Controlled study of the effect of angiotensin converting enzyme inhibition versus calcium-entry blockade on insulin sensitivity in overweight hypertensive patients: Trandolapril Italian Study (TRIS)

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Objective **The aim of this study was to evaluate the effect of trandolapril, an angiotensin converting enzyme inhibitor, on blood pressure, forearm blood flow and insulin sensitivity in comparison with nifedipine gastrointestinal therapeutic system.**

Patients and methods **This is a multicentre, two-way parallel-group, open-label comparative study in 90 overweight hypertensive patients, who were randomly assigned to treatment for 8 weeks with either trandolapril or nifedipine. At baseline and after treatment, all patients underwent an oral glucose tolerance test, an evaluation of their metabolic profiles and a euglycaemic hyperinsulinaemic clamp test. In a subgroup of 18 patients, a forearm study was carried out.**

Results **Blood pressure fell by the second week of treatment and remained significantly reduced compared with baseline in both treatment groups. Plasma triglyceride levels were also significantly reduced after trandolapril therapy, but no significant changes occurred in the other metabolic parameters during treatment with either drug. During the euglycaemic hyperinsulinaemic clamp, whole-body glucose use was similar in the two treatment groups at baseline, and a moderate but statistically significant increase in insulin sensitivity was observed after trandolapril treatment (trandolapril: 5.0 $\pm$ 0.2 versus 4.5 $\pm$ 0.2 mg/kg per min; nifedipine: 4.1 $\pm$ 0.3 versus 4.2 $\pm$ 0.3 mg/kg per min; $P < 0.05$, versus baseline and trandolapril versus nifedipine treatment). Skeletal muscle glucose uptake was significantly higher after trandolapril than after nifedipine therapy (5.0 $\pm$ 0.7 and 3.0 $\pm$ 0.4 mg/min, respectively; $P < 0.01$). As forearm blood flow was similar in the two treatment groups at baseline and was unchanged after 8 weeks of therapy, skeletal muscle glucose extraction was significantly greater in the ACE inhibitor treated-group than in the nifedipine comparative group (trandolapril: baseline 21 $\pm$ 2, treatment 24 $\pm$ 3 mg/dl; nifedipine: baseline 18 $\pm$ 3, treatment 16 $\pm$ 2 mg/dl; $P < 0.05$, trandolapril versus nifedipine treatment).**

Conclusions **During short-term treatment, ACE inhibition with trandolapril was able to moderately improve insulin sensitivity, in comparison with calcium blockade, and this effect appeared to be independent of the haemodynamic action of the drug.** *J Hypertens* **1999, 17:439–445 © Lippincott Williams & Wilkins.**

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Keywords: trandolapril, angiotensin converting enzyme inhibition, hypertension, blood pressure, insulin, insulin sensitivity, glucose uptake, nifedipine-GITS, calcium blockade

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Introduction

Essential hypertension is very often associated with metabolic abnormalities which are powerful risk factors for coronary heart disease [1], and insulin resistance appears to be a key factor in this association [2–5]. Failure to effectively control these metabolic correlates of hypertension may be one of the reasons why antihypertensive treatment achieved less than the expected benefit in some intervention trials. In recent years, increasing attention has been focused on the metabolic effects of commonly used antihypertensive drugs [6,7]. It appears that antihypertensive therapy is best tailored to the individual patient, and that in patients with concomitant metabolic abnormalities,

antihypertensive drugs with adverse metabolic effects should be avoided [8].

The metabolic profile of the most effective antihypertensive drugs has been investigated extensively [8]. Although it is clear that calcium blockers are metabolically neutral [5,9–12], there is still debate over the question of whether angiotensin converting enzyme (ACE) inhibitors can ameliorate insulin sensitivity [13–31].

To investigate this question, we set up a randomized trial to determine the effects of the ACE inhibitor trandolapril on blood pressure and insulin sensitivity in comparison with nifedipine gastrointestinal therapeutic system (GITS). Since peripheral vasodilation allows a greater supply of glucose and insulin to skeletal muscle, and has been proposed as a possible mechanism for the putative effect of ACE inhibition on insulin sensitivity, we also evaluated regional blood flow and insulin-stimulated glucose uptake by forearm skeletal muscle in a subgroup of patients during short-term treatment with the two study drugs.

Patients and methods

Study design and patient selection

The study followed a multicentre, randomized, two-way parallel-group, open-label comparative design. Five centres participated, and all obtained approval from the local ethical committees. The study population consisted of patients with mild or moderate essential hypertension referred to outpatient clinics, and all gave informed consent. Entry criteria included age 35–65 years, blood pressure consistently over 140 mmHg systolic and/or 90 mmHg diastolic on three consecutive visits and a body mass index (BMI) of 25–30 kg/m^2. Patients with congestive heart failure, cardiac or cerebrovascular disease, known diabetes or a plasma creatinine concentration greater than 140 μmol/l were excluded. Ninety patients who met the above criteria entered a 2 week wash-out period, during which any antihypertensive treatment was withdrawn, followed by 2 weeks of placebo administration (single daily capsule). At the end of this period, the patients were randomly assigned to active treatment for 8 weeks with either 2 mg trandolapril (Gopten; Knoll, Muggiò, MI, Italy) or 30 mg nifedipine-GITS (Adalat Crono 30; Bayer, Milan, Italy) every morning at 8 a.m.

Blood pressure was measured at the end of the placebo run-in period, after 2 and 5 weeks of therapy and at the end of the treatment period. At the end of the placebo run-in and after the 8-week treatment period, venous blood was collected for the evaluation of fasting serum glucose, insulin, total and high-density lipoprotein (HDL) cholesterol and triglyceride levels; an oral glucose tolerance test and a euglycaemic hyperinsulinaemic clamp test were carried out; and a forearm study was performed in a subgroup of 18 patients (nine taking trandolapril and nine taking nifedipine-GITS).

Oral glucose tolerance test

The oral glucose tolerance test was performed by administering a standard load of 75 g glucose, in the morning after a 12 h fast. A venous blood sample was obtained before and 60 and 120 min after the glucose load for measurement of glucose and insulin concentrations. Glucose tolerance was defined according to National Diabetes Data Group criteria [32].

Euglycaemic hyperinsulinaemic clamp

After a 12 h overnight fast, a polyethylene cannula was inserted into an antecubital vein for insulin and glucose infusion. A second cannula was placed retrogradely into a hand vein for intermittent blood sampling, the hand being warmed in a heated box (60°C) to ensure arterialization of venous blood. Regular insulin was administered intravenously at a constant rate of 1.2 mU/kg body weight per min for 2 h to induce a physiological increase in peripheral insulin concentration. A solution of 20% glucose in water was infused simultaneously to maintain the blood glucose concentration at its basal level. The glucose infusion rate was adjusted according to plasma glucose levels, which were measured every 5 min with a Beckman glucose analyser (Beckman Instruments, Fullerton, California, USA). Blood samples for insulin measurements were taken in the basal state immediately before the clamp and every 40 min during the clamp. The amount of glucose infused to maintain euglycaemia is considered equal to the amount of glucose metabolized, provided hepatic glucose production is totally suppressed. Although we did not measure hepatic glucose output in our patients, previous studies have shown that the insulin-inhibitory effect of hepatic glucose output is well preserved in hypertensive patients [2], and that at insulin concentrations similar to those achieved in our study, hepatic glucose output is completely suppressed [2]. We therefore assumed that in our study patients, the glucose infusion rate during the last 40 min of the clamp represented whole-body glucose disposal and this measurement was taken as an index of insulin sensitivity.

Forearm study

A teflon catheter was introduced retrogradely into a large antecubital vein and threaded as deeply as possible (under these conditions, the effluent venous blood predominantly drains muscle tissue). A second catheter was inserted into the ipsilateral brachial artery for blood sampling and for infusion of indocyanine green dye (Cardio-Greeen; Westcott of Dunning, Baltimore, Maryland, USA) to measure blood flow. Insulin and glucose were infused through a contralateral vein, and simultaneous blood samples were taken from the

arterial and the deep-venous catheter every 40 min for 2 h. Five minutes before each blood collection, a sphygmomanometer cuff placed around the wrist was inflated 100 mmHg above the arterial blood pressure to exclude the hand from the circulation. Soon after blood collection, indocyanine green dye was infused through the arterial catheter, while keeping the cuff inflated around the wrist. After 5 min, two venous blood samples were taken, at 1 min intervals, to measure the plasma concentration of the dye.

Biochemical measurements

All biochemical measurements were carried out in the laboratories of the Department of Clinical and Experimental Medicine, Federico II University of Naples. Plasma glucose was measured by the glucose-hexokinase method using a Cobas-Mira spectrophotometer (Roche, Basel, Switzerland). Plasma insulin was measured by radioimmunoassay, using a commercially available kit (Techno Genetics, Milan, Italy). Lipids were measured by enzymatic-colorimetric methods using a Cobas-Mira spectrophotometer (Roche).

Calculations and definitions

Mean blood pressure was calculated as [one-third (systolic minus diastolic blood pressure) plus diastolic blood pressure]. BMI was calculated as weight (kg)/height (m^2). Insulin-induced whole-body glucose uptake was calculated as mg glucose infused per kg body weight per min, during the last 40 min of the clamp. Forearm plasma flow was estimated by dividing the dye infusion rate by its concentration in venous plasma, and converted to blood flow (ml/min) according to haematocrit levels. The forearm glucose uptake was calculated by multiplying the arteriovenous glucose difference by forearm blood flow, and was normalized to the forearm volume in litres. Forearm glucose uptake in response to insulin was measured as the mean of two observations taken after 80 and 120 min of the clamp. Insulin-stimulated glucose clearance was calculated as insulin-induced whole-body glucose uptake divided by the mean plasma glucose level during the last 40 min of the clamp, normalized to the concomitant plasma insulin concentration [13].

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences. One-way analysis of variance was used to detect possible differences between the two therapies. Two-tailed Student's paired *t* test was used to compare the differences between baseline and the end of the treatment period. Data are expressed as means ± SEM.

Results

The two treatment groups were fully comparable at baseline with regard to sex distribution, age, BMI, fasting plasma glucose and plasma insulin levels, total cholesterol and HDL cholesterol and triglyceride levels (Table 1). Blood pressure was similar at the end of the placebo run-in period in the two groups, fell to a similar extent by the second week of treatment and remained significantly reduced compared with baseline in both groups (Fig. 1). No significant changes occurred in any anthropometric or metabolic parameters during treatment with either drug, except that serum triglyceride concentrations were significantly lower after trandolapril therapy (Table 1). Table 2 gives the results of the oral glucose tolerance test performed before and after treatment with each drug. There was a trend for an improvement in glucose tolerance after trandolapril therapy, as glucose levels were 9% lower in the presence of plasma insulin concentrations similar to baseline values. This difference in blood glucose response to the oral glocose tolerance test was of borderline significance.

Euglycaemic hyperinsulinaemic clamp

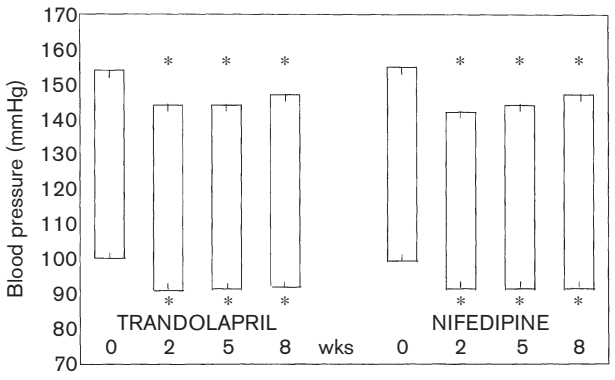
The basal glucose level was 4.89 ± 0.10 and 4.84 ± 0.10 mmol/l for the trandolapril group before and after treatment, respectively, and 5.06 ± 0.10 and 5.11 ± 0.10 mmol/l for the nifedipine group. These values remained virtually unchanged during the clamp. The coefficient of variation for blood glucose during

Table 1 **Anthropometric and metabolic data of overweight hypertensive patients by treatment group at baseline and at the end of treatment**

	Trandolapril		Nifedipine	
	Baseline	During treatment	Baseline	During treatment
n (males/females)	45 (26/19)		45 (28/17)	
BMI (kg/m^2)	28.4 ± 0.3	28.4 ± 0.3	28.6 ± 0.3	28.7 ± 0.3
IRI (μU/ml)	9.4 ± 0.8	10.8 ± 1.8	10.9 ± 2.0	10.1 ± 0.6
GLU (mmol/l)	4.88 ± 0.11	4.94 ± 0.11	5.05 ± 0.11	4.99 ± 0.11
CHOL (mmol/l)	5.61 ± 0.15	5.66 ± 0.15	5.66 ± 0.15	5.74 ± 0.15
TG (mmol/l)	1.40 ± 0.10	1.34 ± 0.08*†	1.44 ± 0.13	1.53 ± 0.13
HDL (mmol/l)	1.11 ± 0.05	1.14 ± 0.05	1.09 ± 0.05	1.14 ± 0.05

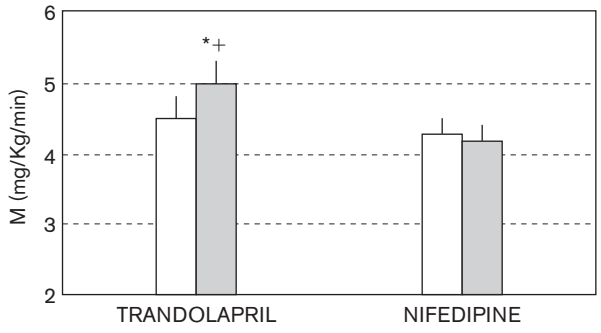
Values are means ± SEM. BMI, body mass index; IRI, immunoreactive insulin; GLU, glucose; CHOL, cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol. * $P < 0.05$, versus baseline; † $P < 0.01$, versus nifedipine.

Fig. 1



Systolic (tops of bars) and diastolic (bottoms of bars) blood pressure before and during therapy. wks, Weeks. $^{*}P < 0.0001$, versus baseline (0).

Fig. 2



Insulin-stimulated whole-body glucose use in the two treatment groups. White bars represent values at the end of placebo run-in period and shaded bars represent values during treatment. M, mg glucose infused per kg body weight per min during the last 40 min of the clamp. $^{*}P < 0.05$, versus baseline; $^{+}P < 0.05$, versus nifedipine.

the clamp was 8%. Plasma insulin concentrations were comparable before the clamp in the two treatment groups (baseline 10 ± 1 and 11 ± 2 μU/ml; during treatment 10 ± 2 and 10 ± 1 μU/ml, for the trandolapril and nifedipine groups, respectively) and increased to a similar extent during the clamp (trandolapril group: 47 ± 2 and 49 ± 2 μU/ml; nifedipine group: 46 ± 2 and 47 ± 2 μU/ml, before and after treatment, respectively). As shown in Figure 2, whole-body glucose use during the last 40 min of the clamp was not different in the two treatment groups at baseline. After trandolapril treatment, a significant increase in insulin sensitivity was observed in comparison with baseline and with nifedipine-GITS therapy (Fig. 2). When the data were expressed in terms of mean insulin-stimulated glucose clearance, the increase in plasma insulin sensitivity was still significantly higher for the trandolapril group compared with baseline (1.31 ± 0.11 versus 1.16 ± 0.08 ml/min per kg, $P < 0.05$) or with nifedipine treatment (increase in insulin-stimulated glucose clearance: 0.15 ± 0.07 versus 0.02 ± 0.1 ml/min per kg, $P < 0.05$).

A significant inverse correlation was detected in the group as a whole between changes in insulin sensitivity and concomitant changes in serum triglyceride concentrations ($r = -0.27$, $P < 0.02$), an improvement in insulin sensitivity being associated with a fall in serum triglyceride levels. A trend towards a reciprocal association between the improvement in insulin sensitivity and the blood glucose response to the oral glucose tolerance test was also apparent ($r = -0.30$), but did not reach statistical significance.

Forearm study

Skeletal muscle blood flow was similar in the two treatment groups, both at baseline and after 8 weeks of therapy, and remained unaltered in response to an infusion of insulin (Table 3). As the drug-induced blood pressure fall was comparable in the two groups, we conclude that vascular resistance was reduced to the same extent with each drug. Insulin-stimulated glucose uptake was significantly higher after trandolapril than after nifedipine treatment (5.0 ± 0.7 versus 3.0 ± 0.4 mg/min, respectively, $P < 0.01$). This indicates that skeletal muscle glucose extraction was greater after trandolapril treatment, as forearm glucose uptake is calculated by multiplying the arteriovenous glucose

Table 2 **Plasma insulin and glucose levels during oral glucose tolerance test, by treatment group**

	Trandolapril			Nifedipine		
	0 min	60 min	120 min	0 min	60 min	120 min
Glucose (mmol/l)						
Basal	4.99 ± 0.11	8.11 ± 0.33	5.72 ± 0.33	5.05 ± 0.11	8.44 ± 0.39	5.83 ± 0.22
On therapy	4.89 ± 0.11	7.55 ± 0.33	5.77 ± 0.28	4.94 ± 0.11	8.55 ± 0.39	5.77 ± 0.28
Insulin (μU/ml)						
Basal	9 ± 1	54 ± 6	39 ± 8	11 ± 1	68 ± 7	50 ± 8
On therapy	10 ± 1	54 ± 3	42 ± 5	10 ± 1	68 ± 8	44 ± 6

Values are means ± SEM.

Table 3 **Forearm blood flow (ml/l per min) during euglycaemic hyperinsulinaemic clamp, by treatment group**

	Baseline				During treatment			
	0 min	40 min	80 min	120 min	0 min	40 min	80 min	120 min
Trandolapril	22 ± 1	25 ± 2	26 ± 2	24 ± 2	22 ± 2	22 ± 1	22 ± 2	21 ± 2
Nifedipine	24 ± 2	22 ± 2	23 ± 2	21 ± 2	19 ± 2	19 ± 2	20 ± 3	20 ± 2

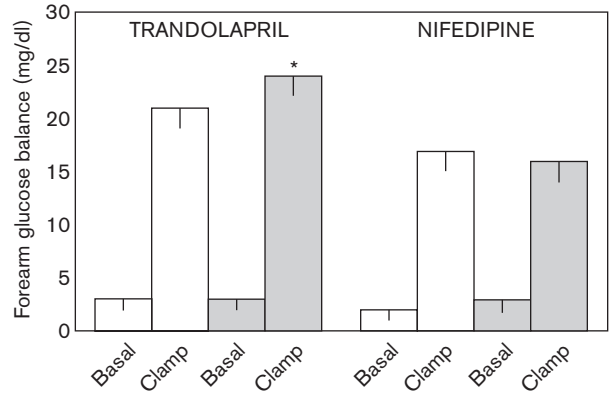
Values are means ± SEM.

extraction by the forearm blood flow. Insulin infusion, as expected, remarkably increased forearm glucose extraction in both groups, both before and during treatment (Fig. 3). However, while no significant difference in the effect of insulin was detectable between the two groups at baseline, at the end of the 8 week treatment period, the effect of insulin infusion was significantly greater in the ACE inhibitor-treated group than in the nifedipine comparative group (Fig. 3).

Discussion

A number of studies have investigated the metabolic effects of ACE-inhibiting drugs, with a particular focus on insulin sensitivity [13–31]. The results of these studies are generally controversial. Many of them used less sensitive methods for detecting insulin sensitivity and largely found no effect of ACE inhibitors on glucose metabolism [16–22], with the exception of two studies [14,15] that suggested a positive effect. Among the trials that used the euglycaemic hyperinsulinaemic clamp for the measurement of insulin sensitivity [13,23–31], only eight were placebo-controlled or comparative studies (versus other antihypertensive drugs). The results of one of these studies were not conclusive due to a carryover effect from previous antihypertensive medications [24], while others found that ACE inhibitors improved insulin sensitivity during both short- [25,26] and longer-term treatment [27,28].

Fig. 3



Effect of insulin on forearm glucose balance before (white bars) and after 8 weeks of therapy (shaded bars) in the two treatment groups. * $P < 0.05$, versus corresponding nifedipine value.

In a comparison of the effects of ACE inhibition with α_1-adrenergic blockade, both classes of drugs ameliorated insulin sensitivity, although the effect was greater for the α_1-adrenergic blocker doxazosin [29–30]. Yet another study of different ACE inhibitor drugs suggested that this class of drugs has a generally favourable effect on insulin sensitivity, although the effect varied with different drugs [31].

The present study, which included the largest patient population so far, showed that trandolapril and nifedipine-GITS had significantly different effects on whole-body insulin sensitivity for a similar blood pressure fall. The improvement in insulin sensitivity with the ACE inhibitor was relatively small in absolute terms, yet is probably biologically meaningful given that the study patients had only a modest degree of insulin resistance overall in the absence of severely obese and diabetic individuals. The effect of ACE inhibition on insulin-stimulated whole-body glucose uptake was associated with an improvement in glucose tolerance of borderline significance and with a statistically significant fall in serum triglyceride levels. Furthermore, a low-grade but statistically significant correlation was seen between the changes in triglyceride levels and those in whole-body glucose uptake.

Although the study design did not include a placebo control, it is clear that ACE inhibition ameliorated insulin resistance in comparison with nifedipine-GITS therapy. This conclusion is clinically relevant because the bulk of the available evidence supports the metabolic neutrality of calcium blockers in hypertensive patients.

The very least that can be said for the ameliorative effect of trandolapril on insulin sensitivity is that its vasodilating potential presumably leads to an increase in glucose and insulin supply to skeletal muscle or visceral organs as a consequence of increased blood flow [16,33]. Nevertheless, the concomitant observation

that during short-term treatment with both drugs, no substantial changes in blood flow to foream skeletal muscle were detected either under basal conditions or during the hyperinsulinaemic state appears to detract from this hypothesis. In this respect, our findings are in line with a report by Santoro *et al.* [13] that after 7 days of ACE inhibition there was a significant fall in blood pressure but no change in forearm blood flow, and with a study by Bijlstra *et al.* [34], who found that the forearm blood flow response to endothelium-dependent vasodilation was unaffected by 6 months of ACE inhibition in diabetic patients. Several other studies dealing with a possible direct vasodilating effect of insulin have provided controversial results [35–40]. In particular, our finding that peripheral blood flow did not increase during systemic hyperinsulinaemia is in agreement with reports by DeFronzo *et al.* [35] and Natali *et al.* [36]. Our present data suggest that the improvement in whole-body insulin-mediated glucose use during ACE inhibition was associated with increased forearm skeletal muscle glucose extraction in comparison with calcium blockade, independently of changes in regional blood flow. This finding is in keeping with results reported by Jacob *et al.* [41], who assessed skeletal muscle glucose metabolism in obese Zucker rats without the potentially confounding influence of changes in blood flow, by using an isolated epitrochlearis muscle preparation. These authors [41] reported that during both short- and long-term administration, trandolapril improved the activity of the insulin-sensitive transport system GLUT-4 in insulin-resistant skeletal muscle. Similarly, in insulin-resistant obese rats, both the ACE inhibitor captopril and trandolapril increased glucose transport [42] and insulin-stimulated 2-deoxyglucose uptake by isolated skeletal muscle [43]. It is clear that further investigation is needed to elucidate the cellular mechanisms responsible for the improvement in skeletal muscle insulin action following ACE inhibitor treatment.

In conclusion, the present study shows that the ACE inhibitor trandolapril improved insulin sensitivity to a moderate degree in comparison with calcium blockade during short-term treatment in hypertensive patients with low-grade insulin resistance. This effect appeared to be independent of the haemodynamic action of the ACE inhibitor and was perhaps related to a direct effect of trandolapril on insulin-sensitive glucose metabolism in skeletal muscle.

Appendix: The TRIS Study Group

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