Diabetes Care Publish Ahead of Print, published online April 28, 2008

PREVENTING LEFT VENTRICULAR HYPERTROPHY BY ACE INHIBITION IN HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES: *A PRESPECIFIED ANALYSIS OF THE BENEDICT TRIAL*

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Running title: *ACE Inhibitors Prevent LVH in Diabetes*

Received for publication 20 February 2008 and accepted in revised form 23 April 2008.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

OBJECTIVE In patients with type 2 diabetes left ventricular hypertrophy (LVH) predicts cardiovascular events and its prevention is cardioprotective.

RESEARCH DESIGN AND METHODS This pre-specified study compared the incidence of electrocardiographic (ECG) LVH by Sokolow-Lyon and Cornell voltage criteria in 816 hypertensive type 2 diabetic patients of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) randomized to at least 3-year blinded angiotensin-converting-enzyme (ACE) inhibition with trandolapril (2 mg/day) or non-ACE inhibitor therapy, who had no ECG-LVH at baseline. Treatment was titrated to systolic/diastolic blood pressure (BP) <130/80 mmHg. ECG readings were centralized and blinded to treatment.

RESULTS Baseline characteristics of the two groups were similar. Over a median (interquartile range) follow-up of 36 (24 to 48) months, 13 of the 423 patients (3.1%) on trandolapril compared to 31 of the 376 (8.2%) on non-ACE inhibitor therapy developed ECG-LVH. [Hazard Ratio (95% CI): 0.34 (0.18 to 0.65), P=0.0012 (unadjusted); 0.35 (0.18 to 0.68), P=0.0018 (adjusted for pre-define baseline covariates)]. The Hazard Ratio was significant even after adjustment for follow-up BP and BP reduction vs baseline. Compared to baseline, both Sokolow-Lyon and Cornell voltages significantly decreased on trandolapril, but did not change on non-ACE inhibitor therapy.

CONCLUSIONS ACE inhibition has a specific protective effect against the development of ECG-LVH that is additional to that of BP lowering. Since ECG-LVH is a strong cardiovascular risk factor in people with hypertension and diabetes, early ACE inhibition may be cardioprotective in this population.

Left ventricular hypertrophy (LVH), a cardinal manifestation of preclinical cardiovascular (CV) disease, strongly predicts myocardial infarction, stroke, and CV death in patients with hypertension (1) or coronary artery disease (2), as well as in the general population (3). In the Framingham Study, LVH as assessed by electrocardiography (ECG-LVH), was associated with a 2-fold increase in mortality over that resulting from hypertension alone (4).

Studies consistently found that antihypertensive therapy may effectively limit the incidence of ECG-LVH, regardless of the treatments used to reduce the blood pressure (BP) (5). However, the Heart Outcomes Prevention Education (HOPE) (6) and the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trials (7) showed that, in patients with ECG evidence of LVH at inclusion, the ACE inhibitor ramipril and the angiotensin receptor blocker (ARB) losartan, respectively, regressed LVH more effectively than drugs that do not directly interfere with the renin angiotensin aldosterone system (RAAS). The finding that in both trials this benefit was significant even after adjustments for the small differences in BP between the two treatment groups provided consistent evidence that RAAS inhibitor therapy has a specific cardioprotective effect that exceeds expectations based on changes in BP alone. However, the HOPE study (6) was not powered to assess the treatment effect on newly onset LVH in the subgroup with no ECG evidence of LVH at baseline, and the LIFE trial (7) included only patients with LVH. Thus, whether RAAS inhibitor therapy may also prevent the new onset of LVH in subjects with normal left ventricular mass to start with, is unknown.

To formally explore this issue we compared the effect of ACE vs. non-ACE inhibitor therapy on incident ECG-LVH in patients from the BErgamo Nephrologic Diabetes Complications (BENEDICT) trial (8-11)., who had no ECG evidence of LVH at inclusion.

RESEARCH DESIGN AND METHODS

Patients and study design: BENEDICT (8) was a prospective, randomized, double blind, parallel group study that evaluated the possibility of preventing the onset of persistent microalbuminuria in 1204 patients with type 2 diabetes (WHO criteria), arterial hypertension (systolic or diastolic BP more than 130 or 85 mmHg, or concomitant antihypertensive therapy), but normal Urinary Albumin Excretion (UAE) rate (UAE <20 μg/min in at least 2 of 3 consecutive overnight urine collections) randomly assigned to at least 3 year treatment with one of the following study drugs: I, a non-dihydropyridine calcium channel blocker (ndCCB): verapamil SR, 240 mg/day; II, an ACE inhibitor: trandolapril 2 mg/day; III, the fixed-dose combination of verapamil SR, 180 mg/day plus trandolapril 2 mg/day: VeraTran; and IV, placebo. The target BP after randomization and throughout the whole study period was less than 130/80 mmHg for all the treatment groups. Other antihypertensive drugs (with the exception of RAAS inhibitors and ndCCBs different from the study drugs) could be used to achieve and maintain the target blood pressure according to pre-defined guidelines (8). The study protocol was in accordance with the declaration of Helsinki and was approved by the institutional review board at each center and by the safety committee of the BENEDICT study. The trial was registered in the US Clinical Trials Registry (Clinical trials.gov NCT00235014). All patients gave written informed consent. Patients were eligible to enter the ECG-LVH sub-study if they had no ECG evidence of ECG-LVH at baseline and had at least one year follow up.

Aims: Analyses were primarily aimed at comparing the incidence of ECG-LVH in patients randomized to ACE-inhibitor or non-ACE inhibitor therapy who had no ECG evidence of LVH at baseline. Secondarily, we evaluated the relationships between incidence of ECG-LVH and baseline and follow-up variables, including treatable risk factors such as BP and HbA1C.

ECG-LVH and other outcome variables: Main outcome variable was ECG-LVH defined as Sokolow-Lyon ($S_{V1}+R_{V5/6}$) voltage ≥3.5 mV (12) and/or Cornell ($R_{aVL}+S_{V3}$) voltage ≥2.0 mV (women) or ≥2.4 mV (men) (13). Secondary outcomes were Sokolow-Lyon and Cornell voltages considered as continuous variables. Standard 12-lead ECGs were recorded at 25 mm/sec, 1 mV/cm calibration, at baseline and every year thereafter. They were centrally and independently evaluated by two investigators who were blinded to treatment allocation and patient data. ECGs with inconsistent readings were evaluated by a third independent cardiologist and his diagnosis was considered for data analysis. Trough systolic and diastolic (Korotkoff phase I/V) BPs were measured in the morning before treatment administration (8).

Data were reported in dedicated case report forms and doubly entered in an ad-hoc database that was eventually merged with the BENEDICT database. Before analyses, all data were monitored by the Monitoring Unit of the Clinical Research Center for Rare Diseases “Aldo & Cele Daccò” of the Mario Negri Institute for Pharmacological Research.

Sample size: We assumed a 10% incidence of ECG-LVH in the non-ACE inhibitor group and a 60% reduction (from 10% to 4%) in the ACE inhibitor group. The expected incidence of ECG-LVH was assumed to be higher than in HOPE controls (6) since, different from HOPE, all BENEDICT patients were hypertensive and diabetic at inclusion (8), and they also had additional risk factors such as older age, systolic hypertension, obesity and, conceivably, insulin resistance. The 60% risk reduction was assumed on the basis of experimental evidence that ACE inhibition fully prevents LVH if treatment is started before the induction of arterial hypertension (14). Since our patients were already hypertensive at study entry and had other risk factors, we considered a conservative assumption of 60% risk reduction as appropriate. Thus, we calculated that 400 patients per group gave the study an 91% power to detect as statistically significant (α=0.05, two-tailed test) the expected between-group difference in ECG-LVH incidence.

Statistical analyses: The analyses were performed by the Laboratory of Biostatistics of the Clinical Research Center. The Authors had full access to the data and take full responsibility for its integrity. All Authors have read and agree to the manuscript as written.

‘Between-groups’ comparisons were performed in continuous variables by unpaired t-test or Wilcoxon’s Rank Sum test and in categorical variables by χ^2 test or Fisher’s Exact test. ‘Within-group’ comparisons were performed in continuous variables by paired t-test or Wilcoxon’s Signed Rank test and in categorical variables by McNemar test. pre-defined (8) baseline covariates were considered: site, age, sex, smoking status (patients who had never smoked versus former smokers and current smokers), diastolic BP, log-transformed urinary albumin excretion (median of three readings) at baseline.

Main study results were reported by a Cox regression model. For graphical representation, Kaplan–Meier curves were plotted for each considered group. Explorative analyses were also conducted including follow-up systolic and diastolic BP measurements and absolute reductions from baseline to follow-up BP in order to help data interpretation. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). P<0.05 was considered statistically significant. No p-value adjustment was carried out for multiple comparisons.

RESULTS

Of 905 patients with readable ECG at baseline and at least one year follow up, 816 (433 on ACE and 383 on non-ACE inhibitor therapy) had no ECG evidence of LVH. Of these, 799 patients (423 on ACE and 376 on non-ACE inhibitor therapy) were available for analyses (Study Profile, on-line Appendix-2, which is available at http://care.diabetesjournals.org). Baseline characteristics and Sokolow-Lyon and Cornell voltages were similar between treatment groups with the exception of the percentage of never smokers and of serum cholesterol levels that were higher in the non-ACE inhibitor group (Table 1).

Incidence of ECG-LVH: Over a median (interquartile range) of 36 (24-48) months of follow-up, LVH developed in 44 patients (5.5%): 13 (3.1%) on ACE and 31 (8.2%) on non-ACE inhibitor therapy (Figure 1). The unadjusted Hazard Ratio (95% Confidence Interval) for ECG-LVH was 0.34 (0.18-0.65), p=0.0012. The Hazard Ratio was statistically significant even after adjustment for pre-defined baseline characteristics [0.35 (0.18-0.68), P=0.0018), and baseline and follow-up systolic and diastolic BP, as well as systolic and diastolic BP reduction vs. baseline (Table 2).

Compared to baseline, both Sokolow-Lyon and Cornell voltages significantly decreased at different years on follow-up in the study group as a whole and in the subgroup on ACE inhibitor therapy (Table 3). In the non-ACE inhibitor group, changes in Sokolow-Lyon voltage were not significant and those in Cornell voltage achieved the statistical significance only at 2 and 3 years (Table 3).

Blood pressure and metabolic control: Follow up systolic (138.4±9.4 mmHg) and diastolic (80.8± 5.2 mmHg) BP were 12.7 and 7.1 mmHg lower than at baseline, respectively (p<0.0001 for both). Follow-up systolic (137.2±9.2 mmHg vs 139.7±9.5 mmHg, respectively, P=0.045) and diastolic (80.0±5.2 mmHg vs 81.7±5.0 mmHg, P=0.005) BP were lower in the ACE than in the non-ACE inhibitor group. Follow up HbA1C levels were lower in the ACE than in the non-ACE inibitor group (5.76±1.17 % vs 5.91±1.23 %, P=0.03), while blood glucose was similar in the two teatment groups (156.1±36.2 mg/dl vs 161.3±39.1 mg/dl, P=0.31) (see BP, HbA1C and blood glucose profiles in on-line appendix-3).

At multivariable analyses known diabetes duration, baseline BMI, Sokolow-Lyon and Cornell voltages were associated with the incidence of ECG-LVH on follow-up, while baseline and follow-up systolic/diastolic BP, HbA1C and blood glucose as well as systolic/diastolic BP, HbA1 and blood glucose changes vs. baseline had no predictive value. No significant correlation was found between changes in Sokolow-Lyon or Cornell voltages on follow-up and concomitant changes in BP, HbA1C and blood glucose (vs baseline).

Comparative analyses between randomization arms: LVH developed in 4 patients on trandolapril (1.9%), 9 on VeraTran (4.2%), 16 on verapamil (8.9%) and 15 on placebo (7.6%). After adjustment for pre-defined covariates, the risk of LVH was significanly lower on trandolapril compared to verapamil [HR (95%CI): 0.22 (0.07-0.65), p=0.007] or placebo [0.25 (0.08-0.78), p=0.017, p=0.017], and on VeraTran compared to verapamil [0.42 (0.19-0.97), p=0.0.043]. Risk reduction on VeraTran compared to placebo was not significant [0.49 (0.21-1.16), p=0.10]. Risk was not significantly different between VeraTran and trandolapril [1.97 (0.60-6.49), p=0.26], and between verapamil and placebo [1.21 (0.58-2.52), p=0.61].

DISCUSSION

In the present study, ACE inhibition with trandolapril compared to non-ACE inhibitor therapy significantly reduced the incidence of ECG-LVH in patients with arterial hypertension and type 2 diabetes. The protective effect of trandolapril against ECG-LVH was already evident at 1 year post-randomization and progressively increased on follow up. Sokolow-Lyon and Cornell voltages consistently decreased on trandolapril therapy, whereas they did not change appreciably on non-ACE inhibitor therapy.

The reduced incidence of ECG-LVH with trandolapril was not explained by the small differences in BP control between the two treatment groups, since risk reduction was highly significant even after adjustments were made for BP control achieved on follow-up and for BP reductions observed versus baseline. Baseline factors potentially involved in LVH development and progression, such as age, body mass index, BP, and Sokolow-Lyon and Cornell voltages were similar in the two groups. All patients were prescribed a low-salt diet and no one performed vigorous physical activities. Altogether, the above data indicate that trandolapril had a specific protective effect against the development of LVH that was additional to the benefit of BP reduction.

Both hemodynamic and non-hemodinamic factors most likely contributed to the cardioprotective effect of trandolapril therapy. ACE inhibitors increase vessel wall compliance and reduce arterial wave reflection amplitude and so reduce aortic and left ventricular BP even more consistently than peripheral artery BP - that is the brachial BP as measured at the arm (15)**.** Thus, at comparable peripheral BP, ACE inhibitors may reduce central pressures and left ventricular after-load more effectively than antihypertensive drugs that do not directly interfere with the RAAS (16)**.** This likely contributed to the regression of LVH observed with RAAS inhibitor therapy in HOPE (6) and LIFE (7) and might also explain why in the BENEDICT trial trandolapril prevented LVH more effectively than non-ACE inhibitor therapy, even at comparable brachial BP (9).

ACE inhibitors may prevent LVH also through direct inhibition of cardiac RAAS. Angiotensin II promotes the growth of myocytes independently of loading conditions (17) and ACE inhibitors may prevent the hypertrophic effect of angiotensin II even at doses that do not affect the BP (14). Renin expression and tissue-converting enzyme activity are increased in hypertrophied hearts of spontaneously hypertensive rats (SHR) (18, 19), and AT1 receptors are over-expressed in cardiomyocytes of mice with cardiac hypertrophy and normal BP (20). Consistently, in rats, cardiac expression of the angiotensin II type 1 (AT_1) receptor antisense transgene attenuated cardiac hypertrophy without affecting the BP (21). However, recent data that cardiac AT1 receptors cannot sustain angiotensin II-dependent hypertension and cardiac hypertrophy after knocking-out renal AT_1 receptors (22) suggest that kidney RAAS activation is also involved and that its inhibition may explain at least part of the cardioprotective effect of ACE inhibitors and ARBs. Unlike ARBs, ACE inhibitors may directly prevent myocardial hypertrophy also by increasing local bradykinin bioavailability through inhibition of the myocardial kallikrein-kinin pathway (23).

Vascular stiffness and RAAS activation (24) are common in patients with type 2 diabetes and this may explain the high prevalence and severity of LVH in this population, even at "normal" BP (8; 9). The synergistic effect on left ventricular structure of arterial hypertension and of the above hemodynamic and metabolic abnormalities most likely explained the relatively high incidence of ECG-LVH we observed in our present controls on non-ACE inhibitor therapy. On the other hand, all the above risk factors for LVH can be controlled by ACE inhibitor therapy. Indeed, in addition to inhibit angiotensin II and aldosterone production, ACE inhibitors may also ameliorate arterial compliance (25). Thus, the co-existence of several abnormalities that can be ameliorated by RAAS inhibitors may also explain the remarkable protective effect of trandolapril against ECG-LVH we observed here, an effect that appears to exceed that of ramipril in HOPE (6).

Post-hoc analyses according to the four original randomization arms showed that trandolapril alone prevented LVH more effectively than verapamil alone or placebo, while trandolapril combined to verapamil was more cardioprotective than verapamil alone. Trandolapril alone tended to be more effective than trandolapril combined to verapamil, while the effect of verapamil was similar to that of placebo. Within the limitations of the limited power and multiple comparisons, these data show - consistently with the results of primary outcome analyses - that the ACE inhibitor is the effective component of the trandolapril-verapamil combination and that verapamil has no specific protective effect against LVH.

A possible limitation of the present study is that, as in previous large studies (4, 6, 7), LVH was assessed by electrocardiography. This likely resulted in a reduced precision of outcome data (ECG may underestimate LVH in obese subjects) that reduced the power of the analyses, but very unlikely introduced a systematic bias. Actually, a posterior power analyses showed that the probability of a false positive finding was less than 0.2%.

In conclusion, hypertensive patients with type 2 diabetes on trandolapril compared to controls on non-ACE inhibitor therapy had a significantly lower incidence of ECG-LVH by Sokolow-Lyon and Cornell voltage, an effect that was highly significant even after adjustments for BP control achieved in the two treatment groups throughout the study. These findings and the observation that ECG-LVH strongly predicts CV morbidity and mortality in people with hypertension and type 2 diabetes, support early ACE inhibitor therapy for effective prevention of left ventricular hypertrophy and, conceivably, cardiovascular morbidity and mortality (6, 7) in this population.

ACKNOWLEDGMENTS

Authors thank Maria Ganeva and Laura Gallizioli for technical support, doctors and nurses of the BENEDICT study group for patient care, and Manuela Passera for help in preparing the manuscript. Abbott (Ludwigshafen, Germany) partially supported the study.

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Table 1. Baseline characteristics of hypertensive patients with type 2 diabetes and normal urinary albumin excretion in the study group as a whole and according to ACE inhibitor therapy YES or NO

Characteristics	**Overall**	**ACEi YES**	**ACEi NO**
	(N = 799)	*(N = 423)*	*(N = 376)*
Age *(yrs)*	61.6±8.0	61.5±7.8	61.7±8.2
Males *(n,%)*	443 (55.4)	238 (56.3)	205 (54.5)
Body-mass index *(kg/m^2)*†	29.1±4.8	29.2±5.1	29.1±4.6
Known duration of diabetes *(yrs)*	7.5±6.5	7.5±6.6	7.6±6.3
Smokers			
Never	435 (54.4)	213 (50.4)	222 (59.0)*
Former	257 (32.2)	147 (34.7)	110 (29.3)
Current	107 (13.4)	63 (14.9)	44 (11.7)
Glycosylated haemoglobin *(%)*‡	5.8±1.4	5.7±1.4	5.7±1.3
Glucose (mg/dl)	160.4±45.7	159.1±45.6	161.9±45.9
Trough Blood pressure *(mm Hg)*			
Systolic	150.4±14.0	150.0±14.0	150.9±14.0
Diastolic	87.6±7.5	87.5±8.0	87.8±7.0
Mean arterial pressure	108.6±8.3	108.3±8.5	108.9±8.0
Urinary albumin excretion *(μg/min)*§	5.2 (3.6-8.9)	5.2 (3.6-9.3)	5.2 (3.6-8.8)
Serum creatinine *(μmol/L)*	79.6±17.7	79.6±17.7	79.6±17.7
Triglycerides *(mmol/L)*	1.65±0.91	1.63±0.83	1.66±1.00
Cholesterol *(mmol/L)*	5.41±0.93	5.33±0.93	5.50±0.93*
Sokolow-Lyon voltage *(mV)*	19.2±5.8	19.2±5.9	19.2±5.7
Cornell voltage *(mV)*	13.4±4.2	13.2±4.2	13.6±4.2

Values are means ± SD. † The body-mass index is the weight in kilograms divided by the square of the height in meters. ‡ Glycosylated hemoglobin was measured by ion-exchange high-performance liquid chromatography (normal range, 3.5 to 5.2 percent). § Values shown are medians (interquartile ranges).*P<0.05 vs ACE yes

Table 2. Hazard Ratio (95% Confidence Interval) of the incidence of ECG-LVH in patients randomized to ACE-inhibitor YES compared to patients randomized to ACE inhibitor NO

	H.R. (95% C.I.)	**p**
Unadjusted	0.34 (0.18 - 0.65)	0.0012
Adjusted		
- Baseline pre-defined	0.35 (0.18 - 0.68)	0.0018
- Baseline SBP	0.36 (0.18 - 0.68)	0.0019
- Baseline DBP	0.36 (0.19 – 0.69)	0.0020
- Follow-up SBP	0.38 (0.20 - 0.73)	0.0036
- Follow-up DBP	0.34 (0.18 - 0.67)	0.0016
- SBP reduction	0.35 (0.18 - 0.68)	0.0018
- DBP reduction	0.34 (0.18 - 0.66)	0.0013

Table 3. Changes in Sokolow-Lyon and Cornell voltages at different years vs baseline in the study group as a whole (Overall) and according to ACE inhibitor therapy YES or NO

	1 year	2 years	3 years	4 years
Solokow-Lyon *(mV)*				
Overall	-0.5±0.1***	-1.1±0.2**	-1.2±0.2**	-1.3±0.3
ACEi YES	-0.6±0.2***	-1.4±0.2****	-1.4±0.2**	-1.7±0.4
ACEi NO	-0.3±0.2	-0.7±0.2	-1.0±0.3	-0.8±0.4
Cornell *(mV)*				
Overall	-0.4±0.1***	-0.5±0.2****	-0.4±0.1****	-0.3±0.2****
ACEi YES	-0.5±0.1**	-0.8±0.1****	-0.6±0.2****	-0.4±0.3****
ACEi NO	-0.2±0.2	-0.2±0.3**	-0.3±0.2***	-0.2±0.4

Values are means ± standard error, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs baseline

Figure 1

Kaplan-Meier curves for the percentages of subjects developing ECG-LVH in patients on ACE inhibitor therapy with trandolapril (ACEi YES) or on non-ACE inhibitor therapy (ACEi NO). The difference in ECG-LVH adjusted for prespecified baseline covariates, was significant (p=0.0018).