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Trandolapril

An Update of its Pharmacology and Therapeutic Use in Cardiovascular Disorders

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Data Selection

Sources: Medical literature published in any language since 1966 on trandolapril, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'trandolapril', 'RU-44570', 'Gopten', 'Mavik', 'Odrik', 'coronary-disorder', 'hypertension' and 'postmyocardial infarction'. Medline and EMBASE search terms were 'trandolapril', 'RU 44570', 'gopten', 'mavik' and 'odrik'. Searches were last updated 18th Sept. 1998.

Selection: Studies in patients with hypertension, congestive heart failure or post-myocardial infarction who received trandolapril. 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, hypertension, congestive heart failure, post-myocardial infarction, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Trandolapril is an orally administered angiotensin converting enzyme (ACE) inhibitor that has been used in the treatment of patients with hypertension and congestive heart failure (CHF), and after myocardial infarction (MI). Trandolapril is a nonsulfhydryl prodrug that is hydrolysed to the active diacid trandolaprilat.

Trandolapril 2mg once daily provides effective control of blood pressure (BP) over 24 hours in patients with mild to moderate hypertension, with a trough/peak ratio of BP reduction (as determined by 24-hour ambulatory monitoring) consistently ≥50%. Trandolapril has similar antihypertensive efficacy to enalapril as indicated by several clinical trials. Combined therapy with trandolapril and sustained-release verapamil has a significantly greater antihypertensive effect than either agent alone.

Only limited data are available on the use of trandolapril in patients with CHF, although ACE inhibitors as a class are recommended as first line therapy in such patients.

In the Trandolapril Cardiac Evaluation (TRACE) study, trandolapril 1 to 4mg once daily resulted in an early and long term reduction in all-cause mortality, including cardiovascular mortality, in patients with left ventricular (LV) dysfunction after an MI. Trandolapril therapy was commenced a mean 4.5 days after acute MI and continued for 24 to 50 months. At study end, the relative risk of death from any cause with trandolapril versus placebo was 0.78 ($p = 0.001$).

The tolerability profile of trandolapril is similar to that of other ACE inhibitors. Most adverse events are mild and transient in nature, and include cough, asthenia, dizziness, headache and nausea. Trandolapril has no adverse effect on lipid or carbohydrate metabolism.

Conclusions: Trandolapril has a favourable pharmacological profile and an antihypertensive efficacy at least comparable to that of other ACE inhibitors. The pharmacological characteristics of trandolapril allow it to provide good 24-hour control of BP with once-daily administration. Trandolapril has also demonstrated some efficacy in a small number of patients with CHF. In addition, trandolapril provides long term protection against all-cause mortality in patients with LV dysfunction after MI. The results of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study will determine its potential as a cardioprotective agent in patients with coronary artery disease and preserved LV function. Thus, trandolapril represents an effective, well-tolerated and convenient

treatment option for patients with mild to moderate hypertension or LV systolic dysfunction after MI.

Pharmacodynamic Properties

The active diacid of trandolapril, trandolaprilat, has a high binding affinity for angiotensin converting enzyme (ACE), producing 50% inhibition at a concentration of 0.374 μg/L. Trandolaprilat is a more potent ACE inhibitor than captopril, enalaprilat and quinaprilat *in vitro*. Trandolapril rapidly inhibits ACE after single doses of 2 or 4mg in both elderly (≥65 years) and younger (<65 years) patients with mild to moderate hypertension. In normotensive volunteers, trandolapril 2mg daily for 7 days inhibited ACE significantly more than enalapril 20 mg/day when measured 24 hours after the last dose. ACE inhibition was still >50% 48 hours after the last dose. Trandolapril is highly lipophilic, more so than captopril, enalaprilat, perindoprilat and ramiprilat.

In patients with mild to moderate essential hypertension, trandolapril markedly reduced both systolic and diastolic blood pressure (BP) throughout the 24-hour post-dose period while generally having no effect on heart rate, stroke volume or cardiac output. Trandolapril 2 to 4 mg/day for 1 year significantly improved diastolic function and reduced left ventricular (LV) hypertrophy in patients with hypertension and LV hypertrophy. Cardioprotective effects of trandolapril have been demonstrated in animal models of hypertension with LV hypertrophy, myocardial infarction (MI) and congestive heart failure (CHF).

In clinical studies, trandolapril generally had no effect on lipid profile in patients with hypertension, but did have a favourable effect in one study in overweight patients. Trandolapril did not significantly affect fasting or post-prandial blood glucose levels or insulin sensitivity in patients with hypertension and type 2 (non-insulin-dependent) diabetes mellitus. However, it did significantly decrease microalbuminuria in these patients.

Pharmacokinetic Properties

After oral administration, trandolapril is rapidly absorbed and converted to its active diacid, trandolaprilat. Peak plasma concentrations (C_{max}) of trandolaprilat in healthy volunteers were reached in approximately 4 to 6 hours. C_{max} for trandolaprilat after a single 2mg dose was 4.2 μg/L in patients with mild to moderate hypertension. The bioavailability of trandolaprilat was between 40 and 60% in healthy volunteers, and this level was not affected by food. Trandolaprilat is highly bound to plasma protein (80 to 94%) in a saturable manner. Trandolaprilat has a biphasic elimination pattern with a prolonged terminal half-life of 16 to 24 hours. The drug has a dual route of elimination and approximately 33% of a dose is excreted in the urine and 66% in the faeces.

The pharmacokinetic profile of trandolapril is similar in elderly and younger patients with hypertension. The effects of renal or hepatic dysfunction on the pharmacokinetics of trandolapril do not require dosage adjustment unless the impairment is severe.

Therapeutic Use

When trandolapril was previously reviewed in *Drugs*, its therapeutic efficacy in patients with essential hypertension was found to be similar to that of other agents used in the management of this condition. However, only single studies were available for most comparisons. Since then, the body of data has grown considerably and trandolapril now has an established therapeutic profile in patients with hypertension.

Trandolapril provides effective 24-hour BP control when administered once daily and the trough/peak ratio of BP reduction for trandolapril 2mg once daily

is consistently ≥50%. In studies where the last dose was missed or replaced by placebo, trandolapril 2mg sustained the significant reduction in BP, compared with baseline or placebo, for a further 4 to 24 hours after the initial 24-hour postdose period.

Trandolapril has similar antihypertensive efficacy to enalapril when administered once daily in patients with mild to moderate hypertension. Responder rates varied from 47 to 65% with trandolapril and from 40 to 67% with enalapril in 2 comparative studies. Systolic BP (SBP) and diastolic BP (DBP) trough/peak ratios adjusted for placebo were 90 and 54% with trandolapril and 49 and 49% with enalapril, respectively. However, after a missed dose, these ratios were 58% for SBP and 36% for DBP with trandolapril and 10% and 19%, respectively, with enalapril. Trandolapril appears to have similar antihypertensive efficacy to lisinopril, amlodipine, sustained-release nifedipine, hydrochlorothiazide and atenolol.

Both diuretics and calcium antagonists have been used in combination with trandolapril to provide greater efficacy with no deterioration in tolerability compared with monotherapy. In particular, the combination of trandolapril and verapamil SR has been extensively studied in patients with hypertension, and to a lesser extent in patients with CHF. The reduction in BP seen with the combination is consistently greater than with either agent alone.

The antihypertensive efficacy of trandolapril is maintained in elderly, Black and overweight patients, and patients with type 2 diabetes mellitus. However, higher dosages are typically needed in Black patients.

In the Trandolapril Cardiac Evaluation (TRACE) study, treatment with trandolapril 1 to 4 mg/day starting within 3 to 7 days of acute MI significantly reduced all-cause mortality compared with placebo in patients with left ventricular (LV) dysfunction (n = 1749). The relative risk of death with trandolapril, compared with placebo, was 0.78 (p = 0.001). In addition, trandolapril reduced the relative risk of cardiovascular mortality (0.75), sudden death (0.76) and CHF (0.71), and there was a trend toward a decreased risk of reinfarction.

Trandolapril, like other ACE inhibitors, has also demonstrated efficacy in patients with CHF, although the number of patients evaluated is small.

Tolerability

Trandolapril has been well tolerated in clinical trials and in a postmarketing cohort study, which together included >24 000 patients with mild to moderate hypertension. The adverse events reported are typical of ACE inhibitors with the most frequently reported events being cough, asthenia, dizziness, headache and nausea. In the postmarketing study (n = 10 820) adverse events that occurred in ≥0.33% of patients were cough (3.6%), asthenia (1.0%), dizziness (0.9%), headache (0.7%), nausea/vomiting (0.6%), orthostatic effects (0.5%) and rash/pruritus (0.4%). Trandolapril was also well tolerated in patients with LV dysfunction post-MI in the TRACE study. Adverse events causing withdrawal from the TRACE study with trandolapril and placebo, respectively, were cough (0.04 *vs* 0.01%), hypotension (0.02 *vs* 0.01%) and reduction in renal function (0.02 *vs* 0.01%).

Dosage and Administration

In patients with mild to moderate hypertension, the recommended starting dosage for trandolapril is 2mg once daily. This may be increased to 4mg once daily if necessary to achieve optimal response. In patients with LV dysfunction after MI, trandolapril 0.5mg is the initial recommended dosage, and this should be slowly titrated to 4mg once daily. Trandolapril should be initiated at 0.5mg once daily in patients with severe renal or hepatic failure.

1. Introduction

Angiotensin converting enzyme (ACE) inhibitors are now an established class of antihypertensives, accepted therapy in the early management of patients after acute myocardial infarction (MI), and recommended as initial therapy in patients with congestive heart failure (CHF).

Trandolapril is a nonsulfhydryl inhibitor of ACE with a similar structure to enalapril. It is a prodrug that is hydrolysed to the active diacid, trandolaprilat, after oral administration. The pharmacology and therapeutic use of trandolapril in essential hypertension were reviewed in *Drugs* in 1994.[1] This review re-examines the role of trandolapril in the treatment of hypertension in the light of recently published clinical trials, as well as reviewing its use in patients after acute MI. In addition, limited available data on the use of trandolapril in patients with CHF are reviewed.

Table I. Overview of the pharmacodynamic properties of trandolapril[1]

High binding affinity for ACE: IC_{50} of trandolaprilat [0.374 μg/L (0.93 nmol/L)] is less than that of enalaprilat, captopril and quinaprilat and similar to that of ramiprilat
Prolongs survival and provides cardiac protection in animal models of hypertension and CHF
Markedly reduces SBP and DBP throughout 24-hour post-dose period in patients with essential hypertension
Does not effect or slightly decreases heart rate without affecting cardiac output or stroke volume in patients with essential hypertension
Causes regression of LVH comparable to enalapril in patients with hypertension and LVH
Improves elastic properties of large arteries in patients with essential hypertension: increases arterial compliance and brachial artery diameter, and decreases forearm vascular resistance and carotid-femoral pulse wave velocity
No adverse effects on carbohydrate and lipid metabolism at rest or during exercise in patients with essential hypertension

ACE = angiotensin converting enzyme; **CHF** = congestive heart failure; **DBP** = diastolic blood pressure; **IC_{50}** = drug concentration required to inhibit ACE activity by 50%; **LVH** = left ventricular hypertrophy; **SBP** = systolic blood pressure.

2. Pharmacodynamic Properties

The pharmacodynamic properties of trandolapril (table I) are well established from preclinical and clinical trials, and were discussed in detail in the previous review in *Drugs*.[1]

2.1 Effects on the Renin-Angiotensin-Aldosterone System

Trandolapril is a weak inhibitor of ACE. However, trandolaprilat has high binding affinity for ACE and produces potent reversible inhibition of the enzyme preventing the conversion of angiotensin I to the active angiotensin II in plasma. As with other ACE inhibitors, this reduction in plasma angiotensin II levels is responsible for the majority of observed pharmacodynamic effects of trandolaprilat, including peripheral vasodilation, reduced blood pressure (BP) and total peripheral resistance, and decreased sodium and water retention by the kidney (via inhibition of aldosterone production). ACE inhibitors (including trandolaprilat) can also increase bradykinin production (by inhibiting kinase II) and inhibit the local formation of angiotensin II by tissue renin-angiotensin systems.[1,2]

Trandolapril rapidly inhibited ACE after single doses of 2 or 4mg in both elderly (≥65 years) and younger (<65 years) patients with mild to moderate hypertension.[3] Maximal ACE inhibition of 85% occurred at 4 hours in younger patients and 6 hours in older patients after a single dose. However, after repeated doses, the time to maximal ACE inhibition decreased significantly in both age groups but to a greater extent in the elderly (from 6 to 1.5 hours) than in younger patients (from 4 to 3 hours).[3]

When measured 24 hours after the last dose at the end of 7 days' treatment, ACE activity was inhibited more with trandolapril 2 mg/day than enalapril 20 mg/day in 36 normotensive volunteers (70 *vs* 64% inhibition; $p = 0.04$).[4] ACE inhibition was still greater than 50% 48 hours after the last dose of trandolapril. Furthermore, 1 week after discontinuation of enalapril there was a rebound of ACE activity but this was not seen with trandolapril. However, only a preliminary report of this study has been published.[4]

A similar level of ACE inhibition was seen in White and Black patients with hypertension who

received trandolapril 1 to 4 mg/day in a randomised, multicentre, double-blind study, despite Black patients requiring 2 to 4 times more trandolapril than White patients to achieve identical BP reductions.[2]

2.1.1 Local Tissue Angiotensin Converting Enzyme Inhibition

Trandolaprilat is highly lipophilic (more so than captopril, enalaprilat, perindoprilat and ramiprilat), and this may facilitate tissue ACE inhibition.[1] Treatment with trandolapril inhibited local ACE activity in the microvasculature of the cremaster muscle of spontaneously hypertensive rats (SHR)[5] and significantly attenuated the increase in left ventricular (LV) ACE activity in rats with chronic CHF after MI.[6] These effects were similar to those with captopril,[6] enalapril[5,6] and perindopril.[5]

2.2 Effects on Blood Pressure and Haemodynamics

Clinical trials have demonstrated that trandolapril 1 to 4 mg once daily provides effective 24-hour BP control in patients with mild to moderate hypertension (see section 4.1).

Trandolapril had no significant effect on heart rate, stroke volume or cardiac output in the majority of clinical studies in patients with hypertension, although a slight but significant decrease in heart rate was reported in some studies.[1,7] Furthermore, trandolapril does not appear to have any adverse effects on the normal physiological response to exercise in patients with hypertension[8] or myocardial ischaemia.[9] However, after a single intravenous dose of trandolapril 2mg, significant reductions in mean LV end-systolic pressure and LV end-diastolic pressure of 9 and 32%, respectively, were seen during pacing in 14 patients with myocardial ischaemia.[9] In addition, diastolic function was significantly improved 3 hours after administration of a single oral dose of trandolapril 2mg in 20 patients with hypertension,[10] and after long term (2 to 4 mg/day for 1 year) administration of trandolapril in 22 patients with both hypertension and LV hypertrophy.[10,11] In these studies, peak early velocity (E), peak atrial (late) velocity (A) and the E/A ratio were measured by echocardiography. Long term trandolapril therapy increased E by 8.5% ($p = 0.05$ versus baseline), the E/A ratio by 5% and LV ejection fraction (LVEF) by 6.9% ($p < 0.05$).[11]

Trandolapril 2 mg/day significantly increased circulation and microcirculation in 17 patients with mild to moderate hypertension, as evidenced by increased femoral artery diameter (assessed by laser Doppler flowmetry), and increased skin flow and venoarteriolar response.[12]

2.3 Effects on Cardiovascular Remodelling

The antihypertensive effect of trandolapril is accompanied by regression of LV hypertrophy and improvement in diastolic function in patients with hypertension and LV hypertrophy. Regression of LV hypertrophy with trandolapril 2 to 4 mg/day has been measured by magnetic resonance imaging (MRI) in 20 patients with hypertension.[7] After 3 months, significant decreases from baseline were seen in mean end-systolic intraventricular septum thickness (9.6%) and end-systolic posterior wall thickness (8%) [$p < 0.01$ *vs* baseline].[7] In addition, the LV mass index, as measured by echocardiography, decreased by 13.3% ($p < 0.01$ versus baseline) in 22 patients with hypertension and LV hypertrophy who received trandolapril 2 to 4 mg/day for 1 year.[11] The thickness of the intraventricular septum decreased by 8.5% ($p < 0.02$) and the posterior wall of the left ventricle by 9% ($p < 0.01$) compared with baseline. However, the results of both these studies need to be considered carefully because of the small patient numbers and lack of blinding.

The cardioprotective effects of trandolapril have been extensively studied in animal models of hypertension with LV hypertrophy, MI and CHF. These effects include a reduction in ventricular arrhythmias[13] and heart rate variability in SHR,[14] inhibition of cyclic coronary flow reductions during ischaemia,[15] decreased arrhythmias and attenuation of β-adrenoceptor desensitisation after ischaemia and reperfusion,[16-18] and attenuation of the reduction in β_1-adrenergic receptor density and sar-

coplasmic reticulum function in rats with CHF.[19,20] Furthermore, trandolapril plus verapamil produced an improvement in antiarrhythmic effects and haemodynamic profile compared with verapamil alone in an experimental porcine model of myocardial ischaemia and reperfusion.[21]

2.4 Renovascular, Metabolic and Neuroendocrine Effects

Trandolapril had no statistically significant effect on the following renovascular, metabolic and neuroendocrine parameters in the types of patients described:

- renal plasma flow in patients with hypertension[1]
- lipid profile in patients with hypertension[1]
- fasting glycaemia, post-prandial glycaemia, fructosaminaemia, serum glycosylated haemoglobin levels or insulin sensitivity in patients with hypertension and type 2 (non-insulin-dependent) diabetes mellitus[22,23]
- early circulating neurohormones in patients with recent onset MI and reduced LV function.[24]

However, trandolapril has improved some of these parameters in other patient groups or shown a benefit over a comparator. In a study published as an abstract, trandolapril 2 mg/day improved renal blood flow without affecting glomerular filtration rate, serum creatinine levels, creatinine clearance or urine osmolality in 8 patients with severe [New York Heart Association (NYHA) class IV] CHF.[25] In a nonblind study, trandolapril 2 mg/day for 4 weeks significantly decreased mean total and low density lipoprotein cholesterol levels (from 217 to 214 mg/dl and from 142 to 138 mg/dl, respectively; $p < 0.05$ *vs* baseline) in 295 overweight patients with hypertension.[26] Trandolapril 1 to 4 mg/day for 3 months to 1 year significantly decreased microalbuminuria in >100 patients with hypertension and type 2 diabetes mellitus in 2 nonblind studies.[22,27]

In contrast to the evidence that insulin sensitivity is not affected by trandolapril in patients with hypertension and type 2 diabetes mellitus,[23] the results of 2 randomised, parallel, comparative studies reported as abstracts indicate that trandolapril may have a more favourable effect than atenolol or nifedipine GITS (gastrointestinal therapeutic system) on insulin sensitivity (as measured by the euglycaemic hyperinsulinaemic clamp technique) in patients with essential hypertension.[28,29] Insulin sensitivity was significantly better with trandolapril 1 mg/day than atenolol 50 mg/day after 4 weeks' double-blind therapy in 53 patients with uncomplicated mild to moderate hypertension.[28] This effect was maintained over an 11-month treatment period. In 90 overweight patients with essential hypertension, insulin sensitivity was significantly better after 8 weeks' treatment with trandolapril 2 mg/day than nifedipine GITS 30 mg/day.[29]

3. Pharmacokinetic Properties

The pharmacokinetic properties of trandolapril have been previously reviewed in detail in *Drugs*.[1] An overview of the pharmacokinetics of trandolapril and trandolaprilat after a single dose is given in table II.

After oral administration, trandolapril is rapidly absorbed and converted in the liver to trandolaprilat, the biologically active diacid. The bioavailability of trandolapril is not affected by concomitant food intake. Nearly all of a dose is excreted in both the urine (33%) and faeces (66%) within 7 days, and steady state is reached in 4 days after once-daily administration of 1 or 2 mg/day.[1,30] Modest accumulation of trandolapril was observed in healthy volunteers during administration of trandolapril 1 or 2 mg/day for 7 to 10 days. Whereas the pharmacokinetics of trandolapril are linear, trandolaprilat is eliminated biphasically because of its saturable binding to plasma ACE.

The pharmacokinetic properties of trandolapril are similar in elderly and younger patients with mild to moderate essential hypertension.[3] The effects of renal or hepatic impairment on the pharmacokinetics of trandolapril are generally not clinically significant unless the impairment is severe. The dual elimination routes of trandolapril allow compensation for reduced renal or biliary excretion without the need to alter the starting dose in

Table II. Summary of the pharmacokinetic properties of trandolapril and trandolaprilat in normotensive volunteers or patients with mild to moderate hypertension after oral administration of trandolapril 2mg as a single dose.[1] Values are mean or range

	Trandolapril	Trandolaprilat
Patients		
C_{max} (μg/L)	3.1	4.2
$t_{½β}$ (h)	1.3	
Volunteers		
C_{max} (μg/L)	1.7-2.9	2.5-2.9
t_{max} (h)	1	4-6
AUC (μg/L • h)	1.9-4.5	38.2-45.7
$t_{½β}$ (h)	0.7	16-24
Bioavailability (%)	9.5	40-60
Plasma protein binding (%)	80 (nonsaturable)	80-94 (saturable)
Excretion[a]:		
urine (%)	<0.5	14
faeces (%)	10	30

a Measured for the first 24 hours after administration.

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = peak plasma concentration; $\mathbf{t_{max}}$ = time to achieve C_{max}; $\mathbf{t_{½β}}$ = terminal elimination half-life.

most patients. The renal clearance of trandolapril is directly proportional to creatinine clearance in patients with chronic renal failure, and dosage reduction is recommended in patients with severe renal impairment (see section 6).[31] In patients with severe hepatic failure, the plasma trandolapril concentration was approximately 10 times higher than in healthy volunteers.[1] However, there was evidence of increased urinary clearance in these patients, suggesting a compensatory mechanism.

Although data on the passage of the blood-brain barrier (BBB) by ACE inhibitors are conflicting, trandolapril (or trandolaprilat) crossed the BBB in SHR after chronic oral administration, in contrast to enalapril.[32]

No significant pharmacokinetic drug interactions were observed when trandolapril was coadministered with sustained release (SR) nifedipine, digoxin, furosemide (frusemide), glibenclamide (glyburide), propanolol or cimetidine in healthy volunteers.[1,33] Multiple doses of trandolapril did not interfere with the anticoagulant effects of warfarin in healthy volunteers.[34]

4. Therapeutic Use

4.1 Essential Hypertension

Trandolapril significantly decreases systolic BP (SBP) and diastolic BP (DBP) in patients with mild to moderate essential hypertension. In placebo-controlled dose-finding studies comparing trandolapril 2, 4 and 8 mg/day for 8 to 28 days, the 2mg dosage caused maximal BP reduction with no significant additional antihypertensive activity observed with the higher dosages.[1] The antihypertensive efficacy of trandolapril has been compared with that of other ACE inhibitors and antihypertensive agents.

In major studies investigating the use of trandolapril as an antihypertensive agent, efficacy was evaluated by determining the percentage of patients with 'normalised' BP (≤160/90mm Hg for SBP/DBP) and/or the percentage of patients 'responding' with a DBP of ≤90mm Hg or a decrease in DBP of ≥10mm Hg. Agents were also compared in terms of the absolute mean decrease in SBP and DBP. Patients in these multicentre, randomised, double-blind studies had mild to moderate hypertension defined as a sitting or supine DBP of ≥90mm Hg, and usually ≤115mm Hg, after a 2- to 4-week washout period. Tables III and IV summarise the results of comparative trials of trandolapril in patients with hypertension.

4.1.1 As Monotherapy

Since the previous review of trandolapril in *Drugs*,[1] 2 further studies[38,39] have confirmed earlier data[36,37] indicating that trandolapril has comparable antihypertensive efficacy to enalapril given once daily (table III). Responder rates varied from 65% with trandolapril and 67% with enalapril in a large Japanese study[36] to 47 and 40%, respectively, in a smaller study using 24-hour ambulatory BP (AMBP) monitoring.[38] In this latter study, BP decreased significantly versus baseline with both agents during the awake period and the sleep period, and antihypertensive efficacy was maintained during the early hours of the morning without affecting the circadian cycle.[38]

Table III. Comparative antihypertensive efficacy of trandolapril (TRA) and other ACE inhibitors in patients with mild to moderate essential hypertension. All studies were multicentre, randomised, double-blind and had a 2- to 4-week run-in period. The mean age of the patients in these studies ranged from 52 to 55 years (when stated). All agents were administered once daily and all measurements were sitting or supine office blood pressure (BP), unless otherwise stated. All reductions in BP were significant versus post run-in baseline

Reference	Duration of treatment (wk)	No. of patients	Dosage (mg/day)	Antihypertensive efficacy		
				mean reduction in SBP/DBP (mm Hg)	patients responding (%)[a]	comparative efficacy
Captopril (CAP)						
Pauly & Safar[35]	16	88	TRA 4	23/16	97*	TRA > CAP
		92	CAP 200[b]	20/14	79	
Enalapril (ENA)						
Arakawa et al.[36]	12	138	TRA 0.5-2		64.9	TRA ≡ ENA
		161	ENA 2.5-10		67.1	
de Leeuw & Pauly[37]	8	81	TRA 4	12[c]		TRA ≡ ENA
		78	ENA 20	14[c]		
Poirier et al.[38][d]	>10	34	TRA 0.5-4	10/6	47	TRA ≡ ENA
		37	ENA 2.5-20	12/8	40	
Vaur et al.[39][d]	3	40	TRA 2	13/9		TRA ≡ ENA
		36	ENA 20	10/8		
Lisinopril (LIS)						
Wiseman & McTavish[1][e]	NR	236 (total)	TRA 1		60	TRA ≡ LIS
			LIS 10		67	
Perindopril (PER)						
Vaur et al.[40][f]	4	57	TRA 2	13†/7		TRA > PER
		62	PER 4	9/5		

a DBP ≤ 90mm Hg or decreased by ≥10mm Hg.

b Administered as a divided dose twice daily.

c Results are given as SDBP which was not defined.

d 24-hour ambulatory BP measurement.

e Review of unpublished paper.

f Home self-measured BP.

DBP = diastolic BP; **NR** = not reported; **SBP** = systolic BP; **>** indicates significantly better antihypertensive efficacy; ≡ indicates equivalent antihypertensive efficacy; * p = 0.003 *vs* CAP; † p < 0.05 *vs* PER.

The BP lowering effect of trandolapril appears to be better maintained than that of enalapril if a dose is missed. In a study that used AMBP monitoring, trandolapril 2 mg/day reduced mean daytime BP by 13/9mm Hg and night-time BP by 12/8mm Hg, and enalapril 20 mg/day reduced daytime BP by 11/8mm Hg and night-time BP by 8/7mm Hg.[39] However, missing a dose decreased the night-time reduction to 4/3mm Hg with enalapril and to 8/5mm Hg with trandolapril. SBP trough/peak ratios adjusted for placebo during treatment and after a missed dose, respectively, were 90 and 58% with trandolapril and 49 and 10% with enalapril. Corresponding ratios for DBP were 54 and 36% with trandolapril and 49 and 19% with enalapril. [39]

The 24-hour antihypertensive efficacy of trandolapril 2 mg/day and perindopril 4 mg/day has been compared over a 4-week period using home self-measured BP in 119 patients.[40] The mean evening BP decreased from 151/97 to 137/89mm Hg with trandolapril, and similarly from 151/97 to 139/90mm Hg with perindopril. However, the reduction in morning (predose) BP was significantly greater with trandolapril than with perindopril [147/96 to 137/90mm Hg *vs* 149/98 to 143/94mm Hg (p = 0.05)], indicating that trandolapril was able to sustain greater BP reductions than perindopril over the full 24-hour period.[40]

Early comparative trials showed that trandolapril had antihypertensive efficacy similar to that of

Table IV. Comparative antihypertensive efficacy of trandolapril (TRA) and antihypertensive agents other than ACE inhibitors in patients with mild to moderate essential hypertension. Unless otherwise stated, all studies were multicentre, randomised, double-blind and had a 2- to 4-week run-in period. The mean age of the patients in these studies ranged from 51 to 57 years (when stated), except for the study by Zannad et al.[41] in which the mean age was 71 years. All agents were administered once daily and all measurements were sitting or supine office blood pressure (BP), unless otherwise stated. All reductions in BP were significant versus post run-in baseline

Reference	Duration of treatment	No. of patients	Dosage (mg/day)	Antihypertensive efficacy		
				mean reduction in SBP/DBP (mm Hg)	patients responding (%)[a]	comparative efficacy
Hydrochlorothiazide (HYD)						
Meyer & Pauly[42]	16wk	68	TRA 2	12/11	63	TRA + HYD > TRA ≡ HYD
		68	HYD 25	14/11	60	
		69	TRA 2 + HYD 25	21†/15†	77	
Atenolol (ATN)						
Wiseman & McTavish[1]b	16wk	295 (total)	TRA 2 or 4		65	TRA ≡ ATN
			ATN 50 or 100		74	
Amlodipine (AML)						
Aranda et al.[27]c,d,e,f,g	12mo	18	TRA 2 or 4	10/12	61	TRA ≡ AML
		18	AML 5 or 10	13/11	66.7	
Winnicki et al.[43]c,e	8wk	20	TRA 2-4	8/6		TRA ≡ AML
		20	AML 5-10	9/6		
Nifedipine (sustained release) [NIF]						
Steiner & Pauly[44]	16wk	54	TRA 2	14/12	67	TRA + NIF > TRA ≡ NIF
		55	NIF 40	18/15	76	
		52	TRA 2 + NIF 40	23‡/19‡	87	
Nitrendipine (NIT)						
Zannad et al.[41]c	75d	30	TRA 2	19/13	70	TRA ≡ NIT
		34	NIT 20	21/15	79	
Verapamil (sustained release) [VER]						
Compagnone et al.[45]h	6wk	424 (total)	TRA 1	11		
			TRA 2	14		TRA + VER > TRA ≡ VER
			VER 120	11		
			VER 180	9		
			TRA 1 + VER 120	15†		
			TRA 1 + VER 180	16†		
			TRA 2 + VER 180	15†		
Levine et al.[46]	6wk	723 (total)	PLA	2/2		TRA + VER > TRA ≡ VER > PLA
			TRA 2	6*/6**	38.8**	
			TRA 8	7**/6**	41.9**	
			VER 180	6*/5**	29.8**	
			VER 240	7*/6**	31.3**	
			TRA 2 + VER 180	10**/8**†	48.5**	
			TRA 2 + VER 240	12**/9**†	62.8**	
			TRA 8 + VER 240	11**/9**†	50**	

Table IV. contd

Reference	Duration of treatment	No. of patients	Dosage (mg/day)	Antihypertensive efficacy		
				mean reduction in SBP/DBP (mm Hg)	patients responding (%)[a]	comparative efficacy
Messerli et al.[47]	6wk	152	PLA	NR		
		155	TRA 4	9**/5**		TRA + VER > TRA ≡ VER > PLA
		155	VER 240	8**/4**		
		163	TRA 4 + VER 240	13**†/8**†		
Nalbantgil et al.[48]j	6wk	20	TRA 2	24/9		TRA + VER > TRA ≡ VER
		20	VER 240	18/6		
		20	TRA 1 + VER 120	31†/12†		
Veratran Study Group[49]j	8wk	51	PLA	4/4		
		50	TRA 1	18**/11**		
		56	VER 180	9/7		TRA + VER ≡ TRA > VER
		77	TRA 1 + VER 180	20**††/12**††		
Viskoper et al.[50]	8wk	310 (total)	TRA 2	13/11		TRA + VER > TRA ≡ VER
			VER 180	10/10		
			TRA 2 + VER 180	18†/13†		

a DBP ≤90mm Hg or decreased by ≥10mm Hg.

b Review of unpublished paper.

c 24-hour ambulatory BP measurement.

d Duration of run-in period not specified.

e Nonblind.

f Patients with type 2 diabetes mellitus.

g Single centre.

h Only mean reduction in DBP reported.

i Obese patients, body mass index >27 kg/m^2.

j Semi-automated BP measurement.

DBP = diastolic BP; **NR** = not reported; **PLA** = placebo; **SBP** = systolic BP; + = combination therapy; **>** indicates significantly better antihypertensive efficacy; ≡ indicates equivalent antihypertensive efficacy; * p < 0.05, ** p < 0.01 *vs* PLA; ‡ p < 0.01 *vs* TRA; †† p < 0.05 *vs* VER; † p < 0.05 *vs* monotherapy with TRA or comparator (HYD or VER).

lisinopril and superior to that of captopril.[1] No further comparisons with these drugs have been published.

Trandolapril has recently shown similar antihypertensive efficacy to the calcium antagonists amlodipine (in patients with diabetes mellitus)[27] and nitrendipine (in elderly patients),[41] [see section 4.1.4] adding to previous data showing similar efficacy between trandolapril and antihypertensive agents other than ACE inhibitors [namely, atenolol, hydrochlorothiazide and nifedipine SR (table IV)].[1,42,44,51]

4.1.2 As Combined Therapy

At the time of the previous review,[1] both diuretics and calcium antagonists had been added to trandolapril monotherapy to control BP when control was not achieved with trandolapril alone.[52] Furthermore, the combinations of trandolapril 2 mg/day plus hydrochlorothiazide 25 mg/day[42] and trandolapril 2 mg/day plus nifedipine SR 40 mg/day[44] reduced BP to a significantly greater extent than monotherapy with these agents (table IV).[42,44] Since then, the combination of trandolapril and verapamil SR has been extensively inves-

tigated in randomised, double-blind, parallel group studies (table IV).[45-50]

A 4 × 4 factorial dosage comparison in 723 patients (16 different treatment groups, each of 35 to 67 patients) over 6 weeks showed that once-daily trandolapril/verapamil SR 2mg/180mg, 2mg/240mg and 8mg/240mg produced significantly greater decreases in sitting DBP at the end of the dosage interval (7.1, 7.4 and 7.7mm Hg, respectively) than monotherapy with either drug at the same dosage.[46] Furthermore, in a 4 × 3 multifactorial study in 424 patients over 6 weeks, DBP was reduced by 16, 15.1 and 15.2mm Hg with trandolapril/verapamil SR 1/180, 2/180 and 1/120 mg/day, respectively.[45] Again, these reductions were significantly greater than those with monotherapy.

The antihypertensive efficacy of trandolapril 1 to 4 mg/day plus verapamil SR 180 to 240 mg/day has been compared with the individual agents at the same dosages in >1100 patients.[47,49,50] Both monotherapies and the combination therapy produced a significant reduction in BP after 3 to 8 weeks compared with baseline. However, the reduction in BP was significantly greater for trandolapril/verapamil SR recipients than for patients receiving trandolapril or verapamil SR alone.[47,49,50] Furthermore, the trough/peak ratio for 24-hour mean DBP was 67 to 77% with trandolapril/verapamil SR compared with 50 to 75% with trandolapril and 47 to 56% with verapamil alone.[47,49]

Trandolapril 2 to 8 mg/day has also been successfully administered as sequential therapy with verapamil SR 180 mg/day then hydrochlorothiazide 12.5 to 25 mg/day in White (n = 58) and Black (n = 32) patients with severe hypertension.[53] The percentages of patients responding to treatment with trandolapril, trandolapril/verapamil SR and trandolapril/verapamil SR/hydrochlorothiazide were 45, 56 and 78%, respectively.

4.1.3 24-Hour Control of Blood Pressure

The trough/peak ratio of BP reduction provides a guide as to whether 24-hour BP control can be achieved with once-daily administration. During steady-state treatment, any antihypertensive drug should retain most of its peak BP lowering effect over the dosage interval, and specifically the trough effect should be no less than half of the peak effect.[54-56]

Trough/peak ratios for trandolapril in individual clinical trials were consistently >50% (table V).[57,58] A literature analysis that selected papers published from 1974 to 1994 included studies in patients with mild to moderate hypertension receiving ACE inhibitor monotherapy (for ≥2 weeks after a ≥2 week run-in period) in which BP was measured by 24-hour ambulatory monitoring and hourly mean BP values were reported.[58] The trough/peak ratios in 6 trandolapril, 8 enalapril and 10 lisinopril studies were compared.[58] Although the trough/peak ratios varied greatly from study to study, they were ≥50% for trandolapril in all 6 studies with a mean SBP trough/peak ratio of 72% and DBP trough/peak ratio of 70%. Both SBP and DBP trough/peak ratios were ≥50% in 7 of 10 studies with lisinopril, while with enalapril SBP and DBP trough/peak ratios were ≥50% in 2 of 8 and 3 of 8 studies, respectively. In a follow-up analysis of studies of ACE inhibitors or calcium antagonists administered once a day after a placebo run-in and published from 1986 to 1994 (all other criteria the same), average trough/peak ratios were ≥50% with trandolapril (range 50 to 100%), cilazapril, enalapril, fosinopril and ramipril (range 51 to 84%), and with the calcium antagonists amlodipine, diltiazem SR, nifedipine CC (coat core), nifedipine GITS, lacidipine and verapamil SR (range 51 to 82%).[57]

Trandolapril provides effective 24-hour BP control when administered once daily.[39,41,49,59,60] When 24- and 48-hour AMBP monitoring was used in patients with mild to moderate hypertension to evaluate the duration of antihypertensive action of trandolapril, significant reductions in both SBP and DBP were evident throughout the 24-hour interval.[38-41,49,59,61,62] In studies where the last dose was missed or replaced by placebo, trandolapril 2mg sustained the significant decrease in BP, compared with baseline or placebo, for a further 4 to 24 hours after the initial 24-hour postdose period.[39,59,61,62]

Table V. 24-hour control of blood pressure (BP) with trandolapril. Trough/peak ratio of BP reduction with trandolapril in patients with mild to moderate hypertension. Summary of results from randomised, double-blind studies

Reference	No. of patients	Trandolapril dosage in mg/day (treatment duration weeks)	Trough/peak ratio (%)	
			SBP	DBP
Cesarone et al.[59]	14	1 (2)	100	100
	13	2 (2)	75	86
Messerli et al.[47]	155	4 (6)	NR	75
Omboni et al.[60]	62	2 (6)	60	70
Vaur et al.[39]	88	2 (3)	90	54
Veratran Study Group[49]	39	1 (8)	43	41
Zannad et al.[41]	64	2 (75 days)	70	71

DBP = diastolic BP; **NR** = not reported; **SBP** = systolic BP.

4.1.4 Specific Patient Groups

Previous findings from a subgroup analysis of a large multicentre trial (n = 1042)[52] suggested that the antihypertensive efficacy of trandolapril in elderly (n = 100), glucose intolerant (n = 56), renally impaired (n = 65) and overweight (n = 227) patients is comparable to that seen in the general population. Several subsequent studies have further investigated these findings.[2,22,26,27,41,48,53,63,64]

Elderly Patients

Trandolapril is an effective antihypertensive agent when used as monotherapy in elderly patients with mild to moderate hypertension.[41,63] It has also been successfully combined with calcium antagonists in this patient group. In a large (n = 13 147) multicentre general practice study of patients >60 years of age (mean 68 years), trandolapril 2 or 4 mg/day lowered mean SBP by 22mm Hg and DBP by 12mm Hg compared with baseline after 8 weeks.[63] 82% of patients were considered responders. Calcium antagonists were added after 4 weeks' treatment in some nonresponders, and in this group of patients (n = 1712) mean BP decreased by 21/12mm Hg after 8 weeks' total treatment, with a responder rate of 84%.[63] The antihypertensive efficacy of trandolapril 2 mg/day was similar to that of nitrendipine 20 mg/day when administered once daily for 75 days in 64 patients aged ≥65 years (see table IV).[41] Trandolapril trough/peak ratios for SBP and DBP were 70 and 71%, respectively, compared with 26 and 28%, respectively, for nitrendipine.[41]

Black Patients

In general, ACE inhibitors and β-blockers are thought to be less effective antihypertensive agents in Black patients than diuretics and calcium antagonists.[56] However, a reduction in salt intake, an increase in drug dosage or the addition of a diuretic have been used to overcome this when an ACE inhibitor or β-blocker are indicated for other therapeutic reasons.[56] Trandolapril is effective in Black patients at higher dosages than those required for White patients.[2,53] Trandolapril 4 mg/day was required to produce a 6.5mm Hg decrease in mean DBP compared with baseline in Black patients (n = 91), whereas in White patients (n = 207), trandolapril 1 mg/day achieved a similar decrease (6.1mm Hg).[2] Trandolapril has also been successfully used in Black patients with severe hypertension in double (trandolapril plus verapamil SR) and triple (trandolapril plus verapamil SR plus hydrochlorothiazide) combinations.[53]

Overweight Patients

Trandolapril appears to have antihypertensive efficacy in patients with a body mass index (BMI) ≥24 kg/m^2 as evidenced by responder rates of 85 to 92% in 2 short term nonblind studies involving a total of >500 patients.[26,64] In a small (n = 20), double-blind, crossover study, both trandolapril 2 mg/day and verapamil SR 240 mg/day produced significant decreases in BP of up to 24/9mm Hg.[48] However, even greater decreases were seen with the lower dose combination of trandolapril/verapamil SR 1/180 mg/day.

Patients with Diabetes Mellitus

Trandolapril effectively reduced BP long term (≥3 months) in patients with hypertension and type 2 diabetes mellitus without producing adverse metabolic effects in 2 small studies (total n = 103) [see also section 2.4].[22,27] In 36 patients receiving glibenclamide (glyburide), mean 24-hour BP

was reduced by 11/12mm Hg with trandolapril 2 or 4 mg/day and by 13/11mm Hg with amlodipine 5 or 10 mg/day for 12 months.[27]

4.2 Post-Myocardial Infarction

The use of trandolapril to improve outcome after acute MI in patients with LV dysfunction has been investigated in the Trandolapril Cardiac Evaluation (TRACE) study.[65] In this study, trandolapril significantly reduced the risk of mortality from all causes, including cardiovascular mortality.

4.2.1 TRACE Study Design

TRACE investigated the efficacy of trandolapril initiated 3 to 7 days after acute MI, and continued for 24 to 50 months, in patients with LV dysfunction.[65] The design of this study is summarised in table VI. The sample size needed was calculated as 1500 based on an expected 25% relative reduction in mortality in the active group compared with placebo and an expected 1-year mortality of 30%.[66] 2606 of 6676 patients with acute MI screened had LV dysfunction. After exclusions, 1749 patients (mean age 68 years) from 27 centres in Denmark were randomised a mean of 4.5 days after MI to trandolapril [1 mg/day for 2 days, then 2 mg/day for 4 weeks, then 4 mg/day for 24 to 50 months (n = 876)] or placebo (n = 873).[65,66]

Table VI. Design of the TRACE (Trandolapril Cardiac Evaluation) study investigating the efficacy and tolerability of trandolapril (TRA) in patients with LV dysfunction after MI[65]

Inclusion criteria	Chest pain or ECG changes indicative of MI or myocardial ischaemia, and an increase in ≥1 cardiac enzyme levels to ≥2 times the upper limit of normal. A WMI ≤1.2 (corresponding to an LVEF of ≤35%) measured by echocardiography[67]
Study design	Randomised, double-blind, parallel-group, placebo-controlled, multicentre
Patient age	Mean 67.5 years.
Patient numbers	876 received TRA and 873 received placebo
Treatment regimen	Oral TRA 1 mg/day for 2 days, then 2 mg/day for 4 wks, then 4 mg/day for 24 to 50mo. The dosage of TRA could be reduced to 1 or 2 mg/day if the 4 mg/day dosage was not tolerated
Treatment duration	24 to 50mo
Concurrent medication	Aspirin, β-blockers, calcium antagonists, diuretics, nitrates, digoxin or digitalis, if indicated
Primary efficacy endpoint	All-cause mortality assessed on an intent-to-treat basis
Secondary efficacy endpoints	Cardiovascular death, sudden death[a], progression to severe CHF (admission to hospital with CHF, death from CHF, or requirement for nonblind ACE inhibitor therapy), recurrent fatal or nonfatal MI[b], and change from baseline in WMI
Statistical significance level	Final analysis of the primary endpoint used an asymmetric, one-sided test with a significance level of 0.0225 in favour of TRA and 0.10 in favour of placebo. Two-sided p values are cited.

a Sudden death was defined as death within 1 hour of new symptom onset.

b Reinfarction was defined as the onset of new symptoms or typical ECG changes accompanied by elevated cardiac enzyme levels (or both), or as the development of a new Q wave accompanied by typical symptoms.

ACE = angiotensin converting enzyme; **CHF** = congestive heart failure; **ECG** = electrocardiographic; **MI** = myocardial infarction; **LV** = left ventricular; **LVEF** = LV ejection fraction; **WMI** = wall motion index.

4.2.2 Results of TRACE

The TRACE study demonstrated that treatment with trandolapril starting within 3 to 7 days of acute MI significantly reduces all-cause mortality and cardiovascular mortality among patients with LV systolic dysfunction.[65] At study end, 34.7% of trandolapril recipients had died compared with 42.3% of placebo recipients. The relative risk of death from any cause with trandolapril, as compared with placebo, was 0.78 (95% confidence interval, 0.67 to 0.91; p = 0.001). Furthermore, the relative risk of cardiovascular mortality [0.75 (0.63 to 0.89); p = 0.001], sudden death [0.76 (0.59 to 0.98); p = 0.03] and progression to severe CHF [0.71 (0.56 to 0.89); p = 0.003] were all significantly reduced with trandolapril compared with placebo (fig. 1). In addition, there was a trend for the risk of reinfarction to be reduced with trandolapril compared with placebo [0.86 (0.66 to 1.13); p = 0.29].

At 3 months, mean change from baseline in wall motion index (WMI) was +0.09 with trandolapril and +0.06 with placebo (p = 0.03). However, no statistically significant difference in WMI change

from baseline was evident between treatment groups at 6 and 12 months.[65]

Subgroup analysis

Trandolapril was associated with a reduction in the relative risk of death from any cause in all subgroups of patients examined.[65] Characteristics investigated included age, gender, WMI, site of infarction, previous infarction, residual angina, Killip class, and diuretic, thrombolytic, aspirin, β-blocker and nitrate therapy. Importantly, the survival benefit with trandolapril was seen in patients with and without CHF.[65] CHF was diagnosed in patients with a Killip class >1 or a history of CHF treated medically.[68] The relative risk for trandolapril compared with placebo was 0.82 (95% CI, 0.69 to 0.98) and 0.70 (0.52 to 0.96), respectively, in patients with and without a Killip class value ≥1 recorded between MI and randomisation.[65]

Furthermore, the beneficial effect of trandolapril appears more marked in patients with a history of hypertension.[69] The relative risk for total mortality with trandolapril versus placebo in patients with a history of hypertension was 0.59 (0.44 to 0.80) compared with 0.85 (0.72 to 1.02; p = 0.03) for those without hypertension.[69]

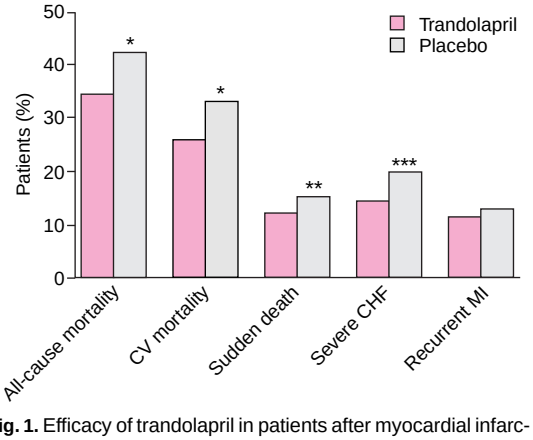

Fig. 1. Efficacy of trandolapril in patients after myocardial infarction (MI). Event rates (percentage of patients) for all-cause mortality, cardiovascular (CV) mortality, sudden death, severe congestive heart failure (CHF) and recurrent MI among patients receiving trandolapril 1 to 4 mg/day (n = 876) or placebo (n = 873) for 24 to 50 months; results from the Trandolapril Cardiac Evaluation (TRACE) study.[65] * p = 0.001, ** p = 0.03 and *** p = 0.003 *vs* placebo.

4.2.3 Pharmacoeconomic Evaluation of TRACE

A cost-effectiveness analysis has recently been conducted using individual raw data from TRACE.[70] The analysis was differential and from a payer perspective in a French setting. The cost variables (programme costs) were simply the acquisition cost of trandolapril versus the cost of additional medication and clinical events likely to be prevented by treatment with trandolapril, i.e. reinfarction, percutaneous transluminal angioplasty, coronary artery bypass graft surgery and severe CHF. The effectiveness indicator was the number of life-years saved. No additional survival benefit with trandolapril beyond the follow-up period of TRACE was assumed.

The total programme cost was 22 080 500 French francs (FF; 1996 value) in patients receiving trandolapril compared with FF20 317 300 in the placebo group. Thus, the difference between groups was FF1 763 200 for 65 lives saved (304 deaths with trandolapril *vs* 369 with placebo; p = 0.001) or FF27 100 per life saved. The life expectancy at the end of the trial was calculated as 5.52 years. Thus, the average cost per life-year saved was FF4910, and the use of trandolapril in post-MI patients was considered to be cost-effective.[70]

A recent French study compared several relevant trials [TRACE, AIRE (Acute Infarction Ramipril Efficacy study), GISSI-3 (Gruppo Italiano per lo Studio della Sopravvivenzia nell'Infarto Miocardico), ISIS-4 (International Study of Infarct Survival Collaborative Group) and SAVE (Survival and Ventricular Enlargement)] from a medico-economic standpoint and concluded that trandolapril in the TRACE study was a significantly more cost-effective treatment than lisinopril in GISSI-3, ramipril in AIRE or captopril in ISIS-4 and SAVE.[71] However, the designs of these studies and the risk levels of patients included in them were different, and the validity of the methods used in this analysis cannot be confirmed as it has only been published as an abstract.[71]

4.3 Congestive Heart Failure

Guidelines from both the US and Europe recommend that ACE inhibitors be used as the mainstay of therapy for CHF.[72,73] The results of TRACE show that trandolapril has long term benefits in patients with CHF after MI.[65] However, only 1 study has been published specifically assessing the efficacy of trandolapril alone in the treatment of patients with CHF.[74] In this noncomparative multicentre study, trandolapril titrated from 0.5 to 4 mg/day for 10 weeks improved NYHA functional class in 15 of 27 (56%) patients with NYHA class II (n = 17) or III (n = 10) CHF at baseline.[74]

Combined treatment with trandolapril and verapamil SR may be beneficial in patients with CHF as indicated by the results of 2 small pilot studies.[75] These multicentre, randomised, nonblind studies were performed consecutively. After a 2-week dose titration, trandolapril 4 mg/day plus verapamil SR 360 mg/day was administered for 10 weeks to 14 patients with NYHA class II or III CHF and angina pectoris. Mean exercise duration improved from 6.9 minutes at baseline to 7.7 minutes ($p \leq 0.05$). In a follow-up study in 100 patients with CHF between 3 and 10 days post MI, trandolapril plus verapamil (1/240mg for 4 weeks then 2/360mg for 8 weeks) significantly improved the reinfarction rate compared with trandolapril alone after 3 months of treatment (2 *vs* 14%; $p = 0.03$).[75] A 2% death rate was seen in both treatment groups. The hazard ratio for the combined endpoint of death, recurrent MI, unstable angina and readmission for CHF was 0.35 (95% confidence interval 0.15 to 0.85; $p = 0.01$) for trandolapril plus verapamil versus trandolapril alone. Concomitant medication in this latter study included diuretics in all patients, and aspirin, digoxin and long-acting nitrates in 91, 22 and 40 patients, respectively. More studies are needed to better define the role of this combination therapy in patients with CHF after MI.

5. Tolerability

Trandolapril is generally well tolerated and produces adverse effects typical of ACE inhibitors as a class. It has yet to be established if the pharmacodynamic and pharmacokinetic differences between trandolapril and other ACE inhibitors have any clinically significant effect on tolerability. Cough, asthenia, dizziness, headache and nausea are the most frequently reported events with trandolapril.[1,52]

The incidence and type of adverse event in 2 recent studies in a large number of patients with hypertension (n = 23 967)[63,76] are consistent with those reported in an earlier large multicentre study of long term (3 months to 1 year) trandolapril use (n = 786).[52] The overall incidence of adverse events was 10% (n = 1081) in a postmarketing observational cohort study in 10 820 patients receiving trandolapril 0.5 to 4 mg/day for ≥6 months.[76] Adverse events which occurred in ≥0.33% of patients in this study are shown in figure 2. Cough was the most common event (3.6%), followed by asthenia (1.0%), dizziness (0.9%), headache (0.7%), nausea and/or vomiting (0.6%), orthostatic effect (giddiness, syncope and possibly hypotension; 0.5%) and rash/pruritus (0.4%). The majority of adverse events were mild and transient. 4.9% of patients discontinued treatment as a result of adverse events. Only 5 patients had a serious event considered to have been caused or exacerbated by trandolapril.[76]

Trandolapril therapy was equally well tolerated in elderly patients (n = 13 147) receiving trandolapril 2 or 4 mg/day for 8 weeks in a multicentre clinical study.[63] The overall incidence of adverse events in this study was 9.7% and the withdrawal rate was 2.8%. The most frequent adverse events in this population were cough (2.8%), headache (0.8%), vertigo (0.8%) and nausea (0.5%). Trandolapril was well tolerated in Black patients,[2] overweight patients,[26,64] and patients with diabetes mellitus[22] in comparative clinical trials. Adverse events occurring in >1% of 1069 patients in placebo-controlled trials conducted in the US were cough (1.9 *vs* 0.4%), dizziness (1.3 *vs* 0.4%) and diarrhoea (1 *vs* 0,4%) for trandolapril *vs* placebo, respectively.[77]

Trandolapril was at least as well tolerated as enalapril in clinical studies comparing these 2

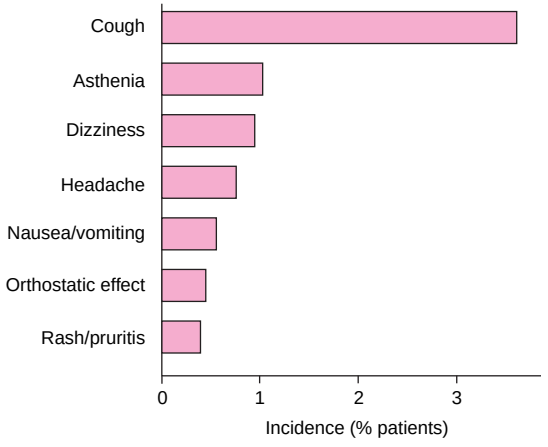

Fig. 2. Tolerability of trandolapril. Incidence of adverse events occurring in ≥0.33% of patients with hypertension (n = 10 820) receiving trandolapril 0.5 to 4 mg/day for ≥6 months in a post-marketing surveillance study. All adverse events not considered unlikely to be associated with trandolapril were included, i.e. all doubtful, possible, probable and certain adverse events.[76]

agents,[36-38] with no difference in the type or severity of adverse events reported. In a single multicentre study, trandolapril 4 mg/day was better tolerated than captopril 200 mg/day, with 9 versus 23% of patients experiencing an adverse event.[35] Six captopril but no trandolapril recipients withdrew from treatment because of adverse events. Interestingly, in a small observational study, cough occurred in 15 to 20% of patients with hypertension receiving captopril 40 to 100 mg/day (n = 40), enalapril 10 to 20 mg/day (n = 36) or trandolapril 2 to 4 mg/day (n = 46), regardless of treatment group.[78] However, cough occurred a mean of 3 to 6 weeks after the start of captopril or enalapril therapy but was not seen before 12 weeks with trandolapril.

The incidence and severity of adverse events with trandolapril was similar to that observed in patients receiving atenolol,[51] hydrochlorothiazide,[42] amlodipine,[27] nitrendipine,[41] and verapamil in clinical trials.[47] In 1 study, 17% of 54 trandolapril recipients experienced an adverse event considered probably or possibly related to treatment compared with 35% of 55 nifedipine SR recipients ($p < 0.05$), and there were 4 trandolapril-related withdrawals compared with 8 related to nifedipine SR.[44]

Trandolapril was generally well tolerated in patients with LV dysfunction after MI in the TRACE study. Adverse events necessitating withdrawal of trandolapril and placebo recipients, respectively, were cough (0.04 *vs* 0.01%), hypotension (0.02 *vs* 0.01%) and reduction in renal function (0.02 *vs* 0.01%).[65] Adverse events occurring significantly more frequently with trandolapril than with placebo were cough (33.9 *vs* 21.0%), hypotension (31.1 *vs* 22.2%), renal dysfunction (13.7 *vs* 10.8%), peripheral vascular disorder (3.8 *vs* 1.8), hyperkalaemia (4.9 *vs* 2.6) and atrial flutter (1.8 *vs* 0.7).[65] It should be noted that patients were specifically asked about cough at each follow-up visit. The test dose of trandolapril 0.5mg was not tolerated in 4.5% of the 859 patients screened as appropriate for inclusion but then excluded from TRACE (i.e. 1.5% of the total 2060 screened).[65]

6. Dosage and Administration

An initial oral trandolapril dosage of 2mg once daily is recommended in adult patients with hypertension or CHF without renal or hepatic failure. The dosage may be increased to 4mg once daily to achieve optimal BP reduction. If BP is still not controlled, the addition of a thiazide diuretic or calcium antagonist should be considered. In patients with LV hypertrophy post-MI, the initial dosage recommended is 0.5mg once daily, slowly titrated to 4 mg/day.[79]

Trandolapril dosage should be reduced in patients with severe renal failure (creatinine clearance <1.8 L/h/1.73m^2) because of decreased renal elimination.[31] The initial dosage recommended in these patients is 0.5 mg/day, increasing to 1 mg/day if required, with monitoring of renal function. The initial dosage of trandolapril should also be reduced to 0.5 mg/day in patients with severe hepatic failure (Pugh's classification 8 to 13) and then adjusted if necessary according to therapeutic response.

Trandolapril is contraindicated in patients with a known hypersensitivity to trandolapril or another

ACE inhibitor, or a history of angioneurotic oedema. It should not be administered to children, or pregnant or breastfeeding women.

Concomitant administration of NSAIDs can attenuate the antihypertensive effect of ACE inhibitors.[1,80] However, indomethacin 75 mg/day for 3 weeks did not attenuate the efficacy of trandolapril 2 mg/day in 23 patients with mild to moderate hypertension during a randomised, placebo-controlled study.[80] As with other ACE inhibitors, trandolapril should be used with caution in patients already receiving potassium salts or potassium sparing diuretics because of the predisposition to hyperkalaemia.[81] Precautions should also be taken when coadministering trandolapril with lithium (as the elimination of lithium may be reduced), probenecid (as the combination may augment renal excretion of uric acid) and narcotics, antipsychotics and antidepressants (because of an increased risk of postural hypotension).[33,81]

7. Place of Trandolapril in the Management of Cardiovascular Disorders

7.1 Hypertension

ACE inhibitors are now established as an important class of antihypertensives and are widely prescribed. The 1997 Sixth Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommends ACE inhibitors as first line agents in patients with hypertension and concomitant LV dysfunction, CHF or coronary artery disease (CAD), and in patients with diabetic nephropathy.[56] JNC-VI also recommends long acting formulations that provide 24-hour efficacy for reasons of increased compliance, possible decreased cost, smoother BP control and protection against the risk of hypertensive crisis after arising from overnight sleep.

For optimal control of hypertension, BP needs to be consistently reduced over a full 24-hour period without increasing variability in BP itself, i.e. BP still follows the normal circadian cycle, with a lower BP during sleep and the ability to increase when the patient is awake, but with minimal or no risk of a sharp increase in BP in the early morning (which is associated with morbidity related to cardiovascular events and the incidence of LV hypertrophy).[54] Ideally, BP control should extend beyond the 24-hour dosing period because many patients inadvertently miss ≥1 dose of medication each week.[56]

Pharmacological characteristics that distinguish trandolapril from other ACE inhibitors are its high binding affinity to ACE, high lipophilicity and long elimination half-life.[1] The most clinically relevant result of these characteristics is a duration of action that is longer than that of other ACE inhibitors. Trandolapril provides effective 24-hour BP control when administered once daily and such administration may increase compliance. It should be noted that other ACE inhibitors are also administered on a once-daily basis, but comparative studies indicate that trandolapril maintains BP reduction for longer than enalapril when a dose is omitted.

The trough/peak ratio for trandolapril 2mg once daily was consistently ≥50% (50 to 100%), and this effect was maintained for SBP after a missed dose in 1 study. Trough/peak ratios ≥50% after once-daily administration have been reported for cilazapril, enalapril, fosinopril and ramipril.

Up to 50% of patients with mild to moderate hypertension require more than 1 antihypertensive agent to achieve and sustain BP control.[82,83] Therefore, combination therapy is an important aspect of disease management. The aim of combining 2 agents with different modes of action is to increase antihypertensive efficacy while decreasing the likelihood of adverse events which may occur with higher doses of monotherapy.[82] It has been shown that trandolapril can be effectively combined with hydrochlorothiazide, nifedipine SR and verapamil SR. This latter combination has been extensively studied and consistently reduces BP to a greater extent with a trough/peak ratio higher than monotherapy with either agent.

Trandolapril produces effective BP control in Black patients (albeit at higher dosages than those needed in White patients) and in overweight pa-

tients. Trandolapril is also as effective in elderly (≥65 years) as younger (<65 years) patients with hypertension.

One of the most important advantages of ACE inhibitors over other antihypertensive agents is their relative lack of adverse effects, including metabolic effects, and trandolapril has a tolerability profile typical of the class. Trandolapril is a well tolerated and effective long term antihypertensive agent for patients with diabetes mellitus, and improves renal function in these patients.

The majority of ACE inhibitors are eliminated primarily via the kidneys and dosage adjustments are required in patients with moderate to severe impairment of renal function.[84] However, a compensatory mechanism is evident for trandolapril and fosinopril, which have a dual biliary/renal route of elimination.[79,85] Therefore, in general, trandolapril dosage adjustments are only required in patients with severe renal or hepatic failure.

7.2 Post-Myocardial Infarction

ACE inhibitors are now established therapy in the early management of patients after acute MI.[51,65,86-94] However, there is ongoing debate over which patients should be selected for treatment with these agents and the timing of administration of ACE inhibitors.[86]

The TRACE study showed an early and persistent reduction in mortality among patients with reduced LV function receiving trandolapril starting 3 to 7 days after an acute MI. Furthermore, trandolapril significantly reduced the risk of the secondary endpoints of cardiovascular mortality, sudden death and CHF compared with placebo. Although the reduction in risk of reinfarction with trandolapril compared with placebo was not statistically significant in TRACE, it should be noted that the definition of recurrent MI in this study was strict. The TRACE study is also significant in that benefits were seen in patients followed for 2 to 4 years and that it enrolled a substantial 25% of all screened patients, i.e. exclusion criteria were minimal.

A substantial long term survival benefit with ACE inhibitor therapy initiated several days after MI has also been shown in patients with LV dysfunction without CHF in the SAVE trial,[93] and in patients with CHF with or without LV dysfunction in the AIRE study.[87] Moreover, a significant short term benefit was also demonstrated when ACE inhibitors were administered unselectively to all patients without contraindications within 24 hours of MI in ISIS-4[92] and GISSI-3.[91]

A recent report by the ACE Inhibitor Myocardial Infarction Collaborative Group, who conducted a systematic overview of 4 megatrials [GISSI-3, ISIS-4, CONSENSUS-II (Cooperative New Scandinavian Enalapril Survival study) and CCS-1 (Chinese Cardiac Study)],[89-92] has helped to clarify the issue of timing.[95] The recommendation of this collaborative group was for the early (day 1 or 2 after MI) initiation of ACE inhibitor therapy in patients with acute MI. However, there was less unanimity within the group concerning patient selection.[95,96] One suggested strategy was to administer early ACE inhibitor therapy to all patients without contraindications until discharge from hospital or for a few weeks, and then to continue therapy long term only in patients at high risk of complications, i.e. with extensive LV damage or CHF. An alternative strategy suggested by this group was the early initiation of ACE inhibitor therapy only in high risk patients, e.g. those with an anterior infarct or tachycardia.

To examine the issue of whether patients at lower risk would also benefit from ACE inhibitor therapy, the Prevention of Events with ACE Inhibition (PEACE) study is being conducted by the National Heart, Lung and Blood Institute in the US on the efficacy and tolerability of trandolapril in patients with CAD and preserved LV function (LVEF ≥40%).[97] The primary endpoint of the PEACE study is the incidence of cardiovascular death, nonfatal MI or the need for coronary revascularisation procedures. 8100 patients will be enrolled from 208 centres to ensure a 90% power to detect a 10% relative reduction in this primary outcome, assuming a 19% incidence of this end-

point in the control group. Enrolment has commenced and the study is expected to be completed in the year 2003.[97,98]

Cardiovascular disorders are a major public health issue in all industrialised countries and the development of cost-effective strategies for the management of patients with MI appears to be essential. A cost-effectiveness analysis conducted in France using raw data from TRACE computed a cost-effectiveness ratio of FF27 100 per life saved corresponding to FF4910 per life-year saved.[70]

7.3 Congestive Heart Failure

In 1994, the Agency for Health Care Policy and Research (AHCPR) published guidelines for the evaluation and management of CHF secondary to LV systolic dysfunction (i.e. LVEF < 40%).[72] These guidelines recommend that pharmacological treatment for the condition should routinely be initiated with ACE inhibitors (unless contraindicated) and that additional agents should be used as required. This approach of using ACE inhibitors as the mainstay of therapy is also recommended in the new European guidelines for the treatment of CHF which were published in 1997.[73] Trandolapril improved the NYHA functional class of 56% of patients with CHF while being well tolerated in the 1 study specifically evaluating its effects in such patients.[74] Clearly, further investigation is required to confirm the beneficial effects of trandolapril in patients with CHF.

7.4 Conclusion

In conclusion, trandolapril has a favourable pharmacological profile (high lipophilicity, high affinity for ACE and long duration of action) and an antihypertensive efficacy at least comparable to that of other ACE inhibitors. The pharmacological characteristics of trandolapril allow it to provide good 24-hour control of BP with once-daily administration. Trandolapril has also demonstrated some efficacy in a small number of patients with CHF. In addition, trandolapril provides long term protection against all-cause mortality in patients with LV dysfunction after MI. The results of the PEACE study will determine its potential as a cardioprotective agent in patients with CAD and preserved LV function. Thus, trandolapril represents an effective, well-tolerated and convenient treatment option for patients with mild to moderate hypertension or LV systolic dysfunction after MI.

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