

# Trandolapril/verapamil combination in hypertensive diabetic patients

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**Abstract:** Cardiovascular diseases are directly affected by arterial hypertension. When associated with diabetes mellitus, the potential deleterious effects are well amplified. Both conditions play a central role in the pathogenesis of coronary artery disease, heart failure, stroke, and renal insufficiency. Prevalence of hypertension is much higher among diabetic than non-diabetic patients, and the hypertensive patient is more likely to develop type 2 diabetes. Current international guidelines recommend aggressive reductions in blood pressure (BP) in hypertensive patients with additional risk factors, including cardiovascular risk factors, and emphasize the relevance of intensive reduction in patients with diabetes mellitus; a goal of 130/80 mm Hg is required. To achieve BP target a combination of antihypertensives will be needed, and the use of long-acting drugs that are able to provide 24-hour efficacy with a once-daily dosing confers the noteworthy advantages of compliance improvement and BP variation lessening. Lower dosages of the individual treatments of the combination therapy can be administered for the same antihypertensive efficiency as that attained with high dosages of monotherapy. Angiotensin-converting enzyme inhibitors and calcium-channel blockers as a combination have theoretically compelling advantages for vessel homeostasis. Trandolapril/verapamil sustained release combination has showed beneficial effects on cardiac and renal systems as well as its antihypertensive efficacy, with no metabolic disturbances. This combination can be considered as an effective therapy for the diabetic hypertensive population.

**Keywords:** hypertension, trandolapril, verapamil, diabetes, renin-angiotensin system, combination therapy

## Introduction

Prevalence of hypertension in the diabetic population is 1.5–3 times higher than in the non-diabetic population after adjusting for age and weight (HDS 1993). Extensive evidence indicates that in diabetic individuals, arterial hypertension greatly contributes to an increase in the risk of atherosclerosis (Sowers et al 1994; Adler et al 2000). People with type 2 diabetes have a greater incidence of cardiovascular (CV) disease, cerebrovascular disease, and renal disease than the general population (Kannel and McGee 1979; Knuiman et al 1986; Klein 1995). Epidemiological studies suggest that relative hyperglycemia accounts for part but not all of the increased CV risk. Raised BP is a major risk factor for myocardial infarction and stroke in people with and without diabetes (Hanefeld et al 1996; Lehto et al 1997). A difference of 5 mm Hg in either systolic blood pressure (SBP) or diastolic blood pressure (DBP) accounts for an increase in cardiovascular events or death of 20%–30% in diabetic patients (McMahon et al 1990). A strict BP control is critical in diabetic people in order to prevent organ damage due to the rising cardiovascular risk that accompanies small BP elevations (Vasan et al 2001). It is accepted that BP values above 130/85 mm Hg, or even 130/80 mm Hg, deserve to be treated based on the existing epidemiological data showing reduced cardiovascular risk at SBP less than 130 mm Hg

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(Bakris et al 2000; JNC 2003). Nevertheless, it has been suggested that physicians accept an elevated SBP in their patients that could facilitate a passive attitude in type 2 diabetic patients (Oliveira et al 2002). Antihypertensive therapy has been shown to be of great value in order to diminish the cardiovascular, renal, and ocular complications of diabetes (Schrier et al 2002; Zanchetti and Ruilope 2002). The metabolic alterations that are likely to be present in diabetic hypertensive patients can concomitantly accelerate or precipitate CV complications. Therefore, the metabolic effects and associated consequences of antihypertensive treatments on insulin resistance, glycemia, lipids, or potassium homeostasis must be considered in choosing a therapeutic regimen (Teuscher and Wiedmann 1997). The attention paid to identifying the optimal antihypertensive agent for type 2 diabetics may appear rather questionable in view of the need for multiple drugs in order to lower BP to the difficult goal of <130/80 mm Hg. The positive effects are enhanced by the presence of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) when the kidney is damaged (Ravid et al 1993). The issue is not that clear for cardiovascular complications where the benefit seems to depend on the drop in BP and not so much the type of therapy employed. Moreover, the need for a combination of different antihypertensive agents to achieve the BP goal has been shown in the great majority of participants with hypertension in clinical trials (Hilleman et al 1999; Ruilope et al 1999). According to current international guidelines, in most hypertensive patients, therapy must be initiated gradually, and target BP values achieved progressively through several weeks. To reach target BP, it is likely that a large proportion of patients will require combination therapy with more than one agent (ESH-ESC 2003). Combining two drugs may reduce BP by several mechanisms of action and obtain additive or strengthened effects. By using low doses of drugs, side-effects are minimized and patient compliance improves.

ACE inhibitors and calcium-channel blockers (CCB) have favorable hemodynamic profiles and both have beneficial cardiovascular effects with no significant adverse metabolic effects (Cifkova et al 2000; PROCOPA Study Group 2002). A combination of these treatments offers benefits over every drug on monotherapy and may potentially be better than other combined regimens.

## Target organ damage protection in hypertensive diabetics

Various randomized controlled trials comparing antihypertensive regimens that included both patients with and

without type 2 diabetes helped explain the influence on cardiovascular risk of having type 2 diabetes in association with hypertension. Among placebo-treated patients in two trials on elderly patients with isolated systolic hypertension (the Systolic Hypertension in the Elderly Program [SHEP] and the Systolic Hypertension in Europe trial [SystEur]), the incidence of major cardiovascular events, and the relative risks for coronary events, stroke, and all deaths was higher in the presence than in the absence of diabetes (Curb et al 1996; Tuomilehto et al 1999). With regard to diastolic BP, the Hypertension Optimal Treatment (HOT) study showed a 51% reduction in cardiovascular events in diabetic participants randomized to a target DBP of 80 mm Hg when compared with a group randomized to a target of 90 mm Hg (Hansson et al 1998). In the Heart Outcomes Prevention Evaluation study (HOPE) incidence of major cardiovascular events was 1.2 times higher in diabetic than in non-diabetic subjects, although only 46.8% of subjects also had hypertension (HOPE 2000b). However, in this study, when diabetes was linked to another powerful predictor of cardiovascular events, such as impaired renal function, incidence of cardiovascular events among placebo-controlled patients was almost twice as high that in non-diabetic subjects with a comparable reduction in renal function (Ruilope et al 2001). Nevertheless, the high cardiovascular risk demonstrated in type 2 diabetics is not just as a result of the high prevalence of hypertension among these patients. For instance, in the Appropriate Blood Pressure Control in Diabetes study (ABCD-NT), which enrolled diabetic patients with blood pressure <140/90 mm Hg, subjects in the placebo arm with an average blood pressure of 137/81 mm Hg had an incidence of major cardiovascular events of approximately 16% in 5 years (Schrier et al 2002).

Further evidence of the close association between type 2 diabetes and renal damage has been shown in a number of trials. Among the placebo-treated elderly hypertensives of the SystEur trial, incidence of proteinuria was much higher in diabetic than in non-diabetic subjects (58.0 vs 15.1 cases per 1000 patient years). In the HOT study, incidence of renal dysfunction (defined as an increase of baseline creatinine  $\geq 30\%$  with final values  $>176 \mu\text{mol/L}$  or  $2.0 \text{ mg/dL}$ ) was rare, but was 45% more frequent in diabetic than in non-diabetic patients. Also, in the MICRO-HOPE substudy (HOPE 2000a), incidence of clinical proteinuria among diabetic patients receiving placebo was high (8.4% during 4.5 years) and, in further studies (Brenner et al 2001; Lewis et al 2001) on type 2 diabetic subjects with hypertension and

nephropathy (the Irbesartan Diabetic Nephropathy Trial, IDNT, and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, RENAAL), patients randomized to normal treatment plus placebo had a very high incidence of doubling of baseline serum creatinine, end stage renal disease, and death (cumulative endpoint incidence of 39% during 3 years in the IDNT and 47% during 3.4 years in the RENAAL). In the diabetic hypertensives of the Irbesartan Microalbuminuria study (IRMA-2) with milder initial nephropathy (microalbuminuria only), 15% of the placebo-treated patients developed proteinuria in 2 years (Parving et al 2001).

The positive effects are enhanced by the presence of an ACE inhibitor or an angiotensin receptor blocker when the kidney is damaged. This benefit has been tested for preventing the development of microalbuminuria in hypertensive diabetics. The multicenter, double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether ACE inhibitors and non-dihydropyridine CCBs, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes, and normal urinary albumin excretion (Ruggenenti et al 2004). The primary endpoint was the development of persistent microalbuminuria (overnight albumin excretion,  $\geq 20$   $\mu\text{g}$  per minute at 2 consecutive visits). More than 1200 subjects were randomized to receive at least 3 years of treatment with trandolapril (2 mg/day) plus verapamil sustained-release (TV SR) formulation (180 mg/day), trandolapril alone (2 mg/day), verapamil alone (sustained-release formulation, 240 mg/day), or placebo. The main results showed that TV and trandolapril alone significantly decreased the incidence of microalbuminuria to a similar extent.

## Metabolic control and antihypertensive treatment

The widely described association between hypertension and diabetes is promoted by interplay of hereditary and acquired disturbances. Up to 50% of diabetic patients become hypertensive, whereas patients with essential hypertension are prone to develop type 2 diabetes. Treatment-associated metabolic alterations are crucial in hypertensive diabetic patients. Consequently, the optimal drug for hypertensive diabetic patients should not only lower blood pressure, but also concomitantly improve, or at least not worsen, associated risk factors (Jarrett et al 1994). The need for a combination of different antihypertensive agents to achieve the BP goal has been shown

in the great majority of hypertensives. An emerging body of evidence in mixed populations suggests that fixed-dose combination therapy is more effective than commonly used monotherapies in achieving target BP goals. Among them the combination of an ACE inhibitor and a CCB has widely proven in clinical practice in diabetic patients (Schneider et al 1996). Fixed combinations have to be considered within the new strategies developed to increase the percentage of diabetic patients achieving an adequate BP control. The ultimate goal of treatment is to prevent diabetes and hypertension without detrimental metabolic side-effects.

In a subgroup of patients, lifestyle modifications might prevent or delay the onset of hypertension and diabetes. In contrast to some proven prognostic benefit of thiazide-type diuretics and/or  $\beta$ -blockers in non-diabetic patients with uncomplicated essential hypertension, the influence of these agents on the prognosis of diabetic patients may be deleterious. The TRAVEND study was designed to compare, at equal BP reduction, the effect of TV SR 2/180 mg and enalapril/hydrochlorothiazide (EH) 20/12.5 mg during a 6-month period on metabolic control and albuminuria in type 2 diabetic hypertensive patients with albuminuria (Fernandez et al 2001). Overall BP was significantly reduced and albuminuria significantly decreased, both without significant differences between treatments. Glycated hemoglobin was not modified on TV, but increased on EH. At the end of the study, a blood glucose  $< 126$  mg/dL was attained in 72.7% of the TV group (improving in 29.5% and worsening in 6.8% of patients [ $p = 0.021$ ]) and in 50% of the EH group, 13.6% of patients improved and 11.4% worsened ( $p = 1.000$ ). Similarly, in a 3-month randomized, controlled trial, there were no significant changes from baseline in plasma glycated hemoglobin, fasting plasma glucose, insulin levels, or the insulin sensitivity index in recipients of TV (mean dosage 1.6/180 mg/day). However, inpatients treated with atenolol/chlortalidone (mean dosage 71/18 mg/day), there was a reduction in the insulin sensitivity index compared with baseline. Lipid indices did not change during TV treatment. In contrast, serum total triglyceride levels increased and HDL cholesterol decreased in atenolol/chlortalidone recipients. ACE inhibitors (or ARB) and/or certain calcium antagonists have emerged as the preferred antihypertensive agents in diabetic patients. Although the comparative influence of different calcium antagonists on important factors other than blood pressure is insufficiently delineated, verapamil or diltiazem seem to be preferable to dihydropyridines, because the latter may be less effective in reducing proteinuria. Furthermore,

certain CCB/ACE inhibitor combinations, such as TV, that provide supplementary antihypertensive efficacy, metabolic neutrality, and probably also synergistic nephroprotection, may become an attractive therapeutic approach to the diabetic population with hypertension and/or renal or other target-organ disease (Bakris et al 1998). The main effects of both drugs are summarized in Table 1.

## Cardiovascular effects of TV

Hypertension and diabetes play central roles in the pathogenesis of coronary heart disease, congestive heart failure, stroke, and renal failure. The main goal of the treatment should be to reduce morbidity and mortality, and decrease collateral effects. Aggressive reductions in BP are recommended in hypertensive diabetic patients and achievement of <30/80 mm Hg is required to diminish global CV risk. The results of recent randomized trials on diabetic patients with major cardiovascular events, cardiovascular death, and total mortality as primary endpoints, in which more or less intensive BP lowering was tested or an active regimen was compared with placebo, assert that more intensive BP lowering is beneficial in reducing the aggregate of major cardiovascular events in type 2 diabetic patients. The PRADID study (Ruilope et al 2004) was a multicentric, double-blind, placebo-controlled study with a 16-week follow-up including 438 previously untreated type 2 diabetics; the primary endpoint was to attain the recommended guideline goals of a systolic and diastolic BP. Patients were randomized to receive a TV fixed dose of 180/2 mg, versus trandolapril 2 mg, versus placebo. Both active groups were more effective than placebo in decreasing SBP and DBP. At the end of the study, 36.5% in the trandolapril group, 37.8% in the TV group, and 14.9% placebo ( $p = 0.009$ ) had attained the primary endpoint. Control rate on the DBP was significantly

higher in the TV (88.8%), when compared with trandolapril (79.1%) or placebo (63.5%) ( $P = 0.002$ ). Therefore, these results support the concept that antihypertensive treatment is more effective than placebo for BP control in previously untreated type 2 diabetic patients, and a TV fixed-dose combination could be more effective than trandolapril alone for preventing increases in DPB. The Combination of an ACE inhibitor and a CCB should be safely used in clinical practice for diabetic patients. The combination of an ACE inhibitor such as trandolapril, and a CCB such as verapamil, is very attractive due to their common ability to reduce peripheral vasoconstriction without distressing cardiac output, and to facilitate salt and water excretion by different mechanisms (Muijsers et al 2002). The use of two long-acting drugs provides control over a 24-hour period. This quality can contribute to a increased therapy adherence, minimization of BP variation, and, therefore, a higher protection against the risk of major CV events and the development of target organ damage. TV combination can be particularly beneficial in hypertensive diabetic patients with cardiac or renal disease. Data from a number of studies point to significant reductions in albuminuria in patients receiving TV and, interestingly, Bakris et al (2004) reported that the reduction appears to be independent of the BP-lowering effect. As mentioned above, the BENEDICT study has reported a beneficial primary prevention of renal disease as microalbuminuria, in hypertensive diabetics (Ruggenti et al 2004).

Moreover, this combination has demonstrated other CV benefits in a limited number of randomized trials by reducing left ventricular hypertrophy, total peripheral resistance, and pulse wave velocity. The INternational VERapamil SR-Trandolapril study (INVEST) was designed to compare morbidity and mortality in hypertensives with coronary artery disease treated with a CCB or a non-CCB (atenolol-based)

**Table 1** Summary of the clinical properties of trandolapril and verapamil in hypertensives

Trandolapril	Verapamil
Neutral effect on heart rate	Moderating effect on heart rate
Reduces the breakdown of bradykinin	Inhibits sympathetic nervous cell activation
Reduces blood pressure by inhibiting the renin-angiotensin system. Induces decreased vasopressor activity, aldosterone secretion.	Reduces blood pressure by inhibiting the calcium flow across the vascular and cardiac smooth muscle cells.
Reduces left ventricle hypertrophy	Reduces left ventricle hypertrophy
Neutral effect on lipid metabolism and neutral or beneficial effect on insulin sensitivity	Neutral effect on glucose and lipid metabolism
Decreases water and sodium retention. Induces a modest increase in kaliemia	Neutral effect on water and ion control
Improves elastic properties of large arteries	

regimen (Pepine et al 2003). Diabetic patients comprised 6400 out of 22 576 (28.3%) at entry. During a mean follow-up of 2.7 years, 913 diabetic patients suffered a primary outcome event (a composite of first occurrence of all-cause death, non-fatal myocardial infarction, or non-fatal stroke), with no significant difference between treatment strategies. Risk for the primary outcome increased with presence of baseline heart failure, renal impairment, age, previous stroke/transient ischemic attack, previous myocardial infarction, peripheral vascular disease, or smoking. High SBP and DBP during follow-up also were associated with increased risk, as were low DBP. Antihypertensive treatment with a verapamil SR or atenolol strategy resulted in similar rates of cardiovascular outcomes in coronary artery disease (CAD) patients with diabetes. Therefore, a verapamil SR-based antihypertensive treatment strategy can be considered as an alternative to a  $\beta$ -blocker-based strategy in adults with CAD and diabetes (Muijsers et al 2002).

In conclusion, TV SR combination is an effective treatment for hypertensive diabetics.

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