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Trandolapril/Verapamil Sustained Release

A Review of its Use in the Treatment of Essential Hypertension

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Data Selection

Sources: Medical literature published in any language since 1980 on trandolapril/verapamil, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company that markets the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'trandolapril/verapamil' or 'trandolapril plus verapamil'. Searches were last updated 7 June 2005.

Selection: Studies in patients with hypertension who received trandolapril/verapamil sustained release. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Trandolapril, verapamil, verapamil SR, trandolapril/verapamil SR, coronary artery disease, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Trandolapril/verapamil sustained release (SR) [Tarka®] is an oral, fixed-dose combination of the ACE inhibitor trandolapril and the SR formulation of the phenylalkylamine calcium channel antagonist verapamil. It is indicated for the treatment of hypertension in patients who require more than one agent to achieve blood pressure (BP) targets. In the large, randomised, multicentre INVEST (INternational VErapamil SR/trandolapril STudy), a verapamil SR-based treatment strategy that included trandolapril in most patients was as effective as an atenolol-based treatment strategy in reducing the risk of the primary outcome (first occurrence of death [all-cause], nonfatal myocardial infarction [MI] or nonfatal stroke) in patients with hypertension and coronary artery disease (CAD) and was as well tolerated. Trandolapril/verapamil SR is generally more effective at controlling hypertension than either component as monotherapy, and is as effective as a number of other fixed-dose combination therapies. The combination is as well tolerated as trandolapril monotherapy and is at least as well tolerated as verapamil SR monotherapy. In hypertensive patients with type 2 diabetes mellitus in the BENEDICT (BErgamo NEphrologic DIabetes Complications Trial), trandolapril/verapamil SR prolonged the time to the onset of persistent microalbuminuria compared with placebo, as did trandolapril monotherapy. Thus, trandolapril/verapamil SR is an effective option for the treatment of essential hypertension in patients requiring more than one agent to achieve BP targets, including those with compelling indications, such as CAD or type 2 diabetes.

Pharmacological Properties

Trandolapril, a prodrug of the active metabolite trandolaprilat, reduces vasopressor activity and aldosterone release and provides negative feedback for renin secretion by inhibiting the conversion of angiotensin I to angiotensin II. The phenylalkylamine calcium channel antagonist verapamil causes dilation of peripheral and coronary vasculature, and thus a decrease in BP, by inhibiting the influx of calcium ions through the L-type calcium channels. Trandolapril/verapamil SR improves left ventricular (LV) wall structure and function in patients with hypertension and preserves LV function in patients with heart failure. Cardiac events are less common with trandolapril/verapamil SR than trandolapril monotherapy in patients with heart failure following an acute MI.

Peak plasma concentrations (C_{max}) of trandolapril and trandolaprilat are achieved 0.5–1.5 and 3–12 hours after a single oral dose of trandolapril 2mg in healthy volunteers. The C_{max} of trandolapril at steady state is double that after a single dose. Trandolapril is converted to trandolaprilat by hepatic metabolism. The absolute bioavailability of the parent drug is ≈10% and that of the active metabolite is 70%; both are highly protein-bound. The respective terminal elimi-

nation half-lives ($t_{1/2}\beta$) of trandolapril and trandolaprilat are 6 and 10 hours, with the majority of a dose excreted in the faeces. Verapamil SR C_{max} is achieved in ≈5 hours. Due to extensive first-pass metabolism in the liver, verapamil SR has an oral bioavailability of 10–35%. Verapamil is highly bound to plasma proteins. The primary metabolite of verapamil is the active desmethyl species, norverapamil. The SR formulation has a $t_{1/2}\beta$ of 8 hours after repeated administration, with the majority of a dose excreted in urine as metabolites.

There are no clinically relevant pharmacokinetic interactions between verapamil SR and trandolapril when the two agents are coadministered.

Therapeutic Efficacy

A verapamil SR-based treatment strategy in which most patients also received trandolapril was as effective as an atenolol-based treatment strategy at preventing the primary outcome (first occurrence of death [all-cause], nonfatal MI or nonfatal stroke) [9.9% vs 10.2%; mean follow-up 2.7 years] in patients with hypertension and CAD in the large (n = 22 576), randomised, multicentre INVEST. Similar proportions of patients receiving either treatment strategy achieved US Joint National Committee (JNC) VI BP targets (current consensus guidelines when INVEST was conducted) or BP control <140/90mm Hg.

In randomised, double-blind, multicentre studies (n > 100), trandolapril/verapamil SR 1mg/180mg, 2mg/180mg, 2mg/240mg or 4mg/240mg per day was more effective than placebo, and generally more effective than the corresponding dosages of trandolapril or verapamil SR monotherapy, at reducing mean sitting BP from baseline in adult patients with hypertension. The 1mg/180mg or 2mg/180mg dosages of trandolapril/verapamil SR were more effective at reducing mean 24-hour ambulatory systolic BP or diastolic BP than corresponding dosages of monotherapy. Trandolapril/verapamil SR was generally as effective at reducing BP as other fixed-dose combination therapies (metoprolol/hydrochlorothiazide, atenolol/chlortalidone, lisinopril/hydrochlorothiazide, enalapril/hydrochlorothiazide). Trandolapril/verapamil SR was effective at reducing mean sitting BP from baseline in patients unresponsive to either agent administered as monotherapy, and in special patient populations, such as Black or elderly patients or those with type 2 diabetes.

Compared with placebo, trandolapril/verapamil SR prolonged the time to onset of persistent microalbuminuria in patients with hypertension and type 2 diabetes in the large, double-blind, multicentre BENEDICT, as did trandolapril monotherapy.

Tolerability

Trandolapril/verapamil SR was generally well tolerated in clinical trials in patients with hypertension and had a tolerability profile similar to that of the individual components or respective class of drug. The incidence of adverse events (9–46%) and withdrawal rates due to adverse events (2.0–11.7%) in patients receiving trandolapril/verapamil SR was generally similar to that of comparator treatment arms. In INVEST, the verapamil SR-based and atenolol-based treatment strategies were equally well tolerated.

The most common adverse events occurring more frequently with trandolapril/verapamil SR than placebo were cough, first-degree atrioventricular block and constipation. Gastrointestinal tract adverse events and/or constipation were more

likely with trandolapril/verapamil SR or verapamil SR than with trandolapril in two studies.

1. Introduction

Hypertension is the leading treatable cause of stroke and coronary artery disease (CAD).[1] A recent epidemiological study reported a prevalence of hypertension (blood pressure [BP] ≥140/90mm Hg or the use of antihypertensive therapy) in those aged 35–64 years of 28% in North America and 44% in Europe.[1] Reductions in high BP decrease mortality and morbidity caused by myocardial infarction (MI), heart failure, stroke and kidney disease.[1] The cause of essential hypertension is unclear, but includes factors such as diet, obesity, physical activity, alcohol intake, environmental toxins, psychological stress and genetic susceptibility.[1]

Consensus guidelines from the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP (JNC 7),[2] the European Society of Hypertension-European Society of Cardiology (ESH-ESC),[3] the World Health Organization/International Society of Hypertension (WHO/ISH),[4] and the British Hypertension Society (BHS)[5] suggest that treatment be initiated in patients with a BP of ≥140/90mm Hg; however, a lower treatment threshold (≥130/80mm Hg) is advocated in patients with diabetes mellitus, renal impairment or established cardiovascular disease, because of the increased risk of cardiovascular events in these populations. For example, hypertensive patients with diabetes have approximately double the risk of cardiovascular disease as nondiabetic patients with hypertension and may develop other vascular complications, such as nephropathy and retinopathy.[6]

The consensus guidelines generally agree that most patients require at least two agents to achieve BP targets.[2,3,5] Indeed, the JNC 7 suggests the initial use of two-drug combination therapy, either as separate or fixed-dose combination formulations in patients with a BP ≥160/100mm Hg.[2] Greater efficacy is likely when two agents with different mechanisms of action are used to control BP; in addition, both drugs can be given at a lower dose than either drug as monotherapy, which is more likely to minimise adverse events.[7] The use of a fixed-dose combination of two agents in a single tablet or capsule improves compliance,[7] and is recommended by several groups, provided the combination replicates the intended treatment plan for the patient at no additional cost.[2,4,5]

Trandolapril/verapamil sustained release (SR) [Tarka®][1] is a fixed-dose combination of trandolapril, a prodrug of the active metabolite trandolaprilat, and an SR formulation of verapamil,[8] both of which are well established therapies in the management of hypertension. This article provides an overview of the use of trandolapril/verapamil SR in the treatment of essential hypertension, and includes data for the two agents administered as the fixed-dose combination or as separate formulations.

2. Pharmacodynamic Properties

The cardiovascular and metabolic properties of the ACE inhibitor trandolapril and the phenylalkylamine calcium channel antagonist verapamil are well established and are, therefore, described only briefly in this section. The active moiety of trandolapril, trandolaprilat, inhibits the conversion of angiotensin I to angiotensin II, which results in decreased vasopressor activity and aldosterone secretion, and provides negative feedback for renin secretion.[9] Verapamil inhibits the influx of calcium ions through the L-type calcium channels, which causes dilation of peripheral and coronary blood vessels and results in decreased BP.[9]

Trandolapril/verapamil SR generally does not affect heart rate in patients with mild-to-moderate essential hypertension.[10-12] The combination treatment has a positive effect on aortic elastic proper-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ties[10,13,14] and reduces total peripheral resistance.[10] Importantly, trandolapril/verapamil SR improves left ventricular (LV) wall structure and function in patients with hypertension,[13,15,16] and preserves LV function in patients with heart failure.[17] Moreover, trandolapril/verapamil SR significantly reduces the incidence of cardiac events (death, reinfarction, unstable angina or readmission due to worsening congestive heart failure [CHF]) compared with trandolapril monotherapy in patients with CHF after an acute MI.[18]

Trandolapril/verapamil SR does not adversely affect lipid or glucose metabolism in patients with mild-to-moderate hypertension,[14,19-21] including in those with type 2 diabetes.[20,21]

2.1 Pharmacodynamic Interactions

Several important pharmacodynamic interactions between calcium channel antagonists and/or ACE inhibitors and a number of other drugs have been identified.[8,22,23] As a consequence, concomitant administration of trandolapril/verapamil SR with some drugs is not recommended (e.g. potassium-sparing diuretics, potassium supplements and dantrolene), and close monitoring or dosage adjustments may be required with others (see the manufacturer's prescribing information[8,22,23] for more details).

3. Pharmacokinetic Properties

Few data are available on the pharmacokinetics of trandolapril/verapamil SR in patients with hypertension. Most are from the manufacturer's prescribing information,[8,22] although several small, noncomparative trials are also available.[24-26] The pharmacokinetic properties of trandolapril/verapamil SR,[9] trandolapril and its active metabolite trandolaprilat,[27,28] and verapamil[29,30] have been reviewed previously in *Drugs*; as such, they are only briefly described below. A summary of the pharmacokinetics of trandolapril, trandolaprilat and verapamil SR (based on data from two of the noncomparative trials[24,25] and the manufacturer's prescribing information for the combination therapy[8,22] and individual components[31,32]) is presented in table I.

3.1 Trandolapril

Peak plasma concentrations (C_{max}) of trandolapril and trandolaprilat were reached in a time (t_{max}) of 0.5–1.5 and 3–12 hours following a single oral 2mg dose in healthy volunteers.[24,25] Although 40–60% of an oral dose is absorbed, the absolute bioavailability of trandolapril is approximately 10% and is not affected by food.[22] The absolute bioavailability of trandolaprilat is 70%.[32] Both trandolapril

Table I. Pharmacokinetic parameters of trandolapril, trandolaprilat and verapamil sustained release (SR)[8,22,24,25,31,32]

Parameter	Trandolapril	Trandolaprilat	Verapamil SR
C_{max}[a] (μg/L)	1.7–1.9	2.0–2.8	164
t_{max}[a] (h)	0.5	6	4–5
AUC_{24}[a] (ng • h/mL)			1478
F (%)	≈10	70	10–35
Plasma protein binding (%)	80	65–94[b]	≈90
Effect of grapefruit juice			↑ Plasma concentration
Major metabolic pathway	Hepatic cleavage of the ester group		Cytochrome P450
$t_{½β}$	6	10	8[c]
Urinary excretion (% of a dose)	34		70 (as metabolites), 3 (unchanged drug)
Faecal excretion (% of a dose)	66		≈16 (metabolites)

a Mean values after a single oral dose of trandolapril 2mg[24,25] or verapamil SR 240mg[31] in healthy, fasted[25,31] volunteers.

b Concentration-dependent protein binding that is saturable at higher dosages.

c After repeated administration.[22]

AUC_{24} = area under the plasma concentration-time curve from time 0 to 24h after administration; **C_{max}** = peak plasma concentration; **F** = mean absolute bioavailability; **$t_{½β}$** = terminal elimination half-life; **t_{max}** = time to C_{max}; ↑ indicates increase.

and trandolaprilat are highly bound to plasma protein.[32]

The biotransformation of trandolapril to trandolaprilat primarily occurs in the liver,[32] and metabolism is rapid (plasma half-life of <1 hour).[22] The terminal elimination phase of trandolaprilat at steady state (effective half-life of 16–24 hours)[22] is prolonged and elimination occurs in a triphasic manner, probably because of binding/dissociation kinetics of the trandolaprilat/angiotensin-converting enzyme complex in plasma and tissue.[32] The drug is excreted in both faeces (predominant route) and urine, mainly as metabolites.[32] Following the administration of a radioactive oral dose of trandolapril, approximately 82% of the radioactivity is excreted after 48 hours and elimination is almost complete (99.2%) after 7 days.[27]

3.2 Verapamil Sustained Release (SR)

As is the case with immediate-release formulations of verapamil, approximately 90% of the administered oral dose of verapamil SR is absorbed, albeit at a delayed rate.[8] In fasted, healthy volunteers who received a single oral dose of verapamil SR 240mg, C_{max} was achieved in a t_{max} of approximately 5 hours.[31] Verapamil undergoes extensive first-pass metabolism in the liver and, therefore, has a low oral bioavailability.[31] It is highly bound to plasma protein.[31]

In vitro, verapamil is metabolised by the cytochrome P450 (CYP) isoenzymes CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18.[31] The primary metabolite of verapamil is the active desmethyl species, norverapamil;[31] 11 other metabolites have been identified in very small quantities.[31] The $t_{1/2}\beta$ of verapamil SR is 8 hours after repeated administration.[22] Most of a dose of verapamil is excreted as metabolites within 5 days of administration, predominantly in urine.[31]

3.3 Trandolapril/Verapamil SR

The pharmacokinetics of trandolapril and trandolaprilat are unaffected when administered concomitantly with verapamil SR.[8,22] However, concomitant administration of trandolapril increases verapamil and norverapamil C_{max} (by 54% and 30%) and area under the plasma concentration-time curve (AUC) [by 65% and 32%; single oral dose of trandolapril/verapamil SR 4mg/240mg]; t_{max} is unaffected.[8]

Steady-state plasma concentrations of trandolaprilat and verapamil after approximately 1 week of once-daily administration of trandolapril/verapamil SR are up to twice those after a single dose of the fixed-dose combination formulation.[8]

Administration of trandolapril/verapamil SR with food decreases the bioavailability of verapamil, but does not affect the absorption of trandolapril.[8] C_{max} and AUC values of verapamil are decreased by 37% and 28% and t_{max} of both verapamil and norverapamil are increased by ≈7 hours following the administration of trandolapril/verapamil SR 4mg/240mg with a high-fat meal.[8] The US manufacturer's prescribing information[8] recommends that trandolapril/verapamil SR be administered with food (see section 6).

3.4 Special Populations

3.4.1 In the Elderly

After the administration of trandolapril/verapamil SR, the bioavailability of trandolapril, verapamil and norverapamil is increased by 35%, 87% and 77%, respectively, in older (aged ≥65 years) compared with younger patients.[8] Nevertheless, no dosage adjustment is required in the elderly.

3.4.2 In Patients with Renal or Hepatic Impairment

The clearance of trandolapril and trandolaprilat decreases with worsening renal function;[8,32] in patients with severe renal impairment (creatinine clearance [CL_{CR}] ≤1.8 L/h [≤30 mL/min]) and in those on renal dialysis, trandolapril and trandolaprilat C_{max} values are approximately double those in patients with normal renal function and renal clearance is reduced by approximately 85%. The pharmacokinetics of verapamil are not affected by the presence of renal impairment.[22,26]

In patients with severe hepatic impairment, verapamil clearance is reduced by approximately 30% and $t_{1/2}\beta$ is prolonged by 14–16 hours.[8] In those with

moderate-to-severe hepatic impairment, plasma concentrations of trandolapril and trandolaprilat are increased 9- and 2-fold; however, this is not considered clinically important.[8,22]

Trandolapril/verapamil SR has not been evaluated in patients with impaired renal or hepatic dysfunction; nevertheless, based on assessments of the individual components, the combination should be used with caution in patients with moderately impaired renal function[8,22] and, in Europe, it is contraindicated in patients with severe renal impairment (CL_{CR} <0.6 L/h [<10 mL/min]) or receiving haemodialysis.[22] In the US, caution is required when trandolapril/verapamil SR is used in patients with hepatic impairment,[8] whereas in Europe, it is not recommended in patients with severe hepatic impairment and is contraindicated in those with cirrhosis and ascites.[22]

3.5 Pharmacokinetic Interactions

Clinically important pharmacokinetic interactions between trandolapril or verapamil SR and a number of other agents are shown in table II.[8,22,31,32] As a consequence of these interactions, close monitoring or dosage adjustments may be required (see the manufacturer's prescribing information[8,22,31,32] for more details). Trandolapril and trandolaprilat have no clinically significant interactions with furosemide, nifedipine or warfarin.[32]

Table II. Clinically relevant pharmacokinetic interactions between oral trandolapril or verapamil sustained release (SR) and various other agents when administered concomitantly[8,22,31,32]

Concomitant agent	Nature of interaction
Effect of trandolapril or verapamil SR on concomitant agent	
Carbamazepine	Verapamil ↑ plasma concentrations
Ciclosporin (cyclosporine)	Verapamil ↑ serum concentrations
Digoxin	Verapamil ↑ serum concentrations, potential for toxicity
Ethanol	Verapamil ↓ elimination
Metoprolol or propranolol	Verapamil ↓ clearance
Quinidine	Verapamil ↑ concentrations
Theophylline	Verapamil ↓ clearance, ↑ plasma concentrations
Lithium	ACE inhibitors (e.g. trandolapril) ↑ serum concentrations, potential for toxicity
Effect of concomitant agent on trandolapril or verapamil SR	
Cimetidine	Possible ↓ verapamil clearance
Erythromycin, ritonavir (CYP 3A4 inhibitors)	↑ Plasma verapamil concentrations (oral administration)
Grapefruit juice	↑ Plasma verapamil concentrations
Phenobarbital	↑ Verapamil clearance
Rifampicin (rifampin) [CYP3A4 inducer]	↓ Verapamil bioavailability (oral administration)
Antacids	↓ Bioavailability of ACE inhibitors, including trandolapril

CYP = cytochrome P450; ↑ indicates increase; ↓ indicates decrease.

4. Therapeutic Efficacy

The effect of a calcium channel antagonist (verapamil SR)-based treatment strategy on mortality and morbidity in patients with essential hypertension and CAD has been compared with that of a non-calcium channel antagonist (atenolol)-based strategy in INVEST (INternational VErapamil SR/trandolapril STudy) [section 4.1]; in this study, most patients receiving the verapamil SR-based strategy also received trandolapril.[33,34] The antihypertensive effects of trandolapril/verapamil SR have been compared with placebo and trandolapril or verapamil SR monotherapy,[12,35-44] or combination antihypertensive therapies,[10,11,14,20,21] and have been evaluated in Black patients[45,46] and the elderly (section 4.2.1).[47] The effect of trandolapril/verapamil SR on renal function in patients with type 2 diabetes was the focus of several studies,[48-50] including the BENEDICT (BErgamo NEphrologic DIabetes Complications Trial)[50] [section 4.2.2].

This review focuses mostly on large (n > 100), randomised, double-blind[11,12,20,35-44] or open-label blinded-endpoint,[34] multicentre studies, although a small double-blind,[21]and several nonblind[10,14,45,48] or noncomparative[46,47,49] trials are also included. Several subgroup analyses of INVEST,[51-56] two of which are fully published,[51,56] are discussed in section 4.1. INVEST was a 5.4-year study (mean follow-up 2.7 years; the study was stopped 2 years after the last patient was enrolled);[34] other studies[10-12,14,20,21,35-49] were of 6–24 weeks' duration. Trandolapril/verapamil SR 1mg/240mg, 2mg/180mg, 2mg/240mg and 4mg/240mg was adminis-

tered once daily orally. Data on combinations not commercially available are reported occasionally.

Apart from in INVEST (see section 4.1 for additional study design details),[33,34] eligible patients aged 24–90 years (mean age 48–61 years), most of whom had received antihypertensive therapy prior to study entry, underwent a 2- or 4-week placebo run-in period (prior to randomisation in comparative studies), after which they generally had mild-to-moderate hypertension (sitting diastolic BP [DBP] 90–115mm Hg); patients with severe (supine DBP 115–135mm Hg) hypertension were included in one study.[45] Where stated, patients were excluded from some studies evaluating the antihypertensive effects of trandolapril/verapamil SR if they had evidence of CAD or cerebrovascular disease,[12,21,37-41,45,47-49] prior therapy with an ACE inhibitor (including trandolapril),[10,38,48] or required concomitant therapy, including other antihypertensives or agents with antihypertensive properties.[10-12,21,35,36,38,41,45,47,49] In INVEST,[33,34] patients were only eligible if they had documented evidence of CAD.

The primary endpoint in INVEST was the first occurrence of death (all-cause), nonfatal MI or nonfatal stroke (hereafter referred to as the primary outcome) by intent-to-treat analysis.[33,34] Secondary efficacy endpoints included the incidences of these three components individually, the time to the most serious event (death was most and MI least serious), and the incidences of cardiovascular death, cardiovascular-related hospitalisation, BP control, angina and new diagnosis of diabetes (added in the early stages of patient recruitment). These endpoints were assessed at each visit and are reported for the entire duration of the study. Several tolerability outcomes were also measured as secondary endpoints,[34] and these are discussed in section 5.

In most studies where the antihypertensive effect of trandolapril/verapamil SR was measured, the primary endpoint was the mean reduction from baseline in trough (24 hours after administration) sitting DBP values;[11,12,37-41,44,47] two trials[35,36,45] assessed reductions in trough supine DBP and one[46] assessed ambulatory BP. A number of trials did not clearly specify the primary endpoint[10,21] and/or whether BP was assessed as sitting, supine or standing.[14,42,43,49] Other endpoints differed between studies, and included reductions in trough sitting or supine systolic BP (SBP), standing DBP and SBP, trough supine DBP and 24-hour ambulatory BP. In several studies, patients were classified as responders (sitting DBP ≤95mm Hg,[37] or <90mm Hg or reduction of ≥10mm Hg,[10,11,35,36,38,41] or SBP <130mm Hg and DBP <85mm Hg[44]) or nonresponders (co-primary endpoint in two studies[11,35,36]). Response according to JNC VI guidelines (target BP <140/90mm Hg or <130/85mm Hg in patients with diabetes or renal impairment) was reported in INVEST.[33,34] Where stated,[20,48,50] mean reduction from baseline in albuminuria or proteinuria was the primary endpoint of trials examining the effect of trandolapril/verapamil SR on renal function.

4.1 International Verapamil SR/Trandolapril Study

INVEST was designed to assess whether the risk of the occurrence of the primary outcome with a verapamil SR-based treatment strategy was equivalent to that with an atenolol-based strategy.[33,34] The trial included patients aged ≥50 years (mean age 66 years) with essential hypertension requiring drug treatment and documented CAD for ≥3 months prior to enrolment.[33,34] Approximately 50% of the patients included in the study were Caucasian (n = 10 925), 36% were Hispanic (n = 8045) and 13% were Black (n = 3029).[57] Most patients (83% of Caucasian, 91% of Hispanic and 89% of Black participants) were taking antihypertensive therapy at baseline, however few had controlled SBP (20–23%), DBP (44–56%) or overall BP (17–20%) levels, according to JNC VI guidelines (the current BP treatment guidelines when INVEST was conducted).[57]

Patients were excluded if they had certain conduction abnormalities, severe (New York Heart Association [NYHA] class IV) heart failure or unstable angina, angioplasty, coronary artery bypass grafting or stroke in the month prior to study entry. Those who had received β-blockers (β-adrenoceptor antag-

onists) within the previous 2 weeks or for an MI that had occurred in the previous 12 months were excluded to avoid withdrawal effects in individuals randomised to the verapamil-based strategy.[33,34] Baseline characteristics of patients in either treatment group were similar, including the number of patients taking antihypertensive therapy (both ≈86%), and those with NYHA class I–III heart failure (both 6%), diabetes (both ≈28%) or renal impairment (both 2%).[34]

Patients received treatment according to a stepwise strategy that was designed to achieve JNC VI BP targets.[33,34] As a first step in treatment, patients were randomised to receive either verapamil SR 240 mg/day (n = 11 267) or atenolol 50 mg/day (n = 11 309). Those with diabetes, renal impairment or heart failure in either treatment strategy also received trandolapril 2 mg/day (starting dose was reduced to 0.5 mg/day in patients with serum creatinine levels >177 μmol/L). If BP targets were not achieved, trandolapril 2 mg/day was added to the verapamil SR strategy and hydrochlorothiazide was added to the atenolol strategy (step two). If this was not effective, drug dosages in either strategy were increased (step three); in step four, the patients in the verapamil-based strategy group could also receive hydrochlorothiazide 25 mg/day and those in the atenolol-based strategy group could receive trandolapril 2 mg/day.[33,34] Additional nonstudy antihypertensive drugs were permitted in those patients who did not achieve BP control at the fourth stage; patients were deemed to have crossed over to the other treatment strategy if they were in the verapamil-based strategy and received a β-blocker or were in the atenolol-based strategy and received a calcium channel antagonist.[33,34]

During the study, titration ranges for the study drugs were verapamil SR 120–480 mg/day, atenolol 25–200 mg/day, trandolapril 0.5–8 mg/day and hydrochlorothiazide 12.5–100 mg/day. In the calcium channel antagonist strategy, patients could receive fixed-dose formulations of trandolapril/verapamil SR 2mg/180mg, 1mg/240mg or 4mg/240mg at a frequency determined by the step of the strategy.[34] Investigators recognised that patients would generally require more than one drug to achieve satisfactory BP levels and most would receive either verapamil SR plus trandolapril or atenolol plus hydrochlorothiazide.[34] At the 24-month assessment, 82% and 78% of patients were receiving verapamil SR or atenolol; the distribution of the number of study and nonstudy drugs was similar in both treatment strategies (table III) and a minority of patients (6% and 7%) had crossed over to the other treatment strategy. Approximately 50% of patients required at least three antihypertensive drugs (study or nonstudy) and 31% required two drugs, irrespective of treatment strategy. Only 2% of patients in either group required no medication.[34]

Clinical outcomes with a verapamil SR-based treatment strategy were equivalent to those with an atenolol-based treatment strategy in patients with hypertension and CAD.[34,52-54] Similar rates of the primary outcome (first occurrence of death [all-cause], nonfatal MI or nonfatal stroke) [9.9% vs 10.2%], and overall rates for each component of the primary outcome were seen with either treatment strategy (figure 1)[34] and no between-group difference in time to primary outcome was reported in Kaplan-Meier analysis.[34] Subgroup analyses[51-55] (including a prespecified analysis in the cohort of patients with diabetes at baseline [n = 6400],[51] and

Table III. Antihypertensive medication use in INVEST (INternational VErapamil SR/trandolapril STudy).[34] Percentages of patients with hypertension and coronary artery disease randomised to verapamil sustained release (SR)- or atenolol-based treatment strategies receiving study (n = 7842 and 7850) and nonstudy (n = 6793 and 6822) drugs at 24 months in this open-label, blinded-endpoint trial

Treatment	Patients (%)	
	verapamil SR-based therapy	atenolol-based therapy
Study drugs [mean dosage (mg/day)]		
Verapamil SR (288)	82	—
Atenolol (76)	—	78
Trandolapril (4)	63	52
Hydrochlorothiazide (29)	44	60
Nonstudy drugs		
Diuretic	19	21
ACE inhibitor	19	19
Calcium channel antagonist	17	7
β-Blocker	6	14

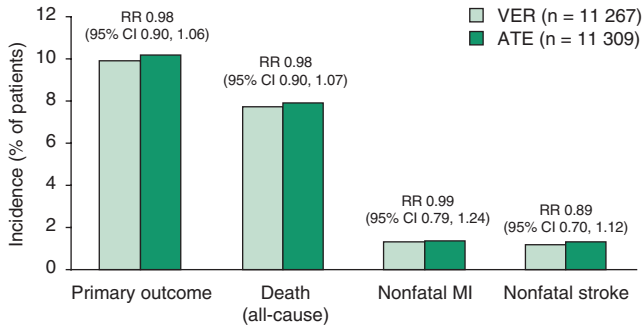

Fig. 1. Clinical efficacy of a calcium channel antagonist versus a non-calcium antagonist treatment strategy in patients with hypertension and coronary artery disease. Incidence of first occurrence of death (all-cause), nonfatal myocardial infarction (MI) or nonfatal stroke (primary outcome) and of the three components individually in INVEST (INternational VErapamil SR/trandolapril STudy).[34] This open-label, blinded-endpoint, multicentre trial randomised patients with hypertension and coronary artery disease to treatment strategies based on verapamil SR (VER) or atenolol (ATE); trandolapril was the most common study drug added in the verapamil-based treatment strategy. Mean duration of follow-up was 2.7 years. Relative risk (RR) stated for VER vs ATE.

analyses in patients with ischaemia at study entry [n = 10 617][52] and in Black patients [n = 4535][55]) showed that the risk of the primary outcome with either treatment strategy was similar (mostly available as abstracts and/or posters[52-55]). Patients with diabetes at baseline had an increased risk of the primary outcome occurring compared with nondiabetic patients (14.3% vs 8.4%; hazard ratio 1.77; 95% CI 1.63, 1.93).[51]

In general, there were no between-strategy differences in INVEST for other secondary outcomes. Patients receiving either the verapamil SR-based or atenolol-based treatment strategy experienced a similar incidence of cardiovascular-related death (3.83% vs 3.81%) or hospitalisation (6.44% vs 6.27%) and a similar time to the most serious event.[34] A clinically important decrease from baseline in the incidence and mean frequency of angina episodes was seen at month 24 with both treatment strategies.[34] Nevertheless, the mean frequency of angina episodes was lower with the verapamil SR-based treatment strategy than the atenolol-based treatment strategy at month 24 (0.77 vs 0.88 episodes/week; $p = 0.02$),[34] and the mean number of angina episodes per month reported in a subgroup of patients with ischaemia at baseline were 2.4 and 2.7 ($p = 0.05$).[52] Subgroup analysis also showed that quality of life was improved with either treatment strategy and showed some association with the extent to which angina symptoms were controlled.[52] The incidence of repeat coronary revascularisation did not differ between treatment strategies.[54]

At 24 months, in the whole treatment population, similar proportions of patients receiving verapamil SR- or atenolol-based treatment strategies in INVEST achieved JNC VI SBP (65.0% vs 64.0%) and DBP (88.5% vs 88.1%) treatment goals.[34] Likewise, BP <140/90mm Hg was achieved in similar proportions of patients receiving either strategy (71.7% vs 70.7%).[34] Subgroup analyses,[51-53] including analyses in patients with diabetes[51] or ischaemia[52] at baseline, showed that there were no differences between the two treatment strategies in achieving BP control. In all patients, those with greater mean follow-up SBP levels during the follow-up period had an increased risk of the primary outcome.[51] The risk of the primary outcome was higher in those who did not achieve BP control in the first 6 months of treatment (10.3% vs 6.9%; $p < 0.001$).[53]

The inclusion of trandolapril in a verapamil SR-based treatment strategy may influence the onset of type 2 diabetes in hypertensive patients with CAD.[34] In INVEST, a smaller proportion of patients without diabetes at trial entry who received the verapamil SR-based treatment strategy were diagnosed with diabetes during follow-up compared with those receiving the atenolol-based treatment strategy.[34]

The effect of a verapamil SR- or an atenolol-based treatment strategy on depressive symptoms (according to the Center for Epidemiologic Studies-Depression [CES-D] scale) was assessed after 1 year of therapy in a subgroup of 2317 patients in INVEST.[56] CES-D scores were improved from baseline in recipients of the verapamil-SR-based strategy (1.45 points; $p < 0.001$ vs baseline), whereas the change in atenolol-based treatment strategy recipients (0.27-point increase from baseline) was not significant. At baseline, none of the patients receiving either treatment strategy had CES-D scores consistent with clinical depression.

4.2 Other Studies

4.2.1 Effect on Blood Pressure

Comparisons with Placebo or Monotherapy

The commercially available fixed-dose combination dosages of trandolapril/verapamil SR are more

Table IV. Comparative efficacy of trandolapril/verapamil sustained release (TRA/VER) versus TRA, VER or placebo (PL) in adult patients (pts) with mild-to-moderate hypertension, some of whom had type 2 diabetes mellitus. All agents were administered once daily in randomised, double-blind trials (one crossover study[37]). Where additional comparisons were reported,[39] only data for commercially available fixed-dose combination dosages and the corresponding monotherapies are shown

Study	Treatment duration (wk)[b]	Dosage (mg/day)	No. of pts evaluated	Mean sitting SBP/DBP[a] (mm Hg)		Responders (%)[c]
				baseline	reduction at endpoint	
Placebo-controlled trials						
Messerli et al.[38]	6	TRA/VER 4/240	163	152.3/101.4	12.9†§§/8.1†§§	64†§§
		VER 240	155	151.1/100.8	8.0§§/4.3§§	37§§
		TRA 4	155	151.8/101.3	9.0§§/4.5§§	41§§
		PL	152	153.6/100.5	NR	18
Scholze et al.[39]	6	TRA/VER 2/180	50	NR/100–115[d]	18.8**§§/15.2**‡‡§§[e]	
		VER 180	29	NR/100–115[d]	9.3**/8.9**[e]	
		TRA 2	30	NR/100–115[d]	16.4**/13.9**[e]	
		PL	30	NR/100–115[d]	8.1**/8.7**[e]	
Veratran Study Group[40]	8	TRA/VER 1/180	77	160.3/104.1	18.9*§/13.4*§	
		VER 180	56	156.0/104.2	10.5*/10.0*	
		TRA 1	50	159.3/103.6	21.2*§/13.0*§	
		PL	51	158.2/103.5	9.7*/6.1*	
Versus monotherapy						
Karlberg et al.[37]	8	TRA/VER 2/180	192	166.1/102.0[d]	19.6††/15.1††	93
		VER 240	96	166.1/102.0[d]	13.3/12.4	89
		TRA 2	96	166.1/102.0[d]	14.2/10.5	79
Viskoper et al.[41]	8	TRA/VER 2/180	103	164.7/103.3	17.6†/13.2†[e]	70
		VER 180	102	162.2/103.1	10.3/9.6[e]	49
		TRA 2	105	161.6/103.3	12.5/10.9[e]	59
In pts with type 2 diabetes						
Ruilope et al.[44]	16	TRA/VER 2/180	172	143.9/84.7	10.9§§/7.0†§§[e]	38§§
		TRA 2	165	143.7/85.1	10.1§§/5.3§[e]	37§§
		PL	84	144.6/85.3	3.9/3.0[e]	15

a Primary endpoint was mean sitting DBP.

b Prior to randomisation, pts underwent 2-[44] or 4-[37-41] wk PL run-in periods.

c Pts with sitting DBP ≤95mm Hg,[37] or <90mm Hg or reduction of ≥10mm Hg,[38,41] or SBP <130mm Hg and DBP <85mm Hg;[44] some values estimated from graph.[38]

d Baseline values not reported; mean value for all pts[37] or inclusion criteria[39] shown.

e Adjusted mean value.

DBP = diastolic blood pressure; **NR** = not reported; **SBP** = systolic blood pressure; * $p < 0.01$, ** $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.001$ vs monotherapy components; ‡ $p < 0.05$, ‡‡ $p < 0.001$ vs VER 180; § $p < 0.05$, §§ $p < 0.01$ vs PL.

effective than placebo and generally more effective than the corresponding dosages of either drug as monotherapy at reducing BP in adult hypertensive patients. Trandolapril/verapamil SR 1mg/180mg, 2mg/180mg, 2mg/240mg or 4mg/240mg per day produced significantly greater reductions from baseline in mean supine DBP (primary endpoint) and SBP[35,36] and mean sitting DBP (primary endpoint) and SBP (table IV),[38-40,44] than placebo in adult patients with mild-to-moderate hypertension, including those with type 2 diabetes in studies of 6–16 weeks' duration. Furthermore, a significantly greater proportion of patients receiving trandolapril/verapamil SR 2mg/180mg, 2mg/240mg or 4mg/240mg per day responded to treatment (sitting DBP <90mm Hg or reduction of ≥10mm Hg,[35,36,38] or SBP <130mm Hg and DBP <85mm Hg[44]) compared with placebo recipients (38–64% vs 5–18%; all $p < 0.01$) in the three studies reporting this. In the study investigating the trandolapril/verapamil SR 1mg/180mg per day dosage,[40] trandolapril/verapamil SR recipients experienced significant ($p < 0.01$) reductions from baseline in 24-hour ambulatory mean DBP and SBP at day 1 and at 8 weeks, whereas no significant reductions from baseline were seen in placebo recipients at either timepoint.

Trandolapril/verapamil SR 2mg/180mg, 2mg/240mg or 4mg/240mg recipients generally experienced significantly greater reductions from baseline in mean sitting DBP and/or SBP than patients receiving trandolapril or verapamil SR monotherapy at corresponding dosages.[12,35-39,44] In two studies,[35,36,38] a significantly ($p < 0.05$) greater percentage of patients receiving trandolapril/verapamil SR (51–64%) responded to therapy (sitting DBP <90mm Hg or reduction of ≥10mm Hg) than recipients of the corresponding dosages of trandolapril (41% and 46%) and/or verapamil SR (29–37%); however, no significant differences in response rate were seen between active treatment groups in three other studies (table IV).[37,41,44] The trough : peak sitting DBP ratios in patients receiving trandolapril/verapamil SR 4mg/240mg, trandolapril 4mg or verapamil SR 240mg daily were 0.67, 0.75 and 0.47, respectively;[38] those for trandolapril/verapamil SR 1mg/180mg, trandolapril 1mg or verapamil SR 180mg daily were 0.59, 0.41 and 0.35, respectively.[40]

Patients receiving trandolapril/verapamil SR 1mg/180mg[40] or 2mg/180mg[12] (in a subset of 90 patients from a trial previously described[41]) per day generally experienced significantly (all $p < 0.05$) greater reductions from baseline in mean ambulatory 24-hour DBP (9.6[12] and 11.1mm Hg[40]) and SBP (16.7[12] and 14.3mm Hg[40]) than patients receiving monotherapy with trandolapril (DBP 5.4[12] and 7.1mm Hg;[40] SBP 10.1[12] and 11.1mm Hg[40]) or verapamil SR (DBP 3.8[12] and 6.1mm Hg;[40] SBP 2.6[12] and 7.9mm Hg[40]) at corresponding dosages in two 8-week trials (some data estimated from graph[40]).

Fixed-dose combination trandolapril/verapamil SR was effective in lowering BP in hypertensive patients unresponsive to either drug as monotherapy.[42,43] Trandolapril/verapamil SR 2mg/180mg[42] or 2mg/240mg[43] significantly reduced DBP and SBP from baseline (all $p < 0.001$) in patients unresponsive (DBP ≥95mm Hg[42,43] or improvement ≤5mm Hg[42]) to 8 weeks' treatment with trandolapril 2 mg/day [42] or 12 weeks' treatment with verapamil SR 240 mg/day[43] monotherapy in two 12-week studies available as abstracts (n = 381[42] and 463[43]). At trial endpoint, both SBP and DBP were reduced to a greater extent ($p < 0.001$ for all comparisons) with trandolapril/verapamil SR than verapamil (SBP/DBP reductions of 9.6/7.2 vs 4.8/3.4mm Hg)[43] or trandolapril (adjusted mean SBP/DBP reductions of 8.0/6.2 vs 0.6/2.3mm Hg) monotherapy.[42]

Comparisons with Combination Antihypertensive Therapy

The effect of trandolapril/verapamil SR on BP in patients with mild-to-moderate hypertension, some of whom had type 2 diabetes, was generally similar to that of other fixed-dose combination therapies (metoprolol/hydrochlorothiazide,[10] atenolol/chlortalidone,[11,14,21] lisinopril/hydrochlorothiazide,[11] enalapril/hydrochlorothiazide[20]) in studies of 8–24 weeks' duration (table V). Patients receiving combination antihypertensive therapy experienced de-

Table V. Comparative efficacy of trandolapril/verapamil sustained release (TRA/VER) versus other fixed-dose combination therapies in adult patients (pts) with mild-to-moderate hypertension, some of whom had type 2 diabetes mellitus. All agents were administered once daily in randomised, mostly double-blind trials (two trials nonblind[10,14]; one available as an abstract[14])

Study	Treatment duration (wk)[a]	Dosage (mg/day)	No. of pts evaluated	Mean sitting SBP/DBP (mm Hg)		Responders (%)[b]
				baseline	reduction at endpoint	
Breithaupt-Grögler et al.[10]	24	TRA/VER 1/180	26	155.9/101.0	22.3*/14.4‡	81
		MET/HCT 100/12.5	25	149.9/100.8	15.9*/9.2*	64
de Leeuw et al.[11][c]	8	TRA/VER 2/180	50	170/106	27†/13†	72
		ATE/CHL 100/25	50	171/107	28†/13†	76
		LIS/HCT 20/12.5	52	169/107	23†/12†	69
		PL	53	169/107	3/3	32
Ramos et al.[14]	24	TRA/VER 2/180	19	149/102	15/15	
		ATE/CHL 100/25	22	156/103	33‡/22‡	
In pts with type 2 diabetes						
Fernández et al.[20]	24	TRA/VER 2/180	48	157.9/97.4	16.0**/11.2**	
		ENA/HCT 20/12.5	45	156.8/99.2	17.7**/13.2**	
Schneider et al.[21]	12	TRA/VER 1/180 or 2/180	12	171/108	20**/9	
		ATE/CHL 50/12.5 or 100/25	12	159/106	18*/12*	

a Prior to randomisation, pts underwent 2-[10,14] or 4-[11,20,21] wk PL run-in periods.

b Pts with sitting DBP <90mm Hg or reduction of ≥10mm Hg.

c Mean sitting DBP and % of responders identified were co-primary endpoints.

ATE = atenolol; **CHL** = chlortalidone; **DBP** = diastolic blood pressure; **ENA** = enalapril; **HCT** = hydrochlorothiazide; **LIS** = lisinopril; **MET** = metoprolol; **PL** = placebo; **SBP** = systolic blood pressure; * $p < 0.05$, ** $p < 0.01$ vs baseline; † $p < 0.0001$ vs PL; ‡ $p < 0.05$ vs comparator.

creases in mean sitting DBP and SBP from baseline and, in the one placebo-controlled study,[11] the decrease was greater than that seen in placebo recipients (table V). The mean reduction in sitting DBP and SBP in patients receiving trandolapril/verapamil SR 1mg/180mg per day was greater than in metoprolol/hydrochlorothiazide 100mg/12.5mg per day recipients in a 24-week trial (table V).[10] Reductions in BP were similar in recipients of trandolapril/verapamil SR or atenolol/chlortalidone in 8-[11] and 12-week[21] studies; however, in a 24-week study,[14] atenolol/chlortalidone was associated with greater reductions in mean sitting DBP and SBP than trandolapril/verapamil SR (table V). Broadly similar percentages of patients receiving trandolapril/verapamil SR or metoprolol/hydrochlorothiazide,[10] atenolol/chlortalidone[11] or lisinopril/hydrochlorothiazide[11] attained normalisation of BP (sitting DBP <90mm Hg) or responded to treatment (normalisation plus decrease in sitting DBP ≥10mm Hg) [table V].

In Black Patients

Black patients not only have a higher incidence of hypertension compared with other ethnic groups, but the disease is more severe and they are considered to have a different response to pharmacological treatment.[58] Trandolapril/verapamil SR was effective in Black patients with mild-to-moderate hypertension in a noncomparative study[46] and in those with severe hypertension in a nonblind, multicentre study comprising a multiple drug regimen sequentially added for nonresponders.[45] Following a 14-day wash-out and a 14-day placebo run-in period in the noncomparative study, 21 Back patients with mild-to-moderate hypertension were treated with a titrated dosage of trandolapril/verapamil SR (2mg/180mg to 4mg/360mg per day or 4mg/360mg per day plus hydrochlorothiazide 12.5 mg/day), with a target DBP of <90mm Hg.[46] At trial endpoint (16 weeks), mean 24-hour ambulatory BP decreased from baseline (150/96 vs 131/82mm Hg; $p < 0.001$).[46] Furthermore, mean 12-hour daytime DBP (100 vs 87mm Hg) and SBP (154 vs 136mm Hg) decreased from baseline (both $p < 0.001$); 76% of patients achieved the target mean DBP.[46] The addi-

tion of hydrochlorothiazide was required in two patients.[46]

The addition of verapamil SR, and subsequently hydrochlorothiazide, to trandolapril monotherapy was effective in Black or Caucasian patients.[45] In a 24-week study, 30 Black and 57 Caucasian patients with severe hypertension received a titrated dosage of trandolapril 4–8 or 2–4 mg/day, respectively. Because Black patients have a lesser response to ACE inhibitors than Caucasian patients, the initial titration dosage in Black patients was double that in Caucasian patients.[45] After 2 weeks' therapy, verapamil SR was added to trandolapril in nonresponders, who thus received trandolapril/verapamil SR 8mg/180mg or 4mg/180mg per day.[45] Hydrochlorothiazide 12.5–25 mg/day was also added, when necessary, to achieve a target DBP of ≤90mm Hg.[45]

Black or Caucasian patients receiving trandolapril/verapamil SR (n = 26 and 49) experienced significant reductions from baseline in supine SBP and DBP (14.5/13.1 [Black patients] vs 14.6/14.3mm Hg [Caucasian patients]; both p = 0.001); mean baseline BP in trandolapril/verapamil SR recipients was 181.8/119.6mm Hg.[45] Greater reductions in mean supine SBP and DBP were seen in all patients receiving trandolapril/verapamil SR compared with those receiving trandolapril (14.6/13.9 vs 5.3/9.0mm Hg; p = 0.001).[45] The addition of hydrochlorothiazide to trandolapril/verapamil SR resulted in greater reductions in mean supine SBP (27mm Hg) and DBP (19mm Hg) than with trandolapril/verapamil SR (both p = 0.001).[45]

In Elderly Patients

Trandolapril/verapamil SR was effective in the treatment of elderly patients (aged 63–92 years; n = 254) with mild-to-moderate hypertension in a noncomparative, multicentre trial.[47] A 4-week placebo run-in period was followed by treatment with trandolapril/verapamil SR 0.5mg/120mg, 1mg/180mg or 2mg/180mg per day in a three-step dosage titration, with a target DBP of <90mm Hg.[47] Following treatment with trandolapril/verapamil SR, mean sitting BP decreased from 174.5/102.5mm Hg at baseline to 150.9/84.2mm Hg at trial endpoint; most of the BP reduction occurred within the first 3 months of treatment (mean sitting BP at 3 months 152.6/86.8mm Hg).[47] Normalisation of BP (sitting DBP <90mm Hg) occurred in 82% of patients and overall response (normalisation or reduction of sitting DBP ≥10mm Hg) was seen in 85%.[47]

4.2.2 Effect on Renal Function in Patients with Type 2 Diabetes Mellitus

Trandolapril/verapamil SR, like trandolapril monotherapy, prolongs the time to onset of persistent microalbuminuria in hypertensive patients with type 2 diabetes. The BENEDICT included 1204 patients with hypertension (DBP ≥85mm Hg or SBP

Table VI. Effect of trandolapril/verapamil sustained release (TRA/VER) or TRA or VER on proteinuria in adult patients (pts) with hypertension and type 2 diabetes mellitus. Agents were administered once daily orally. At baseline, pts had proteinuria (>300 mg/day[48,49]) or albuminuria (30–3000 mg/day)[20]

Study	Study design	Treatment duration (wk)	Dosage (mg/day)[a]	No. of pts evaluated	Mean urinary albumin excretion (mg/day)		Mean urinary protein excretion (mg/day)	
					baseline	endpoint	baseline	endpoint
Bakris et al.[48]	r, nb	52	TRA/VER 2–4/180–240[b]	14	672	234*†	1403	592*†
			TRA 2–8[b]	12	616	399*	1274	840*
			VER 180–360[b]	11	604	421*	1349	985
Fernández et al.[20]	r, db	26	TRA/VER 2/180	51	601.5	339.8		
			ENA/HCT 20/12.5	52	409.9	161.5		
Rubio-Guerra et al.[49]	nc	24	TRA/VER 2/180	30	4564.7	2096.9**		

a Prior to randomisation, pts underwent 2-[48] or 4-[20] wk placebo run-in periods or a 4-wk antihypertensive-free period.[49]

b Furosemide 40 mg/day was added when necessary.

db = double-blind; **ENA** = enalapril; **HCT** = hydrochlorothiazide; **nb** = nonblind; **nc** = noncomparative; **r** = randomised; * p < 0.05, ** p < 0.001 vs baseline; † p < 0.05 vs comparators.

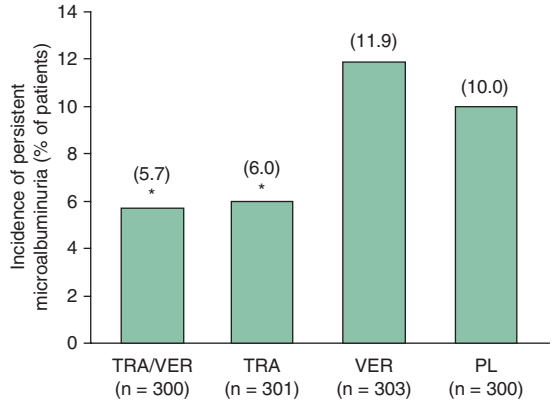

Fig. 2. Effect of trandolapril/verapamil sustained release (TRA/VER) on microalbuminuria in hypertensive patients with type 2 diabetes mellitus. Incidence of persistent microalbuminuria (urinary albumin excretion ≥20 μg/min in ≥2 of 3 consecutive overnight urine collections) in the BENEDICT (BErgamo NEphrologic DIabetes Complications Trial).[50] This double-blind, multicentre study randomised patients with hypertension, type 2 diabetes mellitus and albuminuria <20 μg/min to TRA/VER 2mg/180mg per day, TRA 2 mg/day, VER 240 mg/day or placebo (PL); additional antihypertensives were added, where necessary, to achieve a target BP of 120/80mm Hg. Median duration of follow-up was 3.6 years. * p = 0.01 vs PL.

≥130mm Hg or the requirement for antihypertensive therapy to achieve a BP lower than these values; mean value at baseline of ≈151/88mm Hg), a history of type 2 diabetes of ≤25 years duration and normal renal function, evidenced by albumin excretion within normal limits (albuminuria <20 μg/min) and a serum creatinine level ≤133 μmol/L (1.5 mg/dL).[50] Patients with a glycosylated haemoglobin level ≥11% or nondiabetic renal disease were excluded from the study.[50]

Following a 6-week washout period during which drugs that inhibit the renin-angiotensin system were discontinued and a 3-week period in which nondihydropyridine calcium channel antagonists were stopped, patients were randomised to double-blind treatment with trandolapril/verapamil SR 2mg/180mg per day, trandolapril 2 mg/day, verapamil SR 240 mg/day or placebo, plus additional antihypertensive therapy, where necessary, to achieve a target BP of 120/80mm Hg.[50] Statistical analysis was based on an accelerated failure-time model, which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression and adjusts for patient baseline variables, including DBP and urinary albumin excretion.[50]

Persistent microalbuminuria (primary endpoint; urinary albumin excretion ≥20 μg/min in ≥2 of 3 consecutive overnight urine collections), adjusted for predefined baseline variables, was less likely with trandolapril/verapamil SR than placebo;[50] analyses of secondary endpoints showed that trandolapril, but not verapamil SR, reduced the incidence of persistent microalbuminuria versus placebo to a similar extent (figure 2). The use of trandolapril/verapamil SR or trandolapril instead of placebo prolonged the time to the onset of persistent microalbuminuria by factors of 2.6 and 2.1 (p = 0.01).[50]

The beneficial effect of trandolapril/verapamil SR on proteinuria and/or albuminuria was also seen in smaller, earlier studies. Trandolapril/verapamil SR reduced proteinuria and/or albuminuria from baseline in noncomparative[49] and comparative, randomised, nonblind[48] or double-blind (p-values for each treatment arm not reported)[20] trials of between 24 and 52 weeks' duration in patients with type 2 diabetes, hypertension and varying degrees of proteinuria (table VI) and in a small, randomised, double-blind, 12-week comparison that reported the proportion of patients achieving a reduction in albuminuria.[21] In the latter study, patients receiving trandolapril/verapamil SR experienced a greater reduction from baseline in albuminuria than atenolol/chlortalidone recipients (33% vs 11%; $p < 0.025$);[21] in another double-blind study, reductions in albuminuria were similar to those with enalapril/hydrochlorothiazide (table VI).[20] Greater reductions in albuminuria and proteinuria were seen with trandolapril/verapamil SR 2–4mg/180–240mg per day than with trandolapril 2–8 mg/day or verapamil SR 180–360 mg/day monotherapy in a nonblind study (table VI).[48]

5. Tolerability

Tolerability data for trandolapril/verapamil SR are available from studies presented in section 4,[10,11,20,21,34,35,37-47,49,50] a pooled analysis of four

double-blind trials presented in a review,[59] and the manufacturer's prescribing information.[8,22] The tolerability profile of trandolapril/verapamil SR is the same as that for the individual components and the respective class of drugs.[8,22] Notably, the incidence of verapamil SR-related, but not trandolapril-related, adverse events appears to be dose-related.[35]

Both the calcium channel antagonist (verapamil)- and the non-calcium channel antagonist (atenolol)-based treatment strategies were generally well tolerated in INVEST (see section 4.1 for treatment strategy details).[34] None of the adverse events specifically considered as secondary endpoints (cancer, Parkinson's disease, Alzheimer's disease and gastrointestinal [GI] tract bleeding) were common (each event reported by <2% of patients receiving either treatment strategy) and between-group differences were not evident.[34] Constipation (1.73% vs 0.13%; $p < 0.001$) and cough (1.78% vs 1.34%; $p = 0.01$) were more frequent with the verapamil-based treatment strategy, whereas symptomatic bradycardia (1.26% vs 0.66%; $p < 0.001$), dyspnoea (1.01% vs 0.73%; $p = 0.03$) and wheezing (0.39% vs 0.15%; $p < 0.001$) were more common with the atenolol-based treatment strategy.[34]

Trandolapril/verapamil SR was well tolerated in patients with hypertension, including those with type 2 diabetes in clinical trials of 6–24 weeks' duration.[10,11,20,21,35,37-47,49,50] The incidence of adverse events in patients receiving trandolapril/verapamil SR was 9–46%[11,20,38-42,44,45,50] and was generally similar to that of comparator treatment arms. However, in one study,[44] a higher incidence of adverse events was reported by patients receiving trandolapril/verapamil SR 2mg/180mg per day compared with trandolapril 2 mg/day recipients (16.6% vs 7.6%; $p = 0.01$). The withdrawal rates because of adverse events in patients receiving trandolapril/verapamil SR (2.0–11.7%) were similar to those in comparator treatment arms.[10,11,20,36,39-41,44,45]

The adverse effects occurring most frequently (incidence ≥1.5%) in placebo-controlled trials ($n = 747$) in which patients received trandolapril 0.5–8 mg/day and verapamil SR 120–240 mg/day are presented in figure 3 (reported in the manufacturer's prescribing information; statistical analysis not given); cough (4.6% vs 2.4%), first degree atrioventricular block (3.9% vs 0.5%) and constipation (3.3% vs 1.0%) were the most common adverse events occurring more frequently with trandolapril/verapamil SR than placebo.[8] A higher incidence of GI tract adverse events and/or constipation was reported by patients receiving trandolapril/verapamil SR (3.7%[35] and 16%[37]) or verapamil SR (3.5%[35] and 27%[37]) compared with trandolapril (0.4%[35] and 8%[37]) [both $p < 0.05$] in two studies.

In a pooled analysis of four double-blind trials in which patients received trandolapril/verapamil SR 2mg/180mg per day ($n = 208$), trandolapril 0.5–8 mg/day ($n = 411$), verapamil SR 120–240 mg/day ($n = 263$) or placebo ($n = 199$), the incidence of adverse events in the respective groups were similar (28%, 27%, 34% and 26%).[59] The most common adverse events observed in these studies that occurred more frequently with trandolapril/verapamil SR, trandolapril or verapamil than with placebo were constipation (2.9%, 0.2%, 3.4% vs 0%), cough (1.9%, 2.4%, 2.7% vs 1.5%) and asthenia (1.4%, 1.9%, 1.1% vs 0.5%). The rate of withdrawal because of adverse events was similar in patients receiving trandolapril/verapamil SR (3.4%), trandolapril (1.9%), verapamil SR (4.9%) or placebo (3.0%).[59] The incidence of PQ interval prolongation was similar in each treatment group in this review; the PQ interval increased from <200ms at baseline to >200ms during treatment in 2.0%, 1.8%, 1.2% and 1.1% of patients treated with trandolapril/verapamil SR 2mg/180mg, trandolapril, verapamil SR or placebo, respectively.[59] No clinically relevant changes in laboratory parameters were seen during treatment with trandolapril/verapamil SR.[59]

6. Dosage and Administration

In the US, trandolapril/verapamil SR 1mg/240mg, 2mg/180mg, 2mg/240mg and 4mg/240mg is approved for the treatment of adults with hypertension who have not achieved BP targets at the maximum recommended dosage of trandolapril or verapamil SR monotherapy, or in whom dosages of the individual components cannot be increased fur-

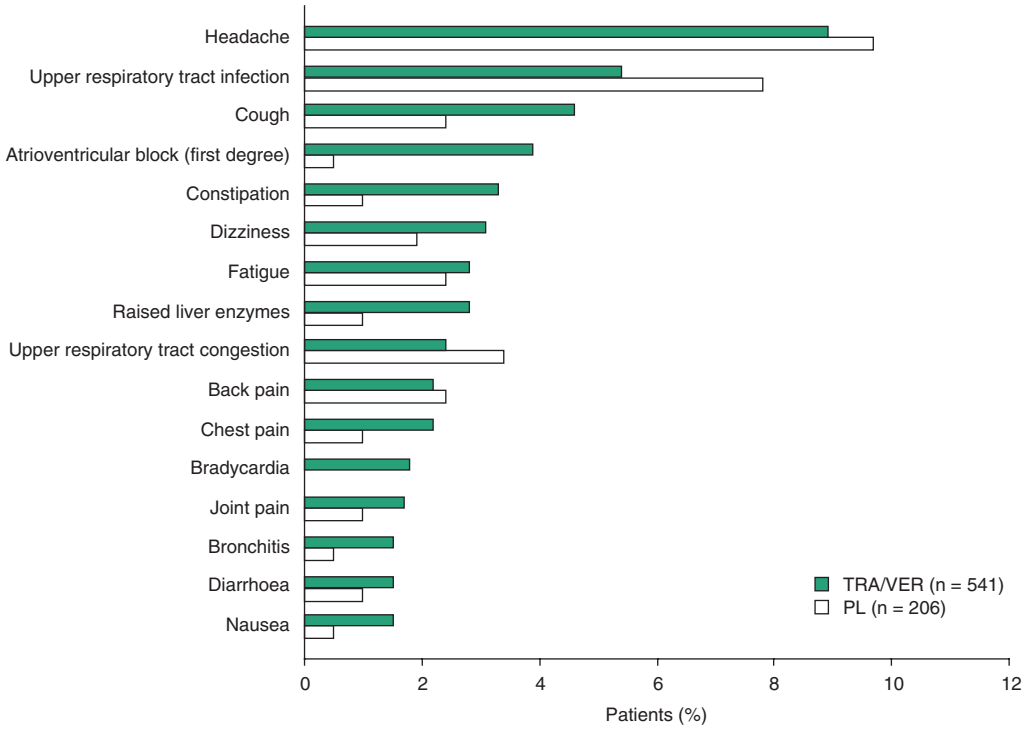

Fig. 3. Tolerability of trandolapril/verapamil sustained release (SR) [TRA/VER] in patients with hypertension. Incidence of the most common adverse events and laboratory abnormalities occurring in ≥1.5% of patients in placebo (PL)-controlled trials in which patients received trandolapril 0.5–8 mg/day and verapamil SR 120–240 mg/day (reported in manufacturer's prescribing information[8]); statistical analysis not reported.

ther because of adverse effects.[8] Trandolapril/verapamil SR is not indicated as initial therapy for the treatment of hypertension.[8] The recommended dosage of trandolapril is 1–4 mg/day and of verapamil SR is 120–480 mg/day; both should be administered either as a single dose or twice a day with food.[8] However, clinical trials have only investigated once daily administration of trandolapril/verapamil SR.[8]A boxed warning indicates that ACE inhibitors can cause injury or death to the developing foetus during the second and third trimesters of pregnancy, and trandolapril/verapamil SR should be discontinued as soon as possible after pregnancy is detected.[8]

In Europe, the 2mg/180mg presentation of trandolapril/verapamil SR is currently available in both capsule and tablet formulations. The indications for the product vary by market, from the treatment of essential hypertension where combination therapy is justified (Switzerland[60]) or where monotherapy with an ACE inhibitor has failed (France[61]), to the treatment of essential hypertension in patients whose BP has been stabilised on the individual components (UK[22]). The dosage and administration instructions vary according to the formulation (capsule or tablet) available in each market, and the local manufacturer's prescribing information should be consulted for specific details.

No data on the use of trandolapril/verapamil SR in children are available.[8,22] For specific recommendations in other special patient populations, contraindications, warnings, precautions and drug interactions in addition to those discussed in sections 2 and 3, see the manufacturer's prescribing information for the relevant country.[8,22]

7. Place of Trandolapril/Verapamil SR in the Treatment of Essential Hypertension

Consensus guidelines[2-5] generally agree on the goals of treating hypertension (the reduction of cardiovascular and renal morbidity and mortality) and the thresholds above which pharmacological management of the disease is required; however, treatment strategies for achieving satisfactory BP control vary. For instance, the ESH-ESC[3] and BHS[5] guidelines agree that, overall, most drug classes are similarly tolerated and effective in the treatment of uncomplicated hypertension, and indeed, the ESH-ESC guidelines recommend any of the major drug classes as initial therapy. Conversely, the JNC 7 [2] and WHO-ISH[4] guidelines advocate the use of diuretics (thiazide-type in JNC 7) as the basis for treatment, either alone or in combination with other agents. BHS guidelines recommend an agent that inhibits the renin-angiotensin system (ACE inhibitors, angiotensin receptor antagonists, β-blockers) in young (aged <55 years), non-Black patients, because they have higher renin concentrations than older (aged ≥55 years) or Black patients, who should receive an agent that does not inhibit this system (calcium channel antagonists or thiazide or thiazide-type diuretics) as first-line therapy.[5]

Despite the divergence in treatment strategies, all consensus guidelines recommend that if combination therapy is indicated, a drug that inhibits the renin-angiotensin system should be combined with one that does not inhibit it.[3-5] Importantly, combination therapy with diuretics and β-blockers may induce more new-onset type 2 diabetes than other combinations;[5] in addition, diuretic/β-blocker combination therapy should be used with caution in patients with metabolic syndrome, as high dosages may worsen insulin resistance and atherogenic dyslipidaemia.[62]

Consensus guidelines also identify compelling indications for specific antihypertensive drugs,[2-5] although treatment strategies for each indication vary:

- ACE inhibitors are recommended for patients with chronic renal disease (including those with type 1 diabetic nephropathy), diabetes, CHF, LV dysfunction, high CAD risk, for secondary stroke prevention and post MI;
- calcium channel antagonists are advised for those with angina (rate-limiting agents), diabetes, high CAD risk, isolated systolic hypertension and in the elderly;
- thiazide or thiazide-type diuretics are recommended in the elderly and in Black patients, in patients with isolated systolic hypertension, high CAD risk, CHF or diabetes and for secondary stroke prevention;
- β-blockers are advised for patients with angina, CHF, high CAD risk, diabetes or post MI;
- angiotensin receptor antagonists are advised in patients with CHF, chronic renal disease (including those with type 2 diabetic nephropathy), diabetes, hypertension with LV hypertrophy and post MI.

The BHS guidelines also recommend that the drug or formulation chosen for the treatment of hypertension should provide 24-hour control following a once-daily dose.[5] This not only provides more consistent control of hypertension, with less variation in BP levels, but once-daily administration is likely to optimise compliance; in addition, the risk of major cardiovascular events and hypertensive renal disease is likely to be reduced.[3,5] Although, in theory, fixed-dose combination preparations lack dose administration flexibility, this may not be a great concern in practice.[7] Trandolapril and verapamil SR are both long acting (section 3), provide 24-hour BP control (section 4.2.1) and allow once-daily administration (section 6).

In INVEST, a verapamil SR-based treatment strategy in which most patients also received trandolapril was as effective as an atenolol-based treatment strategy at preventing the primary outcome (first occurrence of death [all-cause], nonfatal MI or nonfatal stroke) in patients with hypertension and CAD (section 4.1), including in patients with type 2 diabetes (approximately one-third of study entrants) or ischaemia at baseline (approximately one-half of study entrants). Likewise, similar proportions of patients achieved overall BP control. That these two treatment strategies are equivalent is consistent with

the outcomes of meta-analyses of recent large clinical trials, which indicate that treatment with any of the most frequently used strategies will reduce the risk of major cardiovascular outcomes or cardiovascular mortality, irrespective of drug class.[63]

Nevertheless, INVEST has some limitations: for instance, target blood pressure levels recommended in current treatment guidelines[2-5] are now lower than those used in this study,[64] which were based on JNC VI guidelines.[65] In addition, it is difficult to draw firm conclusions from INVEST about the efficacy of trandolapril/verapamil SR relative to atenolol/hydrochlorothiazide because direct comparisons of these treatment strategies are not available.

Subgroup analyses of INVEST data suggest that the onset of new diabetes appeared to be slowed by the addition of trandolapril to verapamil SR, compared with adding trandolapril to atenolol (section 4.1). This outcome is consistent with results from other large, randomised clinical trials in which a lower incidence of new diabetes was seen with treatment strategies using agents that modify the renin-angiotensin system (ACE inhibitors, angiotensin receptor antagonists) and/or calcium channel antagonists than with strategies based on diuretics and/or β-blockers.[63,66-68] Also of interest, trandolapril/verapamil SR recipients maintained baseline glycosylated haemoglobin levels, whereas enalapril/hydrochlorothiazide recipients showed a slight deterioration in metabolic control in a well designed trial in hypertensive patients with type 2 diabetes.[20] Further investigation of these outcomes is, therefore, warranted.[64]

Trandolapril/verapamil SR generally produced greater reductions from baseline in mean sitting BP than trandolapril or verapamil SR administered at corresponding dosages as monotherapy (section 4.2.1) and is well tolerated (section 5), with a tolerability profile similar to that of the individual components or the respective drug class. These findings are consistent with a recent meta-analysis of 20 trials evaluating trandolapril/verapamil SR versus either agent as monotherapy (available as an abstract).[69] Significant reductions in mean sitting BP were seen with trandolapril/verapamil SR in patients previously unresponsive to either agent as monotherapy, and the combination was more effective than either component at reducing mean ambulatory 24-hour BP (section 4.2.1). In addition, trandolapril/verapamil SR is as effective as other frequently used combination antihypertensive therapies, such as metoprolol/hydrochlorothiazide, atenolol/chlortalidone, lisinopril/hydrochlorothiazide and enalapril/hydrochlorothiazide (section 4.2.1). Preliminary evidence also suggests that trandolapril/verapamil SR is effective in the elderly (section 4.2.1).

Although Black patients with hypertension may have a better response to monotherapy with diuretics or calcium channel antagonists than β-blockers, ACE inhibitors or angiotensin receptor antagonists, the addition of an adequate dosage of a diuretic to combination therapy based on the latter drug classes usually overcomes the problem.[2] Preliminary evidence suggests that trandolapril/verapamil SR-based strategies are effective at lowering BP in Black patients, although higher dosages of the trandolapril component are required in Black patients than in Caucasian patients (section 4.2.1).

The American Diabetes Association recommends the use of antihypertensive agents in patients with microalbuminuria to prevent progression to overt nephropathy and end-stage renal failure.[70] In patients with microalbuminuria or clinical albuminuria, an ACE inhibitor is the initial drug of choice in hypertensive or nonhypertensive patients with type 1 diabetes, whereas angiotensin antagonists are preferred in hypertensive patients with type 2 diabetes.[70] Nondihydropyridine calcium channel antagonists may reduce albuminuria, but have not been shown to halt the decline in renal function.[70] In the BENEDICT, trandolapril/verapamil SR prolonged the time to onset of persistent microalbuminuria in hypertensive patients with type 2 diabetes compared with placebo to the same extent as trandolapril monotherapy, whereas verapamil had no effect, confirming results from smaller, earlier trials (section 4.2.2).

Preliminary data from pharmacoeconomic analyses suggest that the direct medical costs of trandolapril/verapamil SR compare favourably with those

of the fixed-dose combination product benazepril/amlodipine for the treatment of hypertension,[71] and that health economic benefits are associated with trandolapril/verapamil SR in comparison with ACE inhibitors or calcium channel antagonists in the prevention of renal failure[72] in patients with type 2 diabetes. Studies comparing trandolapril/verapamil SR with other fixed-dose products, including other ACE inhibitor/calcium channel antagonist combinations in terms of clinical endpoints, such as cardiovascular or renal morbidity and mortality, and subsequent pharmacoeconomic analyses, would be of benefit in establishing the place of trandolapril/verapamil SR relative to other fixed-dose combination treatment options in hypertension.

In conclusion, trandolapril/verapamil SR is an effective and well tolerated therapy for the treatment of patients with essential hypertension and CAD, including in those with type 2 diabetes. In INVEST, a verapamil SR-based treatment strategy that included trandolapril in most patients was as effective as an atenolol-based treatment strategy in reducing the risk of the primary outcome (first occurrence of death [all-cause], nonfatal MI or nonfatal stroke) in patients with hypertension and CAD and was as well tolerated. Trandolapril/verapamil SR is generally more effective at controlling hypertension than either component as monotherapy, and is as effective as a number of other fixed-dose combination therapies. The combination is as well tolerated as trandolapril monotherapy and is at least as well tolerated as verapamil SR monotherapy. In hypertensive patients with type 2 diabetes in the BENEDICT, trandolapril/verapamil SR prolonged the time to the onset of persistent microalbuminuria compared with placebo, as did trandolapril monotherapy. Thus, trandolapril/verapamil SR is an effective option for the treatment of essential hypertension in patients requiring more than one agent to achieve BP targets, including those with compelling indications, such as CAD or type 2 diabetes.

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