ADIS DRUG EVALUATION

Drugs 1999 Jul; 58 (1): 143-157
0012-6667/99/0007-0143/$15.00/0

Trimetazidine

A Review of its Use in Stable Angina Pectoris and Other Coronary Conditions

Karen J. McClellan and *Greg L. Plosker*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

W.S. Aronow, Hebrew Hospital Home, Bronx, New York, USA; ***C. Guarnieri***, Università Bologna, Bologna, Italy; ***C. Knight***, St George's Hospital, London, England; ***G. Kober***, Clinic Nordrhein, Bad Nauheim, Germany; ***S. Lévy***, Hôpital Nord, University of Marseille School of Medicine, Chemin des Bourrellys, Marseilles, France; ***G.D. Lopaschuk***, University of Alberta, Edmonton, Alberta, Canada; ***S.C. Manchanda***, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India; ***A.P. Michaelides***, Zografou, Athens, Greece; ***F.V. Mody***, UCLA School of Medicine and West Los Angeles VA Medical Center, Los Angeles, California, USA; ***J-M Vedrinne***, Hôpital Edouard Herriot, Place d'Arsonval, Lyon, France.

Data Selection

Sources: Medical literature published in any language since 1966 on trimetazidine, 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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 'trimetazidine', 'trimetazidine-hydrochloride', trimetazine-hydrochloride', 'trimethazidine' and 'ischaemic-heart-disorders'. Medline and EMBASE search terms were 'trimetazidine'. Searches were last updated 12 May 1999.

Selection: Studies in patients with ischaemic heart disorders who received trimetazidine. 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: trimetazidine, ischaemic heart disorders, pharmacokinetics, pharmacodynamics, therapeutic use.

Contents

Abstract

The orally administered antianginal agent trimetazidine increases cell tolerance to ischaemia by maintaining cellular homeostasis. In theory, this cytoprotective activity should limit myocyte loss during ischaemia in patients with angina pectoris.

Data from studies in patients with coronary artery disease indicate that, unlike the effects of other antianginals, the anti-ischaemic effects of trimetazidine 20mg are not associated with alterations in haemodynamic determinants of myocardial oxygen consumption such as heart rate, systolic blood pressure and the rate-pressure product. Furthermore, limited evidence suggests trimetazidine may improve left ventricular function in patients with chronic coronary artery disease or ischaemic cardiomyopathy and in patients experiencing acute periods of ischaemia when undergoing percutaneous transluminal coronary angioplasty.

Clinical studies have shown that oral trimetazidine 20mg 3 times daily reduces the frequency of anginal attacks and nitroglycerin use and increases exercise capacity when used as monotherapy in patients with angina pectoris. Its clinical effects are broadly similar to those of nifedipine 40 mg/day and propranolol 120 to 160 mg/day but, unlike these agents, trimetazidine does not affect the rate-pressure product during peak exercise or at rest.

Adjunctive trimetazidine 60 mg/day reduces the frequency of anginal attacks and nitroglycerin use and improves exercise capacity in patients with angina pectoris not sufficiently controlled by conventional antianginal agents. Furthermore, the drug appears to be more effective than isosorbide dinitrate 30 mg/day when used adjunctively in patients with angina pectoris poorly controlled by propranolol 120 mg/day.

The tolerability profile of trimetazidine 60 mg/day was similar to that of placebo when used as add-on therapy in patients with angina pectoris insufficiently controlled by other antianginal agents and was superior to that of either nifedipine 40 mg/day or propranolol 120 to 160 mg/day when used as monotherapy. The most frequently reported adverse events in trimetazidine recipients were gastrointestinal disorders, although the incidence of these events was low.

Conclusions: Trimetazidine is an effective and well tolerated anti-ischaemic agent which, in addition to providing symptom relief and functional improvement in patients with angina pectoris, has a cytoprotective action during ischaemia. The drug is suitable for initial use as monotherapy in patients with angina pectoris and, because of its different mechanism of action, as adjunctive therapy in those with symptoms not sufficiently controlled by nitrates, β-blockers or calcium antagonists. The role of trimetazidine in other coronary conditions has yet to be clearly established.

1. Introduction

Angina pectoris is a symptomatic manifestation of ischaemic heart disease and is usually caused by atheromatous narrowing of 1 or more of the coronary arteries. Characteristic chest pains or crushing sensations arise when there is an imbalance between myocardial perfusion and metabolic demand; angina pectoris is generally considered stable when symptoms have occurred for several weeks without major deterioration.[1]

Myocardial ischaemia has several metabolic consequences: the production and retention of acid metabolites leading to intracellular acidosis, a reduction in intracellular content of adenosine triphosphate (ATP) and phosphocreatine, accumulation of free fatty acids and the generation of oxygen free radicals.[2] These may lead to myocyte loss and, ultimately, a poor prognosis.

Whereas conventional antianginal agents act haemodynamically to restore the imbalance between myocardial oxygen supply and demand, the piperazine derivative trimetazidine (fig. 1) has a novel anti-ischaemic mechanism of action. This review evaluates the therapeutic efficacy of oral trimetazidine when used as monotherapy or adjunctive therapy in patients with stable angina pectoris. In addition, its use in patients with other coronary conditions such as those with ischaemic cardiomyopathy and those undergoing coronary revascularisation is briefly examined.

2. Pharmacodynamic Profile

2.1 Mechanism of Action

Findings from *in vitro* and *ex vivo* studies of myocardial ischaemia have demonstrated that trimetazidine:

- limits intracellular acidosis[3-6]
- limits sodium and calcium accumulation[4,7,8]
- maintains intracellular ATP levels[3,6,9] and reduces creatine phosphokinase release[6,10]
- preserves mitochondrial function[11-16]
- reduces myocardial fatty acid metabolism[17-20] and increases myocardial glucose metabolism[19-21]

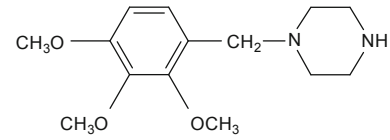

Fig. 1. Chemical structure of trimetazidine.

- protects against oxygen free radical-induced membrane damage[13,22,23]
- inhibits neutrophil infiltration.[24,25]

By inhibiting fatty acid metabolism and secondarily stimulating glucose metabolism, trimetazidine optimises cardiac metabolism and thus protects the heart against the harmful effects of ischaemia. However, the definitive mechanism of action of trimetazidine has yet to be determined.

Consistent with a cytoprotective effect, trimetazidine exhibited anti-ischaemic effects *in vivo*. It limited the extent of necrosis in a rat model of myocardial ischaemia[26] and reduced the extent of nephropathy in a rat model of renal ischaemia.[27] In addition, trimetazidine had a direct anti-ischaemic effect in patients undergoing coronary angioplasty (section 4.2.3).[28]

2.2 Haemodynamic Effects

Data from studies in animals and in patients with coronary artery disease indicate that the anti-ischaemic effects of trimetazidine are not associated with any effects on haemodynamic determinants of myocardial oxygen consumption such as heart rate (HR) or blood pressure.

Intravenous administration of single doses of trimetazidine 0.25 to 1.0 mg/kg had no effects on HR, cardiac output, mean arterial pressure, femoral blood flow or left ventricular (LV) systolic and end-diastolic pressures in closed-chested anaesthetised dogs[29] or on coronary blood flow in open-chested anaesthetised dogs.[29] A higher dose of trimetazidine (2.0 mg/kg) did cause statistically significant (albeit minor and mostly transient) haemodynamic alterations; however, peak plasma drug concentrations after this dose (720 to 1060 μg/L) were markedly higher than those seen after the recommended

therapeutic dosage in humans (84.8 μg/L after 20mg twice daily; section 3.1).

A single oral dose of trimetazidine 60mg had no effects on resting HR or systolic blood pressure (SBP) compared with placebo in 10 men with stable angina pectoris.[30] 15 days' treatment with oral trimetazidine 20mg 3 times daily had no effects on HR or SBP compared with placebo, either at rest or during stress-induced ischaemia, in 15 patients with coronary artery disease (fig. 2).[31] Similarly, oral trimetazidine 20mg 3 times daily had no significant effects on SBP during peak exercise when used on a longer term basis (3 months) as adjunctive therapy in 17 men with stable angina pectoris poorly controlled by β-blockers.[32]

Because HR and SBP during exercise were not affected by trimetazidine, the rate-pressure product (HR × SBP) similarly remained unchanged after a single oral 60mg dose[30] or after repeated administration of a 20mg dose (section 4.1.1)[33-36] in patients with angina pectoris. In contrast, the antianginal agents nifedipine[35] and propranolol[36] significantly reduced the rate-pressure product during exercise in these patients (section 4.1.1).

In 20 patients undergoing percutaneous transluminal coronary angioplasty (PTCA), an intracoronary injection of trimetazidine 6mg had no significant effects on HR and systemic or intracoronary blood pressure compared with placebo.[28]

3. Pharmacokinetic Profile

Few published studies have assessed the pharmacokinetic profile of trimetazidine. Table I presents the main pharmacokinetic properties of the drug after oral administration in healthy volunteers.

3.1 Absorption and Distribution

Trimetazidine is rapidly absorbed from the intestinal mucosa after oral administration. In 13 healthy volunteers, the mean peak plasma trimetazidine concentration (C_{max}; 53.6 μg/L) was reached 1.8 hours after a single 20mg oral dose.[37] After twice daily administration of trimetazidine 20mg for 15 days, C_{max} (84.8 μg/L) was reached in 1.7 hours.[37] The area under the plasma trimetazid-

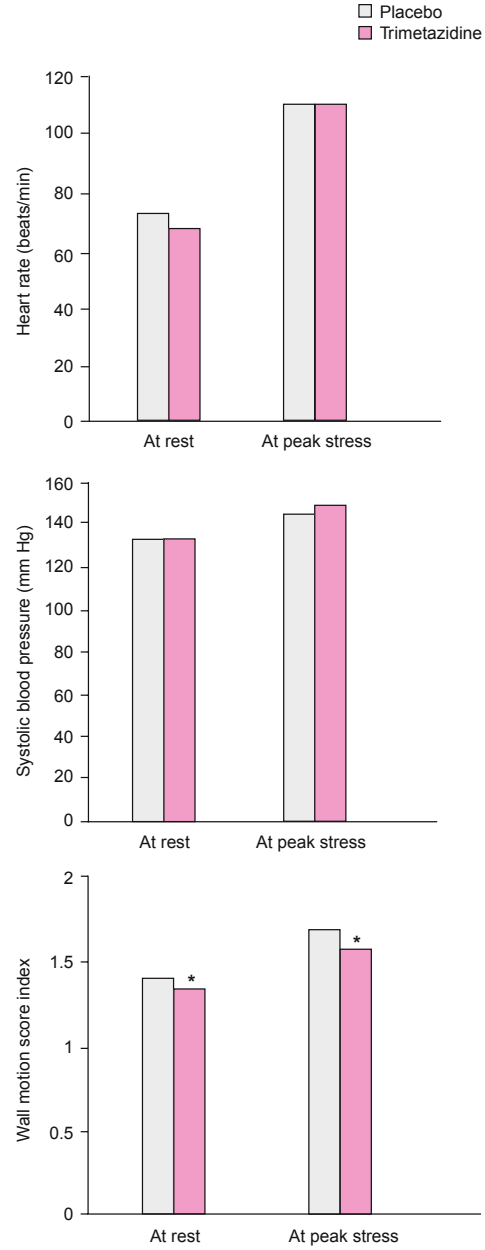

Fig. 2. Effects of oral trimetazidine on ischaemic left ventricular dysfunction and haemodynamic parameters during rest-stress echocardiography in patients with coronary artery disease. Patients (n = 15) were randomised in a double-blind manner to either trimetazidine 20mg 3 times daily or placebo for 15 days before switching to the alternative regimen for 15 days.[31] Heart rate, systolic blood pressure and wall motion score index were assessed at rest and during dobutamine stress echocardiography. * $p < 0.02$ *vs* placebo.

ine concentration-time curve ($AUC_{0-\infty}$) was 508.9 μg/L • h after a single 20mg dose and 831.4 μg/L • h after repeated administration.[37] Steady-state levels were reached within 24 hours and remained stable for the study duration.[37] The bioavailability of a 40mg tablet of trimetazidine in 11 healthy volunteers was 88.7% relative to an intravenous dose.[38]

Trimetazidine is only weakly protein bound in plasma (≈16%)[37] and therefore is widely distributed throughout the body. In 11 healthy volunteers, the volume of distribution (Vd) of trimetazidine was 318.6L after a 40mg intravenous dose.[38]

Table I. Pharmacokinetic profile of trimetazidine after oral administration in healthy volunteers (mean values)

Parameter	Dosage		
	20mg single dose[37]	40mg single dose[38]	20mg bid for 15 days[37]
C_{max} (μg/L)	53.6	127.5	84.8
$AUC_{0-\infty}$ (μg/L • h)	508.9		831.4
t_{max} (h)	1.8	2.73	1.7
$t_{½}$ (h)	6.0		6.2
Bioavailability (%)		88.7	

$AUC_{0-\infty}$ = area under the plasma concentration-time curve; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **$t_{½}$** = elimination half-life; **t_{max}** = time to reach C_{max}.

3.2 Metabolism and Elimination

The elimination half-life of trimetazidine 20mg is ≈6 hours after single or repeated oral administration.[37] More than 80% of an administered dose of trimetazidine is excreted in the urine within 48 hours, with 62% of the drug eliminated unchanged.[37] Eight metabolites (including 4 phase II metabolites) have been detected in urine,[39] but little is known of their properties.

The total clearance of trimetazidine was 37.45 L/h after a 40mg intravenous dose in 11 healthy volunteers.[38]

3.3 Drug Interactions

Oral trimetazidine 20mg twice daily for 25 days had no effects on the half-life of phenazone (antipyrine; administered as a single 500mg oral dose) in 13 healthy male volunteers, indicating that the antianginal agent is neither an inducer nor an inhibitor of drug hydroxylation.[40] In the same individuals, coadministration of trimetazidine 20mg had no effects on the pharmacokinetics of single oral doses of digoxin 0.5mg or theophylline 375mg.[40]

4. Therapeutic Efficacy

4.1 Stable Angina Pectoris

The therapeutic efficacy of oral trimetazidine, both as monotherapy and when used as adjunctive therapy in patients with angina pectoris not sufficiently controlled by other antianginal agents, has been evaluated in a number of well-controlled clinical trials of up to 6 months' duration. All these studies were conducted in patients aged <75 years with stable angina pectoris confirmed by a positive exercise test and/or coronary angiography prior to inclusion. Because of the low diagnostic ability of exercise testing in women, they were excluded from all but 1 study.[41] In general, studies excluded patients with unstable angina pectoris, LV dysfunction, or a history of myocardial infarction within the previous 3 months. In the monotherapy studies, drugs that could interfere with antianginal treatment (e.g. β-blockers or calcium antagonists prescribed for hypertension or amiodarone prescribed for arrhythmias) or interpretation of ST segment changes (e.g. antiarrhythmics or digoxin) were not permitted.

Whether used as monotherapy or in combination with other antianginals, trimetazidine was administered orally as a 20mg dose 3 times daily (except for 1 study[36] in which the dosage was titrated to 80 mg/day if necessary).

Changes in the number of anginal attacks per week and nitroglycerin (glyceryl trinitrate) consumption per week were used as clinical end-points and were supported by the findings of exercise (either bicycle or treadmill) stress testing. Parameters assessed during exercise testing included HR and SBP (from which the rate-pressure product was calculated), time to onset of angina, time to 1mm ST segment depression and total work performed. Several studies also assessed the effects of trimetazidine on

LV function, either at rest or during dobutamine echocardiographic testing (DET).

4.1.1 Monotherapy

Clinical Effects

Trimetazidine monotherapy reduces the frequency of anginal attacks and nitroglycerin use in patients with angina pectoris. Its effects appear to be greater than those of placebo and broadly similar to those of short-acting nifedipine and propranolol.

Compared with placebo, 2 weeks' treatment with trimetazidine 20mg 3 times daily significantly reduced the weekly rate of angina episodes and nitroglycerin consumption ($p \leq 0.001$) in 54 patients with angina pectoris (table II).[33] The drug also reduced these parameters after 1 month in a smaller placebo-controlled study[34] although between-group differences did not reach statistical significance (table II). A well-controlled trial showed that both trimetazidine 60 to 80 mg/day and propranolol 120 to 160 mg/day significantly reduced anginal episodes and nitroglycerin use from baseline in patients with angina pectoris ($p < 0.05$; table II).[36] The absolute reductions in both parameters were greater with propranolol than with trimetazidine in this study, but between-group differences were not statistically significant.[36] Another comparative study showed that the effects of trimetazidine on the frequency of anginal attacks were similar to those reported with short-acting nifedipine 40 mg/day (table II).[35]

Effects on Exercise Capacity

Consistent with the effects of a single dose,[30] repeated administration of trimetazidine 20mg 3 times daily increases exercise capacity in patients with angina pectoris. Unlike nifedipine and propranolol, however, the drug has no effects on myocardial oxygen consumption during peak exercise.

Trimetazidine (usual dosage 60 mg/day) increased exercise duration by up to 19%, the time to 1mm ST segment depression (ischaemic threshold) by up to 18% and total work performed during exercise by up to 62% in patients with stable angina pectoris treated for 1 to 3 months (table II).[34-36] The improvements in these measures of exercise capacity were similar to those reported with short-acting nifedipine 40 mg/day[35] and propranolol 120 to 160 mg/day[36] but in general were significantly ($p < 0.05$) greater than those reported with placebo (table II).[34]

Unlike nifedipine and propranolol, trimetazidine had no significant effects on the rate-pressure product during exercise (table II) or at rest.[35,36]

Effects on LV Function

In a randomised, double-blind, crossover study in 15 patients with coronary artery disease (≥50% stenosis of a major coronary artery) and a positive response to DET,[31] 15 days' treatment with oral trimetazidine 20mg 3 times daily improved LV function compared with placebo. The drug reduced the mean LV wall motion score index both at rest (1.34 *vs* 1.40; $p = 0.013$) and at peak dobutamine infusion (i.e. at peak stress) [1.61 *vs* 1.71; $p = 0.018$] compared with placebo (fig. 2). Trimetazidine administration was also associated with the achievement of higher doses of dobutamine (28.7 *vs* 22.7 μg/kg/min; $p = 0.003$) and longer infusion time (17.9 *vs* 15.3 min; $p = 0.019$) until ischaemia developed compared with placebo. Usual antianginal medications (nitrates, calcium antagonists and β-blockers) were withdrawn at least 2 days before stress echocardiography.[31]

4.1.2 Combination Therapy

Clinical Effects

Adjunctive trimetazidine (20mg 3 times daily) reduces the frequency of anginal attacks and nitroglycerin use in patients with angina pectoris not sufficiently controlled by other antianginal agents. Furthermore, the drug is a more effective addition than isosorbide dinitrate 30 mg/day in patients with angina pectoris not sufficiently controlled by propranolol 120 mg/day.

In men who had a positive exercise test (exercise induced angina and/or ischaemic ST segment depression) despite treatment with diltiazem 180 mg/day[42] or a β-blocker (propranolol, pindolol or oxprenolol),[32] the addition of trimetazidine significantly reduced the mean number of anginal at-

Table II. Efficacy of oral trimetazidine (TRI) compared with that of placebo (PL) or other antianginal agents in patients with stable angina pectoris. Data are expressed as mean values

Reference	Study design	No. of pts	Dosage (mg/day)	Time point	Angina episodes (per wk)	NTG consumption (tablets per wk)	Exercise parameters				Comparative efficacy
							time to onset of angina (sec)	time to 1mm STD (sec)	total work (kpm)	RPP (mm Hg • beats/min)	
Comparisons with PL											
Passeron[33]	r, db, pg	27	PL	Baseline	7.6	7.9			2772	21 929	TRI > PL
				2wk	4.9	5.4			3456	21 052	
		27	TRI 60	Baseline	8.1	9.1			2430	21 656	
				2wk	2.9††	3.1††			3939†	19 068	
Gallet[34]	mc, r, db, pg	14	PL	Baseline	4.9	6.3	612	504	4191	23 324	TRI ≥ PL
				1mo	3	4.6	642	540	4564	24 764	
		18	TRI 60	Baseline	5.1	5.7	612	498	4200	24 592	
				1mo	2.6	2.7	726†	588†	5620†	27 274	
Comparison with nifedipine (NIF)											
Dalla-Volta et al.[35]	r, db, co	35	NIF 40	Baseline	2.2		462	342	520.7 W • min	23 555.1	TRI ≡ NIF
				6wk	0.9		540	408	677.9 W • min	21 885.2†	
		35	TRI 60	Baseline	2.5		468	348	529.3 W • min	22 984.1	
				6wk	1.2		528	408	657.1 W • min	22 604.8	
Comparison with propranolol (PRO)											
Detry et al.[36]	mc, r, db, pg	78	PRO 120-160 (mean 132)	Baseline	9.4	6.6	554	446	3674	23 683	TRI ≡ PRO
				3mo	3.9**	3.2**	588*	510**	4002	18 579**	
		71	TRI 60-80 (mean 67)	Baseline	10.1	8.6	536	432	3472	22 387	
				3mo	6.6**	6.2*	569*	483**	3802*	23 089	

co = crossover; **db** = double-blind; **kpm** = kilopound-metres; **mc** = multicentre; **NTG** = nitroglycerin; **pg** = parallel group; **pts** = patients; **r** = randomised; **RPP** = rate-pressure product; **STD** = ST segment depression; **W** = watts; **>** indicates significantly greater efficacy; ≥ indicates significantly better on some but not all efficacy parameters; ≡ indicates equivalent efficacy. † $p < 0.05$, †† $p \leq 0.001$ *vs* change from baseline with comparator; * $p < 0.05$, ** $p \leq 0.001$ *vs* baseline.

tacks and nitroglycerin consumption compared with placebo or baseline ($p < 0.05$; table III). Trimetazidine also reduced these clinical indices in patients poorly controlled by nifedipine 40 mg/day,[45] although in this small study these reductions were not significantly different from those achieved after the addition of placebo (table III).

The results of a large noncomparative study (TRIMPOL-1) in 700 men and women with a positive exercise test despite treatment with a conventional antianginal agent (either a long-acting nitrate, β-blocker or calcium antagonist) showed that anginal attacks and nitroglycerin use were significantly reduced after the addition of trimetazidine (table III).[41] These significant clinical effects were also evident in the subgroup of TRIMPOL-1 participants who had coexisting diabetes mellitus.[46]

In men who had a positive exercise test after a 2-week run-in period with propranolol 40mg 3 times daily, the addition of trimetazidine reduced anginal attacks and nitroglycerin use significantly more effectively than the addition of isosorbide dinitrate 30 mg/day ($p < 0.05$; table III).[43]

Effects on Exercise Capacity

Trimetazidine 20mg 3 times daily significantly increases exercise capacity compared with placebo when used as add-on therapy in patients with angina pectoris not sufficiently controlled by other antianginal agents. In addition, the drug appears to be more effective than isosorbide dinitrate when used adjunctively in patients with angina pectoris not sufficiently controlled by propranolol.

In men with a positive exercise test despite treatment with diltiazem 180 mg/day, the addition of trimetazidine for 28 days resulted in a significant increase in the exercise time to 1mm ST depression and angina onset (both $p < 0.05$ *vs* placebo; table III) as well as the mean maximum work at peak exercise (+1.4 metabolic equivalents; $p < 0.05$ *vs* placebo).[42] A longer term (6 months) study reported similar effects (table III).[44]

Adjunctive trimetazidine significantly enhanced exercise capacity in patients receiving nifedipine 40 mg/day,[45] β-blockers (propranolol, pindolol and oxprenolol)[32] or a broad range of antianginal agents (long-acting nitrates, β-blockers or calcium antagonists)[41] [table III]. Similar results were reported when the drug was added to metoprolol 100 mg/day in TRIMPOL II, a multicentre, randomised, double-blind study involving 227 patients. An abstract report of this study[47] showed that the addition of trimetazidine for 12 weeks increased the exercise time to 1mm ST segment depression by 28.5%, total walking time by 16.3% and work capacity by 15.6% (fig. 3). Exercise time to onset of angina increased by 27.4%. All increases were significant versus baseline and placebo ($p < 0.01$).

Exercise duration improved by 15% ($p < 0.01$) and the time to ST segment depression improved by 19% ($p < 0.01$) after the addition of trimetazidine to conventional antianginals in the subgroup of TRIMPOL-1 participants who had coexisting diabetes mellitus.[46]

Trimetazidine tended to be more effective than isosorbide dinitrate 30 mg/day when used as add-on therapy in men with angina poorly controlled by propranolol 40mg 3 times daily (table III), but between-group differences did not reach statistical significance.[43]

Effects on LV Function

In a study involving 40 men with stable angina pectoris who were taking long-acting nitrates,[48] the addition of oral trimetazidine 20mg 3 times daily for 12 weeks significantly improved mean LV ejection fraction (LVEF) from 49.2 to 59.9% ($p < 0.05$). In contrast, LV ejection fraction remained unchanged in those who received adjunctive placebo.

4.2 Other Coronary Conditions

Because of its anti-ischaemic activity, the effects of trimetazidine have been assessed in other coronary conditions such as ischaemic cardiomyopathy and in patients undergoing coronary revascularisation. This section reports the results of these studies. It should be noted, however, that data are limited and few conclusions can be drawn.

4.2.1 Ischaemic Cardiomyopathy

The results of 1 study suggest that trimetazidine 60 mg/day may improve LV ejection fraction,

Table III. Efficacy of oral trimetazidine (TRI) when used as adjunctive therapy in patients with angina pectoris not sufficiently controlled[a] by other antianginal agents. Data are expressed as mean values

Reference	Study design	Run-in (drug; days)	No. of pts	Adjunctive therapy (mg/day)	Time point	Angina attacks (per wk)	NTG use (units/wk)	Exercise parameters			Comparative efficacy
								time to onset of angina (sec)	time to 1mm STD (sec)	total work (kpm)	
In combination with β-blockers (BB)											
Michaelides et al.[32]	nb	BB[c] + PL; 30	18	TRI 60	Baseline	7.6	7.1	550.9	432.4	10.8 MET	BB + TRI > BB + PL
					3mo	2.7**	2.3**	643.9*	517.8*	12.3* MET	
Michaelides et al.[43]	r, db, pg	PRO 120 mg/day; 14	23	ISO 30	Baseline	4.3	3.6	701	550		PRO + TRI ≥ PRO + ISO
					60 days	3.0*	2.4*	717	565		
			26	TRI 60	Baseline	4.5	3.7	679	526		
					60 days	1.7*†	1.1*†	774**	607**		
In combination with diltiazem (DIL)											
Levy et al.[44]	mc, r, db, pg	DIL 180 mg/day; 15	35	PL	Baseline			644	479	4678	DIL + TRI ≥ DIL + PL
					6mo			661	521	4899	
			32	TRI 60	Baseline			557	373	3637	
					6mo			607*	534**†	4207*	
Manchanda et al.[42]	mc, r, db, pg	DIL 180 mg/day; 15	32	PL	28 days						DIL + TRI > DIL + PL
			32	TRI 60	28 days	–4.8‡b	–2.6†b	+113.1†b	+94.2†b		
In combination with nifedipine (NIF)											
Brochier et al.[45]	mc, db, r, pg	NIF 40 mg/day; 15	15	PL	Baseline	3.04	2.18			4472	NIF + TRI ≥ NIF + PL
					15 days	1.65	1.43			4548	
			13	TRI 60	Baseline	2.82	3.15			3956	
					15 days	1.21	1.31			5177‡‡	
In combination with conventional antianginals (AA)[d]											
Szwed et al. (TRIMPOL-1)[41]	mc, nb	AA; >7	700	TRI 60	Baseline	3.66	2.94	443.7	337.8		AA + TRI > AA
					4wk	2.47*	1.80*	486.4*	389.9*		

a Demonstrated by a positive exercise test (exercise-induced angina and/or ischaemic ST segment depression in response to an exercise test).

b Net effect after adjustment for PL.

c Propranolol mean 120 mg/day (n = 11), pindolol mean 7.5 mg/day (n = 4), oxprenolol mean 60 mg/day (n = 3).

d Long-acting nitrates (n = 331), β-blockers (n = 293) or calcium antagonists (n = 76).

db = double-blind; **ISO** = isosorbide dinitrate; **kpm** = kilopound-metres; **mc** = multicentre; **MET** = metabolic equivalents; **nb** = nonblind; **NTG** = nitroglycerin; **pg** = parallel group; PL = placebo; **PRO** = propranolol; **pts** = patients; **r** = randomised; **STD** = ST segment depression; **>** indicates significantly greater efficacy; ≥ indicates significantly better on some but not all efficacy parameters; * $p < 0.01$, ** $p < 0.001$ *vs* baseline; † $p < 0.05$ *vs* comparator; ‡ $p < 0.01$ *vs* PL; ‡‡ $p = 0.024$ *vs* change from baseline with PL.

cardiac volume and clinical status compared with placebo when added to an existing regimen in patients with severe ischaemic cardiomyopathy.[49] The study involved 20 patients, 6 of whom had dyspnoea in New York Heart Association (NYHA) class IV and 14 of whom had dyspnoea in class III. Trimetazidine or placebo was added to the existing treatment regimen for 180 days. At study end, mean cardiac volume had decreased by 7.1% with trimetazidine and increased by 3.7% with placebo ($p = 0.034$), and LVEF had increased by 9.3% with trimetazidine and decreased by 15.6% with placebo ($p = 0.018$).[49]

The improvements in LV function reported with trimetazidine were associated with significant gains in clinical status; dyspnoea improved by at least 1 NYHA functional class in all 9 trimetazidine recipients but only 1 of 11 placebo recipients ($p < 0.001$). Trimetazidine reduced the need for treatment modification during the study compared with placebo: regimen adjustments were necessary in 1 versus 8 patients in the respective groups ($p < 0.01$).

However, these results should be interpreted with caution for several reasons: LVEF was higher at baseline in trimetazidine than in placebo recipients; more placebo than trimetazidine recipients had calcium antagonists added (4 *vs* 0) which may have contributed to the reduction in LVEF in this group; the absolute change in LVEF in trimetazidine recipients was not statistically significant. Therefore, the findings of this study are inconclusive and required confirmation in further well controlled studies.

Another placebo-controlled study in patients with ischaemic cardiomyopathy (n = 22) showed that trimetazidine 20mg 3 times daily improved the contractile response of dysfunctional myocardium to low dose dobutamine.[50] In this study, the mean systolic wall thickening score index (SWTI) during DET improved from 1.66 at baseline to 1.32 at 2 months in trimetazidine recipients ($p < 0.05$) but was not significantly altered in placebo recipients. Similarly, the SWTI at rest improved during the 2-month treatment period in trimetazidine recipients (from 2.05 to 1.61; $p < 0.05$) but not in placebo recipients. Patients' usual medications were not altered during the study.

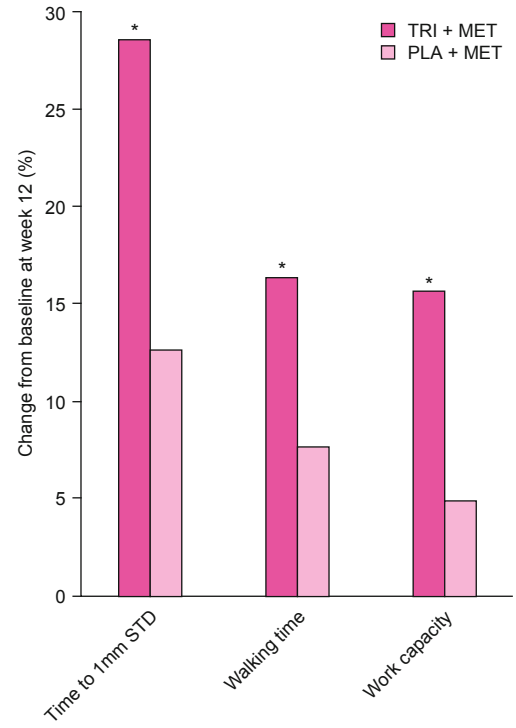

Fig. 3. Effects of adjunctive trimetazidine (TRI) on exercise capacity in patients with persistent angina pectoris. 227 patients who had a positive exercise test despite 1 week's treatment with metoprolol (MET) had TRI 20mg three times daily (n = 114) or placebo (PLA; n = 113) added for 12 weeks in a randomised, double-blind manner.[47] Exercise capacity was assessed during treadmill exercise tests. * $p < 0.01$ *vs* placebo.

4.2.2 Coronary Artery Bypass Grafting

Trimetazidine may improve preoperative LV function in patients undergoing coronary artery bypass graft (CABG) surgery.

Three weeks' double-blind treatment with oral trimetazidine 20mg 3 times daily improved preoperative LV function compared with placebo in a study involving 19 patients scheduled for CABG.[51] Mean LV stroke work index was higher in trimetazidine than placebo recipients prior to surgery (0.0391 *vs* 0.0282 g/min/m^2/beat; $p < 0.01$). During the CABG procedure, patients in the trimetazidine group received trimetazidine 10^{-6} mol/L

with the cardioplegic solution. 20 minutes after reperfusion, malondialdehyde accumulation in the coronary sinus (a marker of lipid peroxidation) was less in patients who received trimetazidine 10^{-6} mol/L with the cardioplegic solution than in those who received placebo (+0.19 *vs* +1.67 μmol/L from baseline; $p < 0.05$). Four hours after surgery, myosin was detected in venous blood of all placebo recipients compared with 5 out of 10 trimetazidine recipients ($p = 0.036$).

These data suggest that trimetazidine reduces the production of oxygen-derived free radicals during reperfusion but are inconsistent with those reported in a larger randomised, double-blind study in 40 evaluable patients undergoing CABG.[52] In this study, the effects of trimetazidine (40mg bolus before skin incision then 2.5 mg/h intravenously until the sixth postoperative hour and 10^{-6} mol/L with the cardioplegic solution) on malondialdehyde accumulation 20 minutes after unclamping were not significantly different from those of placebo.[52]

4.2.3 Angioplasty

Limited evidence suggests that trimetazidine significantly delays the development and reduces the magnitude of the ischaemic response during PTCA and improves LV contractility when administered after PTCA.

In a placebo-controlled study,[28] 20 patients with refractory angina pectoris who were undergoing PTCA received an intracoronary injection of placebo or trimetazidine 6mg 3 minutes prior to balloon inflation. Trimetazidine significantly delayed the mean onset (46.3 *vs* 36.1 sec; $p = 0.024$) and decreased the magnitude (0.85 *vs* 1.39mV; $p = 0.023$) of the maximum ST segment shift on intracoronary electrocardiogram during PTCA compared with a pretreatment balloon inflation.[28]

Compared with untreated controls, oral trimetazidine 20mg 3 times daily for 3 months beginning 24 hours after PTCA improved LV contractility in patients with mild angina pectoris.[53] Mean LV ejection fraction was greater in trimetazidine recipients ($n = 26$) than in the untreated control group ($n = 25$) at study end (66.0 *vs* 55.2%; $p < 0.0001$).[53]

An abstract report of a study in 51 evaluable patients with acute myocardial infarction undergoing PTCA showed that intravenous trimetazidine (40mg bolus then 60 mg/day for 48 hours) may result in earlier and more complete myocardial reperfusion than placebo.[54] ST segment deviation was higher in trimetazidine than placebo recipients prior to treatment (355 *vs* 278μV) but decreased more rapidly after reperfusion in the former group (181 *vs* 208μV at 1 hour and 104 *vs* 124μV at 3 hours).[54]

5. Tolerability

Oral trimetazidine was better tolerated than nifedipine or propranolol when used as monotherapy in clinical trials in patients with stable angina pectoris. Furthermore, the drug was as well tolerated as placebo when used as adjunctive therapy in patients with angina pectoris poorly controlled by other antianginals. Mild gastrointestinal disorders such as gastric burning were the most frequently reported treatment-related events in trimetazidine recipients but their overall incidence was low.

5.1 Monotherapy

Six weeks' treatment with trimetazidine 20mg 3 times daily was better tolerated than nifedipine 40 mg/day in a crossover study involving 39 patients with stable angina pectoris (5 *vs* 13 patients in the respective groups reported adverse events; $p = 0.03$).[35] All events related to trimetazidine involved the gastrointestinal system (e.g. gastric burning) whereas those of nifedipine were predominantly related to peripheral vasodilation.[35]

Trimetazidine was better tolerated than propranolol 40mg 3 times daily in a double-blind study involving 149 men with angina pectoris treated for 3 months.[36] In this study, 29.6% of trimetazidine compared with 38.5% of propranolol recipients spontaneously reported adverse events which were generally of mild to moderate severity. The most frequently reported events in trimetazidine recipients were fatigue (7.0%), dizziness (7.0%), muscular cramps (7.0%) and effort-induced discomfort (5.6%), although their relationship to treatment

was not established. No withdrawals related to adverse events occurred in the trimetazidine group, whereas 6 occurred in the propranolol group.[36]

Trimetazidine 20mg 3 times daily had no clinically significant effects on haematological[35,41] or biochemical[35] parameters.

5.2 Combination Therapy

The incidence of adverse events reported with adjunctive trimetazidine was similar to that with placebo in a double-blind study involving 64 patients with angina pectoris not sufficiently controlled by diltiazem.[42] During the 4-week treatment period, a small number of trimetazidine recipients reported constipation (n = 2) and increased appetite (n = 1), whereas placebo recipients reported constipation (n = 1), depression (n = 1) and bradycardia (n = 1).[42] No adverse event-related withdrawals occurred in the trimetazidine group but there were 2 in the placebo group.[42]

A longer study in 67 patients with angina pectoris poorly controlled by diltiazem confirmed that adjunctive trimetazidine was as well tolerated as placebo.[44] Only 2 patients in each group reported a treatment-emergent adverse event during the 6-month study: myalgia and lower limb oedema in the trimetazidine plus diltiazem group and somnolence and lower limb oedema in the placebo plus diltiazem group.[44]

In addition to being well tolerated when added to diltiazem, trimetazidine was well tolerated when added to other antianginal agents. Of 700 patients with angina pectoris who had trimetazidine added for 4 weeks to conventional therapy (long-acting nitrates, β-blockers or calcium antagonists), only 5% reported adverse events that may have been related to treatment. The most frequently reported events were headache (n = 10) and gastrointestinal disorders (n = 9).[41]

6. Dosage and Administration

Oral trimetazidine is indicated for the preventive treatment of anginal attacks. The recommended daily dosage of the drug is 40 or 60mg (in 2 or 3 divided doses) which should be administered with meals.[55]

Trimetazidine has not shown teratogenic effects in animals but, in the absence of clinical data, its use should be avoided during pregnancy. In addition, breast feeding is not recommended during treatment with trimetazidine until data on its excretion into breast milk are available.[55]

7. Place of Trimetazidine in the Management of Coronary Conditions

7.1 Stable Angina Pectoris

The aim of the management of angina pectoris is to reduce the frequency and severity of anginal attacks and to improve functional capacity. Ultimately, the aim should also be to improve prognosis.[1]

Management regimens ideally include nonpharmacological approaches such as bodyweight reduction, exercise and cessation of smoking which may also result in symptomatic improvement.[1] Low dose aspirin is recommended, unless contraindicated, because it has been shown to reduce the risk of myocardial infarction in patients with stable angina pectoris.[56,57] In addition, lipid-lowering therapy should be considered if serum total cholesterol levels remain elevated despite dietary modification.[1]

Acute anginal attacks are almost always treated with sublingual nitroglycerin, which provides rapid symptomatic relief. For long term prophylaxis, however, 3 main drug classes have proved effective: nitrates, calcium antagonists and β-blockers. These agents ultimately all work to restore the balance between myocardial metabolic demand and myocardial blood supply. Although they act via different mechanisms, there is little to distinguish between the 3 classes in terms of efficacy, and drug selection will often depend on coexisting medical conditions.

Nitrates such as isosorbide di- or mononitrate are vasodilators and may be particularly useful in patients with low or normal blood pressure, mitral regurgitation, congestive heart failure, overt vasospastic angina or in those with contraindications

to β-blockers or calcium antagonists.[58] A major drawback associated with the long term use of nitrates is the development of tolerance to their therapeutic effects but this can generally be averted by altering the dosage interval.

Like nitrates, calcium antagonists are also vasodilators. Their use is associated with minimal adverse metabolic effects and they are therefore suitable for most patients with angina pectoris, with the exception of short-acting nifedipine, which is not recommended as monotherapy because of the increased risk of myocardial infarction associated with its use in some patients.[59]

β-Blockers reduce HR and myocardial contractility, thereby reducing myocardial oxygen demand. As a class they are very effective in the treatment of angina pectoris and few differences exist between individual agents. Rebound ischaemia may occur after sudden β-blocker withdrawal in some individuals and is a potential problem associated with their use.[60]

Although monotherapy is optimal for compliance reasons, the severity of angina may necessitate treatment with a combination of therapeutic agents in some patients. Combinations of a long-acting nitrate and a β-blocker or calcium antagonist, or a β-blocker with a dihydropyridine calcium antagonist, are commonly used because the haemodynamic effects of these classes are different and complementary. However, certain combinations, such as β-blockers with diltiazem or verapamil, should be used with caution because of the risk of bradycardia and LV failure.[61]

Furthermore, although combined haemodynamic treatment is conventional for the treatment of angina, there has been conflicting evidence in the literature about its benefits. A review of controlled clinical trials of combined β-blocker and calcium antagonist therapy in angina pectoris called for a critical re-evaluation of the trend towards the routine prescribing of multiple antianginal agents.[62] Recently published studies have continued to raise doubts about the efficacy and tolerability of combined haemodynamic treatment.[63,64]

Trimetazidine is an antianginal agent which increases cell tolerance to ischaemia. In theory, its cytoprotective activity should limit myocyte loss during ischaemia and hence possibly improve prognosis in patients with angina pectoris.[2]

The beneficial effects of oral trimetazidine 20mg 3 times daily on the frequency and severity of anginal attacks as well as exercise capacity have been shown to be broadly similar to those of short-acting nifedipine (although this is no longer a standard therapy) and propranolol in clinical studies in patients with angina pectoris. Unlike these agents, trimetazidine has no effects on myocardial oxygen consumption at rest or during exercise. It should be noted, however, that monotherapy with trimetazidine has yet to be compared with the calcium antagonists diltiazem and verapamil or the cardioselective β-blockers metoprolol and atenolol.

Trimetazidine has a different mechanism of action from that of nitrates, β-blockers or calcium antagonists. Not surprisingly, therefore, in patients with angina pectoris not sufficiently controlled by conventional antianginals, the addition of trimetazidine led to a reduction in the frequency of anginal attacks and nitroglycerin use and an increase in exercise capacity. Interestingly, trimetazidine is possibly more effective than isosorbide dinitrate when used as adjunctive therapy in patients with angina poorly controlled by propranolol. Therefore, trimetazidine is likely to be a useful adjunctive therapy in patients with angina pectoris refractory to other antianginal agents.

Trimetazidine is generally well tolerated, with transient gastrointestinal events being the most commonly reported adverse events in clinical trials.

7.2 Other Coronary Conditions

Limited evidence suggests that trimetazidine has anti-ischaemic effects during angioplasty. Beneficial effects have also been reported when the drug is added to an existing regimen in patients with ischaemic cardiomyopathy. However, the use of trimetazidine in these indications requires clarification, as does its effect on oxygen free radical-

induced reperfusion injury in patients undergoing CABG surgery.

7.3 Conclusions

In conclusion, clinical studies have shown trimetazidine to be a reasonably effective and well tolerated anti-ischaemic agent which, in addition to providing symptom relief and functional improvement in patients with angina pectoris, has a cytoprotective action during ischaemia. The drug is suitable for initial use as monotherapy in patients with angina pectoris and, because of its different mechanism of action, as adjunctive therapy in those with symptoms not sufficiently controlled by nitrates, β-blockers or calcium antagonists. The role of trimetazidine in other coronary conditions has yet to be clearly established.

References

1. Task Force of the European Society of Cardiology. Management of stable angina pectoris: recommendations of the Task Force of the European Society of Cardiology. Eur Heart J 1997 Mar; 18: 394-413
2. Knight C, Fox K. From antianginal drugs to myocardial cytoprotective agents. Am J Cardiol 1995 Aug 24; 76: 4B-7B
3. Lavanchy N, Martin J, Rossi A. Préservation par la trimétazidine du potentiel énergétique du myocarde au cours de l'ischémie et de la reperfusion. Etude par spectroscopie RMN du phosphore sur le coeur isolé [in French]. Presse Med 1986 Oct 16; 15: 1758-61
4. Renaud JF. Internal pH, Na^+, and Ca^{2+} regulation by trimetazidine during cardiac cell acidosis. Cardiovasc Drugs Ther 1988 Mar; 1: 677-86
5. Lagadic-Gossmann D, Le Prigent K, Feuvray D. Effects of trimetazidine on pH_i regulation in the rat isolated ventricular myocyte. Br J Pharmacol 1996 Mar; 117: 831-8
6. Ponchaut S, Goudernant J-F, Demeure R, et al. Anti-ischemic effects of trimetazidine (TMZ): 31P- and 23NA-NMR spectroscopy in the working rat heart. Servier 1998. (Data on file)
7. Kiyosue T, Nakamura S, Arita M. Effects of trimetazidine on action potentials and membrane currents of guinea-pig ventricular myocytes. J Mol Cell Cardiol 1986 Dec; 18: 1301-11
8. Hisatome I, Ishiko R, Tanaka Y, et al. Trimetazidine inhibits Na^+, K^+-ATPase activity, and overdrive hyperpolarization in guinea-pig ventricular muscles. Eur J Pharmacol 1991 Apr 3; 195: 381-8
9. Allibardi S, Chierchia SL, Margonato V, et al. Effects of trimetazidine on metabolic and functional recovery of post-ischemic rat hearts. Cardiovasc Drugs Ther 1998; 12: 543-9
10. Libersa C, Honoré E, Adamantidis M, et al. Effects of trimetazidine on a model of *in vitro* myocardial ischemia [in French]. Presse Med 1986 Oct 16; 15: 1765-9
11. Kay L, Finelli C, Aussedat J, et al. Improvement of long term preservation of the isolated arrested rat heart by trimetazidine: effects on the energy state and mitochondrial function. Am J Cardiol 1995 Aug 24; 76: 45B-9B
12. Guarnieri C, Finelli C, Zini M, et al. Effects of trimetazidine on the calcium transport and oxidative phosphorylation of isolated rat heart mitochondria. Basic Res Cardiol 1997 Apr; 92: 90-5
13. Guarnieri C, Muscari C. Effect of trimetazidine on mitochondrial function and oxidative damage during reperfusion of ischemic hypertrophied rat myocardium. Pharmacology 1993 Jun; 46: 324-31
14. Elimadi A, Settaf A, Morin D, et al. Trimetazidine counteracts the hepatic injury associated with ischemia-reperfusion by preserving mitochondrial function. J Pharmacol Exp Ther 1998 Jul; 286: 23-8
15. Morin D, Elimadi A, Sapena R, et al. Evidence for the existence of [^{3}H]-trimetazidine binding sites involved in the regulation of the mitochondrial permeability transition pore. Br J Pharmacol 1998 Apr; 123: 1385-94
16. Guarnieri C, Muscari C. Beneficial effects of trimetazidine on mitochondrial function and superoxide production in the cardiac muscle [abstract]. Cardiovasc Drugs Ther 1990 Aug; 4 Suppl. 4: 814-5
17. Lopaschuk GD, Kozak R. Trimetazidine inhibits fatty acid oxidation in the heart [abstract]. J Mol Cell Cardiol 1998; 30: A112
18. Sentex E, Sergiel JP, Lucien A, et al. Is the cytoproctive effect of trimetazidine associated with lipid metabolism? Am J Cardiol 1998; 82: 18K-24K
19. Lopaschuk GD. Treating ischemic heart disease by pharmacologically improving cardiac energy metabolism. Am J Cardiol 1998; 82: 14K-7K
20. Mody FV, Singh BN, Mohiuddin IH, et al. Trimetazidine-induced enhancement of myocardial glucose utilization in normal and ischemic myocardial tissue: an evaluation by positron emission tomography. Am J Cardiol 1998; 82: 42K-9K
21. Kantor PF, Kozak R, Clanachan AS, et al. Glucose oxidation is enhanced by the anti-anginal agent trimetazidine [abstract no. 363]. Can J Cardiol 1998 Sep; 14 Suppl. F: 169F
22. Maridonneau-Parini I, Harpey C. Effect of trimetazidine on membrane damage induced by oxygen free radicals in human red cells. Br J Clin Pharmacol 1985 Aug; 20: 148-51
23. Catroux P, Benchekroun N, Robert J, et al. Influence of trimetazidine on deleterious effect of oxygen radical species in post-ischemic acute renal failure in the rat [abstract]. Cardiovasc Drugs Ther 1990 Aug; 4 Suppl. 4: 816-7
24. Williams FM, Tanda K, Kus M. Trimetazidine inhibits neutrophil accumulation after myocardial ischaemia and reperfusion in rabbits. J Cardiovasc Pharmacol 1993 Dec; 22: 828-33
25. Tritto I, Wang P, Giraldez R, et al. Trimetazidine prevents neutrophil-mediated myocardial injury in post-ischaemic rat hearts [abstract]. Eur Heart J 1997 Aug; 18 Abstract Suppl.: 53
26. Camilleri JP, Joseph D. Effets de la trimétazidine (Vastarel 20 mg) sur l'infarctus expérimental du rat perfusé [abstract]. Arch Mal Coeur Vaiss 1988; 81: 371
27. Catroux P, Dorian C, Harpey C, et al. Mise en évidence de l'effet protecteur de la Trimétazidine vis-á-vis de l'enzymurie induite par clampage du pédicule rénal chez le rat. Nephrologie 1986; 7: 124
28. Kober G, Buck T, Sievert H, et al. Myocardial protection during percutaneous transluminal coronary angioplasty: effects of trimetazidine. Eur Heart J 1992 Aug; 13: 1109-15
29. Timour Q, Harpey C, Durr F, et al. Is the antianginal action of trimetazidine independent of hemodynamic changes? Cardiovasc Drugs Ther 1991 Dec; 5: 1043-4

30. Sellier P, Audouin P, Payen B, et al. Acute effects of trimetazidine evaluated by exercise testing. Eur J Clin Pharmacol 1987; 33: 205-7
31. Lu C, Dabrowski P, Fragasso G, et al. Effects of *trimetazidine* on ischemic left ventricular dysfunction in patients with coronary artery disease. Am J Cardiol 1998 Oct 1; 82: 898-901
32. Michaelides AP, Vyssoulis GP, Bonoris PE, et al. Beneficial effects of trimetazidine in men with stable angina under beta-blocker treatment. Curr Ther Res 1989; 46: 565-76
33. Passeron J. Efficacité de la trimétazidine dans l'angor d'effort stable de l'insuffisant coronarien chronique. Etude à double insu contre placebo. Presse Med 1986 Oct 16; 15: 1775-8
34. Gallet M. Efficacité clinique de la trimétazidine dans l'angor d'effort stable. Etude contrôlée à double insu contre placebo. Presse Med 1986 Oct 16; 15: 1779-82
35. Dalla-Volta S, Maraglino G, Della-Valentina P, et al. Comparison of trimetazidine with nifedipine in effort angina: a double-blind, crossover study. Cardiovasc Drugs Ther 1990 Aug; 4 Suppl. 4: 853-9
36. Detry JM, Sellier P, Pennaforte S, et al. Trimetazidine: a new concept in the treatment of angina: comparison with propranolol in patients with stable angina. Br J Clin Pharmacol 1994 Mar; 37: 279-88
37. Harpey C, Clauser P, Labrid C, et al. Trimetazidine, a cellular anti-ischemic agent. Cardiovasc Drug Rev 1989; 6 (4): 292-312
38. Goupit P. Pharmacocinétique de la trimétazidine. Concours Med 1987; 109 Suppl. 36: 3447-51
39. Jackson PJ, Brownsill RD, Taylor AR, et al. Identification of trimetazidine metabolites in human urine and plasma. Xenobiotica 1996 Feb; 26: 221-8
40. Edeki TI, Johnston A, Campbell DB, et al. An examination of the possible pharmacokinetic interaction of trimetazidine with theophylline, digoxin and antipyrine. Br J Clin Pharmacol 1988; 26: 657P
41. Szwed H, Pachocki R, Domzal-Bochenska M, et al. Efficacy and tolerance of trimetazidine in combination with a conventional antianginal drug in patients with stable effort angina. Diagn Treat Cardiol 1997; 4: 237-47
42. Manchanda SC, Krishnaswami S. Combination treatment with trimetazidine and diltiazem in stable angina pectoris. Heart 1997 Oct; 78: 353-7
43. Michaelides AP, Spiropoulos K, Dimopoulos K. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina. Clin Drug Invest 1997 Jan; 13: 8-14
44. Levy S, Group of South of France Investigators. Combination therapy of trimetazidine with diltiazem in patients with coronary artery disease. Am J Cardiol 1995 Aug 24; 76: 12B-6B
45. Brochier M, Demange J, Ducloux G, et al. Intérêt de l'association de la trimétazidine à un inhibiteur calcique dans le traitement de l'insuffisance coronarienne chronique [in French]. Ann Cardiol Angeiol Paris 1986 Jan; 35: 49-56
46. Szwed H, Sadowski Z, Pachocki R, et al. Anti-ischaemic effects and tolerability of trimetazidine in coronary diabetic patients: a sub-study from TRIMPOL-1. Cardiovasc Drugs Ther. In press
47. Szwed H, Sadowski Z, Pachocki R, et al. TRIMPOL-II – multicenter study. Efficacy and safety of trimetazidine in patients with stable angina pectoris under beta-blocker therapy. Preliminary results [abstract]. 8th International Symposium on Cardiovascular Pharmacotherapy; 1999 Mar 28-Apr 1; Amsterdam
48. Shlyakhto EV, Vakhrameyeva IV, Nifontoff EM, et al. Chronic effects of myocardial cytoprotector trimetazidine for CAD: clinical, biochemical and echocardiographical follow-up [abstract]. Eur Heart J 1998; 19 Abstract Suppl.: 191
49. Brottier L, Barat JL, Combe C, et al. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. Eur Heart J 1990 Mar; 11: 207-12
50. Belardinelli R, Purcaro A. Trimetazidine improves the contractile response of hibernating myocardium to low-dose dobutamine in ischemic cardiomyopathy [abstract no. 3727]. Circulation 1998 Oct 27; 98 Suppl: I-709
51. Fabiani JN, Ponzio O, Emerit I, et al. Cardioprotective effect of trimetazidine during coronary artery graft surgery. J Cardiovasc Surg Torino 1992 Jul-Aug; 33: 486-91
52. Vedrinne J-M, Vedrinne C, Bompard D, et al. Myocardial protection during coronary artery bypass graft surgery: a randomized, double-blind, placebo-controlled study with trimetazidine. Anesth Analg 1996 Apr; 82: 712-8
53. Birand A, Kudaiberdieva GZ, Batyraliev TA, et al. Effects of trimetazidine on heart rate variability and left ventricular systolic performance in patients with coronary artery disease after percutaneous transluminal angioplasty. Angiology 1997 May; 48: 413-22
54. Steg PG, Grollier G, Gallay P, et al. A randomized double-blind trial of trimetazidine as adjunctive therapy to primary PTCA for acute myocardial infarction: evidence for improved myocardial reperfusion from ST-segment analysis [abstract]. Eur Heart J 1998; 19 Abstract Suppl.: 365
55. Servier. Vastarel 20: a new strategic approach to the management of coronary disease. Servier, France
56. Ridker PM, Manson JE, Gaziano JM, et al. Low-dose aspirin therapy for chronic stable angina: a randomized, placebo-controlled clinical trial. Ann Intern Med 1991; 114: 835-9
57. Juul-Möller S, Edvardsson N, Jahnmatz B, et al. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. Lancet 1992; 340: 1421-5
58. Abrams J. Therapy of angina pectoris with long-acting nitrates: which agent and when? Can J Cardiol 1996; 12 Suppl. C: 9C-16C
59. Dougall HT, McLay J. A comparative review of the adverse effects of calcium antagonists. Drug Saf 1996; 15 (2): 91-106
60. Houston MC, Hodge R. Beta-adrenergic blocker withdrawal syndromes in hypertension and other cardiovascular diseases. Am Heart J 1998 Aug: 515-23
61. British National Formulary No. 35. Oxon: The Pharmaceutical Press, Mar, 1998. p562
62. Packer M. Combined beta-adrenergic and calcium-entry blockade in angina pectoris. N Engl J Med 1989 Mar 16; 320: 709-18
63. Fox KM, Mulcahy D, Findlay I, et al. The Total Ischaemic Burden European Trial (TIBET): effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. Eur Heart J 1996; 17: 96-103
64. Savonitto S, Ardissino D, Egstrup K, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. J Am Coll Cardiol 1996 Feb; 27: 311-6

Correspondence: *Karen J. McClellan*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz