The antihypertensive effects of doxazosin: a clinical overview

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1 Doxazosin is a long-acting selective α_1 -adrenoceptor antagonist which has been shown to be effective and well tolerated in the treatment of hypertension given in once-daily doses as monotherapy for up to 1 year or as an adjunct to thiazide or β -adrenoceptor blockers.

2 Doxazosin has a pharmacokinetic profile in both young adult and elderly subjects which is compatible with once-daily administration. This has been confirmed by measurement of steady state pharmacokinetics in patients receiving long-term doxazosin therapy.

3 In controlled double-blind studies involving approximately 550 patients on doxazosin 1–16 mg once daily, significant reductions in both standing and supine BP were maintained throughout the 24 h dosing interval.

4 Effectiveness of doxazosin in terms of BP lowering and proportion of responders was similar to that achieved with hydrochlorothiazide 25–100 mg once daily, atenolol 50–100 mg once daily, nadolol 40–160 mg once daily, metoprolol 100–200 mg per day given twice daily, or prazosin 1–20 mg per day given twice daily.

5 Doxazosin was as effective in elderly patients as in the younger age group and was as effective in blacks as in caucasians.

6 Doxazosin was well tolerated. Side-effects were generally mild to moderate in severity. Overall incidence, including postural effects early in treatment, was similar to that seen with the comparative agents.

7 In comparison with placebo, doxazosin favourably increased ($P < 0.05$) the HDL/total cholesterol ratio. Relative to atenolol in studies over 1 year, doxazosin increased serum HDL cholesterol ($P = 0.0015$) and HDL/total cholesterol ratio ($P = 0.0001$) and decreased serum triglycerides ($P = 0.0001$) in contrast to the neutral or opposing effects of atenolol.

8 The profile of doxazosin suggests that its good toleration and efficacy in control of hypertension is likely to be associated with beneficial effects on overall cardiovascular risk profile.

Keywords coronary risk profile doxazosin hypertension lipids pharmacokinetics

Introduction

The haemodynamic profile of established essential hypertension is now well understood (Lund-Johansen, 1980) and results in a circulation pattern in which an elevated peripheral vascular resistance with a normal cardiac output is responsible for the maintenance of the elevated blood pressure. The mainstays of treatment for essential hypertension in recent years have been the β -adrenoceptor antagonists and the diuretics. However, although reduction of blood pressure using these agents has

been shown to reduce the incidence of death and morbid events associated with stroke, it has not been shown to offer the same protection against myocardial infarction or other events resulting from the progression of the atherosclerotic process. One possible explanation might be found in the effects of β -adrenoceptor antagonists and thiazides on plasma lipid profiles, in particular the decrease in high density lipoprotein (HDL) relative to low density lipoprotein (LDL) and the increase in triglyceride concentrations. Additionally both the thiazide diuretics and β -adrenoceptor antagonists have

secondary effects known to be associated in some populations with the unmasking or exacerbation of other disease processes (e.g. diabetes or gout with thiazides; Raynaud's syndrome, asthma or heart failure with β -adrenoceptor antagonists).

The use of selective α_1 -adrenoceptor blocking agents, such as prazosin, for reducing the increased systemic arteriolar resistance of essential hypertension, offers an alternative and rational drug treatment. Furthermore, prazosin has been shown to change lipid profiles in a favourable direction relative to the other agents. Doxazosin is structurally related to prazosin and has a similar mode of action. Pharmacokinetic studies in man (Elliott *et al.*, 1982; Vincent *et al.*, 1983) showed that the plasma half-life for doxazosin is 9–11 h, compared with approximately 2.5 h for prazosin, suggesting that a once-daily regimen is appropriate. The main objective of the clinical studies reviewed in this paper was to compare the efficacy and safety of doxazosin given once daily with that of placebo and the established antihypertensive agents atenolol, nadolol, metoprolol, hydrochlorothiazide and prazosin.

Methods

The results described in this paper were obtained using 13 different, but similarly designed, protocols. All studies were comparative against placebo and/or active agents and were of double-blind design. All protocols except one, which related to a dose response study, allowed dose titration to the maximum recommended dose of doxazosin and patients from this study were evaluated for safety but were not included in the pooled efficacy analysis.

All studies required a 4-week single-blind placebo run-in, after a washout phase, followed by 9–24 weeks of trial therapy. Patients in the active treatment groups in six of these studies were to continue the same therapy for total durations of up to 62 weeks. The dose ranges of the drugs used were: doxazosin 1–16 mg once daily, hydrochlorothiazide 25–100 mg once daily, atenolol 50–100 mg once daily, nadolol 40–160 mg once daily, metoprolol 100–200 mg per day given twice daily and prazosin 1–20 mg per day given twice daily. Patients were instructed to take the medication at breakfast time and again where appropriate in the early evening. At review visits, blood pressure measurements were made 24 h (12 h for metoprolol and prazosin) after the previous dose and before the first dose of the day. Blood pressure and heart rate were recorded in duplicate (in

triplicate in some protocols) after 5 min in the supine position and after 2 min in the standing position at each review visit. According to response, patients were titrated upwards through the dose range. Patients in the doxazosin group could receive 1, 2, 4, 8 or 16 mg once a day. Upward titration of dose occurred at 2-week intervals, apart from some of the active comparative studies, in which patients could receive doxazosin 8 mg for 6 weeks before titration to the 16 mg dose level. Titration through the dose range continued until either 'goal' blood pressure was achieved or until side-effects prevented further upward titration. Goal blood pressure was defined as a reduction from baseline diastolic BP of at least 10 mmHg and to less than 90 mmHg in both supine and standing positions. Patients were assessed double-blind at 2-week intervals in the early phase of the studies, and thereafter at less frequent but regular intervals up to approximately 1 year. The blinding code was not broken for the investigator until after the final patient review.

Serum cholesterol, HDL cholesterol and triglyceride concentrations were measured at baseline and at intervals throughout the studies. In addition to these parameters, changes in the calculated ratio of HDL/total cholesterol were also assessed. From these four lipid parameters were calculated geometric mean baselines for each treatment group and percentage changes from baseline (derived from geometric means of final/baseline).

Side-effects, observed or volunteered, were recorded at each review visit. Blood samples for haematology and biochemistry examination, together with urine samples, were taken at regular intervals throughout the study and monitored for possible drug-related changes. Other safety assessments comprised measurement of body weight, electrocardiography, ophthalmoscopy and chest X-ray.

Steady state pharmacokinetics of doxazosin were assessed as part of a double-blind 12 month controlled efficacy and safety study. Patients were instructed to eat a normal (light) breakfast on the day of pharmacokinetic assessment but not to take the dose of the day until instructed. Blood samples for doxazosin analysis were taken pre-dose and at selected times after dosing.

Results and discussion

Patients

A total of 1141 patients has been studied in double-blind controlled parallel comparative trials of 9–24

Table 1 Sex, age and weight of patients included in double-blind comparative studies

Number of patients	Doxazosin			Comparative treatment					
	Male	Female	Total	Active			Placebo		
				Male	Female	Total	Male	Female	Total
	327	214	542	225	162	387	121	90	212
<i>Age category</i>									
15–44 years	103	44	147	65	46	111	35	15	50
45–64 years	184	141	325	138	96	234	71	61	132
≥65 years	40	29	69	22	20	42	15	14	29
Not specified			1						1
Mean age (years)	50.2	53.4	51.5	50.3	51.8	51.0	51.7	54.8	53.0
Age range	26–77	28–81	26–81	29–72	29–76	29–76	22–77	30–72	22–77
Mean weight (kg)	85.2	73.5		85.1	72.9		89.2	77.1	
Weight range	48–149	45–127		48–127	46–128		58–156	48–113	
Weight not specified	1	3	5	2	1	3	0	0	0

weeks duration, the shorter durations being used in those studies which included a placebo group. Some of these patients continued to receive doxazosin for approximately 1 year. Of this total, 542 patients were treated with doxazosin, 387 with active comparative agents and 212 with placebo. All protocols were reviewed by Ethics Committees and informed consent was obtained from all patients.

Details of age, sex, weight and race of these 1141 patients are presented in Table 1. Of the 542 patients treated with doxazosin, most (325) were 45–64 years old and 69 patients were elderly (aged ≥ 65 years). Within each protocol, patient populations by treatment group were well matched for physical characteristics and for baseline severity of hypertension (mean of blood pressures measured on the last two visits of the single-blind run-in phase). Based on standing diastolic blood pressure at baseline, approximately two-thirds of patients (67–76%) in all major treatment groups had moderate (100–<115 mmHg) hypertension, 17–28% had mild (90–<100 mmHg) hypertension and 5–9% had severe (115–<130 mmHg) hypertension. The overall mean diastolic blood pressure at baseline for doxazosin-treated patients was 105 mmHg (standing) and 102 mmHg (supine). Patients with baseline blood pressure less than 90 mmHg were excluded from efficacy analysis, as were patients withdrawing from studies prior to completion.

A majority (1092) of the 1141 patients in the main comparative database was studied according to closely similar protocols using a doxazosin 1–16 mg once daily dose titration scheme. Efficacy

results are presented on the evaluable patients (total 903) in this population, comprising 408 patients treated with doxazosin, 323 with active comparative agents and 172 with placebo. Evaluation of safety was made on the full comparative database of 1141 patients.

The mean final daily doses of drugs used in the comparative studies in the efficacy subset of patients (total 903) were doxazosin 11.6 mg ($n = 408$), atenolol 91 mg ($n = 155$), hydrochlorothiazide 77 mg ($n = 55$), metoprolol 187 mg ($n = 33$), nadolol 100 mg ($n = 26$), and prazosin 11.8 mg ($n = 54$).

Blood pressure and heart rate

Efficacy was based on mean changes in blood pressure from baseline (average of readings from final two visits in the single-blind placebo run-in) to the final efficacy review visit at the end of double-blind therapy. Changes in heart rate were assessed similarly. All measurements were made at the end of the dosing interval, which was 24 h post-dose for doxazosin. Results are summarized in Tables 2, 3, 4, 5 and 6.

Clinically relevant falls in standing diastolic BP at the end of the dosing interval were observed for doxazosin both overall and consistently in all studies. In paired comparisons (by study), doxazosin resulted in significantly greater falls in BP than placebo, similar falls relative to nadolol, metoprolol and prazosin, and similar or somewhat lesser falls (depending on study) relative to hydrochlorothiazide and atenolol. Falls in supine diastolic

Table 2 Mean standing diastolic blood pressure

<i>Treatment group</i>	<i>n</i>	<i>Baseline mean (mmHg)</i>	<i>Final mean (mmHg)</i>	<i>Mean change (mmHg) final – baseline ± s.e. mean</i>	
Doxazosin	408	105.3	94.3	–11.1	0.4
Atenolol	155	106.1	94.5	–11.6	0.7
Hydrochlorothiazide	55	105.1	89.9	–15.2	1.6
Prazosin	54	106.5	95.8	–10.6	0.9
Metoprolol	33	105.8	90.5	–15.3	1.8
Nadolol	26	100.9	91.6	–9.3	1.5
Placebo	172	105.1	102.7	–2.4	0.6

Table 3 Mean supine diastolic blood pressure

<i>Treatment group</i>	<i>n</i>	<i>Baseline mean (mmHg)</i>	<i>Final mean (mmHg)</i>	<i>Mean change (mmHg) final – baseline ± s.e. mean</i>	
Doxazosin	378	101.8	92.9	–9.0	0.4
Atenolol	125	101.7	89.7	–12.0	0.7
Hydrochlorothiazide	55	102.6	88.0	–14.6	1.5
Prazosin	54	102.4	93.5	–8.9	0.9
Metoprolol	33	105.0	88.8	–16.2	1.8
Nadolol	26	95.8	86.3	–9.4	1.4
Placebo	172	101.0	97.7	–3.4	0.5

Table 4 Mean standing systolic blood pressure

<i>Treatment group</i>	<i>n</i>	<i>Baseline mean (mmHg)</i>	<i>Final mean (mmHg)</i>	<i>Mean change (mmHg) final – baseline ± s.e. mean</i>	
Doxazosin	408	157.0	142.5	–14.5	0.7
Atenolol	155	154.5	141.0	–13.4	1.1
Hydrochlorothiazide	55	159.6	135.8	–23.9	2.5
Prazosin	54	159.0	147.1	–11.8	1.4
Metoprolol	33	164.2	144.9	–19.3	3.2
Nadolol	26	150.7	141.9	–8.7	3.2
Placebo	172	154.4	151.0	–3.3	1.0

Table 5 Mean supine systolic blood pressure

<i>Treatment group</i>	<i>n</i>	<i>Baseline mean (mmHg)</i>	<i>Final mean (mmHg)</i>	<i>Mean change (mmHg) final – baseline ± s.e. mean</i>	
Doxazosin	378	159.0	148.8	–10.2	0.7
Atenolol	125	157.0	141.6	–15.4	1.2
Hydrochlorothiazide	55	162.1	140.3	–21.7	2.5
Prazosin	54	161.3	151.5	–9.8	1.5
Metoprolol	33	168.5	145.8	–22.7	2.7
Nadolol	26	149.9	137.6	–12.3	2.7
Placebo	172	155.1	153.7	–1.3	0.9

BP with doxazosin were somewhat smaller, overall being 2.1 mmHg less than the mean standing fall (Tables 2 and 3). The mean end of treatment diastolic BPs were similar in both standing (94.3

mmHg) and supine (92.9 mmHg) positions. Doxazosin produced a substantial fall in standing systolic blood pressure (14.5 mmHg, Table 4) but again a somewhat lesser fall in the supine position

Table 6 Mean standing heart rate

Treatment group	Baseline		Final		Mean change (beats min ⁻¹)		n
	mean (beats min ⁻¹)	n	mean (beats min ⁻¹)	n	final-baseline ± s.e. mean		
Doxazosin	79.9	406	78.9	407	-1.0	0.5	406
Atenolol	81.6	151	68.2	153	-13.4	0.8	150
Hydrochlorothiazide	80.3	55	81.5	55	1.2	1.5	55
Prazosin	77.7	54	77.6	54	-0.2	1.3	54
Metoprolol	81.6	33	65.7	33	-15.8	1.7	33
Nadolol	78.4	26	60.1	26	-18.4	1.4	26
Placebo	78.9	172	78.6	171	-0.3	0.6	171

(10.2 mmHg, Table 5). Virtually no change occurred with doxazosin in mean heart rate (Table 6) in contrast to the clinically significant bradycardia produced by the β -adrenoceptor antagonists. Overall mean reductions in standing heart rate for atenolol, metoprolol and nadolol were 13.4, 15.8 and 18.4 beats min⁻¹ respectively, comparable reductions being observed in all studies. Similar changes in heart rate were obtained in the supine position.

Defining a 'responder' as a patient with a fall in standing diastolic BP (1) of 10 mmHg or more, or (2) of 5 mmHg or more and to below 90 mmHg, then responder rates were doxazosin 243/408 (60%), atenolol 93/155 (60%), hydrochlorothiazide 37/55 (67%), prazosin 33/54 (61%), metoprolol 23/33 (70%), nadolol 14/26 (54%) and placebo 33/172 (19%).

The efficacy of doxazosin in elderly patients aged ≥ 65 years was comparable with that found in the population under 65 years old. In the latter population ($n = 349$) mean falls in blood pressure were 14/11 mmHg standing and 10/9 mmHg supine. In the elderly group ($n = 55$), mean falls were 19/13 mmHg standing and 14/10 mmHg supine. The severity of hypertension at baseline was similar for the two patients subgroups in terms of diastolic blood pressure, but systolic pressures were somewhat higher in the elderly.

Haemodynamic and clinical parameters have shown that hypertension differs markedly between black and caucasian patients (Messerli, 1984). The efficacy of doxazosin in blacks was shown to be comparable with that in caucasians. In those studies which included black patients, mean falls in blood pressure for caucasians ($n = 103$) were 15/12 mmHg standing and 10/9 mmHg supine. In the black subgroup ($n = 53$), mean falls were 16/11 mmHg standing and 7/7 mmHg supine. In the small number of black patients ($n = 8$) treated with atenolol or nadolol, the mean falls in blood pressure were 0/5 mmHg standing and 3/5 mmHg supine,

whilst the bradycardia (-12 beats min⁻¹ standing) was similar to that found in the comparative caucasian subgroup (-15 beats min⁻¹ standing).

Lipids

In all studies doxazosin produced favourable changes in key blood lipid parameters relative to the comparative agents. Pooled results (Table 7) from 5 studies of doxazosin ($n = 142$) versus placebo ($n = 155$) showed reductions relative to placebo in total triglycerides (doxazosin -9.1%, placebo -3.0%) and total cholesterol (doxazosin -1.2%, placebo +0.6%). Increases relative to placebo were observed in HDL cholesterol (doxazosin 7.6%, placebo 4.8%) and the calculated ratio HDL/total cholesterol (doxazosin 8.9%, placebo 4.1%). The differences between the two treatments reached statistical significance for the HDL/total cholesterol ratio ($P < 0.05$) and approached statistical significance for total triglycerides ($P < 0.10$). The results of a completed study contributing to these pooled data are reported separately (Torvik & Madsbu, 1986).

The blood lipid results of a double-blind study comparing doxazosin with atenolol have also been reported (Frick *et al.*, 1986; Lehtonen *et al.*, 1986). After 1 year there was a decrease (5.0%) in mean total triglyceride concentration in the doxazosin treated group and an increase (42.7%) in the atenolol treated group. The mean difference in the changes between the two groups was highly statistically significant ($P = 0.0001$). In addition there were mean increases in both HDL cholesterol (3.9%) and the ratio HDL/total cholesterol (5.4%) following doxazosin administration and decreases (7.4% and 9.9%, respectively) following atenolol. Again the mean difference in the changes between the groups was highly significant, $P = 0.001$ for HDL cholesterol and $P = 0.0001$ for the ratio HDL/total cholesterol. Although total cholesterol concentrations were decreased following adminis-

Table 7 Changes from baseline in serum lipids. Doxazosin-placebo comparison. Pooled data

	Doxazosin		Placebo		P
	n	Δ%	n	Δ%	
Triglycerides	142	-9.1	155	-3.0	NS
Cholesterol	142	-1.2	155	0.6	NS
HDL cholesterol	142	7.6	155	4.8	NS
HDL/total cholesterol	142	8.9	155	4.1	P<0.05

Δ% = Percentage change from baseline, derived from the geometric mean of final/baseline

P = Significance of difference between groups

NS = not significant

tration of doxazosin (-1.7%) compared with an increase with atenolol (+2.7%), the difference between the changes for the two treatment groups was not statistically significant.

Pharmacokinetics

In a single dose study in volunteers (Vincent *et al.*, 1983) comparing the pharmacokinetics of intravenous and oral doxazosin, oral bioavailability was found to be 63% and the mean elimination half-lives approximately 9 h. In a similar study (Elliott *et al.*, 1986) in elderly volunteers of mean age 71 years, the results were similar to those found earlier in the younger age group. The calculated bioavailability of the oral form was 69% and the half-lives for intravenous and oral formulations were 8.9 and 11.9 h respectively.

Steady state pharmacokinetics of doxazosin have

been reported (Frick *et al.*, 1986). In patients receiving stable doses of doxazosin (unchanged for at least 1 month), mean plasma concentrations were closely proportional to dose. In a group of 12 patients assessed on two occasions at least 3 months apart, almost identical pharmacokinetic profiles were obtained. Mean elimination half-lives were between 11 and 12 h. Doxazosin was assayed by h.p.l.c. using a fluorescence detection method (Rubin *et al.*, 1980).

Safety

The number of patients with side-effects are summarized in Table 8 for the full comparative database of 1141 patients. The figures quoted for side-effects include those recorded by the investigator as definitely related to treatment, those of uncertain causality and those for which causality

Table 8 Numbers of patients with side-effects

Treatment	Evaluated	With side-effects	Withdrawn with side-effects
Doxazosin ^a	231	118	3
Placebo	212	88	5
Doxazosin	190	118	15
Atenolol	179	86	6
Doxazosin	41	25	6
Metoprolol	39	15	2
Doxazosin	29	14	0
Nadolol	29	14	1
Doxazosin	58	31	0
Prazosin	57	30	1
Doxazosin	117	48	6
Hydrochlorothiazide	83	42	5

^aTotal number of doxazosin patients = 542. Those doxazosin patients in three-way comparisons (doxazosin vs placebo vs atenolol/nadolol) appear twice in the pooled paired comparisons in this Table.

was not recorded. The results are presented as paired comparisons, pooled across studies in the case of the placebo, atenolol and hydrochlorothiazide comparisons.

The incidence of side-effects on doxazosin ranged, depending on study, from an incidence slightly below to somewhat higher than placebo. In paired comparisons with active agents, the incidence of side-effects observed with doxazosin was similar to that observed for nadolol and prazosin, somewhat higher than that observed with atenolol and metoprolol and somewhat lower than that observed with hydrochlorothiazide. There was no observable peaking of side-effects early in doxazosin treatment, as shown by an analysis of side-effects reported during the first 3 weeks of therapy, which revealed a comparable incidence for doxazosin (18%) and placebo (17%). The incidence among the active comparative agents used in these double-blind studies ranged between 10 and 19% during the same period.

Of all side-effects associated with doxazosin, the majority (86%) with recorded severity were in the mild to moderate category. In the great majority of cases these side-effects did not result in an alteration of study therapy. A total of 6% of side-effects resulted in dose reduction and 2% of side-effects resulted in temporary discontinuation of therapy, although in these cases the side-effect either was tolerated or did not recur when therapy was restarted. Similar proportions of patients were withdrawn from therapy due to side-effects in the doxazosin treated group (29/542) and the combined active comparative treatment groups (14/388).

The incidence and profile of side-effects associated with doxazosin in elderly patients were similar to those reported for the total population.

An extensive screening of laboratory safety parameters was carried out on all patients and showed no evidence of doxazosin-related adverse effects.

Coronary risk factors

Three primary risk factors have been shown to predispose to coronary heart disease (CHD), namely high blood pressure, cigarette smoking and hyperlipidaemia. Treatment with doxazosin has been shown to result in a significant improvement in risk for two of the above risk factors, by virtue of its antihypertensive effects and the favourable changes in cholesterol fractions.

The associated risk factors in coronary heart disease are discussed in detail in the *Coronary Risk Handbook* (1973) and also by Gordon & Kannel

(1982). The large Framingham epidemiological study in its 16 year follow-up report provides a substantial independent database from which may be calculated probabilities for the development of coronary heart disease, taking account of the multiple factors contributing to this risk (Keyloun, personal communication). The main characteristics which have been considered to influence coronary heart disease in the Framingham study are systolic blood pressure, serum cholesterol, cigarette smoking, glucose intolerance and left ventricular hypertrophy on the electrocardiogram. Patients with glucose intolerance and left ventricular hypertrophy were excluded from controlled double-blind studies with doxazosin.

Based on the formulae provided in the above publications on coronary risk factors, the average probability of developing coronary heart disease within a 6 year period has been calculated for patients at baseline and at the end of the trial for various populations in the doxazosin clinical programme. Only patients meeting the Framingham inclusion criteria were included in the analysis. The first analysis was carried out on two subsets, including a total of 99 patients treated with doxazosin: those in active drug comparative studies treated for 18–24 weeks and those in placebo-controlled studies treated for 10–12 weeks. The results indicated a substantial mean reduction (15–29%) in the calculated risk of developing heart disease.

The second analysis used comparative data for 75 patients treated for 20–24 weeks with either doxazosin ($n = 38$) or atenolol ($n = 37$) who were evaluable for risk analysis, and showed that doxazosin therapy was associated with a 13% reduction in risk of developing coronary heart disease within 6 years. Despite causing similar reductions in systolic blood pressure in these patients, atenolol therapy was associated with an increase in risk over the 20-week period of 18%. This appears to be primarily related to the substantial and adverse effects atenolol was shown to have on blood lipids. The difference in risk between the two treatment groups was statistically highly significant ($P = 0.001$).

Some caution must be exercised in the interpretation of these analyses based on the Framingham data base. In particular, the applicability of the latter to non-American populations and the possible confounding influence of other risk factors such as cigarette smoking must be considered. Furthermore, the Framingham study was not a prospective trial of risk factor modification.

However, the data presented in this paper are

compatible with the suggestion from epidemiological studies (Freis, 1982; Messerli, 1984; Medical Research Council, 1985) that although established antihypertensive agents will reduce the incidence of haemorrhagic stroke and heart failure, there is little indication that they reduce the risk of coronary heart disease. This is believed to be largely attributable to the adverse effects on blood lipids. Doxazosin has comparable antihypertensive efficacy to the established agents but, in contrast, therapy is also associated with clinically important favourable changes in the lipid parameters. Thus the favourable effects on the two risk factors amenable to therapeutic intervention give doxazosin the potential to reduce the risk of developing coronary heart disease.

The authors gratefully acknowledge the invaluable and expert assistance of Dr T. Lewis and his colleagues for the data handling and statistical inputs.

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