

Clinical Outcomes in Antihypertensive Treatment of Type 2 Diabetes, Impaired Fasting Glucose Concentration, and Normoglycemia

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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Background: Optimal first-step antihypertensive drug therapy in type 2 diabetes mellitus (DM) or impaired fasting glucose levels (IFG) is uncertain. We wished to determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor decreases clinical complications compared with treatment with a thiazide-type diuretic in DM, IFG, and normoglycemia (NG).

Methods: Active-controlled trial in 31 512 adults, 55 years or older, with hypertension and at least 1 other risk factor for coronary heart disease, stratified into DM (n=13 101), IFG (n=1399), and NG (n=17 012) groups on the basis of national guidelines. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, 12.5 to 25 mg/d, amlodipine besylate, 2.5 to 10 mg/d, or lisinopril, 10 to 40 mg/d. We conducted an intention-to-treat analysis of fatal coronary heart disease or nonfatal myocardial infarction (primary outcome), total mortality, and other clinical complications.

Results: There was no significant difference in relative risk (RR) for the primary outcome in DM or NG participants assigned to amlodipine or lisinopril vs chlorthalidone or in IFG participants assigned to lisinopril vs chlorthalidone. A significantly higher RR (95% confidence interval) was noted for the primary outcome in IFG participants assigned to amlodipine vs chlorthalidone (1.73 [1.10-2.72]). Stroke was more common in NG participants assigned to lisinopril vs chlorthalidone (1.31 [1.10-1.57]). Heart failure was more common in DM and NG participants assigned to amlodipine (1.39 [1.22-1.59] and 1.30 [1.12-1.51], respectively) or lisinopril (1.15 [1.00-1.32] and 1.19 [1.02-1.39], respectively) vs chlorthalidone.

Conclusion: Our results provide no evidence of superiority for treatment with calcium channel blockers or angiotensin-converting enzyme inhibitors compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG.

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THE COMBINATION OF HYPERTENSION and type 2 diabetes mellitus (DM) is common and results in a potent milieu for risk of cardiovascular disease (CVD) and end-stage renal disease.¹⁻⁴ Less striking elevations of blood pressure (BP) and impairments of glucose homeostasis such as high normal BP and impaired fasting glucose level (IFG) also increase risk.^{3,5,6} Lowering BP may provide the most effective means to reduce the risk of CVD in patients with DM.^{7,8} Agents that interfere with the renin-angiotensin system, especially angiotensin-converting enzyme inhibitors (ACEIs), have been recommended as first-step antihypertensive treatment in patients with DM and proteinuria.^{9,10} There is less certainty, how-

ever, regarding the optimal choice of first-step antihypertensives in patients with DM and hypertension who have little or no renal damage.^{10,11} The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was designed to determine whether first-step antihypertensive drug therapy with an ACEI, a calcium channel blocker (CCB), or an α -adrenergic blocker would provide better protection against CVD compared with diuretic therapy.¹² A comparison of treatment efficacy in participants with or without DM was prespecified in the ALLHAT protocol.¹² Our group has previously described its experience with first-step antihypertensive therapy using a diuretic compared with an α -adrenergic blocker in ALLHAT participants with and without

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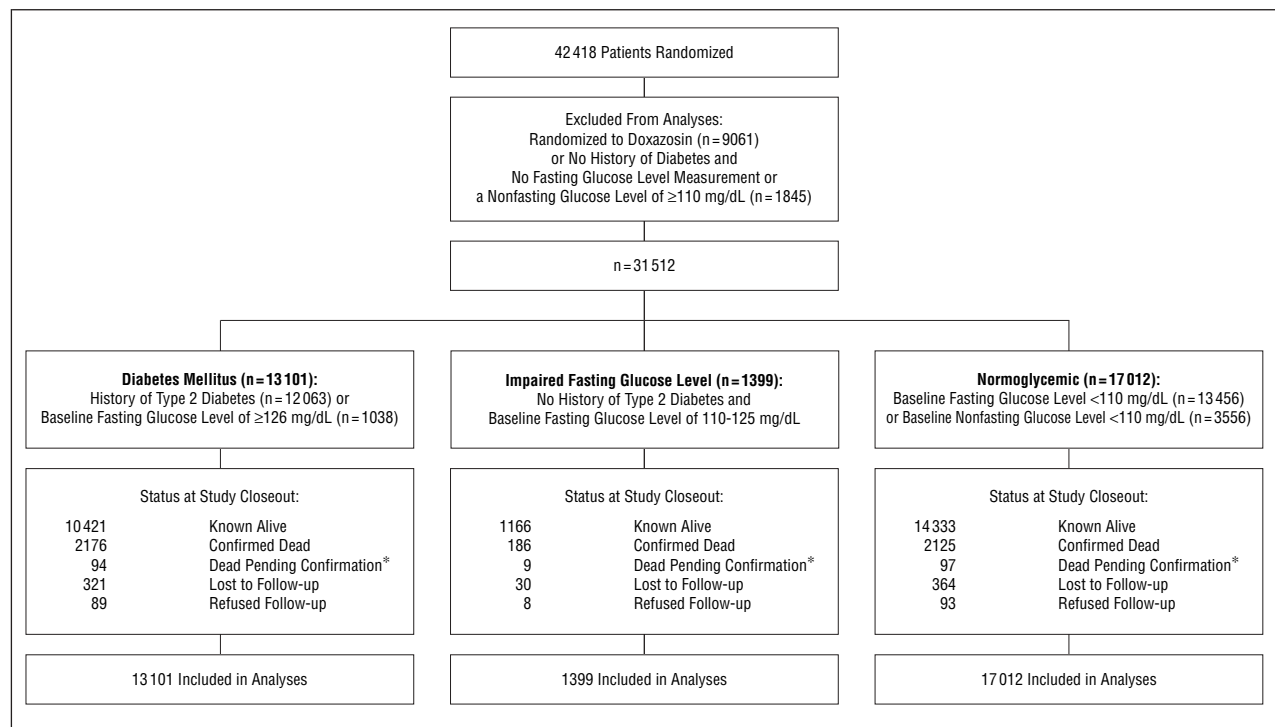


Figure 1. Randomization and follow-up of participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial by baseline glycemic status. To convert glucose levels to millimoles per liter, multiply by 0.0555. Asterisk indicates as of September 30, 2002, database.¹⁴

glucose disorders.¹³ We herein report on the efficacy of first-step antihypertensive therapy with a diuretic compared with a CCB or an ACEI in the following 3 baseline glycemic strata: DM, IFG, and normoglycemia (NG).

METHODS

The ALLHAT participants were men and women 55 years or older who had stage 1 or stage 2 hypertension and at least 1 additional risk factor for coronary heart disease (CHD).¹² Of the 42 418 ALLHAT participants, 33 357 were randomly assigned to therapy with chlorthalidone (n=15 255), amlodipine besylate (n=9048), or lisinopril (n=9054).¹⁴ Baseline fasting glucose level was not available for 1845 of the 33 357 participants, so the present analysis was confined to the remaining 31 512 who could be classified as having DM (n=13 101), IFG (n=1399), or NG (n=17 012) (**Figure 1**). The definition of DM incorporated criteria used in previous ALLHAT publications¹³⁻¹⁵ (history of treatment with insulin or oral hypoglycemic agents during the 2 years preceding randomization, a fasting baseline glucose level >140 mg/dL [>7.8 mmol/L], or a nonfasting baseline glucose level >200 mg/dL [>11.1 mmol/L]) (n=12 063) and a more contemporary criterion (presence of a baseline fasting glucose level ≥ 126 mg/dL [≥ 7.0 mmol/L]),¹⁶ which resulted in 1038 additional DM participants. We defined IFG (n=1399) as a baseline fasting serum glucose level between 110 and 125 mg/dL (6.1-6.9 mmol/L) and no history of DM.¹⁶ Participants with a baseline fasting or nonfasting glucose level less than 110 mg/dL (<6.1 mmol/L) and no history of DM were classified as having NG. The NG group included 13 456 participants with a baseline fasting glucose level less than 110 mg/dL (<6.1 mmol/L) and 3556 with a baseline nonfasting glucose level of less than 110 mg/dL (<6.1 mmol/L).

Lowering of BP was achieved by titrating the dose of the assigned study drug (step 1) and adding study-supplied open-label atenolol, clonidine hydrochloride, or reserpine (step 2); adding hydralazine hydrochloride (step 3); or adding other drugs

when necessary. Nonpharmacological treatment of hypertension was recommended according to national guidelines.^{10,17} Step 1 drugs were encapsulated and identical in appearance, so that each was double-masked at every dosage level. Dosages were 12.5, 12.5 (sham titration), and 25.0 mg/d for chlorthalidone; 2.5, 5.0, and 10.0 mg/d for amlodipine besylate; 10, 20, and 40 mg/d for lisinopril; 25 to 100 mg/d for atenolol; 0.05 to 0.20 mg/d for reserpine; 0.1 to 0.3 mg twice daily for clonidine hydrochloride; and 25 to 100 mg twice daily for hydralazine hydrochloride.

Follow-up visits were conducted at 1, 3, 6, 9, and 12 months and every 4 months thereafter. The primary outcome was a composite of fatal CHD or nonfatal myocardial infarction (MI).¹² Four of the major prespecified secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization, or hospitalized angina), and combined CVD (combined CHD, stroke, other treated angina, heart failure [fatal, hospitalized, or treated nonhospitalized], or peripheral arterial disease). End-stage renal disease (dialysis, renal transplantation, or death due to kidney disease) and individual components of the major outcomes, including heart failure, were also prespecified. We used standardized procedures for reporting and validating study outcomes.^{12,14,18}

We compared baseline characteristics across the 3 treatment groups within each category of glycemic status (DM, IFG, and NG) using the χ^2 test for significance testing of continuous covariates and contingency table analyses for categorical data. We analyzed outcomes using an intention-to-treat approach. Cumulative event rates were calculated using the Kaplan-Meier procedure. The Cox proportional hazards model was used to determine time-to-event hazard ratios (hereafter referred to as relative risks [RRs]) and 95% confidence intervals (CIs). Cox test assumptions were examined using log-log plots and tests of treatment \times time (time-dependent) interaction terms. When the assumptions were violated, a 2×2 table was used to estimate the RR.¹⁹ We examined heterogeneity of treatment effects across the 3 glycemic strata by

Table 1. Baseline Characteristics of 31 512 ALLHAT Participants by Glycemic Status*

Characteristic	Glycemic Status		
	DM (n = 13 101)	IFG (n = 1399)	NG (n = 17 012)
Age, mean (SD), y	66.6 (7.4)†	67.0 (7.5)	67.1 (7.9)
Women	6463 (49.3)†	528 (37.7)†	7719 (45.4)
Black	5077 (38.8)†	413 (29.5)	5468 (32.1)
Education, mean (SD), y	10.7 (4.0)†	11.1 (3.9)	11.2 (4.0)
Cigarette smoker	1762 (13.4)†	329 (23.5)†	4714 (27.7)
Atherosclerotic CVD	4693 (35.8)†	876 (62.6)	10 495 (61.7)
History of MI or stroke	2412 (18.4)†	388 (27.7)	4493 (26.4)
History of coronary revascularization	1403 (10.7)†	215 (15.4)	2479 (14.6)
Other atherosclerotic CVD	1969 (15.0)†	394 (28.2)	4994 (29.4)
Major ST depression/T-wave inversion‡	865 (6.7)†	197 (14.3)	2104 (12.5)
History of CHD at baseline§	2578 (19.8)†	426 (30.8)	2951 (17.3)
History of HDL-C <35 mg/dL	1171 (8.9)†	252 (18.0)†	2250 (13.2)
History of LVH by electrocardiogram or echocardiogram	1656 (15.3)†	322 (26.3)	4061 (27.1)
Taking antihypertensive medication	12 098 (92.3)†	1247 (89.1)	15 107 (88.8)
Aspirin	4415 (33.7)†	533 (38.1)	6451 (37.9)
Estrogen supplements (women only)	914 (14.1)†	82 (15.5)†	1637 (21.2)
Medication to lower lipid levels¶	1682 (13.0)†	215 (15.6)	2423 (14.4)
Systolic/diastolic blood pressure, mean (SD), mm Hg	146.5 (15.4)/82.9 (10.0)†	146.5 (15.7)/84.6 (10.0)	146.0 (15.8)/84.8 (10.0)
Taking antihypertensives	145.8 (15.5)/82.6 (9.9)†	145.1 (15.5)/84.0 (9.8)	144.7 (15.6)/84.1 (9.9)
Not taking antihypertensives	155.2 (11.5)/87.3 (9.6)†	158.4 (12.0)/89.8 (9.9)	156.4 (12.4)/90.4 (8.9)
BMI, mean (SD)	31.1 (6.3)†	30.5 (6.0)†	28.7 (5.8)

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose level; LVH, left ventricular hypertrophy; MI, myocardial infarction; NG, normoglycemic.

SI conversion factor: To convert HDL-C to millimoles per liter, multiply by 0.0259.

*Unless otherwise indicated, data are expressed as number (percentage) of patients. Because of missing or invalid values, some denominators varied.

† $P < .05$ compared with NG participants.

‡Denominators were 12 957 for DM, 1381 for IFG, and 16 878 for NG.

§Denominators were 12 991 for DM, 1376 for IFG, and 16 902 for NG.

||Denominators were 10 797 for DM, 1225 for IFG, and 14 966 for NG.

¶Denominators were 12 927 for DM, 1376 for IFG, and 16 857 for NG.

testing for treatment \times covariate interaction with the proportional hazards model using $P < .05$. Given the many multivariate, subgroup, and interaction analyses performed, statistical significance at the .05 level should be interpreted with caution.

RESULTS

Baseline characteristics were well balanced across the 3 treatment groups (chlorthalidone, amlodipine, and lisinopril) within each glycemic stratum (data not shown). The small number of instances in which differences were noted was consistent with what could be expected on the basis of multiple comparisons and, where present, the differences were modest. The participants' average age was 67 years (**Table 1**), with 58% being 65 years or older. Both men and women and both black and nonblack participants were well represented. Participants with DM had a lower prevalence of other CVD risk factors compared with those with IFG or NG, reflecting the fact that they could be enrolled in the absence of other CVD risk factors. The average baseline systolic/diastolic BP was 146/84 mm Hg for those taking (90.2% of the study group) and 155/89 mm Hg for those not taking antihypertensives. Approximately one third of the participants were taking aspirin, 13% to 16% of them were taking medication to lower lipid levels, and 14% to 21% of the women were

taking estrogen supplements. The average body mass index (calculated as weight in kilograms divided by the square of height in meters) was higher in the participants with DM (31.1) or IFG (30.5) compared with those with NG (28.7).

The mean duration of follow-up was 4.9 years. Annual visits were expected for approximately 94%, 82%, and 48% of the participants at years 3, 4, and 5, respectively, with the lower percentage at year 5 resulting from completion of the trial before that visit. The level of study drug use was high throughout follow-up, with a similar pattern for participants in each glycemic stratum (**Table 2**). Compliance was somewhat better for those assigned to chlorthalidone and amlodipine compared with lisinopril. Over time, an increasing percentage in each treatment group took an agent from 1 of the other 2 classes used for first-step therapy. This was most common in DM participants, especially for addition of a diuretic to assigned amlodipine or lisinopril therapy. Even in the DM group, however, this change was noted in less than 30% at their year-5 visit. Step 2 or step 3 agents were being used by approximately one quarter to slightly more than one third at their year-1 visit. The average number of antihypertensive medications increased from 1.4 at the year-1 visit to 2 at the year-5 visit, with the average being slightly higher for DM compared with IFG or NG participants.

Table 2. Medications During Follow-up by Glycemic Status at Baseline and Study Treatment Assignment*

Medication Regimen by Follow-up	Glycemic Status								
	Diabetes Mellitus			Impaired Fasting Glucose Level			Normoglycemic		
	CHL	AML	LIS	CHL	AML	LIS	CHL	AML	LIS
Assigned study medication									
Year 1	4498 (83.4)	2664 (82.9)	2431 (77.7)†	484 (84.3)	290 (85.6)	303 (80.8)	6038 (84.4)	3567 (84.4)	3240 (77.2)†
Year 2	3960 (78.6)	2330 (78.3)	2083 (71.5)†	430 (80.2)	266 (81.4)	250 (71.8)†	5463 (80.9)	3233 (81.2)	2797 (71.6)†
Year 3	3560 (75.1)	2107 (73.9)	1842 (67.6)†	395 (78.5)	241 (77.5)	236 (71.5)†	4962 (77.0)	3014 (79.0)†	2559 (68.5)†
Year 4	3058 (71.6)	1791 (69.7)	1528 (62.6)†	355 (75.9)	219 (77.9)	194 (66.7)†	4362 (74.1)	2665 (76.2)†	2220 (65.8)†
Year 5	1727 (69.8)	1041 (68.2)	845 (60.7)†	208 (75.1)	135 (77.6)	122 (65.2)†	2496 (72.1)	1543 (74.9)†	1221 (61.1)†
Step 2 or 3									
Antihypertensives									
Year 1	1416 (26.3)	836 (26.0)	1005 (32.1)†	187 (32.6)	97 (28.6)	143 (38.1)	1934 (27.0)	1101 (26.1)	1405 (33.5)†
Year 2	1591 (31.6)	980 (32.9)	1064 (36.5)†	193 (36.0)	126 (38.5)	142 (40.8)	2213 (32.8)	1247 (31.4)	1434 (36.7)†
Year 3	1682 (35.5)	1024 (35.9)	1059 (38.9)†	185 (36.8)	124 (39.9)	139 (42.1)	2317 (36.0)	1335 (35.0)	1481 (39.7)†
Year 4	1638 (38.4)	934 (36.3)	979 (40.1)	180 (38.5)	122 (43.4)	121 (41.6)	2238 (38.0)	1302 (37.2)	1422 (42.2)†
Year 5	979 (39.6)	597 (39.1)	591 (42.5)	117 (42.2)	79 (45.4)	73 (39.0)	1442 (41.7)	819 (39.8)	891 (44.6)†
Diuretic‡									
Year 1	4676 (86.7)	355 (11.0)†	328 (10.5)†	504 (87.8)	26 (7.7)†	32 (8.5)†	6259 (87.5)	358 (8.5)†	356 (8.5)†
Year 2	4236 (84.1)	426 (14.3)†	457 (15.7)†	454 (84.7)	37 (11.3)†	39 (11.2)†	5763 (85.4)	490 (12.4)†	496 (12.7)†
Year 3	3936 (83.0)	508 (17.8)†	531 (19.5)†	422 (83.9)	44 (14.2)†	42 (12.7)†	5342 (82.9)	574 (15.1)†	578 (15.5)†
Year 4	3461 (81.1)	563 (21.9)†	574 (23.5)†	379 (81.0)	43 (15.3)†	54 (18.6)†	4774 (81.1)	618 (17.7)†	609 (18.1)†
Year 5	1992 (80.5)	421 (27.6)†	403 (29.0)†	221 (79.8)	31 (17.8)†	32 (17.1)†	2806 (81.1)	431 (20.9)†	437 (21.9)†
ACEI‡									
Year 1	331 (6.1)	231 (7.2)	2635 (84.2)†	32 (5.6)	12 (3.5)	315 (84.0)†	267 (3.7)	163 (3.9)	3408 (81.2)†
Year 2	508 (10.1)	370 (12.4)†	2323 (79.7)†	40 (7.5)	17 (5.2)	269 (77.3)†	393 (5.8)	208 (5.2)	3037 (77.8)†
Year 3	655 (13.8)	462 (16.2)†	2145 (78.7)†	45 (9.0)	24 (7.7)	258 (78.2)†	488 (7.6)	267 (7.0)	2842 (76.1)†
Year 4	743 (17.4)	503 (19.6)†	1854 (75.9)†	60 (12.8)	30 (10.7)	217 (74.6)†	527 (9.0)	315 (9.0)	2503 (74.2)†
Year 5	524 (21.2)	339 (22.2)†	1045 (75.1)†	39 (14.1)	24 (13.8)	134 (71.7)†	341 (9.9)	213 (10.3)	1418 (71.0)†
CCB‡									
Year 1	270 (5.0)	2795 (86.9)†	231 (7.4)†	29 (5.1)	307 (90.6)†	30 (8.0)	321 (4.5)	3729 (88.2)†	295 (7.0)†
Year 2	364 (7.2)	2507 (84.2)†	307 (10.5)†	42 (7.8)	286 (87.5)†	34 (9.8)	417 (6.2)	3427 (86.4)†	426 (10.9)†
Year 3	413 (8.7)	2320 (81.4)†	347 (12.7)†	48 (9.5)	267 (85.9)†	42 (12.7)	542 (8.4)	3234 (84.8)†	485 (13.0)†
Year 4	439 (10.3)	2013 (78.2)†	378 (15.5)†	55 (11.8)	240 (85.4)†	42 (14.4)	547 (9.3)	2879 (82.3)†	471 (14.0)†
Year 5	272 (11.0)	1190 (77.9)†	243 (17.5)†	32 (11.6)	149 (85.6)†	28 (15.0)	281 (11.0)	1694 (82.3)†	335 (16.8)†
Antihypertensive medications§									
Year 1	1.38 (0.71, 5393)	1.42 (0.73, 3215)†	1.52 (0.84, 3130)†	1.47 (0.74, 574)	1.42 (0.68, 339)	1.61 (0.86, 375)†	1.36 (0.66, 7154)	1.36 (0.67, 4226)	1.48 (0.81, 4199)†
Year 2	1.54 (0.86, 5036)	1.61 (0.86, 2977)†	1.70 (1.01, 2914)†	1.54 (0.79, 536)	1.61 (0.82, 327)	1.67 (0.96, 348)†	1.47 (0.76, 6750)	1.49 (0.76, 3968)	1.64 (0.95, 3904)†
Year 3	1.68 (0.95, 4742)	1.73 (0.96, 2850)†	1.85 (1.10, 2724)†	1.64 (0.86, 503)	1.71 (0.86, 311)	1.78 (1.06, 330)†	1.57 (0.85, 6444)	1.60 (0.84, 3815)	1.74 (1.01, 3734)†
Year 4	1.80 (1.03, 4270)	1.83 (1.02, 2573)	1.96 (1.18, 2442)†	1.73 (0.96, 468)	1.85 (0.99, 281)	1.84 (1.13, 291)	1.64 (0.92, 5886)	1.69 (0.91, 3498)†	1.84 (1.07, 3372)†
Year 5	1.92 (1.07, 2474)	2.00 (1.12, 1527)†	2.12 (1.24, 1392)†	1.77 (1.00, 277)	1.97 (1.12, 174)	1.84 (1.19, 187)	1.77 (0.98, 3461)	1.82 (0.96, 2059)†	1.93 (1.15, 1997)†
Medication to lower lipid levels									
Year 1	1296 (24.0)	806 (25.1)	784 (25.1)	160 (27.9)	113 (33.3)	115 (30.7)	2009 (28.1)	1162 (27.5)	1137 (27.1)
Year 2	1460 (29.0)	856 (28.7)	838 (28.8)	169 (31.5)	108 (33.0)	113 (32.5)	2104 (31.2)	1245 (31.4)	1210 (31.0)
Year 3	1526 (32.2)	938 (32.6)	859 (31.5)	178 (35.4)	119 (38.3)	113 (34.1)	2211 (34.3)	1304 (34.2)	1262 (33.8)
Year 4	1477 (34.6)	903 (35.1)	830 (34.0)	178 (38.1)	117 (41.6)	111 (38.1)	2156 (36.6)	1280 (36.6)	1232 (36.5)
Year 5	954 (38.6)	574 (37.5)	510 (36.6)	122 (44.0)	78 (44.8)	71 (38.0)	1335 (38.6)	782 (38.0)	762 (38.2)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AML, amlodipine besylate; CCB, calcium channel blocker; CHL, chlorthalidone; LIS, lisinopril.

*Unless otherwise indicated, data are expressed as number (percentage) of participants. Denominators for groups and subgroups varied over time.

†P<.05 compared with chlorthalidone.

‡Includes masked study drug or open label from same drug class.

§Expressed as mean number of medications (standard deviation, number of participants).

The DM and NG participants assigned to chlorthalidone were treated with significantly fewer antihypertensive medications compared with their counterparts assigned to amlodipine or lisinopril. Within each glycemic

stratum, an increasing percentage of participants were treated with medication to lower lipid levels over time, but there was no significant difference in this percentage among the 3 treatment groups.

Table 3. Mean Blood Pressure During Follow-up by Glycemic Status at Baseline and Study Treatment Assignment*

Blood Pressure by Medication Regimen and Follow-up	Glycemic Status								
	Diabetes Mellitus			Impaired Fasting Glucose			Normoglycemic		
	CHL	AML	LIS	CHL	AML	LIS	CHL	AML	LIS
SBP, mm Hg									
Baseline	146.4 (15.5, 5994)	146.4 (15.6, 3597)	146.9 (15.5, 3510)	147.0 (15.5, 628)	146.8 (16.1, 364)	145.5 (15.7, 407)	146.0 (15.8, 7791)	146.0 (15.7, 4594)	146.3 (15.8, 4627)
Year 1	138.1 (16.2, 4985)	139.7 (15.1, 2971)†	141.2 (18.2, 2870)†	138.2 (16.2, 537)	137.9 (14.4, 319)	139.9 (18.9, 353)	135.7 (15.3, 6673)	137.3 (14.4, 3936)†	139.0 (18.4, 3888)†
Year 2	137.0 (16.3, 4489)	138.1 (14.9, 2642)†	139.9 (17.9, 2560)†	137.2 (16.5, 493)	136.5 (14.6, 294)	138.0 (18.8, 305)	134.9 (15.4, 6160)	136.2 (14.8, 3596)†	137.4 (17.6, 3479)†
Year 3	135.8 (15.6, 4056)	137.1 (15.7, 2419)†	138.4 (17.8, 2306)†	135.4 (15.1, 440)	135.1 (14.5, 283)	134.8 (16.7, 277)	134.0 (15.2, 5660)	134.4 (14.4, 3356)	135.6 (16.9, 3177)†
Year 4	135.0 (16.1, 3532)	135.8 (15.1, 2104)†	137.2 (17.6, 1988)†	133.0 (16.3, 396)	136.1 (14.2, 248)†	135.0 (16.3, 239)	133.2 (15.4, 5007)	133.9 (14.8, 3020)†	134.4 (17.0, 2824)†
Year 5	135.0 (15.6, 1982)	136.3 (15.9, 1235)†	137.9 (19.0, 1097)†	133.0 (16.1, 226)	134.1 (13.2, 146)	133.5 (15.2, 149)	133.4 (14.9, 2856)	133.5 (14.1, 1686)	134.8 (17.3, 1572)†
DBP, mm Hg									
Baseline	83.9 (9.9, 5994)	82.7 (10.1, 3597)	83.1 (9.9, 3510)	84.6 (10.0, 628)	83.9 (10.3, 364)	85.2 (9.9, 407)	84.8 (10.0, 7791)	84.8 (10.1, 4594)	84.9 (9.9, 4627)
Year 1	78.7 (9.5, 4985)	77.8 (9.6, 2971)†	79.1 (10.3, 2870)†	80.9 (10.3, 537)	79.2 (9.7, 319)†	80.7 (9.9, 353)	79.6 (9.6, 6671)	79.1 (9.3, 3936)†	80.3 (10.6, 3888)†
Year 2	77.6 (9.7, 4489)	76.6 (9.5, 2642)†	77.8 (10.4, 2560)	79.0 (9.0, 493)	78.0 (9.5, 294)	78.9 (10.3, 305)	78.7 (9.4, 6610)	78.3 (9.5, 3596)	79.1 (10.3, 3479)†
Year 3	76.3 (9.5, 4056)	75.7 (9.6, 2419)†	76.5 (10.4, 2305)	77.1 (9.0, 440)	75.7 (9.8, 283)	77.3 (9.9, 277)	77.8 (9.4, 5660)	76.8 (9.4, 3355)†	77.8 (10.3, 3177)
Year 4	75.6 (9.7, 3532)	74.7 (9.7, 2104)†	75.5 (10.4, 1988)	76.4 (9.6, 396)	76.1 (9.5, 248)	76.2 (9.7, 239)	77.0 (9.5, 5005)	76.3 (9.4, 3020)†	77.3 (10.3, 2824)
Year 5	74.4 (9.7, 1982)	73.6 (10.1, 1236)†	74.6 (11.1, 1097)	74.0 (9.8, 226)	74.4 (9.5, 146)	75.1 (11.2, 149)	76.2 (9.8, 2856)	75.3 (9.6, 1686)†	76.1 (10.4, 1572)

Abbreviations: AML, amlodipine besylate; CHL, chlorthalidone; DBP, diastolic blood pressure; LIS, lisinopril; SBP, systolic blood pressure.

*Data are expressed as mean blood pressure (standard deviation, number of participants).

†*P* < .05 compared with chlorthalidone.

In the DM group, systolic BP was significantly lower throughout follow-up in those assigned to chlorthalidone compared with amlodipine (1- to 2-mm Hg difference) or lisinopril (2- to 3-mm Hg difference) (Table 3). Diastolic BP was significantly lower in the DM participants assigned to amlodipine compared with chlorthalidone (approximately 1-mm Hg difference). There was a similar but less consistent pattern for differences in systolic and diastolic BP between the treatment groups in the NG stratum. There was no consistently significant difference in systolic or diastolic BP across the 3 treatment groups for the IFG participants. Differences in systolic BP between chlorthalidone and lisinopril treatment were somewhat greater in black compared with nonblack participants in all 3 glycemic strata. The same was true for the comparison of chlorthalidone with amlodipine in the IFG and NG participants. In the approximately 5000 black participants with DM, systolic BP was about 4 to 5 mm Hg lower during chlorthalidone compared with lisinopril therapy and 1 mm Hg lower during chlorthalidone compared with amlodipine treatment (data not shown).

PRIMARY OUTCOME

There was no significant difference in incidence of the primary outcome (fatal CHD and nonfatal MI) for those

assigned to chlorthalidone compared with lisinopril in any of the 3 glycemic strata or for those assigned to chlorthalidone compared with amlodipine within the DM or NG strata (Figure 2). Within the IFG stratum, the primary outcome was significantly more common (*P* = .02) in those assigned to amlodipine compared with chlorthalidone (RR, 1.73 [95% CI, 1.10-2.72]; *P* = .01 for treatment × glycemic stratum interaction), with the difference emerging after approximately 2 years of follow-up (Figure 3).

SECONDARY OUTCOMES

Within the 3 glycemic strata, there was no significant difference in the incidence of total mortality, end-stage renal disease (Figure 2), or cancer (data not shown) for those assigned to chlorthalidone compared with amlodipine or lisinopril. The incidence of combined CHD was marginally higher (*P* = .05) in the IFG participants assigned to amlodipine compared with chlorthalidone (RR, 1.37 [95% CI, 1.00-1.87]; *P* = .03 for treatment × glycemic stratum interaction), but there was no significant difference for the corresponding treatment comparisons in the DM or NG participants. There was no significant difference in the incidence of combined CHD for those assigned to chlorthalidone vs lisinopril within any of the 3 glycemic strata. The incidence of stroke (RR, 1.31 [95% CI, 1.10-

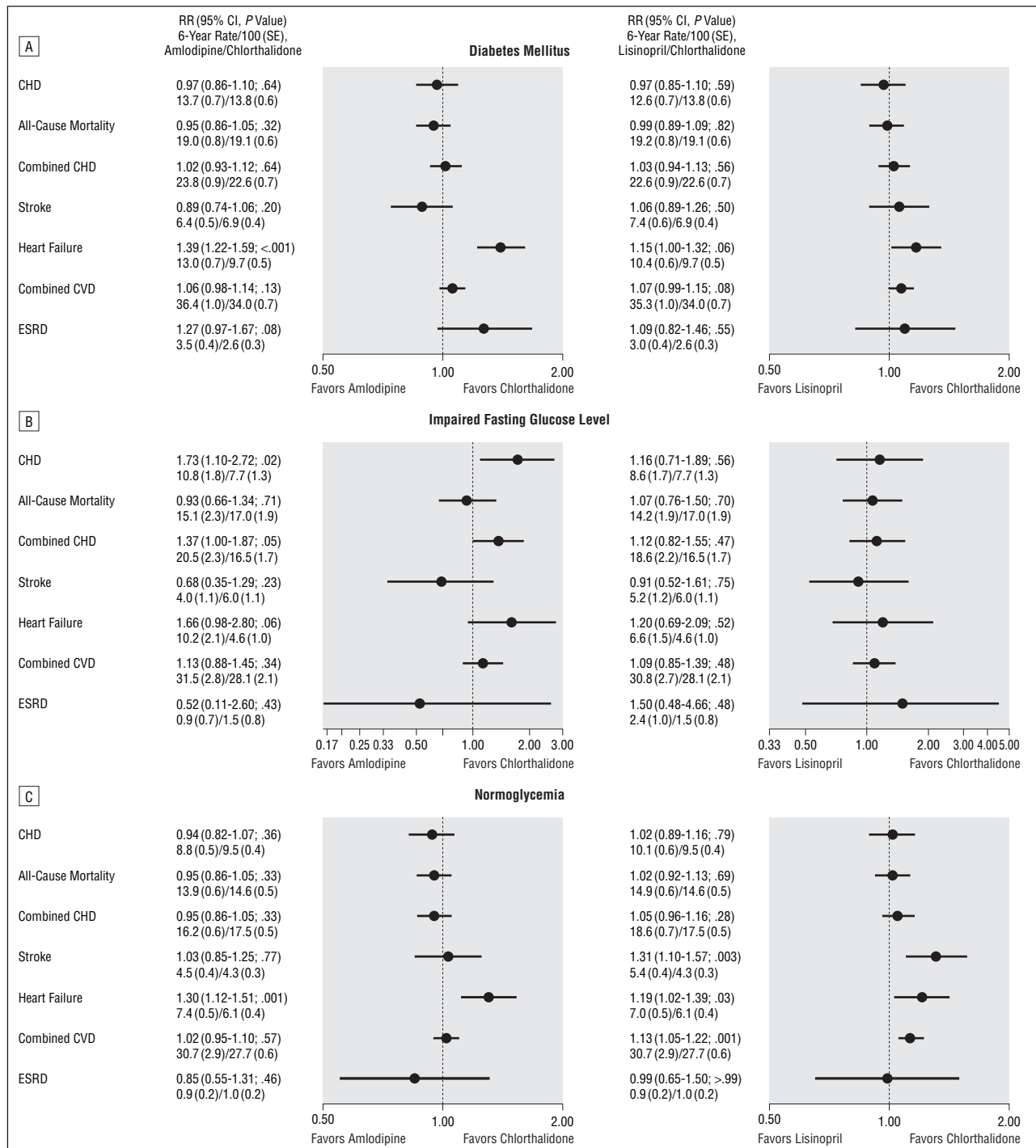


Figure 2. Relative risks (RRs), 95% confidence intervals (CIs), *P* values, and 6-year rates per 100 and standard error (SE) for nondiuretic treatment compared with diuretic treatment for participants with diabetes mellitus (A), impaired fasting glucose level (B), and normoglycemia (C) at baseline, for coronary heart disease (CHD) (includes CHD death plus nonfatal myocardial infarction), all-cause mortality, combined CHD (includes CHD, coronary revascularization, or hospitalized angina), stroke, heart failure, combined cardiovascular disease (CVD) (includes combined CHD, stroke, other treated angina, heart failure, or peripheral arterial disease), and end-stage renal disease (ESRD).

1.57]) and combined CVD (RR, 1.13 [95% CI, 1.05-1.22]) was significantly higher for the NG participants assigned to lisinopril vs chlorthalidone ($P=.17$ and $P=.58$ for treatment \times glycemic stratum interaction for stroke and combined CVD, respectively). Within each of the 3 glycemic strata, Kaplan-Meier plots identified a consistent pattern of higher cumulative stroke rates in black participants assigned to lisinopril compared with chlortha-

lidone, but there was little evidence of a corresponding difference for the nonblack participants (data not shown).

COMPONENTS OF SECONDARY OUTCOMES

There was a significantly higher incidence ($P=.001$) of heart failure for those assigned to amlodipine compared with chlorthalidone in the DM (RR, 1.39 [95% CI, 1.22-1.59])

and NG (RR, 1.30 [95% CI, 1.12-1.51]) groups (Figure 2). There was a significantly higher ($P=.03$) incidence of heart failure for the NG participants assigned to lisinopril vs chlorthalidone (RR, 1.19 [95% CI, 1.02-1.39]).

There was a significant difference ($P=.03$) in coronary revascularization for IFG participants assigned to amlodipine vs chlorthalidone (RR, 1.60 [95% CI, 1.04-2.46]; $P=.53$ for treatment \times glycemic stratum interaction). In the NG participants, there was a significantly higher ($P=.02$) incidence of hospitalized or treated angina for those assigned to lisinopril vs chlorthalidone (RR, 1.14 [95% CI, 1.02-1.28]; $P=.93$ for treatment \times glycemic stratum interaction). The incidence of hospitalized or treated peripheral arterial disease was significantly lower ($P=.04$) in the DM participants assigned to amlodipine vs chlorthalidone (RR, 0.80 [95% CI, 0.65-0.99]; $P=.22$ for treatment \times glycemic stratum interaction).

There was a significant difference in the primary outcome for the comparison of lisinopril with chlorthalidone therapy across the 3 glycemic strata in black compared with non-black participants ($P=.04$ for interaction). Specifically, among participants with IFG, the RR was 1.13 for black and 0.68 for nonblack participants. There was also a significant difference in total mortality for the comparison of amlodipine with chlorthalidone across the 3 glycemic strata in black compared with nonblack participants ($P=.05$ for interaction). Specifically, among participants with IFG, the RR was 1.25 for black and 0.92 for nonblack participants.

COMMENT

ALLHAT provides the largest and most diverse experience for comparing first-step antihypertensive drug therapy in adults with DM and IFG. The present analysis was based on 13 101 adults with DM, of whom 7429 were 65 years or older, 5077 were black, and 4693 had a history of CVD. In addition, 1399 participants had IFG. The ALLHAT comparisons benefit from a high level of adherence to the assigned treatment, for up to 8 years of follow-up, and a substantial number of outcome events.

Overall, the pattern for efficacy of chlorthalidone compared with amlodipine and lisinopril was similar in each of the 3 glycemic strata. The few statistically significant differences must be interpreted with caution, given the large number of treatment comparisons that were examined. Only 2 glycemic stratum \times treatment interactions were statistically significant at the $P<.05$ level (CHD and combined CHD for the IFG participants assigned to amlodipine vs chlorthalidone), and only 1 was significant at the $P<.01$ level (the CHD outcome). One could conservatively interpret the findings in our analysis as failing to demonstrate superiority in protecting against CHD death and nonfatal MI during first-step treatment with an ACEI or a CCB compared with thiazide-type diuretics in those with DM, IFG, or NG. A significantly lower incidence of stroke was observed in those assigned to chlorthalidone compared with those assigned to lisinopril in the NG group. Again, the most conservative interpretation of the data would be that there is no evidence of superiority for treatment with lisinopril or amlodipine compared with chlorthalidone in any of the 3 glycemic strata. There was more consistent evidence that

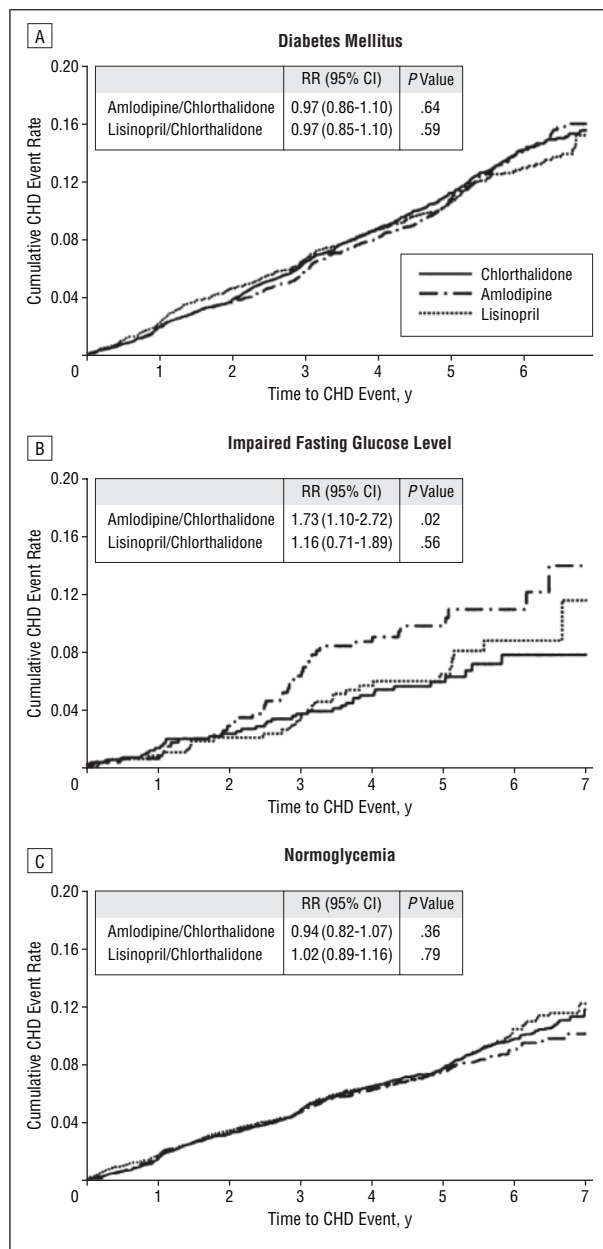


Figure 3. Coronary heart disease (CHD) (includes CHD death plus nonfatal myocardial infarction) by treatment group for participants with diabetes mellitus, impaired fasting glucose level, or normoglycemia at baseline. RR indicates relative risk; CI, confidence interval.

heart failure was less common in those assigned to chlorthalidone compared with amlodipine or lisinopril, although the comparison for lisinopril vs chlorthalidone within the IFG stratum was not statistically significant.

The number of participants with DM in most hypertension trials that have compared a single antihypertensive agent with a placebo or usual care has been modest (1248 in the Hypertension Detection and Follow-up Program; 583 in the Systolic Hypertension in the Elderly Program; 492 in the Systolic Hypertension in Europe Trial; 363 in the Comparison of Amlodipine vs Enalapril to Limit Occurrence of Thrombosis trial; 127 in the Swedish Trial in Old Patients With Hypertension; 98 in the Systolic Hypertension in China trial; and 92 in the European Work-

ing Party on High Blood Pressure in the Elderly trial). Within this limitation, diuretics and CCB have appeared to be equally effective in diabetic and nondiabetic participants in these trials.²⁰⁻²⁵ Almost 4000 patients with DM have been studied in ACEI vs placebo trials, where BP lowering was not the primary intervention (3577 in the Heart Outcomes Prevention Evaluation Study; 280 in the Quinapril Ischemic Event Trial; and 50 in the Simvastatin/Enalapril Coronary Atherosclerosis Trial).²⁶⁻²⁸ In the Heart Outcomes Prevention Evaluation Study, equally beneficial results were noted in the 3577 participants with and the 5720 without DM.²⁶

There have been few differences in clinical outcomes in randomized trials in which patients with DM have been treated with different classes of antihypertensive drug therapy. In the UK Prospective Diabetes Study, cardiovascular and microvascular outcomes were similar in 358 participants assigned to the β -blocker atenolol and their 400 counterparts assigned to the ACEI captopril.²⁹ Likewise, in the Swedish Trial in Old Patients With Hypertension 2 study, there were no significant differences in CVD mortality, fatal MI, stroke, or sudden death among those allocated to traditional antihypertensive treatment (diuretics and β -blockers; $n=253$), a CCB ($n=231$), or an ACEI ($n=235$).³⁰ In the Nordic Diltiazem Study, no significant differences in CVD outcomes were noted between participants assigned to a CCB ($n=351$) or to "conventional" therapy (diuretics or β -blockers; $n=376$).³¹ In the Appropriate Blood Pressure Control in Diabetes trial, nonfatal MI was more common in 235 participants assigned to the CCB nisoldipine compared with 235 assigned to the ACEI enalapril maleate, but total mortality and incidence of heart failure were similar in both groups.^{32,33} In the Captopril Prevention Project,³⁴ the primary end point, a composite of fatal and nonfatal MI and stroke and other CVD deaths, was less common in the 309 diabetic participants assigned to the ACEI captopril compared with the 263 diabetic participants assigned to a diuretic or a β -blocker (RR, 0.59 [95% CI, 0.38-0.91]), but there was no corresponding difference in the trial as a whole ($n=10\,985$). In the Controlled Onset Verapamil Investigation of Cardiovascular End Points, there was no difference in CVD outcomes for 1616 diabetic participants treated with a controlled-onset extended-release form of the CCB verapamil hydrochloride compared with 1623 diabetic participants treated with atenolol or hydrochlorothiazide.³⁵ Likewise, there was no difference in the primary outcome of death or nonfatal MI or stroke in the 3169 International Verapamil-Trandolapril Study diabetic participants assigned to a sustained-release form of the CCB verapamil compared with 3231 diabetic participants assigned to a non-CCB strategy.³⁶ Our ALLHAT experience for participants with hypertension and DM is larger than that in any of the previously mentioned trials. In addition, ALLHAT is the only study of its size, to our knowledge, to have compared a thiazide-type diuretic with representative agents from 3 other classes of antihypertensive medication and to have explored the relative efficacy of different classes of antihypertensive therapy in patients with IFG.

Challenges in interpreting the ALLHAT findings include the complexity of understanding treatment effects in the context of therapy with second- and third-step antihy-

pertensive drugs, the difficulty of generalizing experience with a chosen drug to its entire class, and the challenge of extrapolating trial experience to more prolonged periods of treatment. In an effort to minimize cost and to minimize participant as well as investigator burden, urinary microalbuminuria, glycosylated hemoglobin levels, and other physiological observations of interest were not collected in ALLHAT. In ALLHAT, those treated with chlorthalidone had the highest and those treated with lisinopril had the lowest levels of fasting glucose during follow-up.¹⁴ The biological importance of these differences are unknown, but the average differences in fasting glucose levels were small (<5 mg/dL [<0.3 mmol/L]), tended to diminish over time, and did not result in an increased risk for CVD during an average follow-up of almost 5 years. More detailed ALLHAT analyses of the impact of glucose disorders on clinical outcomes, treatment-related changes in renal function, and experience in subgroups defined by age, race, and sex will be presented in separate papers. Recognizing the constraints in the interpretation of clinical trials, the ALLHAT findings suggest that thiazide-type diuretics should be strongly considered as first-step agents for therapy in patients with hypertension and DM or IFG. These agents are not only efficacious but have been evaluated in many trials and are the least expensive medications to prescribe.

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