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Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: A randomised controlled trial☆

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ABSTRACT

Objective: To assess the effect, tolerability and acceptability of aged garlic extract as an adjunct treatment to existing antihypertensive medication in patients with treated, but uncontrolled, hypertension.
Design: A double-blind parallel randomised placebo-controlled trial involving 50 patients whose routine clinical records in general practice documented treated but uncontrolled hypertension. The active treatment group received four capsules of aged garlic extract (960 mg containing 2.4 mg S-allylcysteine) daily for 12 weeks, and the control group received matching placebos. The primary outcome measures were systolic and diastolic blood pressure at baseline, 4, 8 and 12 weeks, and change over time. We also assessed tolerability during the trial and acceptability at 12 weeks.
Results: In patients with uncontrolled hypertension (SBP ≥ 140 mm Hg at baseline), systolic blood pressure was on average 10.2 ± 4.3 mm Hg ($p = 0.03$) lower in the garlic group compared with controls over the 12-week treatment period. Changes in blood pressure between the groups were not significant in patients with SBP < 140 mm Hg at baseline. Aged garlic extract was generally well tolerated and acceptability of trial treatment was high (92%).
Conclusion: Our trial suggests that aged garlic extract is superior to placebo in lowering systolic blood pressure similarly to current first line medications in patients with treated but uncontrolled hypertension.

1. Introduction

High blood pressure is an important risk factor for cardiovascular disease (CVD). In Australia, 30% or 3.7 million adults are hypertensive (systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure(DBP) ≥ 90 mm Hg) [1]. Only half of the people with hypertension receive antihypertensive medication, however, 60% of patients on treatment are inadequately controlled [2]. Primary prevention of CVD is important; adequate risk factor management is associated with a fourfold larger reduction in deaths than secondary prevention of CVD and with a higher life expectancy of 21 years on average [3].

As hypertension is the most frequently managed problem in Australian general practice, accounting for 9.6% of GP visits [4], and the use of complementary and alternative medicine (CAM) by Australians is high [5], there is scope to explore the integration of CAM in the therapy of patients with treated, but uncontrolled, hypertension.

Garlic supplements have been associated with a blood pressure lowering effect of clinical significance in patients with untreated hypertension. Systolic blood pressure was on average 8 ± 3 mm Hg lower in the garlic group compared to controls in two recent meta-analyses [6,7]. This reduction in blood pressure is of a similar magnitude as that achieved by current first line treatment with antihypertensive medication and is clinically highly relevant; it has been shown that a drop in systolic blood pressure by 5 mm Hg reduces the risk of cardiovascular disease by 8–20% [8,9].

While the majority of trials in these meta-analyses had used garlic in form of garlic powder supplements, current evidence suggests aged garlic extract (AGE) to be a more reliable treatment option. Aged garlic extract is regarded as safe and more tolerable than garlic powder [10,11], and superior to raw or cooked garlic in relation to its antihypertensive properties [10,12]. In addition, the active component S-allylcysteine (SAC) in AGE is less volatile than allicin in garlic powder, and therefore more easily standardised [13].

The antihypertensive properties of garlic have been linked to stimulation of intracellular nitric oxide (NO) and hydrogen sulphide (H_2S) production, and blockage of angiotensin II production, which

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in turn promote vasodilation and thus reduction in blood pressure [14,15].

Our trial is the first to assess the effect, tolerability and acceptability of aged garlic extract as an adjunct treatment to existing antihypertensive medication in patients with treated, but uncontrolled, hypertension.

2. Subjects and methods

2.1. Subjects

Adult patients with uncontrolled hypertension (SBP ≥ 140 or DBP ≥ 90 mm Hg as recorded on their medical record in the last 12 months) from two general practices in metropolitan Adelaide, South Australia, were invited to participate in this double-blind placebo-controlled parallel RCT. We primarily sought patients already taking conventional antihypertensive medication, such as angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (A2RA), beta-blockers (BB), calcium channel blockers (CBB) or diuretics (D), and whose general practitioners (GPs) were not planning to change prescribed medication during the trial. Patients were excluded if they had unstable other medical conditions or serious illness, e.g. dementia, terminal illness, recent bereavement, multiple chronic conditions, secondary hypertension, recent significant medical diagnosis, or pregnancy. Patients with poor comprehension of written or spoken English, or taking daily garlic supplements were also excluded. We identified patients by a search of electronic medical records using the practices' clinical software package and the PEN Computer Systems Audit Tool (CAT) [16], and further assessed eligibility in liaison with the four GPs whose patients were involved in the trial. Patients interested in the trial provided written consent by response to the invitation letter. The trial was approved by the Human Research Ethics Committee at The University of Adelaide.

2.2. Allocation and treatment

Consenting patients were randomly allocated to either the garlic or placebo group using a computer-generated random number table provided by an independent statistical consultant. Patients in the garlic group were assigned four capsules daily of Kyolic® (Garlic High Potency Everyday Formula 112, Wakunga/Wagner®) [17] containing 960 mg of aged garlic extract (AGE) and 2.4 mg S-allylcysteine (SAC) for 12 weeks. The daily dosage is equivalent to about 2.5 g of fresh garlic and comparable to the dosage used in the majority of previous trials on garlic supplements and blood pressure [6,7]. Placebo capsules for the control group were matched to the active capsules in number, size, colour, and odour. Active and placebo capsules were packaged in identical opaque containers. Sachets with a drop of liquid AGE were added to give a garlic odour to all containers. Patients, as well as investigators, research nurses and GPs were blinded to the group allocation. Success of the blinding of patients was evaluated at the end of the intervention by asking patients to which group they thought they had been assigned. Patients were instructed to take all four capsules at the same time of day or two in the morning and two in the evening, preferably with food. Patients' preferences regarding timing of doses were recorded during the trial and any changes in administration and reasons for changes were noted. Patients were reminded to keep taking their usual prescribed medication. Compliance was assessed by daily diary entries.

2.3. Blood pressure monitoring

Primary outcome measures were systolic and diastolic blood pressure at 4, 8 and 12 weeks compared with baseline. Blood pressure (BP) was taken by a trained research nurse using a calibrated and validated digital sphygmomanometer with appropriate sized cuffs (Omron HEM-907, JA Davey Pty Ltd.; calibrated against a mercury sphygmomanometer). Blood pressure was measured with the participant in a seated position and the arm supported at heart level, after 5 min rest, and abstinence from food (including nutritional supplements) and caffeinated beverages for a minimum of 30 min prior to BP measurement [18]. At the participant's baseline assessment, BP was measured using both arms. Thereafter the arm with the higher reading was used. The Omron HEM-907 was set to record three BP readings automatically at intervals of 30 s. If the difference between the SBP readings was more than 8 mm Hg, a further three measures was taken. The mean of whichever set of three BP measurements had the smaller variation was used in the analysis. Following baseline measurement, BP was measured at approximately the same time of day at 4-weekly intervals (baseline, 4, 8 and 12 weeks).

2.4. Tolerability and acceptability

Tolerability of trial medication was monitored throughout the trial by questionnaire at the 4-weekly appointments. An exit questionnaire administered at 12 weeks assessed patient's ease of use and acceptability of the trial medication for the duration of the study, and explored willingness to continue the trial treatment long term, using 5-point Likert-scales and open ended questions. The acceptability questionnaire had been tested in a previous trial [19]. Patients who dropped out from the trial were followed-up by phone to assess acceptability and reasons for withdrawal.

2.5. Audit of medication and cardiovascular risk factors

At enrolment, details of patients' current antihypertensive medication (class, dosage) and cardiovascular risk factors including age, gender, cholesterol levels (total/HDL-C ratio), smoking habits, and diabetic status were obtained from medical records by the research nurse, and by interview of patients to ascertain family history of premature cardiovascular disease (CVD) occurring in male first degree relatives <55 years, or female first degree relatives <65 years of age. Height and weight were measured to calculate Body Mass Index (BMI). Baseline blood pressure and other cardiovascular risk factors were used to calculate absolute cardiovascular risk using the NZ Cardiovascular Risk Calculator [20]. Patients' medical records were audited again at the end of the trial to ascertain any changes in medications during the trial.

2.6. Sample size

A sample size of 25 patients per group was estimated as being able to detect a difference of 8 ± 3 mm in systolic blood pressure between active treatment and control group with a power of ≥80% and 95% confidence, allowing for a 10% drop-out or non-attendance at all appointments, and adjusting for clustering (design effect of 1.2). Assuming a response rate of 20–25%, we estimated that we needed to approach approximately 200–250 patients. Two general practices in metropolitan Adelaide each with access to about 160 adult patients with uncontrolled hypertension were involved.

2.7. Statistical analyses

Analyses were performed using SPSS version 15.0 and SAS version 9.1. Statistical significance was set at $p < 0.05$.

Differences between groups at baseline in continuous variables (age, BMI, cholesterol, BP) were assessed by Student's *t*-test and categorical variables (gender, smoking habits, diabetic status, family

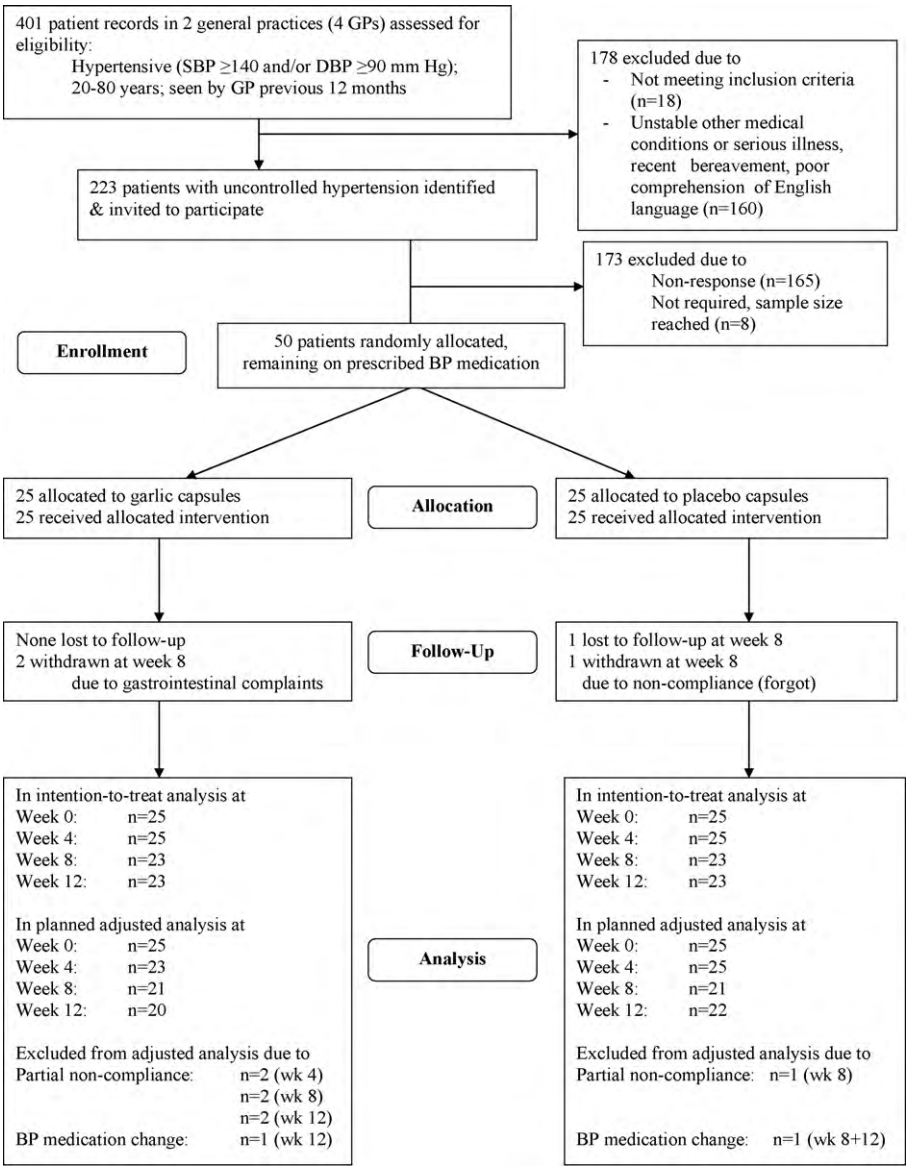

Fig. 1. Flow chart. *Abbreviations*: BP, blood pressure; DBP, diastolic blood pressure; GP, general practitioner; *n*, number; SBP, systolic blood pressure; wk, week.

history of premature CVD, and class of antihypertensive medication) by chi-square test, and absolute CVD risk by Fisher's Exact test.

A mixed model analysis was used to assess differences in mean SBP and DBP between groups over time using data at 4, 8 and 12 weeks compared with baseline while allowing for attrition and cluster effect and inclusion of confounding variables. Compound symmetry was assumed.

Primary analyses were conducted on intention-to-treat group comparisons followed by adjustment for poor compliance or BP medication change, as these factors were expected to influence the primary outcome measure.

Pre-planned subgroup analyses by baseline blood pressure using the mixed model were done, comparing treatment groups within subgroups of patients with (a) SBP ≥ 140 mm Hg at baseline or (b) with SBP < 140 mm Hg at baseline as measured under trial conditions.

Tolerability was analysed qualitatively and differences between the groups assessed by chi-square test. Differences in acceptability of the intervention and willingness for long-term treatment between groups at 12 weeks were assessed by Fisher's Exact test.

3. Results

3.1. Study sample

The trial was conducted in Adelaide, South Australia, between March and September 2009. Fifty patients with uncontrolled hypertension on medical record were enrolled in the trial (response rate 26% of 223 invited), and 25 each randomised to the garlic and placebo groups, respectively (Fig. 1). Comparison of baseline characteristics revealed no significant difference between groups in most parameters, and borderline significance in the mean number of BP medication classes prescribed (Table 1). Forty percent of patients were taking one class of BP medication, 26% were taking two, while 30% were taking three or more BP medication classes. The most prescribed class of BP medication was diuretics (54%); almost half in the garlic group took A2RA alone or in combination with other medication (48%), while 44% of patients in the control group were on ACEI (Fig. 2). Meaningful subgroup analysis by medication class was not possible due to small numbers in each medication regimen.

Table 1
Baseline characteristics.

	Garlic group	Control group
	$n = 25$	$n = 25$
Male [%]	68%	68%
Age [y][a]	66 ± 9	66 ± 9
SBP on medical record [mm Hg][a]	146.2 ± 10.5	151.1 ± 10.4
DBP on medical record [mm Hg][a]	79.3 ± 11.8	80.4 ± 7.9
Number of BP medications[a,b]	2.2 ± 1.1	1.6 ± 0.9[c]
Current smoker	4%	12%
BMI[a]	31 ± 5.8	29.1 ± 4.7
Total cholesterol [mmol/l][a]	5.0 ± 1.1	5.3 ± 0.9
Diabetes	20%	32%
Family history premature CVD	8 (32%)	7 (28%)
Absolute CVD risk		
Mild (5–10%)	8 (32%)	6 (24%)
Moderate (1–15%)	2 (24%)	12 (48%)
High (5–20%)	7 (28%)	3 (12%)
Very high (>20%)	4 (16%)	4 (16%)

Y, years; BMI, Body Mass Index; mmol/l, millimole per litre; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Mean ± SD.

[b] Mean number of prescribed blood pressure medication classes per person. Range 0–4, including ACEI, A2RA, BB, CCB, D.

[c] Significance of difference between the groups was assessed by *t*-test or chi-square test. Differences were insignificant for baseline characteristics, but number of BP medication per person ($p = 0.049$).

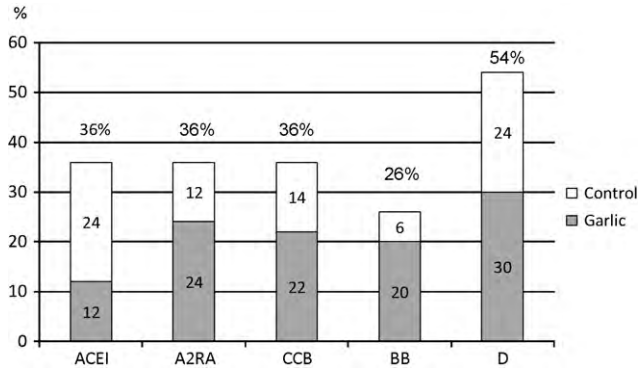

Fig. 2. Antihypertensive medication classes by treatment group at baseline. Some patients took multiple medication classes. See Table 1 for mean ± SD in each group. *Abbreviations*: ACEI, angiotensin converting enzyme inhibitors; A2RA, angiotensin II receptor antagonists; CCB, calcium channel blockers; BB, beta-blockers; D, diuretics.

3.2. Blood pressure

To be included in the trial, participants needed to have a diagnosis of uncontrolled hypertension on medical record: mean of at least two SBP readings of ≥140 ($n = 45$) or DBP ≥ 90 mm Hg ($n = 5$) in the last 12 months (Table 1). However, when measured under trial conditions, after 5 min rest, only 40% of participants displayed a mean SBP ≥ 140 mm Hg at baseline, and 8% a mean of DBP ≥ 90 mm Hg. We subsequently stratified analyses by baseline blood pressure, for SBP: 'uncontrolled hypertensive' subgroup

Table 2
Systolic and diastolic blood pressure (SBP/DBP) outcomes.

Analysis	Week	Garlic group			Control group			Mean difference (SE) between groups over time in mm Hg; *p*-value[a]
		n	Mean (SD) in mm Hg	Change to baseline within group in mm Hg	*n*	Mean (SD) in mm Hg	Change to baseline within group in mm Hg	
SBP								
All participants (ITT)	0	25	135.4 (14.1)		25	140.5 (14.7)		
	4	25	133.2 (13.2)	−2.2	25	142.7 (17.0)	+2.2	
	8	23	131.8 (11.7)	−3.6	23	139.1 (12.4)	−1.4	
	12	23	136.2 (13.8)	+0.8	23	139.3 (12.6)	−1.2	
	0–12							−6.6 (3.3); $p = 0.383$
All participants[b]	0	25	135 .4 (14.1)		25	140.5 (14.7)		
	4	23	132.2 (12.0)	−3.2	25	142.7 (17.0)	+2.2	
	8	21	130.6 (10.5)	−4.8	21	139.4 (12.2)	−1.1	
	12	20	133.5 (11.5)	−1.9	22	139.8 (12.7)	−1.2	
	0–12							−9.0 (3.3); $p = 0.321$
Subgroup[b]: BL ≥ 140 mm Hg	0	8	151.2 (7.7)		12	152.8 (9.3)		
	4	7	139.4 (9.0)	−11.8	12	154.9 (11.8)	+2.1	
	8	7	131.7 (4.3)	−19.5	9	143.4 (5.2)	−9.4	
	12	6	136.0 (8.0)	−15.2	10	145.4 (3.5)	−7.4	
	0–12							−10.2 (4.3); $p = 0.036$[c]
Subgroup[b]: BL < 140 mm Hg	0	17	128.0 (9.4)		13	129.2 (8.0)		
	4	16	129.1 (12.0)	+1.1	13	131.4 (12.9)	+2.2	
	8	14	130.0 (12.6)	+2.0	12	136.4 (15.1)	+7.2	
	12	14	132.4 (12.4)	+4.4	12	135.1 (13.5)	+5.9	
	0–12							−3.6 (3.3); $p = 0.634$
DBP								
All participants[b]	0	25	74.0 (10.3)		25	76.4 (13.2)		
	4	23	72.5 (13.8)	−1.5	25	77.3 (12.6)	+0.9	
	8	22	74.7 (11.6)	+0.7	23	76.6 (10.6)	+0.2	
	12	20	75.5 (13.6)	+1.5	22	73.1 (10.8)	−3.3	
	0–12							+2.5 (3.3); $p = 0.242$

BL, baseline; ITT, intention-to-treat analysis; mm Hg, millimetre mercury.

[a] Mean differences include data at 4, 8 and 12 weeks compared with baseline using mixed model analysis.

[b] Planned analyses adjusted for partial non-compliance and BP medication change.

[c] Significant difference between groups: $p < 0.05$.

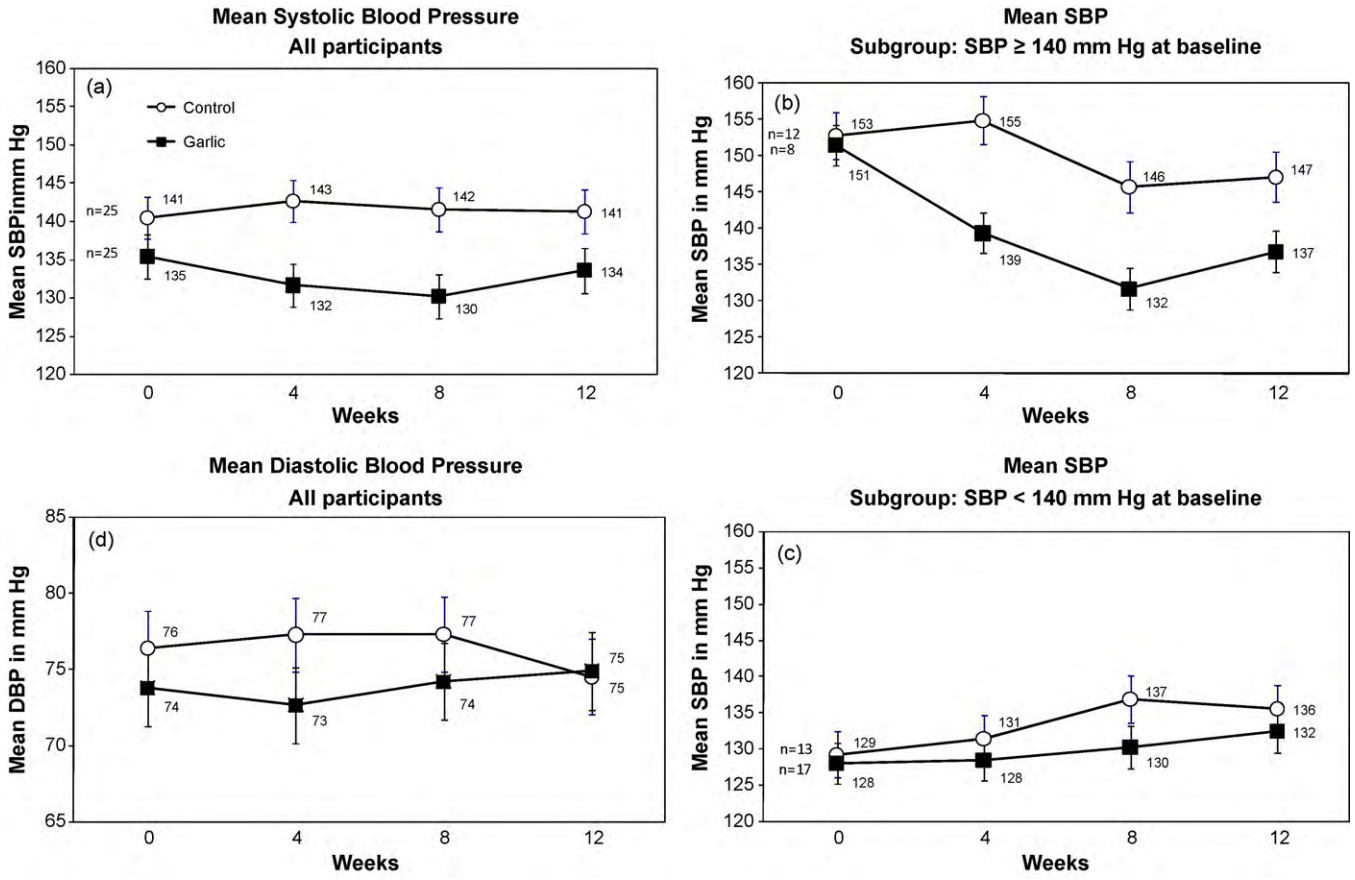

Fig. 3. Mean systolic blood pressure (SBP) ± standard error (SE) over the 12-week intervention period of (a) all participants, (b) subgroup with uncontrolled hypertension (SBP ≥ 140 mm Hg at baseline), (c) subgroup with controlled hypertension (SBP < 140 mm Hg at baseline), and (d) mean diastolic blood pressure (DBP) ± standard error (SE) of all participants.

with mean SBP ≥ 140 mm Hg at baseline and 'controlled hypertensive' subgroup with mean SBP < 140 mm Hg at baseline. Due to the small number of patients with diastolic hypertension, a subgroup analysis of DBP by hypertension status was not meaningful.

Intention-to-treat analyses of SBP including all participants did not reveal a significant difference between the groups over time including data from baseline to 12 weeks (Table 2). Analyses adjusted for partial non-compliance and BP medication change including all participants was consistent with intention-to-treat analyses (Fig. 3a, Table 2).

However, a marked difference in treatment effect was revealed in pre-planned subgroup analyses stratified by baseline SBP. A significant treatment effect over 12 weeks was apparent between garlic and control groups in patients with uncontrolled hypertension at baseline (mean difference in SBP ± SE: −10.2 ± 4.3, $p = 0.0361$), whereas no significant differences between the treatment arms were found in the subgroup of patients with controlled hypertension (Fig. 3b and c, Table 2).

Diastolic blood pressure including all participants was not significantly different between the garlic and control groups over time (Fig. 3d, Table 2).

3.3. Tolerability and acceptability

Attrition was low: one participant was lost-to-follow-up (control), and three participants withdrew during the trial, one due to non-compliance ("kept forgetting"; control group), and two due to experiencing gastrointestinal discomfort (garlic group). Compliance was high: five participants (four in the garlic and one in the control group) were partially non-compliant due to other events such as hospital stays (Fig. 1).

Tolerability of trial capsules was generally high. A quarter (24%) of the participants taking the garlic capsules reported belching, reflux, and taste sensations, while 8% of those taking the placebo capsules reported similar adverse effects ($p = 0.25$). However, these effects were regarded as minor and participants found ways to reduce them including sucking on mints, splitting the daily dosage, or taking the capsules with food. Only two participants (8%) in the garlic group stopped taking their capsules after 2 months because of gastrointestinal complaints (garlic versus control: $p = 0.5$).

Most of the participants in our trial found that taking four trial capsules daily was easy (93%) and acceptable (92%). Two-thirds of participants (65%) preferred to take all four capsules at once, while some (35%) divided the dosage into 2 capsules twice daily. A few participants (14%) found the capsules a little large to take easily. All but two participants in the garlic group (92%) were willing to continue taking garlic supplements if it helped with their blood pressure, compared to two-thirds (66%) in the control group. For 14% of participants a limiting factor for continuation of treatment with garlic capsules were the estimated costs of $1.20 (Australian) for four capsules per day (garlic versus control: $p = 0.05$).

At the end of the intervention, almost 58% of participants in the garlic group guessed their allocated treatment group correctly (4% incorrect, 38% unsure), in comparison to 24% of participants in the control group (24% incorrect, 52% unsure) ($p = 0.02$).

4. Discussion

Our trial suggests that aged garlic extract is superior to placebo in lowering systolic blood pressure in patients with treated, but uncontrolled, hypertension. Aged garlic extract was generally well tolerated, and the level of blood pressure reduction achieved was comparable to that of common antihypertensive medication (-10.2 ± 4.3 mm Hg, $p = 0.03$) over 12 weeks in patients with SBP ≥ 140 mm Hg at baseline. In contrast, no significant difference between the treatment groups was found in the patient subgroup with SBP < 140 mm Hg at baseline. This marked difference in treatment effect dependent on baseline blood pressure is consistent with meta-analyses of trials on garlic supplements in untreated patients [6,7], in which garlic supplements were found to be superior to placebo in lowering blood pressure in hypertensive patients (SBP ≥ 140 mm Hg at baseline) but not in patients with SBP < 140 mm Hg.

Additionally, we found acceptability of trial capsules to be high (92%), and three-quarters (75%) of participants indicated that they would be willing to continue with the treatment in consultation with their physician, if it was available.

Our patient sample represented a general practice population in urban Australia (mean age (SD) 66 ± 9 years, 68% males) with a mean blood pressure on medical record comparable to Australian population with treated hypertension [2]. A greater proportion of patients in our trial were prescribed diuretics compared to the hypertensive Australian population (54% versus 23%) [21], whereas ACEI were less prominent (36%) in our sample if compared nationally (47–56%) [22]. Medication regimen might reflect preferences of physicians involved in the trial.

Our study has a few limitations. First, in this trial we included patients diagnosed with treated, but uncontrolled hypertension according to their medical record. However, an unexpected high proportion (62%) of eligible patients was found to have controlled hypertension under trial conditions. As this study was to assess feasibility of recruitment, as well as tolerability and acceptability of the intervention in addition to efficacy, all patients remained in the study. In order to assess the effect of aged garlic extract on blood pressure in hypertensive patients, we stratified our analyses into subgroups of patients with uncontrolled and controlled systolic hypertension. Due to the small number of patients with diastolic hypertension, subgroup analyses of DBP were not meaningful.

Second, despite randomisation, mean baseline blood pressure differed by 5 mm Hg between treatment groups, albeit this difference was not statistically significant. In addition, mixed model analyses over time were adjusted for baseline blood pressure. In future trials, assessment of baseline blood pressure under trial conditions before enrolment and block randomisation by ranked mean baseline BP might balance BP values between the groups.

Third, blinding of patients might have been hampered to some extent due to some patients in the garlic group experiencing distinctive taste sensations after ingestion of the trial capsules, and/or patients noticing lower than usual blood pressure readings during the intervention period. Blinding of patients may be improved in future trials by instructing patients to take trial capsules with or immediately after a main meal to reduce chances of belching, reflux and taste sensations; and by better blinding of patients to BP readings until the end of the trial.

In our trial, two patients in the garlic group withdrew after 2 months due to gastrointestinal discomfort. While rare, gastrointestinal disturbances have been reported previously when garlic supplements were taken in therapeutic dosages by similar proportions of patients [23,24]. Individual detoxification capacity of sulphur-compounds in garlic is influenced by genetic variation of sulphur-transferase enzymes, in particular sulphite oxidase, as well as inflammatory status [25]. Enzyme capacity is further dependent on molybdenum and vitamin B12 levels [26]. Lower tolerance of sulphur-containing foods such as garlic, onion, and leek, can be reversed by supplementation with molybdenum and/or vitamin B12 [26]. It may be speculated that the two patients in our trial had reduced detoxification capacity; it would be interesting to investigate whether tolerance levels of garlic supplementation can be improved by supplementation with molybdenum and vitamin B12.

Furthermore, it remains to be investigated whether lower dosages of aged garlic extract than those used in this trial may also be effective in reducing blood pressure in treated but uncontrolled hypertensive patients, while at the same time tolerability and blinding might be improved and costs of treatment reduced. Additionally, it would also be of interest to explore whether patients taking ACE inhibitors or A2RA respond differently to aged garlic extract compared with patients taking other antihypertensive medication classes, due to similar blood pressure lowering mechanisms.

Given that popularity of complementary therapies is high [5], and patients' motivation and satisfaction influence persistence to treatment plans [27,28], further research on aged garlic extract for hypertension is warranted.

5. Conclusions

Our trial suggests that aged garlic extract may be a useful adjunct therapy to conventional medications in uncontrolled hypertension. Future larger trials are needed to confirm our findings of effectiveness on systolic hypertension, ascertain the effect on diastolic hypertension, investigate dose–response relationships, examine effect in association to conventional blood pressure medication classes, and explore whether supplementation with molybdenum and vitamin B12 improves some patients' tolerance of garlic.

Contributors

All authors conceptualised the study, obtained funding and oversaw data collection. KR undertook data analysis and interpretation in discussion with co-authors. KR prepared the manuscript with contributions from co-authors. All authors approved the final version. None of the authors had a personal or financial conflict of interest.

Trial material was provided by Vitaco Health (NZ) Ltd., Auckland, New Zealand, who were not involved in study design, data collection, analysis and preparation of manuscript.

Conflict of interest

None.

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