Differences in Glucose Tolerance Between Fixed-Dose Antihypertensive Drug Combinations in People With Metabolic Syndrome

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OBJECTIVE — We sought to test the hypothesis that a fixed-dose combination of trandolapril/verapamil-SR (T/V) is superior to a fixed-dose combination of losartan/hydrochlorothiazide (L/H) on glucose tolerance in hypertensive patients with impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — A prospective, randomized, open-label, blinded–end points design was used to assess the effects of a T/V versus L/H combination in patients with IGT and hypertension ($n = 240$) followed for up to 1 year. Doses were titrated to a systolic blood pressure <130 mmHg. Primary outcome was change from baseline in a 2-h glucose on oral glucose tolerance test (OGTT) at study end (mean [±SD] at follow-up, 46.9 ± 13.5 weeks). Secondary outcomes included changes in insulin sensitivity, office and 24-h ambulatory blood pressure, incidence of new-onset diabetes, lipids, and inflammatory markers. Data are expressed as means ± SE unless otherwise noted.

RESULTS — Changes at study end were noted in 2-h OGTT glucose (T/V −0.21 ± 0.36 vs. L/H +1.44 ± 0.36 mmol/l; $P < 0.001$) and insulin level (−30.13 ± 38.38 vs. +84.86 ± 38.33 pmol/l, respectively; $P = 0.025$). Worsening of insulin resistance occurred by week 12 (T/V 0.000 ± 0.001 vs. L/H −0.005 ± 0.001; $P = 0.016$). A higher incidence of new-onset diabetes (T/V 11.0 vs. L/H 26.6%; $P = 0.002$) and HbA_{1c} >7% (2.6 vs. 9.6%, respectively; $P = 0.05$) occurred at study end.

CONCLUSIONS — In patients with IGT, normal kidney function, and hypertension, the fixed-dose combination of T/V reduces the risk of new-onset diabetes compared with an L/H-based therapy.

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Analyses of clinical trials document a lower risk of new-onset diabetes with use of renin angiotensin system (RAS) blockers (1–3). It is not known, however, whether concomitant use of losartan with a thiazide diuretic (TD) neutralizes the adverse metabolic effects of the TD in people with impaired fasting glucose and metabolic syndrome. Given that verapamil-SR reduces cardiovascular outcomes to a similar degree as TDs and that it has neutral metabolic effects, we hypothesized that blood pressure lowering using a combination of trandolapril/verapamil-SR (T/V) would be superior to losartan/hydrochlorothiazide (L/H) on glucose tolerance in patients with metabolic syndrome. We further evaluated a number of related metabolic and inflammatory markers to help assess the mechanism for possible differences in glucose tolerance.

RESEARCH DESIGN AND METHODS

— The Study of Trandolapril/Verapamil SR And Insulin Resistance (STAR) was a multicenter trial that utilized a prospective, randomized, open-label, blinded-outcome evaluation design. The institutional review boards of participating centers approved the study, and before study enrollment all participants signed informed consent.

At entry, a 4-week washout period, where blood pressure medications were discontinued, 0.1 mg clonidine b.i.d. was permitted if diastolic blood pressure (DBP) was ≥100 mmHg or systolic blood pressure (SBP) ≥160 mmHg. After the washout period, baseline measurements were collected and patients randomized, using a validated in-house program (Web Rando), to a once-daily fixed-dose combination of 2/180 mg T/V or 50/12.5 mg L/H.

Blood pressure was determined from a mean of three sitting measurements with an appropriate sized cuff as described in the Joint National Committee Report 7 (4). If after 4 weeks the patients did not achieve an SBP <130 mmHg, doses were titrated to 4/240 mg T/V or 100/25

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Abbreviations: DBP, diastolic blood pressure; IGT, impaired glucose tolerance; L/H, losartan/hydrochlorothiazide; OGTT, oral glucose tolerance test; RAS, renin angiotensin system; SBP, systolic blood pressure; STAR, Study of Trandolapril/Verapamil SR And Insulin Resistance; TD, thiazide diuretic; T/V, trandolapril/verapamil-SR.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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mg L/H once daily. If the goal SBP was still not achieved, clonidine was added to both arms. Planned treatment duration was 52 weeks. Visits were scheduled every 2 weeks until week 12 and every 4 months thereafter. At each visit, patients were assessed for vital signs, medication adherence (pill counts), and adverse events. An oral glucose tolerance test (OGTT) and laboratory tests were performed at baseline, at 12 and 52 weeks, or at the final visit.

Inclusion and exclusion criteria

Eligibility for inclusion was *1*) age >21 years and *2*) diagnosis of metabolic syndrome defined by fasting blood glucose ≥100 and ≤125 mg/dl, documented controlled hypertension (SBP <140 mmHg) while on two antihypertensive medications or a SBP on monotherapy ≥130 and <160 mmHg, and one of the following criteria: HDL cholesterol <40 mg/dl (men), <50 mg/dl (women); triglycerides ≥150 mg/dl; and waist circumference >40 inches (men), >35 inches (women).

Individuals excluded were those with *1*) diabetes, taking more than two antihypertensive medications; *2*) secondary hypertension; *3*) use of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, niacin >100 mg/day, or loop diuretics; and *4*) renal insufficiency (serum creatinine >1.4 mg/dl and/or urine albumin-to-creatinine ratio >0.3 g/g).

Outcome assessments

The primary outcome was the difference in glucose tolerance, as assessed by change in 2-h blood glucose from baseline to week 52 or final visit (using a 75-g OGTT). The OGTT measurements included blood glucose and insulin levels at 0, 30, 60, and 120 min. The results of these tests were not disclosed to any study investigator or personnel during the course of the trial.

Secondary efficacy end points included changes from baseline in office blood pressure, pulse rate, fasting and postload glucose concentrations during an OGTT, and incidence of diabetes, defined as a fasting glucose ≥126 mg/dl or with 2-h glucose (OGTT) ≥200 mg/dl, while excluding patients meeting one or both of these criteria at baseline, glucose AUC_{0-120} (area under the curve), estimated insulin sensitivity (QUICKI) (5–6), HbA_{1c} (A1C), lipid profile, and proportion achieving blood pressure goal. Change in high-sensitivity C-reactive protein and in 24-h ambulatory blood pressure values from baseline were evaluated in a nested cohort. Adverse events and safety labs were also collected. The central lab analyses of plasma samples were performed (ICON Laboratories, Farmingdale, NY), with biomarker assessments in the laboratory of Doug Vaughan (Vanderbilt University, Nashville, TN).

Statistical analysis

Sample size was calculated assuming a 2-h mean glucose value of 170 mg/dl on the OGTT at randomization and an SD of 25 mg/dl, with a type 1 error rate of 0.05 for a two-tailed test. Based on these assumptions, 100 patients per treatment provided 80% power to detect a treatment difference of 10 mg/dl (6%) in mean change in 2-h OGTT value from baseline to study end (last observation carried forward post first dose of randomized study drug).

All patients who received at least one dose of randomized study drug and for whom both baseline and study end point efficacy assessments were available were included in the intention-to-treat efficacy analyses. Safety analyses included all patients who received at least one dose of randomized study drug. All tests were two tailed with $\alpha = 0.05$.

The primary efficacy variable was analyzed using ANCOVA with terms for baseline, treatment group, and center. Since there was only one intermediate visit to provide data, a mixed-model analysis was not used. In addition, such a method would not capture data for patients discontinuing the trial between weeks 12 and 52. Similar ANCOVA models were used to analyze secondary efficacy variables. For continuous variables, data are expressed as adjusted means ± SE, unless otherwise specified. The Fisher's exact test was used to compare the incidence of each adverse event between treatment groups, in addition to those who developed an A1C >7% at study end. Logistic regression models with factors for treatment group and center were used to compare the proportions of subjects who achieved SBP <130 mmHg and who developed new diabetes.

RESULTS

Patient disposition and baseline characteristics

Of 419 patients screened, 276 were enrolled from 30 primary care or specialty clinics between March 2004 and September 2005, with 240 randomized and receiving at least one dose of study medication (119 on T/V and 121 on L/H). Of these, 77.5% completed the 52-week study (91 of 119 on T/V and 95 of 120 on L/H). Premature discontinuation was similar between groups ($n = 24$ in T/V and $n = 23$ in L/H), with adverse events being the most common cause. In addition, data from seven patients were lost in hurricane Katrina.

No differences in the demographic and baseline characteristics were noted between groups (Table 1). The proportions of patients who received dose titration were similar between groups (91 of 119 [76.5%] vs. 89 of 121 [73.6%], T/V vs. L/H, respectively). Concomitant use of protocol-allowed medication to achieve blood pressure goal was not statistically different between groups (T/V 56 vs. L/H 44%; $P = 0.053$).

Primary outcome

The primary efficacy analysis included 108 of 119 (91%) in T/V and 107 of 121 (88%) in L/H patients who had a baseline and at least one follow-up OGTT performed (Table 2). The mean (±SD) treatment duration for the entire cohort was 46.9 ± 13.5 weeks, and no difference was noted between groups (T/V 45.5 ± 14.9 vs. L/H 48.3 ± 11.9 weeks; $P = 0.13$). A difference in the change from baseline in 2-h OGTT glucose at study end was observed between groups (1.7 ± 0.5 mmol/l; $P < 0.001$). A within-treatment group analysis, utilizing a paired *t* test, demonstrated that baseline and study end 2-h OGTT values were not different for patients receiving T/V (−0.2 ± 0.2 mmol/l; $P = 0.329$) but increased in those receiving L/H (+1.4 ± 0.4 mmol/l; $P < 0.001$).

Secondary efficacy end points

Measures of glucose control. Consistent with the primary outcome, increases in the 2-h OGTT glucose value from baseline to weeks 12 and 52 were noted for L/H but not for T/V (Table 2); treatment-group differences were 1.0 ± 0.3 mmol/l ($P < 0.001$) for week 12 and 1.6 ± 0.5 mmol/l ($P < 0.001$) for week 52. For each time point during the OGTT procedure at study end, differences between groups were noted (Fig. 1). Changes in 2-h OGTT insulin values from baseline to weeks 12 and 52 and study end were also significantly greater in the L/H group (Table 2).

A comparison of change from base-

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Table 1—*Baseline characteristics of the study cohort*

	T/V group	L/H group	*P* value*
n	119	121	
Female	53.8	48.8	0.442
Age (years)	57.7 ± 10.3	55.4 ± 9.7	0.076
Race			0.811
White	70.6	66.9	
Black	28.6	31.4	
Asian/other	0.8	1.7	
Weight (kg)	95.7 ± 21.8	98.3 ± 19.1	0.333
Male waist circumference (inches)	44.1 ± 4.9	44.9 ± 9.1	0.539
Female waist circumference (inches)	41.3 ± 5.2	42.1 ± 6.0	0.429
Height (cm)	167.8 ± 11.0	168.8 ± 11.2	0.477
BMI (kg/m^2)	33.8 ± 6.2	34.6 ± 7.3	0.361
SBP (mmHg)	145.4 ± 15.5	146.7 ± 16.7	0.531
DBP (mmHg)	86.4 ± 10.1	88.2 ± 9.4	0.162
Pulse rate (bpm)	71.5 ± 9.4	70.3 ± 10.8	0.356
eGFR (ml/min)	95.7 ± 19.5	93.6 ± 19.7	0.397

Data are means ± SD or percent. *Fisher's exact test for categorical variables and *t* test for continuous variables. eGFR, estimated glomerular filtration rate.

line in fasting glucose values at each visit noted a difference between groups at 12 weeks but not at 52 weeks or study end (Table 2). Changes in insulin sensitivity at 12 weeks (T/V 0.000 ± 0.001 vs. L/H −0.005 ± 0.001; $P = 0.016$) support the changes in fasting glucose. This was not present at week 52 or study end. More than three times as many patients developed new-onset diabetes by week 12 in the L/H group (6 of 86 [7.0%] vs. 20 of 93 [21.5%], T/V vs. L/H, respectively; $P = 0.007$), with similar results at study end (10 of 91 [11.0%] vs. 25 of 94 [26.6%], respectively; $P = 0.002$).

Mean A1C increased from baseline in L/H patients at all time points and was higher than for T/V patients at week 12 and study end (Table 2). Moreover, the percentage of people that developed an A1C >7% at study end was higher in the L/H group (2.6 vs. 9.6%, T/V vs. L/H, respectively; $P = 0.05$).

Lastly, an analysis of 2-h OGTT values in the subgroup that achieved blood pressure goal with initial, low-dose–fixed combination, i.e., T/V 2/180 mg (22%) and L/H 50/12.5 mg (20.6%), demonstrated a trend for differences in 2-h OGTT glucose values at study end (−1.04 ± 1.99 vs. +0.61 ± 2.40 mmol/l, T/V vs. L/H, respectively). These differences were more pronounced in the remaining cohort that required higher dose combinations, i.e., T/V 4/240 mg and L/H 100/25 mg (−0.01 ± 2.67 vs. +1.65 ± 4.56 mmol/l, respectively).

Blood pressure. No differences were noted between groups at study end for mean office SBP (130.6 ± 15.7 vs. 128.8 ± 14.0 mmHg, T/V vs. L/H, respectively; $P = 0.179$), DBP (78.7 ± 10.0 vs.78.8 ± 8.8 mmHg, respectively; $P = 0.605$), or pulse rate (71.9 ± 10.0 vs.72.1 ± 11.2 mmHg, respectively; $P = 0.457$). There were between-group differences at weeks 12 and 26 in those that achieved an office blood pressure <130 mmHg (L/H 58.9 vs. T/V 47.3% [$P = 0.047$] for week 12 and 59.0 vs. 46.0%, respectively [$P = 0.009$], for week 26). No between-group differences in office SBP <130 mmHg were present at study end (T/V 49.6 vs. L/H 60.8%; $P = 0.06$). Ambulatory blood pressure monitoring performed at baseline and study end in a nested cohort ($n = 32$) demonstrated no significant between-group differences in change from baseline to study end in 24-h SBP ($P = 0.29$), DBP ($P = 0.86$), daytime SBP ($P = 0.44$), or nighttime SBP ($P = 0.95$).

Lipid and inflammatory indexes. No differences between treatment groups were noted for total cholesterol ($P = 0.20$), triglycerides ($P = 0.36$), LDL cholesterol ($P = 0.24$), HDL cholesterol ($P = 0.13$), or high-sensitivity C-reactive protein (T/V group: 5.9 ± 6.1 baseline vs. 6.6 ± 7.6 mg/l study end; L/H group: 5.3 ± 4.6 baseline vs. 6.0 ± 6.0 mg/l study end; $P = 0.76$).

Adverse events

The incidence of adverse events occurring in >5% of either treatment arm was similar between groups. A higher incidence, however, of cough (6 vs. 1%; $P = 0.035$) and extremity pain (5 vs. 0%; $P = 0.014$) was noted for the T/V group. A similar incidence of serious adverse events was observed in each group (6 of 119 [5%] vs. 7 of 121[6%], T/V vs. L/H, respectively). No deaths occurred during the treatment period. Changes in serum potassium (baseline 4.2 ± 0.4 mmol/l) were statistically but not clinically different at study end (+0.01 ± 0.38 vs. −0.17 ± 0.40 mmol/l, T/V vs. L/H, respectively; $P < 0.001$). No association was noted between serum potassium and insulin or glucose levels (data not shown). Additionally, no differences in mean change from baseline to study end occurred in weight (−0.2 ± 5.2 vs. −0.5 ± 4.4 kg, T/V vs. L/H, respectively) or estimated glomerular filtration rate (−10.5 ± 15.5 vs. −9.0 ± 15.2 ml/min, respectively).

CONCLUSIONS— STAR demonstrates that a fixed-dose combination of an ACE inhibitor with a nondihydropyridine calcium antagonist, in contrast to an angiotensin receptor blocker with a TD, achieves blood pressure goals and avoids worsening of 2-h OGTT values in a cohort of patients with IGT and metabolic syndrome. Worsening of 2-h glucose in the L/H group was paralleled by worsening of A1C and fasting glucose values at study end. Moreover, increases in insulin levels paralleled worsening of glycemic control at each time point throughout the study. These between-group differences in glycemic control and worsening of insulin sensitivity were noted as early as 12 weeks following randomization. To our knowledge, this is the first multicenter trial to assess changes in 2-h OGTT comparing a fixed-dose combination of a nondihydropyridine calcium antagonist combined with an ACE inhibitor to an angiotensin receptor blocker combined with a TD for reduction of blood pressure in patients with metabolic syndrome and IGT. The data support the concept that use of a TD in such patients worsens glycemic control, even at low doses, and in the presence of maximally dosed losartan. This effect of TD could not be attributed to changes in potassium, which while significant, were well above the range implicated in worsening glycemic control (7–9). Moreover, a post hoc regression analysis

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Table 2—*Absolute change from baseline to weeks 12 and 52 and study end in blood glucose (primary outcome) and other measures of glucose control*

	n (% of total at baseline)	Baseline (mean ± SD)	Measurement (mean ± SD)	Change ± SE*	*P* value*
Primary outcome†					
Week 12					
T/V	104 (87.4)	7.96 ± 2.47	7.62 ± 2.40	−0.29 ± 0.22	<0.001
L/H	105 (86.8)	7.94 ± 2.50	8.64 ± 2.73	0.72 ± 0.22	
Week 52					
T/V	89 (74.8)	7.99 ± 2.51	7.83 ± 3.11	−0.11 ± 0.36	<0.001
L/H	94 (77.7)	7.75 ± 2.41	9.15 ± 4.08	1.49 ± 0.35	
Study end					
T/V	108 (90.8)	7.98 ± 2.44	7.74 ± 2.98	−0.21 ± 0.36	<0.001
L/H	107 (88.4)	7.89 ± 2.50	9.32 ± 4.52	1.44 ± 0.36	
Absolute change in blood insulin (pmol/l) measured at 2 h during an OGTT					
Week 12					
T/V	100	675.91 ± 405.27	706.40 ± 438.22	33.92 ± 42.48	0.037
L/H	99	631.62 ± 450.20	773.52 ± 510.17	147.67 ± 41.18	
Week 52					
T/V	83	639.01 ± 382.51	585.77 ± 447.92	−52.14 ± 44.79	0.014
L/H	86	648.47 ± 460.15	718.29 ± 511.98	90.15 ± 42.88	
Study end					
T/V	105	672.02 ± 397.71	633.09 ± 456.05	−30.13 ± 38.38	0.025
L/H	102	633.51 ± 444.43	711.34 ± 497.01	84.86 ± 38.33	
Absolute change in fasting blood glucose (mmol/l) at 0 min during an OGTT					
Week 12					
T/V	104	5.90 ± 0.89	5.71 ± 0.69	−0.07 ± 0.08	<0.001
L/H	107	5.77 ± 0.69	6.08 ± 0.89	0.33 ± 0.08	
Week 52					
T/V	89	5.90 ± 0.87	6.26 ± 1.17	0.36 ± 0.23	0.336
L/H	95	5.80 ± 0.71	6.46 ± 2.55	0.65 ± 0.22	
Study end					
T/V	110	5.88 ± 0.88	6.11 ± 1.12	0.24 ± 0.23	0.087
L/H	110	5.77 ± 0.68	6.57 ± 2.95	0.76 ± 0.22	
Absolute change in A1C (%)					
Week 12					
T/V	109	5.8 ± 0.6	5.8 ± 0.5	0.0 ± 0.0	<0.001
L/H	112	5.7 ± 0.5	6.0 ± 0.8	0.3 ± 0.0	
Week 52					
T/V	94	5.8 ± 0.6	5.9 ± 0.6	0.2 ± 0.1	0.055
L/H	97	5.7 ± 0.4	6.1 ± 0.9	0.3 ± 0.1	
Study end					
T/V	115	5.8 ± 0.6	5.9 ± 0.6	0.1 ± 0.1	0.027
L/H	115	5.7 ± 0.5	6.2 ± 1.4	0.4 ± 0.1	

For all study end rows, mean (±SD) 46.9 ± 13.5 weeks. *Adjusted for center and baseline. †Primary outcome is the absolute change in blood glucose (mmol/l) measured at 2 h during an OGTT.

did not identify an association between potassium and glucose levels.

New-onset diabetes is well described with use of TDs in many studies (1–3,7–12). In our study, the change in fasting glucose was increased at 12 weeks and trended toward a significant increase at study end. However, a significantly higher proportion of patients in the L/H group had higher A1C, insulin levels, and 2-h OGTT values, consistent with a diagnosis of diabetes. Additionally, concomitant use of RAS blockers with TDs is thought to protect against worsening of glycemic control (13–15). Thus, our data support the notion that use of a TD at a commonly used dose worsens glucose tolerance in the presence of a high-dose RAS blocker. We recognize that this later analysis may be confounded, since the decision to up-titrate drug doses was determined by on-study blood pressure values and the desire to achieve the goal

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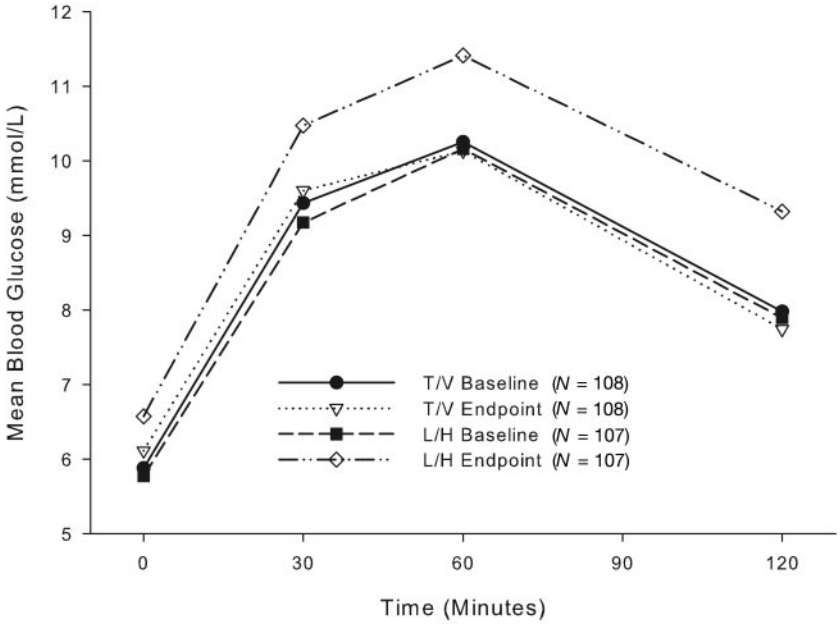

Figure 1— *OGTT results at baseline and study end.*

blood pressure. However, worsening of glycemic control was noted even in the 21% of the L/H study cohort who did not require up-titration for blood pressure control. Thus, this is the first demonstration that even low dose TDs affect glucose control in the presence of RAS blockade.

Combinations of RAS blockers with TDs are advocated for a large number of patients with hypertension and metabolic syndrome to lower blood pressure (4,16). In our study, use of L/H yielded a significantly higher percentage-achieving goal blood pressure at weeks 12 and 26, with no difference noted at 52 weeks or study end. It is important to note that the greatest worsening of glycemic control for the L/H group was observed at the same time point. To our knowledge, there is no evidence that better blood pressure control with a RAS blocker/TD worsens insulin resistance or glucose tolerance. Moreover, this effect could not be accounted for by an earlier titration to a higher TD dose. Thus, worsening of glycemic control in those at high risk for developing diabetes is disturbing, especially since new-onset diabetes is associated with a higher cardiovascular risk (17,18).

When interpreting the data of this study, one must consider its limitations. First, it is not a double-blind, placebo-controlled study; thus, there is a risk for bias in investigator treatment of patients, although investigator sites were blinded to the primary efficacy variable data. Second, while blood pressure control determined by 24-h monitoring confirmed office readings, it was performed in a subset of patients. Third, assessment of new-onset diabetes is based on laboratory values without further confirmation in people with impaired glucose tolerance. However, the data are consistent with the trend observed in fasting glucose based on a separate laboratory value. Lastly, this study was not designed to assess changes in glucose control in the context of cardiovascular outcomes. Despite these limitations, and given that we used 2-h OGTT as the primary end point, this is the first demonstration that examines the metabolic consequences of RAS blocker/TD combinations over 1 year, when used to lower blood pressure in individuals at high risk for developing diabetes.

To help in the understanding of development of new-onset diabetes with this treatment, this trial has continued in an open-label observational phase switching all patients to a T/V. The primary objective is to assess the change in 2-h OGTT glucose values at 6 months.

In conclusion, use of T/V combination therapy in those with IGT, normal kidney function, and metabolic syndrome minimizes the risk of new-onset diabetes at 1 year, which is an effect not seen at similar levels of glucose control utilizing an L/H combination.

APPENDIX

Investigators

George Bakris, Pantelis Sarafidis, Robert Broker, Albert Carr, Christopher Chappel, Eric Cheng, Deanna Cheung, James Doris, Richard Fishman, Thomas Giles, Barry Horowitz, Mark Kipnes, Alan Kivitz, Martin Lester, Andrew Lewin, Thomas Littlejohn, Robert Miles, Rafael Montoro, Stephen Ong, Albert Razzetti, Jane Rohlf, Jeffrey Rosen, Raheela Sadiq, Michael Seidner, Gregory Serfer, Emil Skobeloff, Joel Strom, Cynthia Strout, Danny Sugimoto, Robert Weiss, and Gary Yeoman.

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