Long-Term Effect of Diuretic-Based Therapy on Fatal Outcomes in Subjects With Isolated Systolic Hypertension With and Without Diabetes

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Diuretic-based antihypertensive therapy is associated with the development of diabetes but with improved clinical outcomes. It has been proposed that the duration of clinical trials has been too short to detect the adverse effects of diabetes. We assessed the long-term mortality rate of subjects in the Systolic Hypertension in the Elderly Program (n = 4,732) who were randomized to stepped-care therapy with 12.5 to 25.0 mg/day of chlorthalidone or matching placebo. If blood pressure remained above the goal, atenolol or matching placebo was added. At a mean follow-up of 14.3 years, cardiovascular (CV) mortality rate was significantly lower in the chlorthalidone group (19%) than in the placebo group (22%; adjusted hazard ratio [HR] 0.854, 95% confidence interval [CI] 0.751 to 0.972). Diabetes at baseline (n = 799) was associated with increased CV mortality rate (adjusted HR 1.659, 95% CI 1.413 to 1.949) and total mortality rate (adjusted HR 1.510, 95% CI 1.347 to 1.693). Diabetes that developed during the trial among subjects on placebo (n = 169) was also associated with increased CV adverse outcome (adjusted HR 1.562, 95% CI 1.117 to 2.184) and total mortality rate (adjusted HR 1.348, 95% CI 1.051 to 1.727). However, diabetes that developed among subjects during diuretic therapy (n = 258) did not have significant associations with CV mortality rate (adjusted HR 1.043, 95% CI 0.745 to 1.459) or total mortality rate (adjusted HR 1.151, 95% CI 0.925 to 1.433). Diuretic treatment in subjects who had diabetes was strongly associated with lower long-term CV mortality rate (adjusted HR 0.688, 95% CI 0.526 to 0.848) and total mortality rate (adjusted HR 0.805, 95% CI 0.680 to 0.952). Thus, chlorthalidone-based treatment improved long-term outcomes, especially among subjects who had diabetes. Subjects who had diabetes associated with chlorthalidone had no significant increase in CV events and had a better prognosis than did those who had preexisting diabetes. ©2005 by Excerpta Medica Inc.

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The benefits of antihypertensive therapy in older patients who have hypertension, including isolated systolic hypertension, have been proved in controlled clinical trials.[1–9] In most of these trials, diuretic-based therapy resulted in lower rates of stroke, cardiovascular (CV) events, coronary heart disease and heart failure. However, diuretics have been associated with the development of diabetes.[10–12] Diabetes and hypertension are independently associated with a greater than twofold increase in the risk of CV disease and their combination increases the risk markedly.[13,14] Other reports have suggested increased risks of morbidity and mortality among patients who have diabetes mellitus and are treated with diuretics.[15,16] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the thiazide-like diuretic chlorthalidone was equally efficacious in preventing CV events compared with the angiotensin-converting enzyme inhibitor lisinopril and the calcium channel blocker amlodipine and was associated with a significantly higher rate of developing diabetes.[17] Similarly, diuretic-based therapy was associated with improved outcomes and with the development of diabetes in the Hypertension Detection and Follow Up Program and the Systolic Hypertension in the Elderly Program (SHEP).[18,19] It has been proposed that the diabetes associated with diuretic use in these studies did not result in increased CV events because of a relatively short period of observation after the development of diabetes.[20–23] We report on the 14.3-year mortality rate of subjects in the SHEP who had been randomized to chlorthalidone or placebo according to the presence of diabetes at baseline and to the development of diabetes during the clinical trial.

METHODS

The SHEP was a placebo-controlled, double-blind, randomized, multicenter clinical trial that tested the efficacy of diuretic-based stepped-care antihyperten-

sive management of isolated systolic hypertension in subjects ≥60 years of age.[4,8] The major inclusion criterion was the presence of isolated systolic hypertension, which was defined as a systolic blood pressure of 160 to 219 mm Hg with a diastolic blood pressure <90 mm Hg. Patients who had insulin-dependent diabetes mellitus and those who required diuretic therapy were excluded.

In a randomized, double-blind fashion, subjects received stepped-care therapy with 12.5 to 25.0 mg/day of chlorthalidone or matching placebo to achieve the goal blood pressure (systolic blood pressure decrease of ≥20 mm Hg to <160 mm Hg). If blood pressure remained above the goal, atenolol or reserpine was added. Mean duration of exposure to chlorthalidone was 3.3 years, and 32% of subjects who received active treatment also received atenolol. Potassium supplementation was recommended for subjects in the SHEP who developed hypokalemia and was dictated by the protocol for a confirmed serum potassium level <3.5 mEq/L.[4] Criteria for enrollment and the main results of SHEP, a 36% decrease in stroke, a 27% decrease in coronary heart disease, and a 49% decrease in heart failure, have been described in detail elsewhere.[4,24,25]

Long-term follow-up: The SHEP began in March 1985 and ended in February 1991, with a mean follow-up of 4.3 years. Vital status through 2000 and cause of death of the 4,281 subjects who were alive at the end of the original SHEP trial in 1991 were determined with the National Death Index (NDI) Plus service, which reports codes for causes of death. The institutional review boards of the Robert Wood Johnson Medical School and the University of Texas School of Public Health approved this follow-up study. The SHEP coordinating center at the University of Texas School of Public Health submitted a finder file that contained the personal identifiers of the 4,281 survivors to the National Center for Health Statistics for matching against the NDI for 1991 to 2000. A probabilistic algorithm was used to match subjects in the SHEP to the NDI data. Available matching variables included social security number, birth date, and an acrostic that consisted of the initial letters of the surname, first name, and middle initial. Of the 4,281 records submitted, 2,728 were matched to >1 NDI record and 1,100 were matched to ≥1 NDI record. A class 1 match corresponds to an exact match on social security number (all 9 digits), first name, middle initial, last names, gender, state of birth, birth month, and birth year, and matches of higher order indicate a lesser degree of agreement. A class 2 match corresponds to social security number matches on ≥7 digits, and ≥1 of the other items from class 1 may not match. Complete surnames of subjects and state of birth were not collected by the SHEP coordinating center, so it was not possible to have class 1 matches. With a class 3 match, social security number is unknown, but ≥8 items (first name, middle initial, surname, birth date, birth month, birth year, gender, race, marital status, or state of birth) should match. A class 4 match is the same as a class 3 match, but ≤8 items

match. For a class 5 match, a social security number is known but does not match. Likely matches (classes 2 and 4) were evaluated clerically by applying the probability cut-off score recommended by the NDI to the 1,980 class 2 matches (score ≥44.5) and 51 class 4 matches (score ≥32.5), and 1,535 final SHEP matches were identified. There were no class 3 matches. There were 698 class 5 matches that were assumed by NDI to be false matches. The median length of the extended follow-up after the end of the double-blind phase of the SHEP was ~10 years (119 months). Together with the follow-up data during the double-blind phase, the median length of the extended follow-up from the beginning of the SHEP was 14.3 years (172 months). The SHEP classification of CV death included the following definitions for cause of death (codes from the *International Classification of Diseases, Ninth Revision* are in parentheses): stroke (430, 436 to 438, and 290.4), rapid/sudden death (414, 427.3 to 427.9, and 798.2), myocardial infarction (410), left ventricular failure (425.4 and 428.0 to 428.9), and other CV causes (401, 402, 403, 415, 424, 429.2, 440.9, 441, and 443.9). Causes of death for subjects who resided in New York City (n = 25) or Rhode Island (n = 3) were not available.

Definition of diabetes: The current definition of diabetes (serum glucose ≥126 mg/dl or 7.0 mmol/L) was used in the primary analysis. Analysis performed according to the original SHEP definition (serum glucose ≥140 mg/dl or 7.8 mmol/L) yielded similar results. Subjects were considered to have diabetes at baseline if (1) a history of diabetes was reported by the subject, (2) a subject reported using antidiabetic medication, or (3) a subject had a baseline fasting serum glucose level ≥126 mg/dl. Subjects who did not have diabetes at baseline were considered to have developed diabetes at follow-up if a fasting serum glucose level measured at the first or second SHEP annual visit was ≥126 mg/dl or if they reported use of oral hypoglycemic medication.

Statistical analysis: Statistics were produced with SAS 8.2 (SAS Inc., Cary, North Carolina). Survival analysis was performed with the Kaplan-Meier method using the log-rank test produced by the LIFETEST procedure to compare survival curves. For analyses that considered diabetes, survival times were computed from the time of diagnosis of diabetes. Between-group differences in proportions and their odds ratios were assessed by chi-square test (FREQ procedure), and differences in means were assessed by the TTEST procedure. Median length of follow-up was calculated with the UNIVARIATE procedure. Adjusted hazard ratios for death and CV death associated with treatment assignment and with diabetes were determined by Cox's regression using the PHREG procedure. The reference group for the effect of treatment was the placebo group, and the reference group for the effect of diabetes consisted of subjects who did not have diabetes at baseline and who did not develop diabetes during the SHEP trial. The proportional hazards assumption was checked graphically to see that the curves were roughly parallel. Because

TABLE 1 Length of Follow-up and Mortality Rate by Cause and Treatment Group

Treatment Assignment	SHEP Trial (n = 4,732)[†]		SHEP Plus Extension (n = 4,732)	
	Active	Placebo	Active	Placebo
No. of subjects	2,363	2,369	2,363	2,369
Median follow-up (yrs)	4.4		14.3	
All causes	212	241	969	1,018
%	9.0	10.2	41.0	43.0
HR, 95% CI	0.842	0.697–1.016	0.923	0.844–1.010
CVD causes	89	111	450	515
Percent	3.8%	4.7%	19.0%	21.7%
HR, 95% CI	0.787	0.592–1.046	0.854*	0.751–0.972

*p <0.05.
[†]Four SHEP subjects were excluded from analysis due to indeterminate diabetes status (n = 2) and insulin treatment at baseline (n = 2).
CVD = cardiovascular disease.

diabetes was not included in the original randomization design, we controlled for the introduction of bias into the analyses based on diabetic status by adjusting for demographic and clinical factors associated with increased mortality rate. Cox's models included the following baseline demographic and clinical factors: age, race, gender, smoking status, baseline systolic blood pressure, baseline diastolic blood pressure, history of myocardial infarction, years of education, baseline electrocardiographic abnormalities, baseline alcohol consumption, and body mass index.

RESULTS

Baseline characteristics of the active treatment and placebo groups at randomization have been previously reported.[4,18] Mean age was 71.6 ± 6.7 years, 58% were women, 14% were African-American, 16.9% had diabetes, 4.9% had a history of myocardial infarction, 49.8% were current or previous smokers, and mean blood pressures were 170.3 ± 9.4 mm Hg (systolic) and 77.0 ± 8.0 mm Hg (diastolic).

Long-term follow-up and causes of death: Vital status by the SHEP randomization group is presented in Table 1. Of the 4,732 subjects in the SHEP, 453 (9.6%) died during the clinical trial. Of the remaining 4,279 subjects who were alive at the end of SHEP, 1,534 (35.8%) died during the extended follow-up period. Thus, 1,987 of the original SHEP cohort (42%) were dead at the end of the extended follow-up period (1,018, or 43.0%, of the placebo group vs 969, or 41.0%, of the active therapy group; hazard ratio [HR] 0.923, 95% confidence interval [CI] 0.844 to 1.010).

Approximately half (48.6%) of the deaths was attributed to CV causes. CV mortality rate was lower in the chlorthalidone group (450 deaths, 19.0%) than in the placebo group (515 deaths, 21.7%; HR 0.854, 95% CI 0.751 to 0.972; Table 1).

Development of diabetes in SHEP: At baseline, 384 subjects (16.3%) were diabetic in the active treatment group versus 415 (17.5%) in the placebo group. During follow-up, an additional 258 subjects (13.0%) developed diabetes in the active group versus 169 subjects (8.7%) in the placebo group (p <0.0001).

Subjects who developed diabetes were more likely to have had higher levels of blood sugar at baseline and were more likely to be in the active treatment group (odds ratio 1.56, 95% CI 1.30 to 1.95). Subjects who developed diabetes during diuretic therapy had lower fasting levels of serum glucose at the second annual visit (136.1 ± 30.8 mg/dl) than did those who developed diabetes on placebo (143.8 ± 49.0 mg/dl, p = 0.055) and those who had diabetes at baseline (157.1 ± 55.4 mg/dl, p = 0.001). The follow-up blood sugar levels of those who were not classified as having diabetes at baseline or follow-up were 99.4 ± 10.7 mg/dl for the active treatment group and 97.8 ± 10.5 mg/dl for the placebo group. In subjects who developed diabetes during follow-up, fasting blood sugar levels increased from baseline to the second annual visit by 29.2 ± 31.3 mg/dl in the diuretic group and by 35.2 ± 44.8 mg/dl in the placebo group. In addition, proteinuria (higher than trace levels) occurred less frequently among subjects who developed diabetes in the chlorthalidone group than among those who developed diabetes in the placebo group (14.3% vs 20.6%, p = 0.005). Hemoglobin A1c was not measured in the SHEP. In the active therapy group, subjects who were stepped up to the combination of chlorthalidone and atenolol were more likely to develop diabetes than were those who remained on diuretic therapy alone throughout the double-blind study (16.4% vs 11.8%, p <0.007).

Mortality rate by diabetic status: Figure 1 and Table 2 present the mortality rates of subjects who had diabetes and those who did not. When the extended follow-up was considered, subjects who had diabetes at baseline had significantly higher mortality rates than did those who did not (HR 1.633, 95% CI 1.397 to 1.907 for the placebo group; HR 1.376, 95% CI 1.161 to 1.631 for the active treatment group). Subjects who had been randomized to placebo and developed diabetes during the double-blind phase also had significantly higher mortality rates than did those who did not develop diabetes (HR 1.348, 95% CI 1.051 to 1.727). However, this effect was less pronounced and not statistically significant among subjects who developed diabetes while on diuretic therapy (HR 1.151, 95% CI 0.925 to 1.433). When CV mortality rate rather than total mortality rate was considered (Table 2), the increased risk imposed by diabetes developing in the placebo group was more pronounced (HR 1.562, 95% CI 1.117 to 2.184). A significant increase in risk of CV mortality was not observed among subjects who developed diabetes in the active treatment group (HR 1.043, 95% CI 0.745 to 1.459).

Mortality rate in the chlorthalidone and placebo groups by diabetic status: Subjects who had diabetes (at baseline or during follow-up) and were randomized
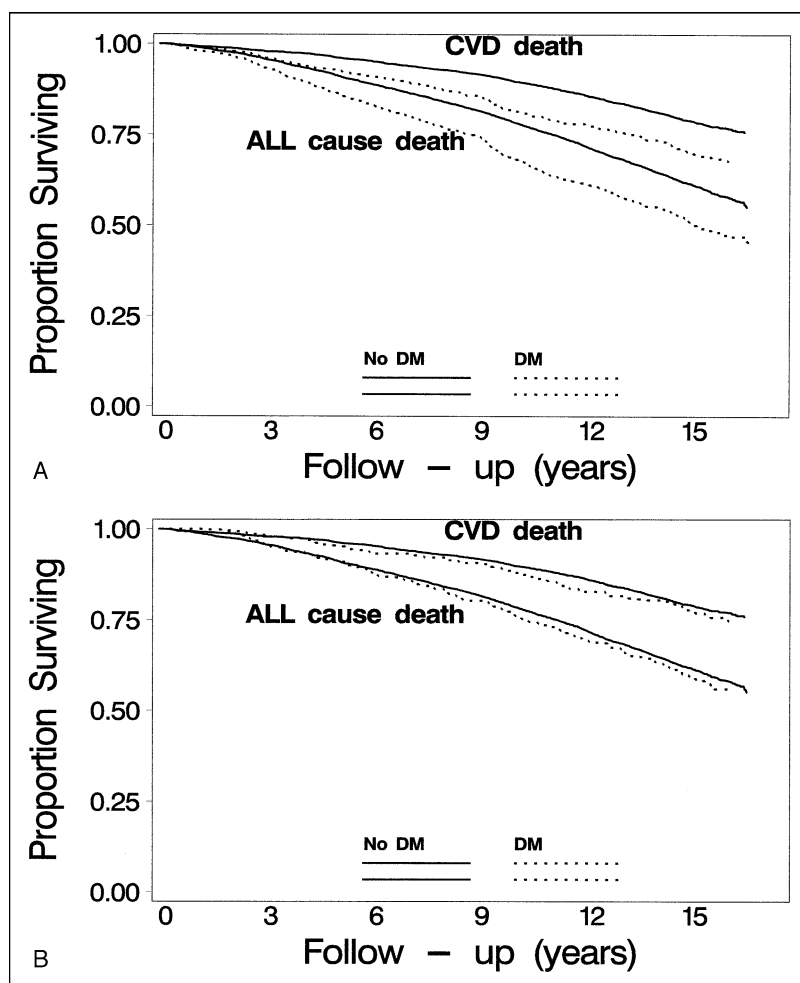
FIGURE 1. Effect of diabetes (DM) on Kaplan-Meier survival plots of all-cause and CV disease (CVD) death in the SHEP trial and the SHEP extension in subjects (n = 799) who had DM (126 mg/dl) at baseline (A) and those (n = 427) who developed DM during the double-blind phase of the SHEP trial (B).

to active therapy had lower mortality rates during the extended follow-up than did those who had been randomized to placebo (HR 0.805, 95% CI 0.680 to 0.952; Figures 2 and 3). This effect was more pronounced when CV mortality rate was considered (HR 0.688, 95% CI 0.526 to 0.848). Statistically significant benefits of active therapy versus placebo were not observed in subjects who did not have diabetes. Subjects who received chlorthalidone plus atenolol did not have mortality rates different from those who remained on chlorthalidone alone regardless of diabetic status.[26]

The results observed when the alternate definition of diabetes (glucose level $\geq$140 mg/dl) was used were directionally similar to those obtained with the current definition (data not presented) and led to the same conclusions.

DISCUSSION

This long-term study of older patients who had isolated systolic hypertension yielded 3 conclusions of clinical significance. First, chlorthalidone-based anti-

hypertensive therapy was associated with a significantly lower rate of CV mortality during long-term follow-up (14.3 years). This was not observed during the double-blind phase of the study. Second, in contrast to diabetes present at baseline, diabetes diagnosed during diuretic therapy was rather mild and not associated with a significant increase in CV or total mortality rates during the extended follow-up. Third, chlorthalidone-based therapy was associated with lower long-term rates of total and CV mortality in patients who had diabetes at baseline or during the clinical trial. These findings support the recommendations of the seventh report by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, in which diuretics (in addition to β blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers) should be considered first-line therapy for hypertension, including in patients who have diabetes.[27] Chlorthalidone, a thiazide-like diuretic, is similar to other thiazide diuretics but differs from hydrochlorothiazide in potency (1.5 to 2.0 times more potent) and has a longer duration of action. Whether these pharmacokinetic and pharmacodynamic features cause differences in outcomes is not known.[28]

The observation of lower rates of long-term CV mortality extends the findings of the SHEP, in which statistically significant mortality effects were not found during the double-blind phase. The continuing divergence of the mortality curves for CV disease after the end of the SHEP could be a manifestation of lesser target organ damage in the active treatment group and a persistence of blood pressure difference between the active treatment and placebo groups after the end of the SHEP, although all patients were advised to begin active therapy. At the end of the SHEP, blood pressure was 11.1/3.4 mm Hg lower in the active treatment group.[4] It is likely that most of the patients in the active treatment group continued active therapy, whereas a smaller proportion of those randomized to placebo initiated active therapy.[4] A significant benefit of active therapy on total mortality rate may not have been observed because of insufficient statistical power to detect mortality differences and competing risks.

The milder long-term course of diabetes that occurred during diuretic therapy is likely related to the lesser degree of metabolic disturbance as judged by fasting glucose levels and proteinuria. In epidemiologic studies, severity of hyperglycemia has been di-

TABLE 2 Mortality Rate by Treatment and Diabetes Status in the SHEP Trial and the SHEP Extension

Diabetes Status	Active (n = 2,363)		Placebo (n = 2,369)		Active Versus Placebo*		Diabetes Versus No Diabetes*		
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Total	Active	Placebo
DM at baseline[†]									
No.	384	1,979	415	1,954					
No. dead	179	790	223	795	0.819 (0.668–1.004)	0.810 (0.576–1.139)	1.510 (1.347–1.693)	1.376 (1.161–1.631)	1.633 (1.397–1.907)
Percent	46.6	39.9	53.7	40.7					
DM developed during follow-up[†]									
No.	258	1,721	169	1,785					
No. dead	100	690	79	716	0.874 (0.638–1.198)	0.969 (0.871–1.078)	1.236 (1.049–1.456)	1.151 (0.925–1.433)	1.348 (1.051–1.727)
Percent	38.8	40.1	46.8	40.1					
DM at baseline or follow-up[†]									
No.	642	1,721	584	1,785					
No. dead	279	690	302	716	0.805 (0.680–0.952)	0.969 (0.871–1.078)	1.431 (1.293–1.584)	1.297 (1.121–1.501)	1.578 (1.369–1.818)
Percent	43.5	40.1	51.7	40.1					
DM at baseline[‡]									
No.	384	1,979	415	1,954					
No. dead	85	365	124	391	0.707 (0.531–0.942)	0.810 (0.576–1.139)	1.659 (1.413–1.949)	1.458 (1.138–1.868)	1.838 (1.484–2.276)
Percent	22.1	18.4	29.9	20.0					
DM developed during follow-up[‡]									
No.	258	1,721	169	1,785					
No. dead	42	323	45	346	0.684 (0.435–1.074)	0.940 (0.805–1.097)	1.256 (0.991–1.591)	1.043 (0.745–1.459)	1.562 (1.117–2.184)
Percent	16.3	18.8	26.6	19.4					
DM at baseline or follow-up[‡]									
No.	642	1,721	584	1,785					
No. dead	127	323	169	346	0.688 (0.526–0.848)	0.940 (0.805–1.097)	1.535 (1.329–1.773)	1.287 (1.037–1.596)	1.809 (1.487–2.200)
Percent	19.8	18.8	28.9	19.4					

*Values are HR (95% CI) according to Cox's model.
[†]All-cause mortality rate.
[‡]Mortality rate from CV disease.
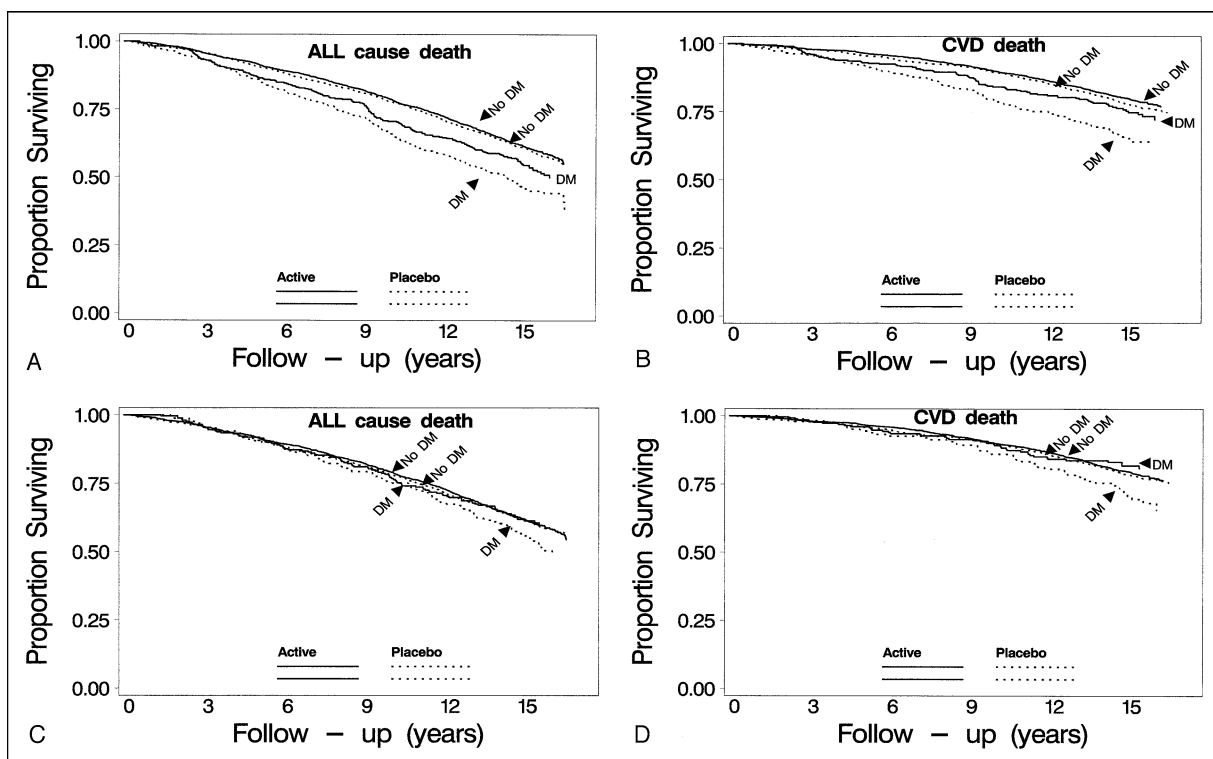CVD = cardiovascular disease.

FIGURE 2. Kaplan-Meier survival plots of the interaction between treatment assignment and DM status for all-cause death and CVD death in (A, B) subjects who had diabetes at baseline (n = 799) and (C, D) those who developed diabetes in the double-blind phase (n = 427) in the SHEP trial and the SHEP extension. Abbreviations as in Figure 1.
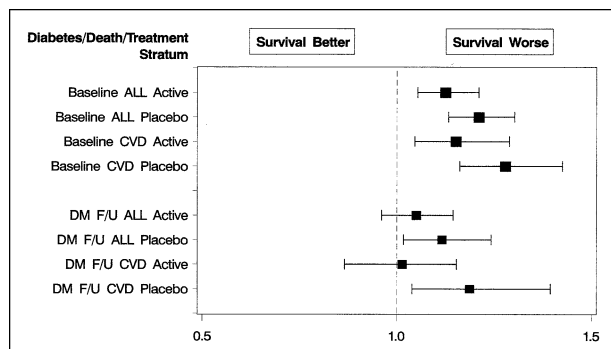

FIGURE 3. Adjusted HR and 95% CI values associated with diabetes for all-cause death and CVD death in the SHEP trial and the SHEP extension, stratified by diabetes definition and treatment assignment. CI bars that cross the line of unity (1) indicate a lack of a statistically significant association of that factor with that mortality outcome. Abbreviations as in Figure 1.

rectly associated with the degree of risk imposed by diabetes.[29] Further, the effects of active treatment versus those of placebo on metabolic parameters in the SHEP were small (fasting glucose level +0.20 mmol/L/+3.6 mg/dl, p <0.01; total cholesterol +0.09 mmol/L/+3.5 mg/dl, p <0.01; high-density lipoprotein cholesterol −0.02 mmol/L/−0.77 mg/dl, p <0.01).[10]

The finding that diuretic-induced hyperglycemia was associated with lower CV risk than with diabetes developing in the placebo group may have been related to different underlying mechanisms. The development of type 2 diabetes in patients who have hy-

pertension and do not receive diuretic therapy is linked to physical inactivity, weight gain, aging, and genetic predisposition.[30] This is associated with endothelial dysfunction, dyslipidemia, hypercoagulability, impaired fibrinolysis, oxidative stress, and hyperglycemia.[29] Diuretics, including chlorthalidone, increase levels of serum glucose and insulin, likely because of decreased glucose-stimulated insulin release due to hypokalemia and insulin resistance related to increased sympathetic activity.[11,12,31]

It is not clear why diuretic-based therapy was associated with a larger risk decrease, especially for CV, in subjects who had diabetes compared with those who did not. Previous clinical trials have suggested that lower blood pressure during follow-up exerts a more pronounced effect on prognosis in subjects who have diabetes. In the Systolic Hypertension in Europe (Syst-Eur) trial, patients who had diabetes reported greater benefit from active treatment than did patients who did not have diabetes, and the initial benefit of active treatment persisted after a median follow-up of 6 years. Therefore, national guidelines have recommended lower blood pressure targets for patients who have diabetes.[27,32,33] Better outcome may be related to better blood pressure control with additional drugs, such as angiotensin-converting enzyme inhibitors. The guidelines in effect during the extended follow-up period (fourth, fifth, and seventh reports by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommended diuretics among the first-line drugs for hypertension and angiotensin-converting enzyme inhibitors

for patients who had hypertension and diabetes.[34–36] Whatever the explanation, the present data associated diuretic-based therapy in patients who had hypertension with lower mortality rates in patients who had diabetes at baseline or developed diabetes during follow-up.

Limitations of this study are its retrospective nature, the lack of information on nonfatal end points, pharmacologic therapy, and blood pressure after the end of the double-blind phase of the SHEP, unavailable data on hemoglobin A1c, and using an administrative database to adjudicate vital status and cause of death. It is also possible that additional patients developed diabetes during the extended follow-up. These patients would have been classified as not having diabetes in the present analysis. It is unlikely that any of these factors would have inserted sufficient bias to invalidate the conclusions of the study. It is unlikely that the placebo group would have been treated more vigorously than the active therapy group after the end of the study. If this were the case, the observed benefit of diuretic therapy would have been underestimated. The reliability of NDI and the matching algorithm have been verified in previous studies.[37,38] This study pertains only to older patients who had isolated systolic hypertension. Therefore, its conclusions may not be extrapolated to younger patients who have diastolic/systolic hypertension and a follow-up of <14 years.

In summary, the present data indicate that diuretic-based therapy of hypertension improves long-term (14.3 year) outcomes, that the diabetes related to diuretic therapy has a much milder course than diabetes at baseline, and that diuretic-based therapy results in lower long-term rates for total and CV mortality in patients who have hypertension and diabetes.

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