Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis

ABSTRACT—*Objective:* to determine the effect of 900 mg/day of dried garlic powder (standardised to 1.3% allicin) in reducing total cholesterol.
Design: double-blind, randomised six-month parallel trial.
Subjects: 115 individuals with a repeat total cholesterol concentration of 6.0–8.5 mmol/l and low-density lipoprotein (LDL) cholesterol of 3.5 mmol/l or above after six weeks of dietary advice.
Intervention: the active treatment group received dried garlic tablets (standardised to 1.3% allicin) at a dosage of 300 mg three times daily. The control group received a matching placebo.
Outcome measures: primary end-point: total cholesterol concentration; secondary end-points: concentrations of LDL and high-density lipoprotein cholesterol, apolipoproteins (apo) A1 and B, and triglycerides.
Results: there were no significant differences between the groups receiving garlic and placebo in the mean concentrations of serum lipids, lipoproteins or apo A1 or B, by analysis either on intention-to-treat or treatment received. In a meta-analysis which included the results from this trial, garlic was associated with a mean reduction in total cholesterol of –0.65 mmol/l (95% confidence intervals: –0.53 to –0.76).
Conclusions: in this trial, garlic was less effective in reducing total cholesterol than suggested by previous meta-analyses. Possible explanations are publication bias, overestimation of treatment effects in trials with inadequate concealment of treatment allocation, or a type 2 error. We conclude that meta-analyses should be interpreted critically and with particular caution if the constituent trials are small.

H A W NEIL, FRCP, *University Lecturer and Honorary Consultant Physician, Department of Public Health and Primary Care, University of Oxford*

C A SILAGY, PhD, *Professor of General Practice, Flinders University of South Australia School of Medicine, Adelaide*

T LANCASTER, MRCP, MRCGP, *Deputy Director, Imperial Cancer Research Fund General Practice Research Group, Radcliffe Infirmary, Oxford*

J HODGEMAN, *Research Nurse, Imperial Cancer Research Group, Radcliffe Infirmary, Oxford*

K VOS, *Research Nurse, Imperial Cancer Research Fund General Practice Research Group, Radcliffe Infirmary, Oxford*

J W MOORE, PhD, *Head of Imperial Cancer Research Fund Assay Laboratory, Radcliffe Infirmary, Oxford*

L JONES, *Computer Scientist, Imperial Cancer Research Fund General Practice Research Group, Radcliffe Infirmary, Oxford*

J CAHILL, MRCP, MRCGP, *General Practitioner, Princes Risborough*

G H FOWLER, OBE, FRCGP, *Clinical Reader in General Practice, Department of Public Health and Primary Care, University of Oxford*

Evidence that garlic may inhibit platelet aggregation, increase fibrinolysis, reduce blood pressure, enhance antioxidant activity and reduce serum lipids suggests that it may have cardioprotective properties [1]. The lipid-lowering action of garlic has been most extensively studied; two meta-analyses of the primary clinical trials showed approximately 10% reduction in total cholesterol attributable to garlic [2,3]. Many of these trials, however, had methodological shortcomings, such as:

- inappropriate methods of randomisation
- lack of a dietary run-in period
- short duration
- failure to undertake intention-to-treat analysis
- inadequate statistical power.

The aim of the study reported here was to conduct a rigorously designed and analysed trial to determine the effect of garlic powder on serum lipids, lipoproteins, and apolipoprotein (apo) A1 and B concentrations in patients with type IIa or IIb hyperlipoproteinaemia.

Study design and methods

The trial, of six months' duration, was a randomised, double-blind parallel comparison of dried garlic powder and placebo. Patients were recruited from a group general practice in Buckinghamshire with 13,453 patients. Men and women of European origin, aged 35–64 years, were eligible for inclusion in the trial if, after receiving dietary advice, they had a total cholesterol concentration of 6.5–9.0 mmol/l on screening and a repeat fasting concentration of 6.0–8.5 mmol/l, with a low-density lipoprotein (LDL) cholesterol of 3.5 mmol/l or above. The exclusion criteria were:

- fasting triglyceride concentration of 5.6 mmol/l or above
- high-density lipoprotein (HDL) cholesterol concentration of 2.0 mmol/l or above

- hyperlipidaemia secondary to any recognised cause
- treatment with a lipid-lowering drug
- hospitalisation for severe illness within the previous three months
- pregnancy or breast feeding.

The primary end-point of the trial was total cholesterol concentration at six months, and the secondary end-points, concentrations of LDL and HDL cholesterol, apo A1 and B, and triglycerides. Assuming a standard deviation (SD) in repeated cholesterol measurements of 1 mmol/l, and based on a two-sided test at a 5% level of significance, the trial was designed to have 90% statistical power to detect a difference of at least 0.6 mmol/l in the total cholesterol concentration between the treatment and placebo groups at the end of the trial. The study was approved by the local research ethics committee.

Recruitment and randomisation

Patients known to have hypercholesterolaemia who had not been treated with a lipid-lowering drug were identified from the practice disease register. Additional potentially eligible patients, identified opportunistically and systematically using the practice age/sex register, were invited to attend a cardiovascular screening clinic appointment. Screening was undertaken by two research nurses and included:

- a brief structured medical questionnaire
- standardised measurement of height, weight and blood pressure (mean of two readings, diastolic pressure as Korotkoff V)
- a non-fasting capillary blood sample, obtained using a dry chemistry analyser (Lipotrend, Boehringer Mannheim, Lewes, UK).

Patients with a cholesterol concentration of 6.5–9.0 mmol/l were given dietary advice to reduce to 30% or less the percentage of total dietary energy contributed from fat, and to consume up to 10% of energy from each of saturated, monounsaturated, and polyunsaturated fats. The recommended percentage of energy derived from carbohydrate was 50–60% and from protein 10–20%. A daily intake of less than 300 mg of cholesterol, and about 35 g of fibre was recommended. Patients were also given a lipid-lowering diet leaflet, and were asked to re-attend six weeks later after an overnight fast.

At the six-week visit, a fasting venous blood sample was obtained for measurement of total and HDL cholesterol, triglycerides, and apo A1 and B. Patients with a total cholesterol of 6.0–8.5 mmol/l who met the entry criteria were informed of the result and invited to participate. The purpose of the trial was explained, and written informed consent obtained.

Garlic tablets and placebo were supplied in identical bottles, using a centrally generated list of consecutive random treatment assignments for blocks of each of 10 patients. The study coordinator issued the bottles consecutively, with no knowledge of the treatment assignment. The results of the lipid and lipoprotein measurements were not entered into the clinical case notes until the end of the trial to avoid the possible confounding effect of dietary advice offered opportunistically.

Intervention

The active treatment group received odour-controlled Kwai (Lichtwer Pharma GmbH) dried garlic tablets (standardised to 1.3% allicin) at a dosage of 300 mg three times daily. The control group received the same number of placebo (lactose) tablets coated with an outer layer impregnated with garlic powder to ensure that they were indistinguishable from the active treatment. Both groups were reviewed by the research nurses eight weeks after randomisation. Remaining tablets were counted to check compliance, and further tablets supplied. A record was made of the possible side effects, acceptability, palatability, and detection of garlic odour. These procedures were repeated after a further four months, and a fasting venous blood sample was taken for measurement of concentrations of total and HDL lipoprotein cholesterol, apo A1 and B and triglycerides. Three attempts were made, by post and telephone, to contact those who did not attend for scheduled follow-up.

Biochemical analysis

Venous blood samples (10 ml) were collected in plain tubes, transported daily to the laboratory on ice and centrifuged immediately on arrival. The laboratory was unaware of the treatment status of the samples. Serum (for analysis of lipids) was removed and stored at minus 50°C in airtight tubes. Serum lipids were measured using a Cobas Farra centrifugal analyser (Roche Diagnostic Systems, Welwyn Garden City, UK). Samples were analysed in a single batch during the week of collection. Cholesterol was measured using Monotest Cholesterol Reagent (Boehringer Mannheim, Lewes, UK), and triglyceride with Peridochrom Reagent (Boehringer Mannheim). HDL cholesterol was measured by precipitation of the non-HDL fraction with phosphotungstic acid. Apo A1 and B were measured by an immunoturbimetric method using standard kits (Boehringer Mannheim). The between-batch coefficient of variation of internal and external quality control material over the range of results found in the study was less than 2% for cholesterol, less than 3% for triglycerides and less than 6% for HDL cholesterol. The interassay coefficient of variation for apo A1 and B was 10% at 33.8 µmol/l and 2.48 µmol/l, respectively. Serum LDL concentrations were calculated using the Friedewald equation [4].

Statistical analysis

Statistical analysis was undertaken using the statistical package SPSS/PC+. Data were analysed on the basis of intention-to-treat, and a secondary exposure analysis was performed. For patients who were randomised but lost to follow-up, the baseline pre-randomisation results were used in the outcome analyses. The triglyceride measurements were log transformed before analysis because the data were positively skewed. For continuously distributed variables, statistical comparisons between the two groups at the end of the trial were made by analysis of variance to adjust for the effects of any imbalance between them. The differences between groups in the mean individual changes in outcome measures from randomisation to the end of the trial were analysed by two-tailed *t*-tests. A χ^2 statistic was used to test for differences between categorical variables, and the 95% confidence intervals (CI) calculated where appropriate.

Results

Screening was carried out from November 1993 to December 1994. Of the 1,293 patients approached, 415 were screened to achieve the final study population of 115, 106 of whom completed the study and returned for a final visit. The baseline characteristics of individuals randomised are given in Table 1. There were no significant differences between the two groups in age, sex, or measured cardiovascular risk factors.

Table 2 shows the mean fasting lipid and lipoprotein concentrations in the garlic and placebo groups at the beginning and end of the trial, with the mean differences and 95% CIs. At the end of the six-month trial, there were no significant differences between the intervention groups in the mean lipid and lipoprotein concentrations or in the mean individual changes from randomisation to the end of the trial.

Table 1. Baseline characteristics of 115 subjects randomly allocated to garlic or placebo

Characteristic	Garlic (n=57)		Placebo (n=58)	
Sex: female: male	21:36		24:34	
Age:				
mean (SD)	53.0	(7.0)	52.6	(7.8)
median	53.0		52.1	
Systolic BP (mmHg): mean (SD)	131.8	(16.1)	133.8	(18.4)
Diastolic BP (mmHg): mean (SD)	81.3	(10.2)	82.6	(10.6)
Body mass index (kg/m²): mean (SD)	27.03	(3.7)	27.67	(4.3)
Weight (kg): mean (SD)	79.52	(14.4)	81.33	(15.2)
Alcohol (units/week):				
mean (SD)	8.3	(9.4)	9.6	(11.5)
median	5.0		5.5	
Current smokers: no. (%)	7	(12.3)	10	(17.2)

BP = blood pressure; SD = standard deviation

Table 2. Mean (SD) fasting plasma lipid and lipoprotein concentrations at the start and end of a six-month trial

Concentration (mmol/l)	Garlic (n=57)		Placebo (n=58)		Difference between groups in mean individual changes (95% CI)
	Baseline	Final	Baseline	Final	
Cholesterol:					
total	6.96 (0.57)	6.91 (0.67)	6.99 (0.61)	7.04 (0.73)	−0.10 (−0.35,0.15)
HDL	1.15 (0.30)	1.17 (0.31)	1.12 (0.30)	1.10 (0.25)	0.03 (−0.03,0.09)
LDL	4.96 (0.62)	4.94 (0.71)	4.94 (0.58)	4.93 (0.69)	−0.02 (−0.22,0.19)
Triglycerides*	1.70 (1.32,2.18)	1.58 (1.06,2.32)	1.87 (1.24,2.53)	1.90 (1.39,2.94)	−0.11 (−0.34,0.12)
Apolipoproteins:					
A1	41.57 (10.18)	41.36 (13.86)	41.29 (11.25)	42.21 (13.25)	−1.16 (−6.36,4.04)
B	2.67 (0.75)	3.06 (1.04)	2.27 (0.79)	3.01 (1.02)	0.10 (−0.34,0.54)

* geometric mean (interquartile range)

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein

Table 3. Mean (SD) fasting plasma lipid and lipoprotein concentrations at the start and end of a six-month trial in patients complying with treatment

Concentration (mmol/l)	Garlic (n=28)		Placebo (n=28)		Difference between groups in mean individual changes (95% CI)
	Baseline	Final	Baseline	Final	
Cholesterol:					
total	7.02 (0.61)	7.10 (0.63)	7.01 (0.64)	7.07 (0.68)	0.03 (–0.33,0.40)
HDL	1.14 (0.27)	1.21 (0.30)	1.12 (0.31)	1.14 (0.27)	0.04 (–0.03,0.12)
LDL	5.08 (0.56)	5.14 (0.69)	4.94 (0.58)	5.06 (0.68)	0.01 (–0.33,0.34)
Triglycerides*	1.63 (1.24,2.10)	1.48 (0.94,2.34)	1.85 (1.14,2.64)	1.78 (1.19,2.95)	–0.05 (–0.32,0.32)
Apolipoproteins:					
A1	41.79 (11.34)	43.50 (15.61)	40.57 (9.57)	41.54 (15.07)	–1.19 (–8.91,8.54)
B	2.63 (0.75)	3.18 (1.10)	2.76 (0.85)	3.06 (1.10)	0.22 (–0.54,0.97)

* geometric mean (interquartile range)

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein

The mean fasting lipid and lipoprotein concentrations in an analysis limited to those subjects who achieved better than 75% compliance with therapy are shown in Table 3. In this on-treatment analysis, there were again no significant differences between the two groups.

Nineteen subjects in the garlic group and five in the placebo group were aware of odour attributable to treatment (odds ratio: 5.90, 95% CI: 1.98–17.50); 34 in the garlic group and four in the placebo group reported that other people had commented on odour (odds ratio: 27.90, 95% CI: 8.44–92.40). Adverse events were the reason for discontinuation of treatment by 16 subjects (Table 4). Compliance with the tablet schedule of better than 75% was achieved by 56 subjects (verified by tablet counts). The main cited reason for failure to comply was the inconvenience of the three times daily dosing schedule.

Table 4. Reasons for discontinuation of treatment

Adverse event	Garlic group		Placebo group	
	no.	%	no.	%
Breath odour	8	14	1	1.7
Abdominal symptoms	4	10.5	2	3.4
Acute myocardial infarction			1	1.7

Discussion

In this double-blind randomised controlled trial, no significant effect of dried garlic tablets (standardised to 1.3% allicin at a dose of 900 mg/day) was detected on lipids and lipoproteins in individuals with type IIa or IIb hyperlipoproteinaemia. Several factors may account for this failure to confirm the moderate effect of treatment suggested by the two previous meta-analyses concerned with the effect of garlic on serum lipids [2,3]. Publication bias is one possible explanation [5]. Figure 1 shows a funnel plot in which the sample size of each trial of standardised garlic was plotted against the difference in mean cholesterol between intervention and control groups at the end of treatment. Without publication bias, the plot should resemble a symmetrical inverted funnel, with results of smaller studies more widely scattered than those of larger studies [6]. In fact, the plot is asymmetric, with a gap at the bottom right of the funnel, raising the possibility of 'missing' negative studies (publication bias) resulting in false-positive meta-analyses.

Another possible explanation may be methodological shortcomings in trials contributing results to pooled estimates of the meta-analyses [2]. Schulz and colleagues [7] recently reviewed 250 reports of randomised controlled trials to determine whether there was a relationship between the quality of reported randomisation procedures and trial outcome. Trials in which there was inadequate reporting of allocation concealment systematically overestimated the benefits of interventions in comparison to trials with adequate concealment.

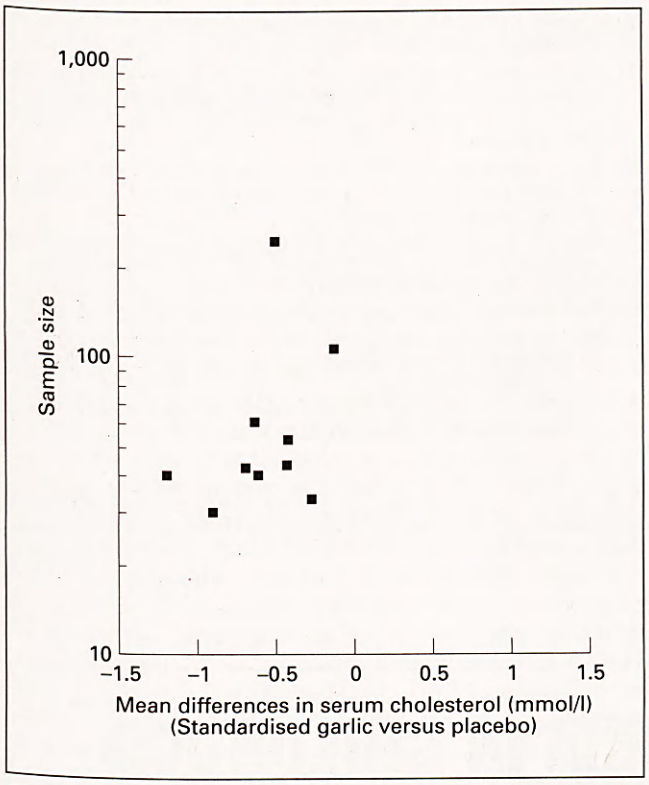

Fig 1. Funnel plot of sample size versus the mean difference in cholesterol between intervention (standardised garlic) and control groups in garlic trials, illustrating how publication bias can affect the results

A third alternative explanation is that we failed by chance to detect a true effect in this particular trial (type 2 error). To address this issue, the results from this trial were included in a re-analysis of our previous overview [2]. The pooled estimate for the effect of standardised garlic compared to placebo (comparison of groups at the end of treatment) remained statistically significant, but was reduced in magnitude from —0.75 mmol/l (95% CI: —0.88 to —0.63) to —0.65 mmol/l (95% CI: —0.53 to —0.76). Any effect of garlic on cholesterol is therefore unlikely to exceed the latter estimate.

The results of our trial are consistent, however, with a recent smaller, rigorously conducted, cross-over study which has also failed to detect an effect of standardised garlic on serum lipids [8].

An effective, safe, inexpensive and naturally occurring compound would be an attractive alternative to lipid-lowering drug therapy for use when dietary measures have proved inadequate, particularly since most trials of dietary advice achieve reductions in cholesterol of less than 4% [9,10]. Our results suggest, however, that the use of garlic for this specific purpose is likely to lead to smaller reductions in serum cholesterol than previously suggested.

Garlic was well tolerated but, predictably, the main side effect reported was breath odour, and its incidence was compatible with that previously reported with dried garlic powder preparations [2]. Other trials have not commented on people's perceptions of odour; not surprisingly, our results suggest that awareness of odour is higher among associates of subjects taking garlic than among the subjects themselves. Although breath odour was the main side effect leading to discontinuation of therapy, the incidence of such events was low.

The results of the study raise more general issues about the size and conduct of clinical trials, and the interpretation of meta-analyses. Some evidence from our study suggests that the previously reported beneficial effects of garlic may partly reflect bias in study design or reporting. However, the only certain method of excluding a significant effect of garlic on serum cholesterol would be to perform a 'mega-trial' [6] in which the number of subjects is sufficient to refute the sum of previous studies (at least 1,000 subjects would be required). Such studies may be feasible for certain—usually common and serious—conditions, but it is unlikely that resources would be available for performing large-scale definitive studies on issues such as the effects of garlic. In these circumstances, a meta-analysis can provide a summary estimate of the effect size of an intervention.

It is important to recognise that the results may be misleading if the constituent trials are methodologically flawed or the data for inclusion are restricted by selective identification of positive studies or publication bias. For example, meta-analyses of randomised controlled trials involving nearly 4,000 patients suggested that prompt intravenous infusion of magnesium could reduce by 50% the mortality from myocardial infarction [11–13]. However, in the fourth international study of infarct survival (ISIS-4) [14] which involved over 58,000 patients, magnesium was subsequently shown to confer no benefit. In the absence of such mega-trials, meta-analyses can provide a useful summary estimate of the effect size of treatment, but they should be subject to critical scrutiny and interpreted with care [15], particularly if the results are based on small trials [6].

Acknowledgements

The study was funded by a project grant from the British Heart Foundation, with additional funding from Lichter Pharma. We thank Drs C Hood, J Durban, AR Maisey, PNJ Appleton and MH Jones, Mrs E Duncombe, and the individuals who participated for their support of the study.

References

1 Neil A, Silagy C. Garlic: its cardio-protective properties. *Curr Opin Lipidol* 1994;**5**:6–10.
2 Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. *J Roy Coll Physicians London* 1994;**28**:39–45.

3 Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. *Ann Intern Med* 1993;**119**:599–605.
4 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;**18**:499–502.
5 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;**337**:867–72.
6 Egger M, Smith GD (editorial). Misleading meta-analysis. *Br Med J* 1995;**310**:752–4.
7 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.
8 Simons LA, Balasubramaniam S, Konigsmark MV, Parfitt A, *et al.* On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis* 1995;**113**:219–25.
9 Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. *Br Med J* 1991;**303**:953–7.
10 Neil HAW, Roe L, Godlee RJ, Moore J, *et al.* Randomised trial of lipid lowering dietary advice in general practice: the effects on serum lipids, lipoproteins, and antioxidants. *Br Med J* 1995;**310**:569–73.
11 Tio KK, Yusuf S, Collins R, Held P, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: an overview of randomised controlled trials. *Br Med J* 1991; **303**:1499–503.
12 Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, *et al.* Cumulative meta-analyses of therapeutic trials for myocardial infarction. *N Engl J Med* 1992;**327**:248–54.
13 Yusuf S, Koon T, Woods K. Intravenous magnesium in acute myocardial infarction. An effective, safe, and inexpensive intervention. *Circulation* 1993;**87**:2043–6.
14 ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669–85.
15 West RR. A look at the statistical overview (or meta-analysis). *J Roy Coll Physicians London* 1993;**27**:111–5.

Address for correspondence: Dr H A W Neil, University of Oxford, Department of Public Health and Primary Care, Radcliffe Infirmary, Oxford OX2 6HE.