contrasted with those at exam 3 (immediately after ALLHAT findings were released) and exam 4 to determine if the relative frequency of specific medications among new users changed given the new guidelines. We assumed that successfully treated prevalent users might be left on their current therapy and so focused the analysis entirely on new users.

Statistical Analysis

Descriptive statistics were used to report on baseline characteristics of the MESA cohort as seen in Table 1. Participants were stratified by their pattern of use of anti-hypertensive medications between baseline and the first follow-up visit. New users began therapy after baseline while users were exposed at both visits. Stoppers were exposed at baseline but not at follow-up. Never users were unexposed to anti-hypertensive medications at both visits.

The differences in the proportion of new users starting each class of anti-hypertensive medications were estimated using Poisson regression with robust standard errors [15]. The proportion of new users at both visits 3 and 4 were compared with the new users in visit 2 to generate a relative risk (RR) of exposure to each drug class. This was done separately for each of the commonly defined classes of anti-hypertensive medication. Participants who were exposed to anti-hypertensive drugs at baseline were excluded from these new user analyses.

Covariates included in the statistical analysis were: systolic and diastolic blood pressure age, race, glucose intolerance, diabetes status and number of different classes of anti-hypertensive medications. Due to the exclusion requirements for the MESA study, cardiovascular disease outcomes, such as Heart Failure (there were $n=14$ incident cases among all new users over follow-up), were extremely rare in the cohort over this time period and thus not appropriate to include as covariates. The potential confounders considered in the models were selected as being participant characteristics that were thought to be associated with selection of type of antihypertensive medication. Testing for interactions was planned for selective subgroups, such as sex, but no *a priori* hypotheses of any specific interactions were stated.

All analyses were done in SAS version 9.1.3.

RESULTS

Table 1 reports on the characteristics of the study participants stratified on the pattern of anti-hypertensive medications at baseline and the first follow-up visit. In general, all participants who reported using anti-hypertensive medications at one or both visits (starters, stoppers and users) were older, had higher baseline blood pressures, were more likely to be diabetic and were at higher cardiovascular risk (as assessed by Framingham risk scores [16]) than non-users.

Prevalent users of anti-hypertensive medications at baseline were exposed to more and different classes of these medications than starters (Table 2). The greater number of classes drugs among users at baseline is due to combining new users with long term users (who would be expected to be on more aggressive treatment regimes). Some drug classes, such as calcium channel blockers, also appear to be less prevalent among new users as compared to the prevalence of medication use reported at baseline.

Table 3 shows the trend in prescriptions over time among new users in the MESA cohort. Sample sizes are slightly smaller than in Table 1 due to loss to follow-up between exams 2 and 4. Vasodilators appeared to be uncommon and mostly used by men. Diuretics become the most frequently prescribed agents in the later part of the study period; this increase is mostly due to use of diuretics among men rising to similar levels as those seen among women at baseline. The data in Table 3 suggest that the changes in first-line anti-hypertensive medications over this time period occurred largely among male participants as rates among female participants appeared to be relatively stable over time.

The new users at the first follow-up exam largely pre-dated the publication of the ALLHAT results and this exam was completed for all participants before the release of the revised guidelines. As seen in table 4, in visits occurring after the publication of the ALLHAT study results and the revised guidelines there was a decrease in the level of ACE inhibitor use and an increase in the rate of diuretic use among male participants. Comparing exam 3 with exam 2 we see an increase in the proportion of male new users taking diuretics (RR:1.65; 95% Confidence Interval (CI):1.21–2.25) and a smaller increase among female new users (RR:1.09; 95% CI:0.86–1.35). Pooling both male and female new users into a single model yields a statistically significant increase in new users of diuretics for the entire MESA cohort comparing exam 3 to exam 2 (RR:1.31; 95% CI:1.09–1.59).

Testing for an interaction between sex and time, by drug yields statistically significant interactions between sex and time for ACE-I (exam 3 vs. exam 2: $p<0.01$; exam 4 vs. exam 2: $p=0.01$) and diuretics (exam 3 vs. exam 2: $p=0.02$; exam 4 vs. exam 2: $p=0.03$). There is not, however, a statistically significant interaction between sex and time for the utilization of calcium channel blockers (exam 3 vs. exam 2: $p=0.28$; exam 4 vs. exam 2: $p=0.45$) or beta blockers (exam 3 vs. exam 2: $p=0.10$; exam 4 vs. exam 2: $p=0.07$). While the numbers in the MESA study are too small to provide reasonable inferences, there is a non-statistically

significant increase in ACE-I use among diabetics for all sub-groups and time periods (data not shown).

This statistically significant increase in the proportion of new users using diuretics persists when comparing the pooled results of exam 4 to exam 2 (RR:1.28; 95% CI:1.04–1.57). However, as in the previous time period, we can see in Table 4 that this effect is also stronger in male new users (RR:1.48; 95% CI:1.06–2.08) than in female new users (RR:1.08; 95% CI: 0.82–1.42). By the end of the study, male new users now look like female new users in the proportion of diuretics used in contrast to the lower rates of use seen at baseline. We excluded vasodilators from the models presented in Table 4 as the very small numbers made these estimates unstable (data not shown).

DISCUSSION

Randomized controlled trial evidence from the ALLHAT trial and the subsequent revision of clinical guidelines for the treatment of hypertension were temporally associated with a moderate increase in diuretic use and a moderate decrease in ACE inhibitor use in this multi-ethnic cohort study. These time trends appeared to be stronger in male participants.

The MESA study is prospective study using a population-based cohort with new users both before and after this time period making it ideal to assess the effects of this new information on patterns of medication use. The MESA study also uses a well-validated inventory approach to the assessment of medication use among the study participants [12,13]. Finally, as the MESA cohort is free of cardiovascular disease at baseline, the use of this cohort enables us to assess the effect of these revised guidelines in a relatively healthy population.

A limitation of the MESA study is the potential under-reporting of medication use. This could occur due to a failure to include a medication in the supply brought to a study visit. This effect is unlikely to be differential by drug class. Another limitation of this investigation is that drug exposure was sampled at visits that were approximately 18 months apart and information about treatments between visits is not available.

The findings of this study are consistent with the findings of Stafford et al. who found a short term boost in diuretic prescriptions following the release of the ALLHAT recommendations [17] and Muntner et al. who found a more sustained increase in diuretic prescriptions post-ALLHAT [18]. The results of this study are also consistent with other cohort studies, such as the Cardiovascular Health Study [19,20] in that they suggest that changes in evidence-based prescribing guidelines can have some impact on physician prescribing behavior.

The reason for the different rate of diuretic prescribing for male participants versus female participants is unknown. The effect of gender could be attributed to differences in how physicians treat male and female patients, differences in comorbid conditions, differences in the indications for starting these drugs, patient preferences, differential treatment for conditions other than hypertension or some other unknown factor. These same factors could also explain why not all patients are started on low-dose diuretics after the release of the guidelines.

The continued use of ACE inhibitors as first line anti-hypertension therapy might be due to the other potential beneficial effects of these drugs that were reported from observational studies during this time period. These drugs were reported to be associated with lower rates of a variety of conditions including renal disease [21], chronic obstructive pulmonary disease [22], headaches [23] and dementia [24]. These possible secondary benefits of ACE inhibitor use might explain the continued use of this drug class among new users despite the changes in recommendations for first line anti-hypertensive therapy.

Calcium channel blockers and alpha-blockers are no longer recommended as first line agents [9]. Consistent with these guidelines, both agents were being prescribed less frequently than diuretics among new users. It is also possible that many of the alpha-blocker prescriptions could be intended for the treatment of benign prostatic hyperplasia [25] instead of hypertension. While the use of these agents did not decrease over the course of this study, the levels of use among new users were already low compared to other anti-hypertensive agents. Conversely, the frequent use of beta blockers as first-line anti-hypertensive therapy was consistent with previous treatment guidelines [2].

This study suggests that the release of important RCT evidence and the consequent revision of clinical guidelines may influence the selection of first-line therapy for hypertension in a population-based, multi-ethnic cohort. Based on the results of this study, we suggest that it is important to ensure that the post-ALLHAT shift to increased first line treatment with low dose diuretics for male patients should be maintained.

Key Points

1. Diuretic use increased in male new users of antihypertensive medications (to the levels seen in female new users) while ACE inhibitor use dropped after the release of key randomized controlled trial evidence supporting low dose diuretic use
2. This increase in diuretic use among male new users persisted for at least one follow-up exam in participants in the Multi Ethnic Study of Atherosclerosis

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Table 1

Comparison of the baseline characteristics of the 5969 subjects with a visit at both baseline (July 2000 to April 2002) and the first follow-up visit (October 2002 to October 2003). Data from the Multi-Ethnic Study of Atherosclerosis.

Baseline Characteristics	Nonusers (n=3,472)	Stoppers (n=192)	Starters (n=441)	Users at both exams (n=1,864)
Age(years)	59.7	63.7	64.2	65.9
Male Gender (%)	47.8	48.4	49.2	46.9
Asian (%)	14.1	13.5	10.2	8.2
African American (%)	21.3	37.5	32.0	36.9
Hispanic (%)	22.8	23.4	22.4	19.2
Body Mass Index(kg/m ²)	27.3	29.8	29.5	29.6
Current Smoker (%)	14.2	9.9	12.5	9.7
Ex-Smoker	34.9	30.7	43.8	38.8
Alcoholic drinks/week (#)	4.0	4.5	3.6	4.0
Systolic Blood Pressure (mmHg)	120.0	130.1	138.9	134.4
Diastolic Blood Pressure (mmHg)	70.5	73.0	76.2	73.2
HDL cholesterol (mg/dL)	51.7	49.9	49.6	50.4
LDL cholesterol (mg/dL)	119.8	114.7	118.7	112.1
Glucose(mg/dL)	99.6	109.5	112.7	110.1
Framingham Risk Score* (%)	9.3	12.3	14.0	13.0
Impaired Glucose** (%)	25.3	28.6	30.4	33.2
Diabetes (%)	7.2	22.4	20.9	22.7
Antihypertensive Medication				
ACE-I (%)	0	24.5	0	38.3
CCB (%)	0	19.3	0	36.5
Diuretic (%)	0	39.1	0	43.5
Beta Blocker (%)	0	18.8	0	28.2
Vasodilator (%)	0	18.8	0	13.3
Number of classes of Antihypertensive Medications***	0	1.60	0	1.20
Multi-Drug Users (%)	0%	19.3	0	44.9

* 10 year risk of any coronary heart disease

** Non-diabetics with fasting glucose ≥ 100 and < 126 mg/dl

*** Number of different agents (ACE-I, CCB, Diuretic, Beta Blocker, Vasodilator) that the participant reports in their medication inventory

Table 2

Prevalence of antihypertensive drug use and recorded blood pressure values by male/female and user/starter status across visits 1 and 2. Data from the Multi-Ethnic Study of Atherosclerosis.

	Women		Men	
	Users (n=989)	Starters (n=224)	Users (n=875)	Starters (n=217)
Systolic Blood Pressure (mmHg)	133.9	131.2	129.2	126.6
Diastolic Blood Pressure (mmHg)	69.5	68.4	73.5	72.9
Antihypertensive Medication				
ACE-I (%)	35.8	26.3	47.2	48.8
CCB (%)	37.7	17.0	36.0	14.3
Diuretic (%)	53.3	37.5	38.1	24.9
Beta Blocker (%)	33.5	34.8	30.1	27.7
Vasodilator (%)	4.3	1.3	22.1	10.6
Number of classes of Antihypertensive Medications	1.65	1.17	1.73	1.26
Multi-Drug Users (%)	44.3	0	45.5	0

Table 3

Comparison of proportion of use by drug class among new users of anti-hypertensive medications at each visit among the participants who completed all 4 study visits *. Data from the Multi-Ethnic Study of Atherosclerosis.

	Visit 2	Visit 3**	Visit 4
All Participants			
Number of new users (percentage of total)	359	278	241
ACE-I	130 (36%)	83 (30%)	78 (32%)
CCB	56 (16%)	44 (16%)	37 (15%)
Diuretic	115 (32%)	122 (44%)	93 (39%)
Beta Blocker	109 (30%)	89 (32%)	80 (33%)
Vasodilator	20 (6%)	18 (6%)	14 (6%)
Women			
Number of new users (percentage of total)	183	145	119
ACE-I	46 (25%)	41 (28%)	34 (29%)
CCB	30 (16%)	21 (14%)	21 (18%)
Diuretic	72 (39%)	67 (46%)	48 (40%)
Beta Blocker	61 (33%)	51 (35%)	38 (32%)
Vasodilator	3 (2%)	0 (0%)	2 (2%)
Men			
Number of new users (percentage of total)	176	133	122
ACE-I	84 (48%)	42 (32%)	44 (36%)
CCB	26 (15%)	23 (17%)	16 (13%)
Diuretic	43 (24%)	55 (41%)	45 (37%)
Beta Blocker	48 (27%)	38 (29%)	42 (34%)
Vasodilator	17 (10%)	18 (14%)	12 (10%)

* There are fewer participants in table 3 and 4 due to loss to follow-up after exam 2

** These are the first new users after the release of the ALLHAT randomized controlled trial results

Table 4

Relative Risks (RR) of participants taking different classes of Antihypertensive medication comparing new users at exams 3 and 4 (post-ALLHAT) to new users at exam 2 (pre-ALLHAT Reference). Data from the Multi-Ethnic Study of Atherosclerosis.

Exam 3 vs. Exam 2 (n=5492)						
Women				Men		
	Crude RR	Adjusted RR *	95% Confidence Interval	Crude RR	Adjusted RR *	95% Confidence Interval
ACE-I	1.13	1.03	0.72 to 1.45	0.66	0.64	0.49 to 0.84
CCB	0.88	0.88	0.53 to 1.47	1.17	1.25	0.78 to 2.02
Diuretic	1.16	1.09	0.86 to 1.38	1.69	1.65	1.21 to 2.25
Beta Blocker	1.06	0.97	0.72 to 1.31	1.05	0.92	0.66 to 1.30
Exam 4 vs. Exam 2 (n=5033)						
Women				Men		
	Crude RR	Adjusted RR *	95% Confidence Interval	Crude RR	Adjusted RR *	95% Confidence Interval
ACE-I	1.15	1.12	0.78 to 1.61	0.76	0.74	0.57 to 0.97
CCB	1.09	0.98	0.59 to 1.63	0.89	1.00	0.53 to 1.75
Diuretic	1.02	1.08	0.82 to 1.42	1.51	1.48	1.06 to 2.08
Beta Blocker	0.97	0.80	0.58 to 1.10	1.26	1.13	0.80 to 1.58

* adjusted for age, race, systolic and diastolic blood pressure at the baseline exam, glucose tolerance, diabetes and number of classes of medications