

# Is New-Onset Diabetes of Clinical Significance in Treated Hypertensive Patients?—Con

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*There is little doubt that diabetes is more common in hypertensive than normotensive individuals. There are also some data suggesting that the use of certain antihypertensive agents, i.e., diuretics and more specifically some  $\beta$  blockers will increase the occurrence of new onset diabetes (NOD) when compared to other medications, especially angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The clinical significance of this 1%–3.5% difference, however, has not been established. Different studies report different outcomes. In large outcome trials the occurrence of NOD did not effect mortality or morbidity outcomes. Although one study reported that NOD had the same prognosis as pretreatment diabetes, another did not. At present, data are insufficient to suggest that NOD is of important clinical significance or that present treatment recommendations, especially*

*regarding the use of diuretics, should be changed. (J Clin Hypertens. 2006;8:126–132) ©2006 Le Jacq Ltd.*

Diabetes is a major cardiovascular (CV) risk factor, but drug-induced new-onset diabetes may not be of important clinical significance and should not be a major determining factor in choosing a treatment for hypertension if the medication is necessary to reduce blood pressure (BP).<sup>1,2</sup> Any recommendation for changing treatment should be based on consistent evidence from well controlled trials.<sup>3</sup> At present, the data on new-onset diabetes do not satisfy these criteria. There are many available studies about this entity, but many are poorly designed with an inadequate follow-up. In addition, there are no randomized controlled trials to date in which new-onset diabetes has been a predefined primary outcome. However, based on a recent study<sup>4</sup> that suggests that new-onset diabetes has the same prognosis as pretreatment diabetes, some investigators have recommended that we reconsider the use of diuretics as initial therapy. It has also been suggested that Food and Drug Administration warnings be put on diuretic prescriptions.

Over the years, for whatever reason, there have been attempts to minimize the benefits of  $\beta$  blockers

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and especially diuretics. Statements have been made that treatment with these agents reduces strokes and heart failure but has had minimal effects on coronary heart disease events, based on epidemiologic data compared with clinical trial data,<sup>5</sup> possibly because of the effect on lipids and insulin resistance. These speculations have been proven to be false.<sup>6-9</sup> There were suggestions that increased ectopy and sudden death resulted from diuretic use.<sup>10</sup> These too have been proven false in carefully done studies.<sup>11</sup> There were studies suggesting that diuretics lowered BP but did not reduce left ventricular mass. Again, this has been refuted by evidence.<sup>12</sup> Other studies also suggest that diuretics are poorly tolerated, but these were observational or retrospective reviews that were not randomized or placebo-controlled. Results from controlled studies have shown that these medications are as well tolerated as other antihypertensive agents.<sup>13</sup>

It has been necessary to defend the use of diuretics in past years.<sup>14</sup> In *The New York Times* on April 28, 1991, a headline appeared, “New Study Says Diuretics Raise Heart Attack Risk.” The next day, the Associated Press urged patients to “ask their doctor about a new study that showed an increased risk of heart trouble with diuretics.” These statements were based on a short-term, 4-month study that noted some increase in cholesterol levels and increase in insulin resistance with a diuretic compared with an angiotensin-converting enzyme inhibitor (ACEI).<sup>15</sup> There were no cases of myocardial infarctions or coronary heart disease events in the trial. Fortunately, no one overreacted to these data. Imagine what the treatment of hypertension would be like today if diuretics had been removed from the market or a “black box warning” placed on each prescription? Throughout the years, numerous clinical trials, including the Systolic Hypertension in the Elderly Program (SHEP), that were diuretic-based compared with control or placebo regimens have reported a reduction in mortality/morbidity.<sup>16</sup> In a more recent comparative, randomized, blinded drug trial, morbidity/mortality was reduced to as great or greater degree with diuretics when compared with other medications.<sup>17</sup>

Some investigators are again suggesting that the use of diuretics be limited despite extensive clinical trial data proving benefit from their use. This suggestion is now based on data indicating that new-onset diabetes is increased with diuretic-based therapy (Table I).<sup>18</sup>

#### HOW SIGNIFICANT IS THE INCREASE IN NEW-ONSET DIABETES?

In a retrospective study in 1993, treatment records of patients were reviewed to determine how many

individuals on various antihypertensive drugs developed hyperglycemia significant enough to warrant the use of antidiabetic drugs.<sup>19</sup> The study reported two findings: 1) hypertensives have an increased risk of developing diabetes compared with normotensive patients (this probably relates to the fact that many of these patients already have other risk factors such as obesity and increased insulin resistance); and 2) there was no difference in the number of patients who developed diabetes with different drugs, including diuretics and  $\beta$  blockers (Figure 1).<sup>19</sup>

A more recent study<sup>20</sup> of 3800 people who were followed to determine the hazard ratio for developing new-onset diabetes was published in 2000. This was also not a randomized double-blind study. No increase was noted with ACEIs, calcium channel blockers (CCBs), or thiazide diuretics. The use of  $\beta$  blockers did, however, show an increase. It is well known that  $\beta$  blockers increase insulin resistance and may have adverse effects on lipids. The authors concluded in this prospective survey that “subjects with hypertension who were taking thiazides were at no greater risk for the development of diabetes than subjects with hypertension who were not receiving antihypertensive drugs;” however, in those taking  $\beta$  blockers, there was an increased risk. They concluded that “concerns should not discourage physicians from prescribing thiazide diuretics to nondiabetic adults. While the use of  $\beta$  blockers appears to increase the risk of new-onset diabetes, this event must be weighed against the possible benefits on CV events.” Outcome rather than new-onset diabetes data should be considered.

In 1993, a review of the placebo-controlled diuretic or diuretic/ $\beta$ -blocker hypertension studies reported that in the 3- to 5-year clinical trials, there was an excess of about six new cases of diabetes per 1000 patients (Table II).<sup>21</sup> In the Hypertension Detection and Follow-up Program (HDFP) study<sup>22</sup> there were 57 new cases in 3500 persons, and in SHEP<sup>23</sup> at 1 year there was no difference between diuretic and control subjects. Thus, there appears to be some change in glucose metabolism in mostly diuretic-based treatment programs. In the 3- to 8-year studies comparing conventional therapy (usually a  $\beta$  blocker or  $\beta$  blocker/diuretic) with ACEI-based treatment, an increase of 1%–3.5% in new-onset diabetes has been reported (Table I).<sup>18</sup> When conventional therapy is compared with a CCB-based regimen, there is an absolute increase of 1%–2%.<sup>1</sup> Differences between an ACEI and CCB in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial (ALLHAT)

**Table I.** Incidence of New-Onset Diabetes in the 3- to 8-Year Hypertension Treatment Trials

TRIAL	THERAPY	DURATION (YR)	NEW-ONSET DIABETES (%)*		ABSOLUTE DIFFERENCE (%)
			ACEI	UC OR D/ $\beta$ -B	
I. ACEI vs. CONVENTIONAL RX			ACEI	UC OR D/ $\beta$ -B	
CAPP	ACEI/ $\beta$ -B/D	6.1	6.5	7.5	1.0
STOP-2	ACEI/ $\beta$ -B/D	6+	4.7	4.9	0.2
ANBP-2	ACEI/D	4+	4.5	6.6	2.1
ALLHAT	ACEI/D	4.9	8.1	11.6	3.5
II. CCB vs. CONVENTIONAL RX			CCB	UC	
NORDIL	CCB/ $\beta$ -B/D	4.5	4.3	4.9	0.6
ALLHAT	CCB/D	4.9	9.8	11.6	1.8
INVEST	CCB/ $\beta$ -B	4.0	6.2	7.3	1.1
INSIGHT	CCB/D	3.5	5.4	7.0	1.6
STOP-2	CCB/ $\beta$ -B/D	6+	4.8	4.9	0.1
III. ARB vs. OTHER RX			ARB	OTHER RX	
VALUE	ARB/CCB	4.2	13.1	16.4	3.3
LIFE	ARB/ $\beta$ -B	4.8	6.0	8.0	2.0
SCOPE	ARB/UC	5	4.3	5.3	1.0
CHARM	ARB/other Rx	3+	6.0	7.4	1.4
IV. ACEI/CCB vs. $\beta$ -B/D			ACEI/CCB	D/ $\beta$ -B	
ASCOT	ACEI/CCB vs. $\beta$ -B/D	5+	11.0	15.9	4.9
V. ACEI vs. CCB			ACEI	CCB	
ALLHAT	ACEI/CCB	4.9	8.1	9.8	1.7

ACEI=angiotensin-converting enzyme inhibitor; UC=usual care; D=diuretic;  $\beta$ -B= $\beta$  blocker; CAPP=Capotopril Prevention Project; STOP-2=Swedish Trial in Old Patients with Hypertension 2; ANBP-2=Second Australian National Blood Pressure trial; CCB=calcium channel blocker; NORDIL=the Nordic Diltiazem study; INVEST=the International Verapamil-Trandolapril Study; INSIGHT=International Nifedipine GITS study; Intervention as a Goal in Hypertension Treatment; ARB=angiotensin receptor blocker; LIFE=Losartan Intervention for Endpoint Reduction in Hypertension study; SCOPE=Study on Cognition and Prognosis in the Elderly; CHARM=the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; other trial names expanded in text. \*Variable definitions. Approximate overall difference ACEI or ARB vs. D/ $\beta$ -B: 2.0%; ACE/CCB: 2.0%; CCB vs. D/ $\beta$ -B: 1.5%. Reproduced with permission from *J Clin Hypertens (Greenwich)*. 2005;7:90–95.<sup>18</sup>

**Table II.** Effects of High-Dose Diuretic Therapy Compared With Control or Placebo on Glucose Metabolism

TRIAL	DURATION (YR)	SERUM GLUCOSE (MG/DL)	HYPERGLYCEMIA OR DIABETES*
Oslo	5	No difference, D vs. Pl	No data
EWPHE MRC HAPPHY	3–4	Increase of 6.6, D vs. Pl	Excess of six new cases/1000 patient-years (NS)
HDFP	5		1.6% (57/3563)
SHEP	1	Difference of 5, D vs.Pl	No difference

EWPHE=European Working Party on High Blood Pressure in the Elderly trial; NS=nonsignificant; MRC=Medical Research Council Working Party trial; HAPPHY=Heart Attack Primary Prevention in Hypertension trial; other trial names expanded in text. \*Diuretics (D) compared with placebo (Pl). From *Cleveland Clin J Med*. 1993;60:27–37.<sup>21</sup>

was about 1.5%. These are small differences, but they could be of clinical significance. When ARB-based treatment was compared with other therapies in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial,<sup>24</sup> 3.3% more patients in the usual care group developed new-onset diabetes compared with the ARB-treated patients. The VALUE trial had a larger number of patients with new-onset diabetes in both groups compared with other studies.

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),<sup>25</sup> in which cases of new-onset diabetes were even higher in both groups than in the VALUE trial, there were 15.9% cases of new-onset diabetes in the diuretic/ $\beta$ -blocker group compared with 11.0% in the CCB/ACEI group (a difference of 4.9%). It should be noted that this trial titrated a  $\beta$ -blocker, atenolol, to a relatively high dose before adding a diuretic to therapy, with the possibility that the greater difference in new-onset

diabetes cases was the result of the high dose of the  $\beta$  blocker. There is no explanation for the large number of cases in both groups.

In a recent observational study of 76,000 patients, no statistically significant differences in new-onset diabetes were found among ACEI-,  $\beta$  blocker-, and CCB-treated patients. In a secondary analysis of more than 100,000 patients, new-onset diabetes was also not significantly different with thiazide diuretics,  $\beta$  blockers, ACEIs, or CCBs.<sup>26</sup>

Thus, there are confusing data regarding the differences in new-onset diabetes with different medications. It should be remembered, however, that none of the clinical trials were monotherapy trials; it is difficult, therefore, to single out a specific agent and compare results with another single medication.

**DOES NEW-ONSET DIABETES AFFECT OUTCOME?**

Conflicting data exist. The new-onset diabetes observational cohort study from Italy reported that the risk of CV events with new-onset diabetes is the same as in diabetics at baseline.<sup>4</sup> There were, however, only 63 CV events in all three groups of patients (Table III). This study examined 795 people at entry and at 3 years and then evaluated them more than 6 years later. There are few data in the interim regarding BPs and medications. The patients who developed new-onset diabetes had

**Table III.** Prognostic Significance of New-Onset Diabetes in Treated Hypertensive Subjects

795 untreated hypertensives (follow-up: median 6.0 yrs)
New-onset diabetes: 5.8%
Plasma glucose and diuretic Rx at follow-up visit (but not $\beta$ blockers) were predictive of new-onset diabetes
Relative risk of cardiovascular event:
2.92 new-onset diabetes
3.57 patients with pre-Rx diabetes
At baseline, nondiabetic patients who developed diabetes:
Systolic blood pressure and diastolic blood pressure higher
More left ventricular hypertrophy
Glucose levels higher (increased fasting glucose 42% vs. 6% who did not develop new-onset diabetes)
Data derived from <i>Hypertension</i> . 2004;43:963–969. <sup>4</sup>

higher systolic and diastolic pressures at baseline, more left ventricular hypertrophy, and higher glucose levels; 42% who developed new-onset diabetes had increased fasting glucose levels compared with only 6% in the control group. In other words, the greater the baseline risk, the more cases of diabetes, which leads to more events.<sup>4</sup> It was of interest that ACEIs and CCBs were given more frequently in patients who developed new-onset diabetes, but results did not achieve significance. Blood glucose levels at entry and diuretic treatment on follow-up were independent predictors of diabetes. “However, while the occurrence of diabetes was an independent

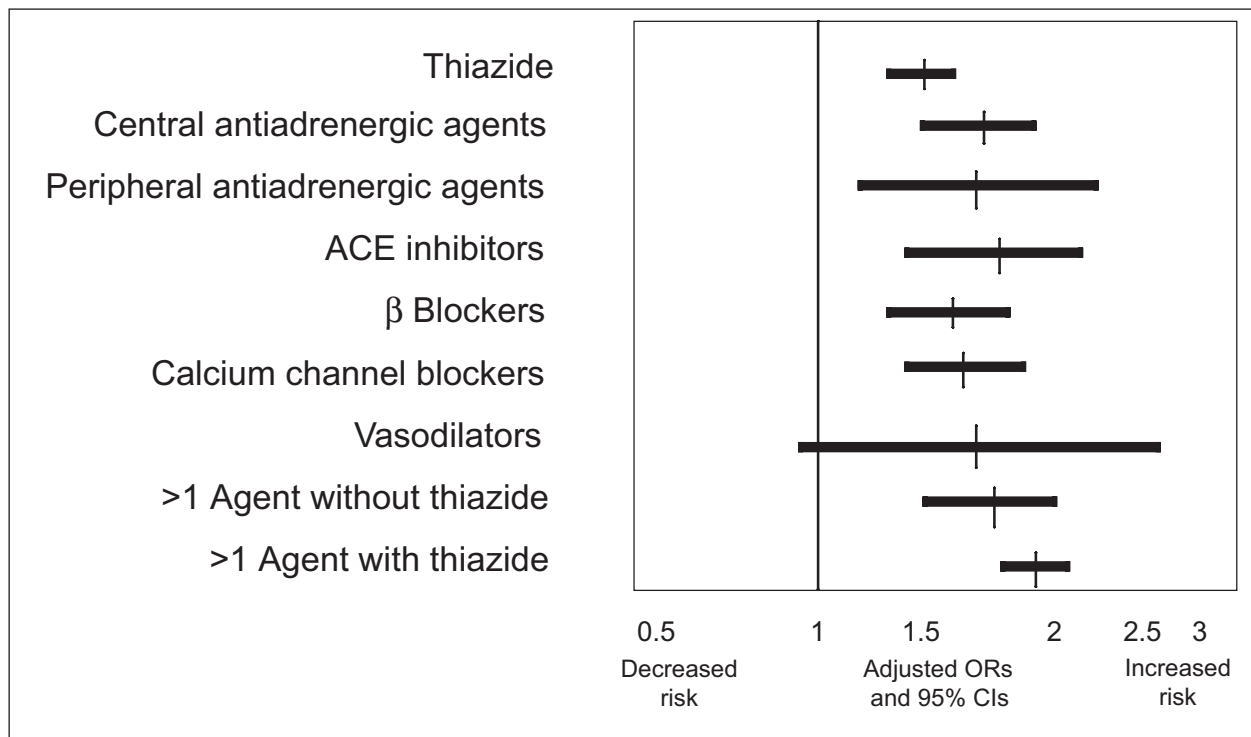


Figure 1. Risk of hyperglycemia in patients receiving antihypertensive drugs. ACE=angiotensin-converting enzyme; ORs=odds ratios; CIs=confidence intervals. Adapted from *Ann Intern Med*. 1993;118:273–278.<sup>19</sup>

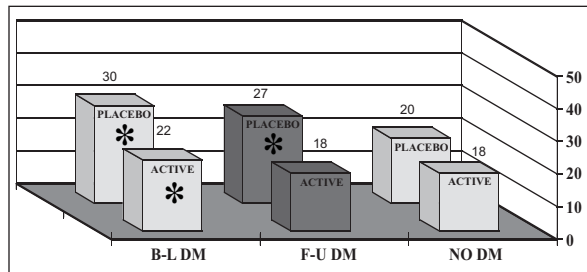


Figure 2. Percentage of cardiovascular deaths in the 14-year follow-up of the Systolic Hypertension in the Elderly Program (SHEP) study. Mortality was evaluated in nondiabetics (NO DM), diabetics at baseline (B-L DM), and in new-onset diabetics (F-U DM). \*Statistically significant difference between B-L DM and F-U DM. Adapted from *Am J Cardiol.* 2005;95:29–35.

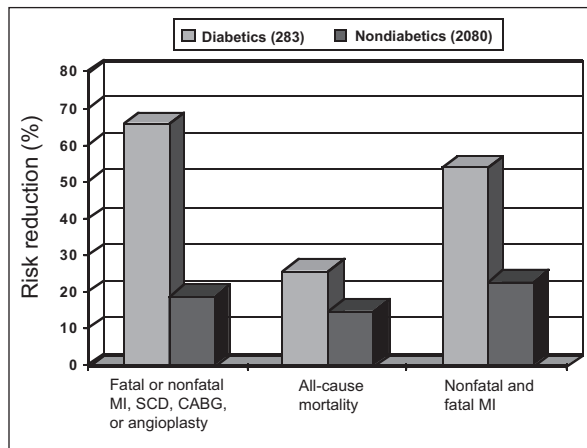


Figure 3. Morbidity and mortality in diabetic and nondiabetic subjects in the Systolic Hypertension in the Elderly Program (SHEP) study. Reduction in risk (%) in treated compared with placebo groups. Therapy included a low-dose diuretic with  $\beta$  blocker added, if necessary;  $n=4736$ ; subjects were 60 years of age or older. MI=myocardial infarction; SCD=sudden cardiac death; CABG=coronary artery bypass grafting. Adapted from *JAMA.* 1996;276:1886–1892.<sup>16</sup>

predictor of CV risk, the use of diuretics, although predictive of new-onset diabetes, did not show any independent relation to the subsequent CV events.” Unlike the Gress et al study,<sup>20</sup>  $\beta$  blockers were not associated with new-onset diabetes. The results of this study do not settle the question regarding the clinical significance of new-onset diabetes. They do, however, provide a clue regarding choice of therapy. They suggest that when choosing medications in patients who are in a high-risk category, we should consider using agents such as an ACEI or ARB as initial therapy.

In ALLHAT, chlorthalidone-treated patients achieved the same primary end point results—fatal and nonfatal infarcts—as amlodipine- or lisinopril-treated subjects despite the fact that there was an increase in serum glucose of 3 mg/dL to 5 mg/dL

and new-onset diabetes was more frequent in the diuretic-based treatment groups.<sup>17</sup> The investigators concluded that “there was no advantage to the use of lisinopril compared with a diuretic despite the difference in new-onset diabetes.” The use of  $\alpha$  blockers does not increase serum glucose and may have a positive affect on lipids; despite this in ALLHAT, there were more CV events with an  $\alpha$  blocker compared with a diuretic.

There is a persistent argument that the 3- to 6-year clinical studies are not going to unmask CV events in patients with new-onset diabetes because they are not long enough, i.e., the CV end point effects of diabetes were not seen because of the relatively short duration of the trials. However, since most hypertensives are middle-aged or older when they enter a clinical trial and a high percentage of them have had some metabolic abnormalities such as insulin resistance for many years, it is reasonable to assume that CV events would be noted in five to six additional years if the degree of increase in serum glucose levels was of clinical importance. It should not take 10 to 15 more years for manifestations of diabetes to become apparent. In a 14-year follow-up of the SHEP study, for example, mortality was evaluated in nondiabetics, diabetics at baseline, and in new-onset diabetics. New-onset diabetics did not have the same prognosis as diabetics at baseline (Figure 2).<sup>27</sup> The results were, therefore, quite different from the results in the Verdecchia study.<sup>4,28</sup> The risk was greater in baseline diabetics compared with new-onset diabetics and nondiabetics, but in patients who developed new-onset diabetes in the actively treated group, an increase in risk comparable to that of diabetics was not seen. Thus, despite an increase in new-onset diabetes in this study, outcome was not adversely affected, i.e., subjects who had diabetes associated with chlorthalidone did not have an increase in CV mortality and had a better prognosis than those with preexisting diabetes. Admittedly, the follow-up data were not controlled, i.e., there were few data about specific medications and interim findings, from the fifth or sixth to the fourteenth year. Thus, the SHEP follow-up suffers from some of the failings of the other studies on new-onset diabetes.

There is a lack of consistency of the available data regarding new-onset diabetes, not only with comparative medications but with outcome. The available data are not consistent enough to make suggestions for a change in the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

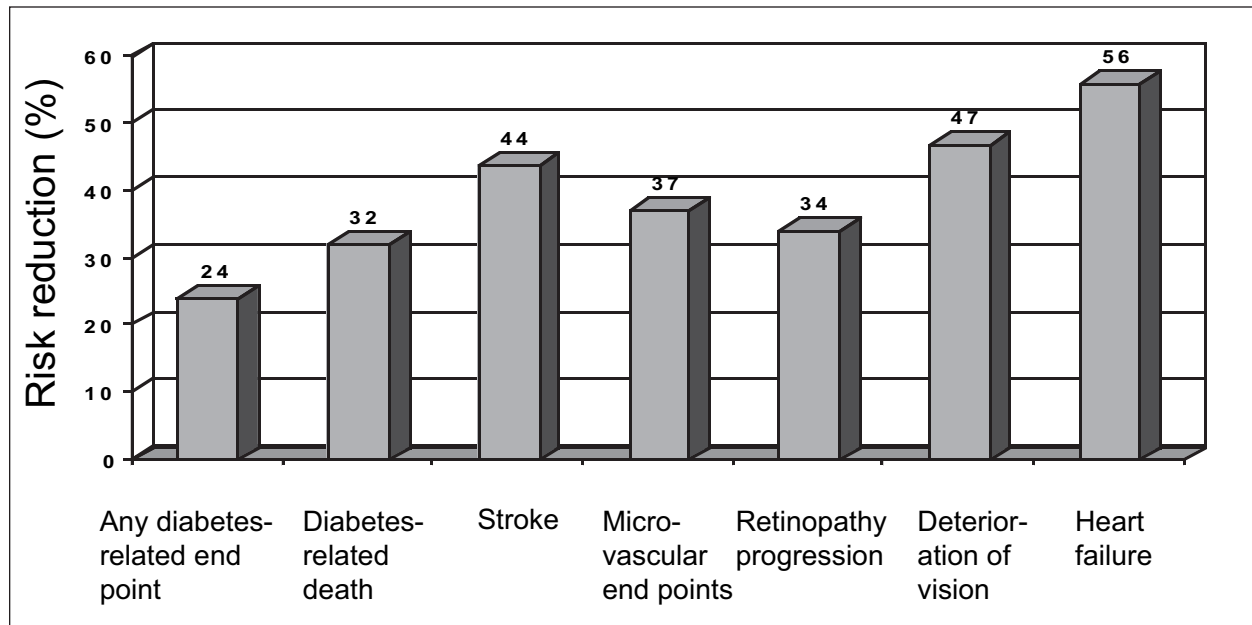


Figure 4. Results of tight blood pressure control compared with less tight blood pressure control in type 2 diabetics. There was no difference in outcome between angiotensin-converting enzyme inhibitor- and  $\beta$  blocker-based treatment groups. Adapted from BMJ. 1998;317:703–713.<sup>29</sup>

recommendations that diuretics be used as initial therapy in most patients. There is no lack of data, however, that intensive BP control reduces mortality/morbidity in diabetic patients regardless of the medication used. BP lowering may be more important than the drugs used as initial therapy regardless of new-onset diabetes.

#### WHAT ABOUT TREATMENT OF HYPERTENSIVE DIABETICS WITH THIAZIDE DIURETICS?

In the SHEP trial, which was diuretic-based, the risk was reduced more in diabetics than in nondiabetics (65% reduction compared with nondiabetics).<sup>16</sup> Diuretic-treated patients did well whether they were diabetic or not (Figure 3).<sup>16</sup> In one group of type 2 diabetics in the United Kingdom Prospective Diabetes Study Group (UKPDS) trial<sup>29</sup> where BP was reduced to 144/82 mm Hg compared with 154/87 mm Hg (a difference of only 10/5 mm Hg), strokes, fatal strokes, deaths, and heart failure were all reduced. There was no difference in outcome between an ACEI- and a  $\beta$  blocker-based program. In this trial, as in many others, it was the achieved BP and not the regimen that made the difference (Figure 4).

#### CONCLUSIONS

Until we have more consistent or definitive data on the significance of new-onset diabetes, this should not be a primary concern when choosing a medication for initial therapy in hypertension. In certain

high-risk patients, the use of a renin-angiotensin system blocker may be the initial drug of choice, but outcome in diabetic as well as nondiabetic patients will be improved if BP is lowered regardless of the medication used.

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