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A CLINICAL PHARMACOLOGICAL COMPARISON OF DICLOFENSINE (Ro 8-4650) WITH NOMIFENSINE AND AMITRIPTYLINE IN NORMAL HUMAN VOLUNTEERS

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1 Ten healthy male volunteers participated in a double-blind placebo-controlled crossover comparison of the pharmacodynamic profiles of single oral doses of diclofensine 25 mg and 50 mg, nomifensine 75 mg and amitriptyline 50 mg.

2 Diclofensine did not influence salivary flow or consistently affect pupil diameter and had no significant effect on subjective measurements of sedation and mood. It had no effect on reaction time, or on critical flicker frequency.

3 By contrast, amitriptyline significantly reduced salivary flow, produced significant sedation and impairment of mood, prolonged reaction time, and appeared to decrease (but not significantly) critical flicker frequency.

4 Nomifensine significantly reduced (i.e. improved) reaction time, and inhibited salivary flow.

5 Diclofensine did not significantly influence heart rate, blood pressure, systolic time intervals or high speed electrocardiogram.

6 No significant treatment-related differences were observed in serum prolactin, cortisol or growth hormone levels.

Introduction

Diclofensine (Ro 8-4650) is a new isoquinoline derivative antidepressive, which is structurally similar to nomifensine but from which it differs in its central and peripheral pharmacological actions (Carruba *et al.*, 1980). It is a potent inhibitor of 5-hydroxytryptamine, dopamine and noradrenaline uptake (Bonetti & Bondiolotti, 1980). Early exploratory, uncontrolled trials suggested the usefulness of this new drug as an antidepressive (Omer, 1982), and controlled trials have demonstrated an effective daily dose of 50 mg in out-patients suffering from moderate to severe depression (Cherpillod & Omer, 1981). The response was characterised by central stimulatory and mood elevating effects, particularly in non-psychotic types of depression (De Paula & Omer, 1980). Few serious side effects occurred in these studies; the most common being insomnia, slight transient drowsiness and constipation. Anticholinergic type symptoms were rare and mild. Since anticholinergic effects such as dry mouth, palpitation, dizziness and drowsiness may also be symptoms of depression, assessment of anticholinergic drug effects in patients can be difficult. It was thought to be necessary, therefore, to establish whether diclofensine in standard therapeutic doses produces anticholinergic side effects in normal subjects.

Animal studies have suggested a reduced potential of diclofensine for cardiotoxic effects as compared with tricyclic antidepressive agents (unpublished data, F. Hoffmann-La Roche & Co Ltd, Basle), and it was of interest therefore to study the effects, if any, of diclofensine on basic cardiovascular parameters in man, using non-invasive methods. This paper describes a study in which diclofensine was compared with nomifensine, amitriptyline and placebo in tests of autonomic, central nervous and cardiovascular function in normal human subjects.

Methods

Subject selection

Ten healthy young male volunteer subjects in the age range 18 to 26 years (mean 21.8 years) of mean weight 74.3 kg were selected on the basis of normal medical

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history and physical examination, ECG and laboratory tests (routine haematology and biochemistry). The subjects were instructed to refrain from taking other drug treatments throughout the study period (about 6 weeks). They were asked to abstain from alcohol, tea, coffee, chocolate and smoking on study days (24 h each). Informed signed consent was obtained from each subject, and the study was approved by the local Ethics Committee.

Study design

Each subject received the following five treatments in matching capsules, in doses considered safe and expected to show biological activity, in a double-blind, cross-over fashion according to two Latin-square designs with an interval of at least 1 week between each treatment:

(1) 25 mg diclofensine (as the hydrochloride)
(2) 50 mg diclofensine (as the hydrochloride)
(3) 75 mg nomifensine (as the maleate)
(4) 50 mg amitriptyline (as the hydrochloride)
(5) placebo

Treatment was given with 100 ml water about 1 h following a light breakfast.

A series of tests as described below were performed before treatment (0 h) and at intervals for up to 24 h following treatment, according to a standard sequence.

Vital functions

Blood pressure, supine (following a 5-min rest) and erect, and radial pulse rate were measured at 0 h and then at hourly intervals until 6 h post-treatment. Blood pressure was measured with the London School of Hygiene sphygmomanometer.

Cardiovascular effects

Cardiovascular effects were measured at pretreatment and at 1.5 h and 3 h. After resting supine on a bed for 15 min the systolic time intervals (STI) and high speed surface ECG were recorded as described by Burgess *et al.* (1978). From these recordings, QS_2 (total electromechanical systole), LVET (left ventricular ejection time), and PEP (pre-ejection period) were calculated from the STI; and PR, QRS and QT intervals were calculated from the ECG. The STI were corrected for heart rate using the formula of Weissler *et al.* (1969). QT interval was corrected for heart rate using the Bazett formula.

Somatic effects

Salivary flow, stimulated by sucking an acid drop for 2 min, was measured according to the procedure described by Kingsley & Turner (1974).

Pupil diameter of both eyes was measured with a ruler under constant lighting conditions, and the values meaned. Both these measurements were made at 0 h and then at hourly intervals until 6 h post-treatment.

Subjective central tests

On a series of 100 mm linear analogue rating scales, subjects were asked to mark the point on the line between the two extremes which would give an indication of their mood, sedation, appetite and dryness of mouth. The extremes of the scales for mood were 'I have never felt more depressed' and 'I have never felt happier'; for sedation the extremes were 'I cannot keep awake' and 'I feel as alert as I have ever been'; the extremes for appetite were 'I am not hungry at all', and 'I am as hungry as I have ever been'; the extremes for dryness of mouth were 'My mouth is completely dry' and 'I have no dryness of mouth whatsoever'. At 0 h and 24 h the subjects also indicated the quality of the previous night's sleep; the extremes of the scales were 'Worst night's sleep' and 'Best night's sleep'.

Objective tests of central function

Critical flicker fusion (CFF) threshold was measured using the method of Turner (1968) as modified by Ogle & Turner (1974). Before the start of the study, subjects were acquainted with the methodology and the normal CFF for each subject was determined. A mean of four readings was taken on each occasion:

(a) ascending threshold from 20 Hz after conditioning to 20 Hz,
(b) descending threshold from 50 Hz after conditioning to 20 Hz,
(c) ascending threshold from 20 Hz after conditioning to 50 Hz,
(d) descending threshold from 50 Hz after conditioning to 50 Hz.

Multiple (complex) reaction time was measured by a standard procedure (Kulshrestha *et al.*, 1978). A total of thirteen visual stimuli were given at randomised intervals. The first three readings were discarded and the subsequent 10 consecutive readings were meaned.

Laboratory tests

Blood samples were drawn at 0, 1, 3 and 24 h for measurements of prolactin, growth hormone and cortisol (Technical Laboratory Services Limited).

Data analysis

Analysis of variance was used to analyse the data for week, time of day and specific *a priori* between drug effects.

A separate analysis of variance was used at each time point in an attempt to isolate the onset and persistence of drug effect. All visual analogue scale data were transformed into arcsine prior to analysis (Cochran & Cox, 1957).

All P values are unadjusted for multiple comparison effects and correlated errors, and consequently only values below 0.001 rather than the more usual 0.05 were considered as reliable evidence of real effects.

Results

Pulse and blood pressure

Pulse rates are shown in Figure 1. Amitriptyline produced a greater fall in pulse rate compared with placebo ($P < 0.001$). There was no significant difference between the mean pulse rates after either dose of diclofensine or nomifensine and placebo.

No significant effects of treatment were seen on systolic or diastolic blood pressure with the exception of an unexplained mean elevation in supine systolic of 7 mm Hg ($P < 0.001$) by 50 mg diclofensine compared with placebo.

Systolic time intervals and ECG

No significant treatment related effects were seen on any component of the systolic time intervals, or ECG.

Salivary volume

Amitriptyline and nomifensine each produced a reduction in salivary volume compared with placebo ($P < 0.001$), but diclofensine produced no significant effect (Figure 2).

Pupil diameter

Amitriptyline and 25 mg diclofensine both produced a significant but small reduction in pupil diameter when compared with placebo ($P < 0.001$). Amitriptyline decreased the mean diameter by 0.5 mm after 2 h, which persisted through to 4 h post-dosing, while diclofensine 25 mg decreased it by 0.2 mm at 6 h post-dosing. Nomifensine and 50 mg diclofensine produced no change compared with placebo.

Subjective tests

Significant treatment effects were seen in the analogue rating scales for mood and sedation (Figures 3 and 4), but not for appetite, dryness of the mouth or for quality of the previous night's sleep. Sedation rating showed the greatest change, with amitriptyline having a highly significant sedative effect compared with placebo ($P < 0.001$) while nomifensine and diclofensine could not be distinguished from placebo. Mood was significantly ($P < 0.001$) affected by amitriptyline, subjects indicating that they were less happy than when receiving placebo, while diclofensine and nomifensine had no significant effect.

Critical flicker frequency and multiple reaction time

Figure 5 illustrates the observed increase in CFF threshold by nomifensine compared with placebo al-

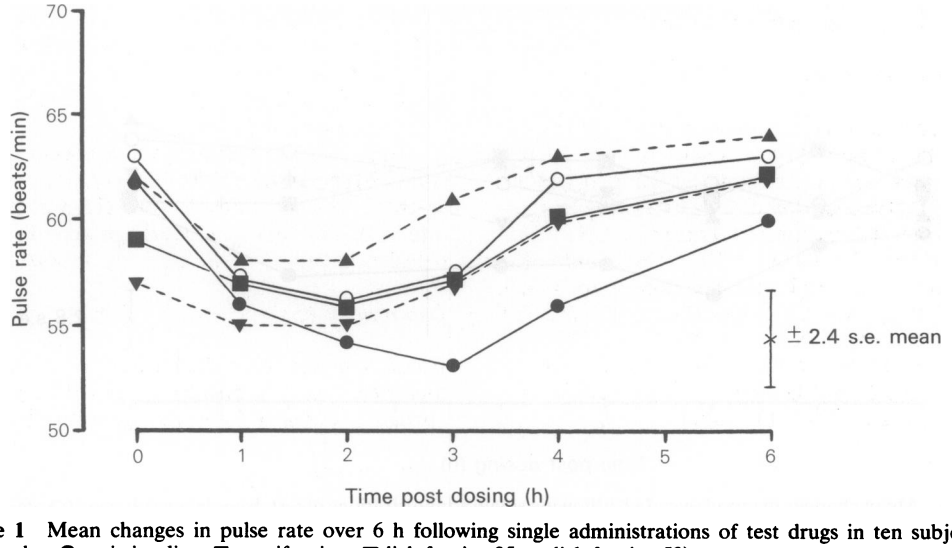

Figure 1 Mean changes in pulse rate over 6 h following single administrations of test drugs in ten subjects. (○ placebo, ● amitriptyline, ■ nomifensine, ▼diclofensine 25, ▲diclofensine 50)
Amitriptyline *vs* placebo ANOVA $P < 0.001$.

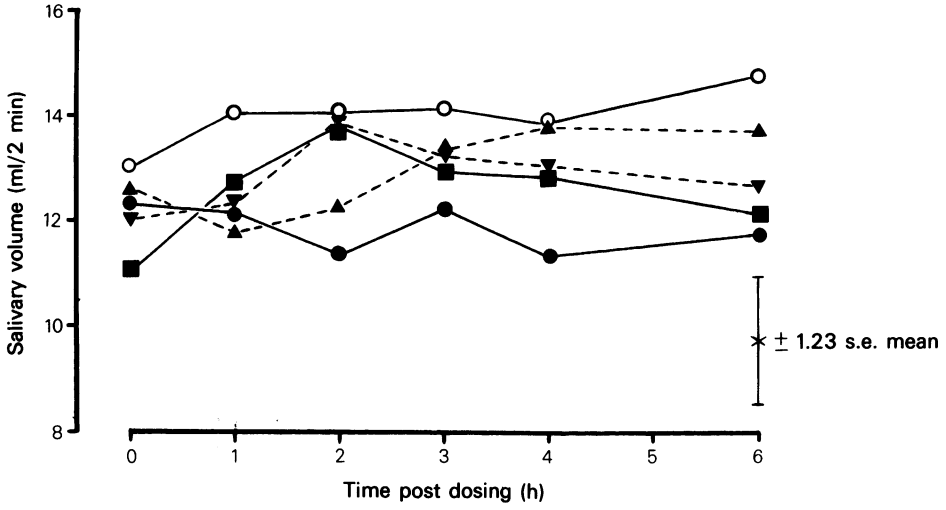

Figure 2 Mean changes in salivary volume over 6 h following single administrations of test drugs in ten subjects. (○ placebo, ● amitriptyline, ■ nomifensine, ▼ diclofensine 25, ▲ diclofensine 50)
Amitriptyline *vs* placebo ANOVA $P < 0.001$.
Nomifensine *vs* placebo ANOVA $P < 0.001$.

though the statistical evidence was slight ($P < 0.05$), while no real effect of amitriptyline was observed compared with placebo. Diclofensine in the higher dosage appeared to decrease CFF threshold, but this also was not statistically significant. Correction for baseline values had only a marginal effect on the analysis.

Multiple reaction time was significantly prolonged ($P < 0.001$) by amitriptyline, the subjects reacting more slowly at 1 h post-dosing and this effect persisted throughout the study day (Figure 6). By contrast, reaction time was significantly shortened by nomifensive ($P < 0.001$), the subjects reacting faster after 1 h. This stimulatory action persisted

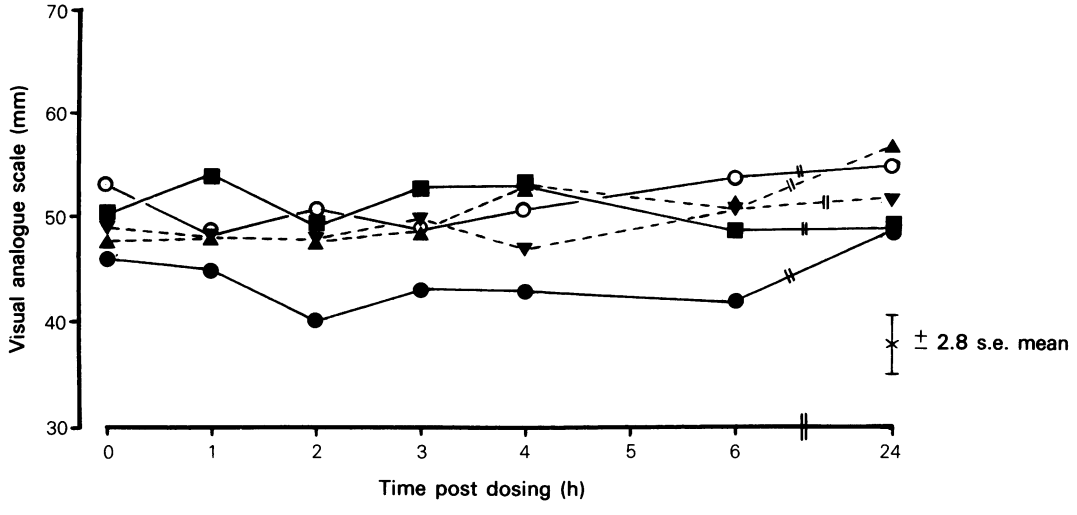

Figure 3 Mean changes in mood over 24 h following single administrations of test drugs in ten subjects. (○ placebo, ● amitriptyline, ■ nomifensine, ▼ diclofensine 25, ▲ diclofensine 50)
(Rating: 0 = depressed, 100 = very happy).
Amitriptyline *vs* placebo ANOVA $P < 0.001$.

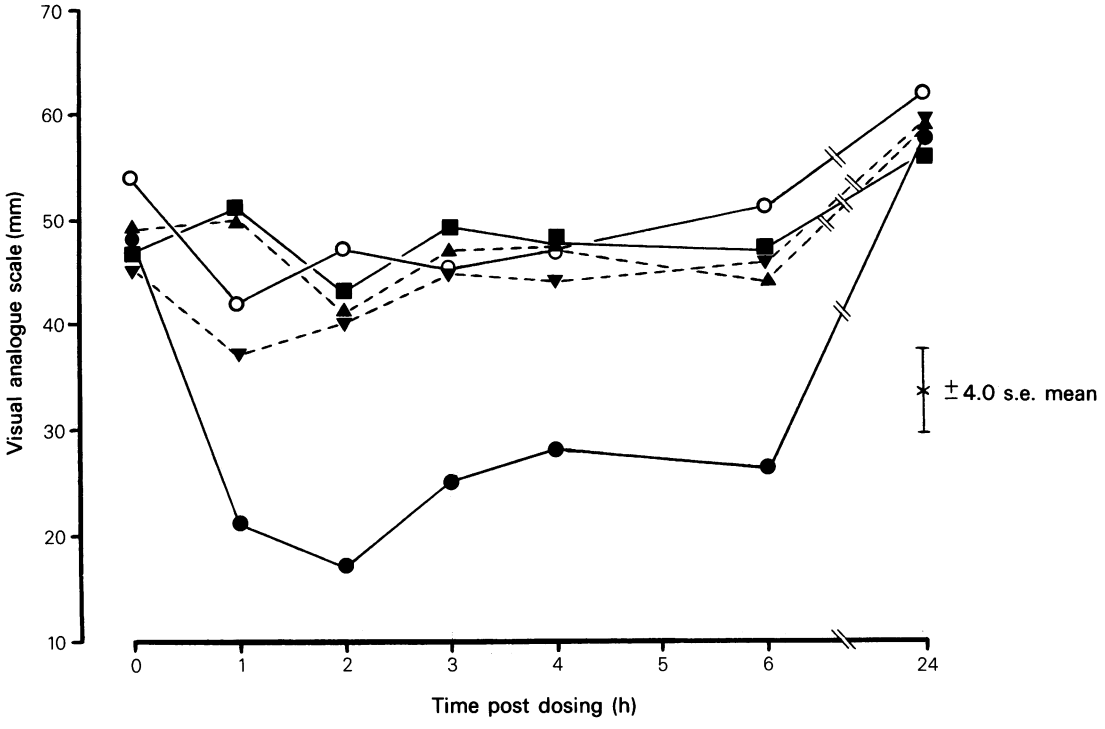

Figure 4 Mean changes in sedation over 24 h following single administrations of test drugs in ten subjects. (○placebo, ● amitriptyline, ■ nomifensine, ▼diclofensine 25, ▲diclofensine 50)
(Rating: 0 = very sleepy, 100 = very alert).
Amitriptyline *vs* placebo ANOVA $P < 0.001$.

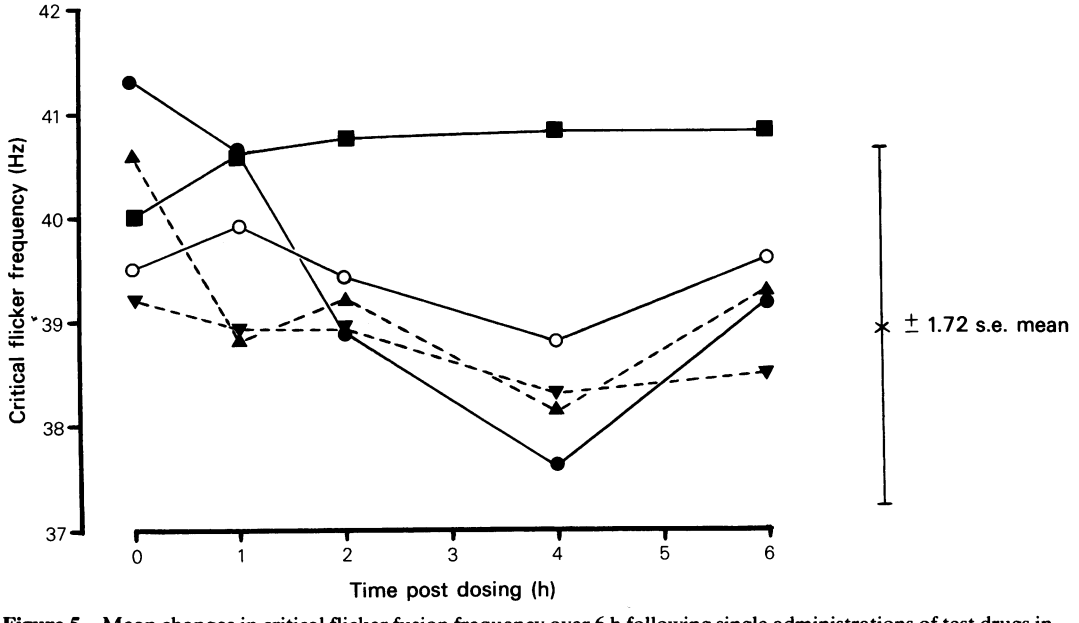

Figure 5 Mean changes in critical flicker fusion frequency over 6 h following single administrations of test drugs in ten subjects. (○placebo, ● amitriptyline, ■ nomifensine, ▼diclofensine 25, ▲diclofensine 50)
Nomifensine *vs* placebo ANOVA $P < 0.05$.

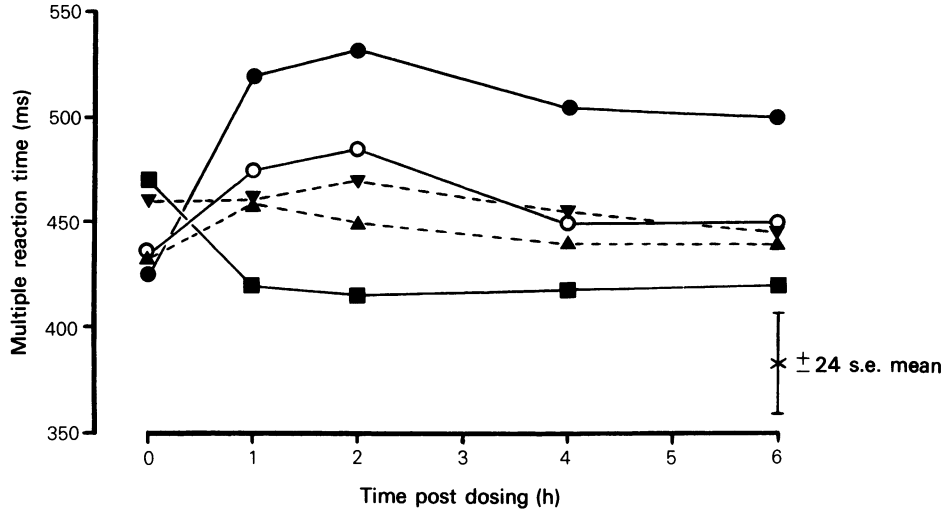

Figure 6 Mean changes in multiple reaction time over 6 h following single administrations of test drugs in ten subjects. (○ placebo, ● amitriptyline, ■ nomifensine, ▼ diclofensine 25, ▲ diclofensine 50)
Amitriptyline *vs* placebo ANOVA $P < 0.001$
Nomifensine *vs* placebo ANOVA $P < 0.001$

through to 6 h post-dosing. Diclofensine showed no effect on reaction time.

Hormone assays

No significant treatment-related effects were seen in serum cortisol, prolactin or growth hormone levels.

Discussion

The tricyclic monoamine reuptake inhibiting group of drugs still remains the most commonly used antidepressives, although treatment is often associated with varying degrees of anticholinergic side effects and sedation (Spencer, 1977). The present study employed amitriptyline as a positive control in this respect.

Salivary flow was inhibited by amitriptyline, as might be expected. In contrast to an earlier observation (Chan *et al.*, 1980), nomifensine was also observed to inhibit salivary flow compared with placebo. No clear evidence was found that diclofensine inhibited salivary flow, suggesting that it has less peripheral anticholinergic activity than amitriptyline following single doses in normal subjects.

The sedative effect of amitriptyline was confirmed in this study, using both subjective visual analogue rating scales and objective measurements such as CFF and reaction time. In contrast, nomifensine showed no sedative action, but rather significantly increased CFF threshold and improved performance, thus confirming the trends seen in a previous study of nomifensine *vs* amitriptyline (Chan *et al.*, 1980), and substantiating the findings of Hindmarch & Parrott (1977), who reported a significant increase in CFF following long-term nomifensine treatment. Diclofensine showed no sedative effect, and neither impaired nor enhanced performance. However, the higher dosage of diclofensine, but not the lower dosage, appeared to decrease (but not significantly) CFF threshold in these volunteers. Thus it would appear that diclofensine, while not showing amitriptyline-like sedative effects, did not show the stimulating or amphetamine-like effects of nomifensine.

Diclofensine was found to have no untoward cardiovascular or hormonal effects confirming similar results in animal studies (unpublished data, F. Hoffmann-La Roche, Basle). It would appear to offer advantages over amitriptyline in older patients and in those with established cardiovascular disease, but this must be confirmed in clinical studies.

Reprint requests should be addressed to R.S.B.E.

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