*British Journal of Nutrition* (2011), **105**, 248–255
doi:10.1017/S0007114510003223


# Influence of dietary modifications on the blood pressure response to antihypertensive medication

Catherine E. Huggins[1], Claire Margerison[1], Anthony Worsley[2] and Caryl A. Nowson[1]*

[1]*Centre for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC 3125, Australia*

[2]*Faculty of Health and Behavioural Sciences, School of Health Sciences, University of Wollongong, Wollongong, NSW 2522, Australia*

*(Received 7 January 2010 – Revised 16 June 2010 – Accepted 26 July 2010 – First published online 1 September 2010)*

## Abstract

Identifying dietary modifications that potentiate the blood pressure (BP)-lowering effects of antihypertensive medications and that are practical for free-living people may assist in achieving BP reduction goals. We assessed whether two dietary patterns were effective in lowering BP in persons on antihypertensive therapy and in those not on therapy. Ninety-four participants (38/56 females/males), aged 55·6 (SD 9·9) years, consumed two 4-week dietary regimens in random order (Dietary Approaches to Stop Hypertension (DASH)-type diet and low-Na high-K (LNAHK) diet) with a control diet before each phase. Seated home BP was measured daily for the last 2 weeks in each phase. Participants were grouped based on antihypertensive drug therapy. The LNAHK diet produced a greater fall in systolic BP (SBP) in those on antihypertensive therapy (−6·2 (SD 6·0) mmHg) than in those not on antihypertensive therapy (−2·8 (SD 4·0) mmHg) ($P$=0·036), and this was greatest for those on renin–angiotensin system (RAS) blocker therapy (−9·5 (SD 6·4) mmHg) (interaction $P$=0·007). The fall in SBP on the DASH-type diet, in those on therapy (overall −1·1 (SD 6·2) mmHg; renin–angiotensin blocker therapy −4·2 (SD 4·7) mmHg), was not as marked as that observed on the LNAHK diet. Dietary modifications are an important part of all hypertension management regimens, and a low-Na and high-K diet enhances the BP-lowering effect of antihypertensive medications, particularly those targeting the RAS.

**Key words: Antihypertensive therapy: Dietary potassium: Dietary sodium: Home blood pressure: Salt**

There is a continuous positive relationship between blood pressure (BP) and CVD risk[1], with a doubling of risk for each increment of 20/10 mmHg above 115/75 mmHg (systolic BP (SBP)/diastolic BP (DBP))[1–3]. Achieving BP control is critical to improve cardiovascular prognosis in hypertensives, and yet many of those on antihypertensive therapy fail to achieve optimal BP levels[2]. The reasons for failure to achieve BP goals with antihypertensive medications are varied and include non-compliance with medication due to side effects, cost of the therapy and risk of orthostatic hypotension[2]. A multifaceted approach to managing BP is required. Identifying dietary modifications that potentiate the BP-lowering effects of antihypertensive medications and that are practical for free-living people may assist in achieving BP reduction goals.

The effectiveness of dietary modifications in reducing BP in persons on antihypertensive therapy is not clear. High salt intake is a major environmental factor that adversely impacts on BP control[4]. There have been conflicting reports that have shown that individual nutrients (largely Na) may either potentiate the BP-lowering effects of some antihypertensive medications or have no additional effect on BP. A synergistic effect of dietary salt restriction and blockers of the renin–angiotensin system (RAS, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) has been reported[5–9], but this is not a consistent finding[10,11]. Moreover, salt restriction can be beneficial in people with BP resistance to angiotensin-converting enzyme inhibition[12]. Interestingly, Ca channel blockers have been shown to have a greater hypotensive effect when combined with a high Na intake and compared with a contrasting low Na intake[13–15], although this has not been an universal finding[16,17]. The effects of contrasting Na intakes (i.e. high and low) in those taking β-adrenoceptor blockers have been shown to have no effect on BP[18]; however, at extremely low intakes of Na

**Abbreviations:** BP, blood pressure; CD, control diet; DASH, dietary approaches to stop hypertension; DBP, diastolic BP; LNAHK, low-Na high-K; NO, no therapy; OAH, other antihypertensive therapy; OD, DASH-type diet; RAS, renin–angiotensin system; SBP, systolic BP.

* **Corresponding author:** Professor, C. A. Nowson, fax +61 3 9244 6017, email nowson@deakin.edu.au

(10 mmol/d), propranolol has been shown to cause a greater BP reduction than at 'usual' Na intakes[19]. A possible explanation for these conflicting observations could be due to the influence of the background diet, which in most instances is poorly described and/or uncontrolled. In addition, a high-K diet has been shown to be effective in controlling BP during tapering of antihypertensive medications down to 50 % of the original medication dose[20]. A limitation of many of these studies is that participants were withdrawn from their usual BP medication regimen and were all provided with a fixed dose of the test drug[5–9], which does not reflect the heterogeneity of antihypertensive medication regimens in free-living people.

The Dietary Approaches to Stop Hypertension (DASH) study tested the efficacy of a comprehensive diet high in fruits, vegetables and low-fat dairy products on BP in a large intervention with all food provided to participants. In that study, large falls in SBP and DBP were demonstrated (11 and 5 mmHg in hypertensives; 5 and 3 mmHg in normotensives); however, hypertensives who were on antihypertensive medications were excluded[21]. We have previously reported on the beneficial effects of a DASH-type diet (OD) and a low-Na high-K diet (LNAHK) on BP in free-living people, who self-selected their own food[22]. In that study, we demonstrated that participants were highly compliant with the dietary advice, and we found (relative to a control diet) an overall significant fall of 2 mmHg in SBP with the OD diet, and a greater fall of 4 mmHg SBP and 2 mmHg in DBP with the LNAHK diet. These BP falls are meaningful at a population level[2] and demonstrate the feasibility of these dietary patterns in free-living individuals who prepared all their own meals. The aim of this investigation was to examine whether the LNAHK and the OD diets lowered BP in participants on antihypertensive therapy than in those not on antihypertensive therapy.

## Methods

This investigation was undertaken as a subanalysis of the cohort presented in our earlier report[22]. Details of the participants, study design, diets and dietary assessment, anthropometry and biochemical assays have been reported previously[22] and will be reported in brief here.

### Participants

Participants were eligible if they were over 25 years of age and had a BP ≥ 120 mmHg SBP or ≥ 80 mmHg DBP at their second visit (mean of last three measurements) or home BP ≥ 116 mmHg SBP or ≥ 78 mmHg DBP (mean of 7 d). Full details of recruitment and retention of the participants have been previously reported[22]. Participants who were taking antihypertensive medication were included, provided they were willing to maintain their current level of antihypertensive therapy. Participants were excluded if they had a BP > 160 mmHg SBP and/or > 90 mmHg DBP, had a cardiovascular event in the past 6 months, had insulin-dependent diabetes, were on medications such as Warfarin or Dilantin, ate their main meal outside the home more than twice per week, drank more than thirty alcoholic drinks per week, were planning to quit smoking or change smoking habits or were unwilling to cease taking dietary supplements (including vitamins) for the duration of the study. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Deakin University Human Research Ethics Committee. Written informed consent was obtained from all the subjects/patients.

### Study design

All the participants were advised to follow two 4-week dietary interventions, each preceded by a 2-week control diet (CD) period, as reported previously[22]. The diets were consumed in random order which minimised the interference of the time-dependent reduction in BP. Participants performed 24 h urine collections every 2 weeks. The mean of two 24 h urine collections in each test diet phase was used in the analysis. Ninety-four participants completed the OD diet phase, and of this forty-three participants also completed the LNAHK diet phase and forty-eight participants completed a high-dairy diet phase. We have previously reported that the high-dairy diet had no significant effects on SBP or DBP[22]. Furthermore, for those on the high-dairy diet phase, there was no significant difference in BP between those who were not taking antihypertensive medication and those who were taking antihypertensive medications change in SBP (0·96 (SEM 0·62) mmHg ($n$ 27) and 0·16 (SEM 0·64) mmHg ($n$ 21), respectively; $P$=0·384), and therefore we have not included data on this diet.

### Diets

The CD diet was a low-K, low-Ca diet. The OD diet, compared with CD diet, was designed to be higher in K, Mg and Ca, and lower in saturated fat, with a moderate reduction in Na together with increased fish intake. The OD diet was based on the United States DASH study[21] and was rich in vegetables, fruits and reduced fat dairy products, with increased fish, nuts and legumes and a moderate Na intake (i.e. salt-reduced products were recommended, ≤ 120 mg/100 g). Compared with the OD diet, the LNAHK diet was similarly plant based and high in fruits and vegetables. The LNAHK diet (compared with OD diet) was designed to be higher in K and Mg with a greater reduction in Na intake, and as there were no specific dietary recommendations for dairy products, it was lower in Ca. To assist with achieving the Na targets during the LNAHK diet phase, the participants were

provided with salt-free bread and margarine. During the CD periods and all test diet phases, a maximum of four caffeine-containing drinks (e.g. cola drinks, diet cola, coffee and tea) and two standard alcoholic drinks were permitted per day. The aim was to maintain body weight for all the participants throughout the study.

### *Blood pressure and antihypertensive therapies*

Home BP was measured using an automated BP monitor (AND Model UA-767 or AND Model UA-767-PC, A&D Company Limited, Tokyo, Japan) on the left arm, and data were either directly downloaded via a computer (Model UA-767-PC) or recorded manually (Model UA-767). Subjects were trained to correctly apply the cuff and instructed to take their BP measurements alone at the same time of the day, after 5 min rest in a quiet room, taking three measurements with 1 min interval (mean of last two measurements on each day used for analysis).

Of the ninety-four participants (thirty-eight females, fifty-six males) who completed the OD diet phase, forty-two were on antihypertensive therapy. There were no significant differences in the baseline BP or urinary electrolytes of those who were on antihypertensive therapy (*n* 42, mean SBP 130·8 (SD 10·7) mmHg; DBP 79·9 (SD 9·0) mmHg) and those who were not on therapy (*n* 52, SBP 128·3 (SD 11·8) mmHg; DBP 81·1 (SD 8·4) mmHg)[22]. The range of medication types were twenty-two participants on single therapy: β-blocker (*n* 2); angiotensin-converting enzyme inhibitor (*n* 3); angiotensin II receptor antagonist (*n* 12); diuretic (*n* 1); Ca channel blocker (*n* 4). A further twelve were on combination therapy either with a single tablet (*n* 4) or with dual tablets (*n* 8), and eight were taking a combination of three drugs. Of the forty-three participants who followed the LNAHK diet, twenty-three were not on antihypertensive therapy and twenty were on antihypertensive therapy including eleven participants on single therapy: β-blocker (*n* 1); angiotensin-converting enzyme inhibitor (*n* 1); angiotensin II receptor antagonist (*n* 6); Ca channel blocker (*n* 3). The remaining nine participants were on combination therapy either with a single tablet (*n* 4) or with dual tablets (*n* 2) or a combination of three drugs (*n* 3). For this analysis, the participants were categorised into one of the three medication groups: (1) no therapy (NO); (2) RAS blockade, which included angiotensin-converting enzyme inhibitor and angiotensin II receptor antagonists as monotherapies; (3) other antihypertensive therapies (OAH), including single and combination therapies (Table 1).

**Table 1.** Class of antihypertensive therapy in each of two test diet groups

| Antihypertensive therapy* | OD (*n*) | LNAHK (*n*) |
|---|---|---|
| No therapy | 52 | 23 |
| RAS | | |
| ACEI | 3 | 1 |
| AT1 blocker | 12 | 6 |
| Other antihypertensive therapy | | |
| Ca channel blocker | 4 | 3 |
| Ca channel blocker, diuretic | 1 | 0 |
| Ca channel blocker + AT1 blocker | 2 | 2 |
| Ca channel blocker, ACEI, diuretic | 1 | 1 |
| Ca channel blocker + (AT1 blocker + diuretic) | 3 | 1 |
| β-Adrenoceptor blocker | 2 | 1 |
| Diuretic | 1 | 0 |
| (AT1 blocker + diuretic) | 2 | 0 |
| (ACEI + diuretic) | 2 | 2 |
| ACEI, diuretic | 2 | 1 |
| Diuretic, β-adrenoceptor blocker | 1 | 0 |
| Diuretic, central acting agent | 1 | 1 |
| AT1 blocker, β-adrenoceptor blocker | 1 | 0 |
| ACEI diuretic, β-adrenoceptor blocker | 2 | 1 |
| ACE-I (ACEI + diuretic) | 1 | 0 |
| Diuretic (ACEI + diuretic) | 1 | 0 |

OD, DASH-type die; LNAHK, low-Na high-K; RAS, renin–angiotensin system blockade; ACEI, angiotensin-converting enzyme inhibitor; AT1, angiotensin II receptor subtype 1.
* Combination medication in parenthesis indicates a single fixed combination medication; multiple different medications are separated by a comma.

### *Statistical analysis*

Data were analysed using SPSS for WINDOWS (version 17.0 SPSS, Inc., Chicago, IL, USA). ANOVA was used to assess the difference in BP between the control diet and test diet phases (within-group factor) across the medication groups (between-group factor), i.e. a separate analysis was completed for the each test diet phase, compared to their respective control diet period. A Sidak's *t* test was used for *post hoc* analysis. One-way ANOVA was used to evaluate the difference in the changes in BP between the OD and LNAHK diet phases. $P<0{\cdot}05$ was considered to be significant. Data are expressed as means and standard deviations.

## Results

### *Baseline characteristics when grouped by class of antihypertensive therapy*

Table 2 shows the baseline characteristics of the participants across the three medication groups (NO, RAS and OAH). The three groups were well matched for baseline SBP and DBP and urinary Na and K (Table 2). Participants in the NO group were younger (mean 52·1 (SD 10·2) years) than the participants in the other two medication groups (RAS 58·7 (SD 8·8) years; OAH 61·7 (SD 6·4) years). Participants in the RAS group had a modestly greater BMI by approximately 10 % than the participants in the NO group ($P=0{\cdot}012$).

### *Dietary compliance: no antihypertensive therapy v. antihypertensive therapy*

Dietary compliance was assessed by comparing the urinary excretion during the dietary intervention period (average of two 24 h urine excretion in weeks 2 and 4) with the

https://doi.org/10.1017/S0007114510003223 Published online by Cambridge University Press

NS British Journal of Nutrition

**Table 2.** Baseline characteristics of participants categorised by antihypertensive therapy
(Mean values and standard deviations)

| | No therapy (*n* 52) | | RAS therapy (*n* 15) | | Other antihypertensive therapy (*n* 27) | | One-way ANOVA |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | *P* |
| Women/men, (*n*/*n*) | 20/32 | | 6/9 | | 12/15 | | |
| Age range (years) | 29–72 | | 49–81 | | 48–74 | | |
| Age (years) | 52·1* | 10·2 | 58·7 | 8·8 | 61·7 | 6·4 | <0·001 |
| Wt (kg) | 82·6 | 13·3 | 93·1* | 16·8 | 81·9 | 9·3 | 0·019 |
| BMI (kg/m$^2$) | 28·2 | 3·6 | 31·1† | 4·6 | 29·5 | 3·3 | 0·033 |
| Home systolic BP (mmHg) | 128·3 | 11·8 | 131·6 | 9·3 | 130·3 | 11·5 | 0·538 |
| Home diastolic BP (mmHg) | 81·1 | 8·4 | 77·9 | 9·4 | 81·1 | 8·7 | 0·412 |
| Pulse (beats/min) | 67·0 | 8·2 | 68·4 | 8·9 | 67·3 | 9·3 | 0·854 |
| Urinary Na (mmol/d)‡ | 142·1 | 49·9 | 167·5 | 37·0 | 154·7 | 54·6 | 0·189 |
| Urinary K (mmol/d)‡ | 76·0 | 25·0 | 86·4 | 27·5 | 75·3 | 21·3 | 0·309 |
| Urinary Na:K | 2·0 | 0·8 | 2·2 | 1·0 | 2·2 | 1·0 | 0·679 |
| Urinary Ca (mmol/d)‡ | 3·9 | 1·8 | 3·6 | 2·4 | 3·1 | 2·3 | 0·287 |
| Urinary Mg (mmol/d)‡ | 4·3 | 1·4 | 4·5 | 2·1 | 4·5 | 1·1 | 0·744 |

RAS, renin–angiotensin system blockade; BP, blood pressure.
* Mean values were significantly different from when compared with that of all other groups ($P<0·05$, *post hoc* Sidak's *t* test).
† Mean values were significantly different from when compared with that of no medication group ($P<0·05$, *post hoc* Sidak's *t* test).
‡ To convert mmol/d into mg/d: multiply by 23 for Na, 39 for $K^+$ and 40 for $Ca^{2+}$.

preceding CD period (Table 3). Urinary Na fell by approximately twice as much in the LNAHK diet phase than in the OD diet phase ($P=0·01$), and there was no significant difference between those not on antihypertensive therapy (LNAHK −63·1 (SD 63·7) mmol/d; OD −29·1 (SD 58·9) mmol/d) and those on antihypertensive therapy (i.e. RAS + OAH groups) (LNAHK −82·2 (SD 57·5) mmol/d; OD −35·3 (SD 65·5) mmol/d). Urinary K and Mg increased with both the test diets by similar amounts and were not significantly different across the medication groups. Taken together, these data indicate that compliance with dietary advice was similar across the groups.

### *Comparison of blood pressure responses to test diets: antihypertensive therapy v. no therapy*

The BP distribution of those not taking antihypertensive therapy and those on therapy was similar at baseline. The LNAHK diet produced the greatest fall in SBP in those on antihypertensive therapy (−6·2 (SD 6·0) mmHg SBP) than in those not on therapy (−2·8 (SD 4·0) mmHg SBP; $P=0·036$ interaction Fig. 1(a)). Overall, the fall in DBP on the LNAHK diet was not significantly different between those on therapy and those not on therapy ($P=0·094$ interaction) (Fig. 1(b)). Overall, the OD diet did not significantly lower SBP (−1·1 (SD 6·2) mmHg) for those on therapy, relative to the preceding CD phase. For those not on therapy, the LNAHK and OD diets lowered SBP by a similar magnitude (LNAHK −2·8 (SD 4·0) mmHg *v.* OD −2·4 (SD 4·4) mmHg SBP; Fig. 1(a)), relative to the CD period.

### *Comparison of test diets on blood pressure responses for classes of antihypertensive therapy*

Those on antihypertensive therapy were divided into two groups: those on RAS therapy and those on other therapies

**Table 3.** Response of participants to low-Na high-K (LNAHK) diet categorised by antihypertensive therapy group
(Mean values and standard deviations)

| | No therapy (*n* 23) | | | | RAS therapy (*n* 7) | | | | All other therapy (*n* 13) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CD | | LNAHK | | CD | | LNAHK | | CD | | LNAHK | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Urinary Na (mmol/d)‡ | 133·9 | 53·2 | 61·9 | 34·0 | 133·6 | 38·9 | 48·1 | 23·1 | 143·9 | 69·7 | 59·5* | 44·2 |
| Urinary K (mmol/d)‡ | 68·9 | 26·7 | 102·2 | 21·2 | 75·1 | 13·6 | 123·2 | 19·8 | 71·6 | 19·0 | 104·2* | 27·9 |
| Urinary Ca (mmol/d)‡ | 3·4 | 2·0 | 2·8 | 1·4 | 3·3 | 2·5 | 2·4 | 1·6 | 2·8 | 1·0 | 2·4* | 2·0 |
| Urinary Mg (mmol/d)‡ | 4·1 | 1·5 | 4·8 | 1·5 | 4·6 | 3·4 | 5·3 | 1·8 | 4·3 | 2·0 | 4·4* | 1·4 |
| Urinary Na:K | 2·1 | 1·1 | 0·7 | 0·5 | 1·8 | 0·4 | 0·4 | 0·3 | 2·1 | 1·5 | 0·7* | 0·9 |
| Wt (kg) | 83·7 | 13·7 | 83·3 | 13·8 | 87·4 | 15·7 | 86·5 | 15·8 | 81·6 | 7·4 | 81·5* | 7·0 |
| Pulse (bpm) | 65·7 | 7·1 | 65·5 | 7·3 | 70·1 | 6·2 | 71·6 | 7·8 | 69·1 | 6·2 | 69·0 | 6·1 |
| Systolic BP (mmHg) | 126·3 | 10·4 | 123·4 | 9·8 | 132·7 | 12·1 | 123·2 | 8·6 | 127·7 | 8·8 | 123·3*† | 8·1 |
| Diastolic BP (mmHg) | 78·5 | 5·6 | 77·4 | 5·6 | 82·2 | 3·2 | 78·1 | 7·5 | 81·9 | 6·7 | 79·4* | 6·7 |

RAS, renin–angiotensin system blockade; CD, control diet; bpm, beats/min; BP, blood pressure.
* Repeated measures ANOVA, between-group factor is antihypertensive medication groups; within-group factor is diet (CD and LNAHK; $P<0·05$).
† Repeated measures ANOVA, between-group factor is antihypertensive medication groups; within-group factor is interaction (diet × medication group; $P<0·05$).
‡ To convert mmol/d into mg/d, multiply by 23 for Na, 39 for $K^+$, 40 for $Ca^{2+}$ and 24·3 for Mg.

British Journal of Nutrition

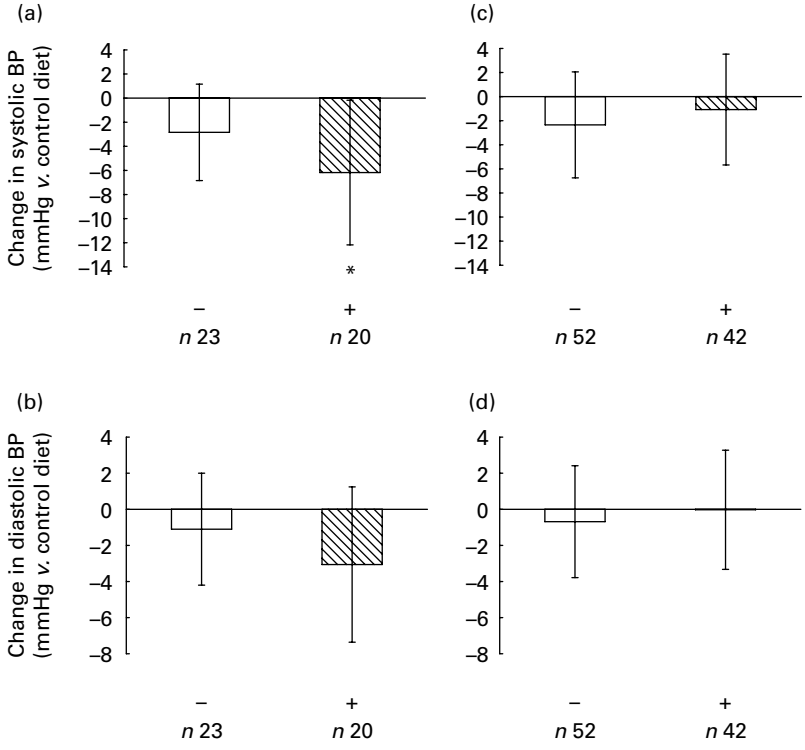


**Fig. 1.** Blood pressure (BP) response to test diets in those not on antihypertensive therapy and those on therapy. Change in home-measured BP relative to control diet phase during the low-sodium high-potassium diet phase (a) systolic BP (b) diastolic BP, and during the DASH-type diet (OD) phases (c) systolic BP and (d) diastolic BP. (−) Not on antihypertensive therapy; (+) taking antihypertensive therapy. Data are means and standard deviations. *Mean values were significantly different ANOVA, $P<0{\cdot}05$ interaction (diet × medication group).

(OAH). During the CD period, there were no significant differences in SBP or DBP across the three medication groups (Tables 3 and 4) . The LNAHK diet lowered SBP (relative to CD) across all the medication groups (ANOVA, $P=0{\cdot}014$). Overall, the fall in BP during the LNAHK diet phase was greater than during the OD diet phase by SBP −1·1 (SD 4·6), −3·8 (SD 5·7) and −7·6 (SD 8·0) mmHg for NO, RAS and OAH, respectively (ANOVA $P<0{\cdot}001$); and DBP −0·3 (SD 3·9), −2·1 (SD 3·4), −4·6 (SD 6·0) mmHg for NO, RAS and OAH, respectively (*n* 43, repeated measures ANOVA $P=0{\cdot}05$).

The LNAHK diet resulted in a greater fall in SBP in the RAS group (−9·5 (SD 6·4) mmHg) than in the NO medication group (−2·8 (SD 4·0) mmHg) ($P=0{\cdot}007$) Fig. 2(a)). This difference remained significant ($P=0{\cdot}015$, ANCOVA) when controlling for the change in Na excretion (between CD and LNAHK diets). This difference was not observed with the OD diet (NO group (−2·4 (SD 4·4) mmHg, *v.* RAS

**Table 4.** Response of participants to DASH-type diet (OD) diet categorised by antihypertensive therapy group

(Mean values and standard deviations)

| | No therapy (*n* 52) | | | | RAS therapy (*n* 15) | | | | All other therapy (*n* 27) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CD | | OD | | CD | | OD | | CD | | OD | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Urinary Na (mmol/d)§ | 143·4 | 47·6 | 114·3 | 51·6 | 166·6 | 75·6 | 119·8 | 46·9 | 139·8 | 47·4 | 118·6* | 49·7 |
| Urinary K (mmol/d)§ | 67·6 | 20·7 | 100·3 | 27·8 | 66·5 | 22·6 | 115·4 | 26·9 | 56·8 | 17·3 | 92·8* | 20·6 |
| Urinary Ca (mmol/d) | 3·7 | 2·1 | 3·8 | 1·8 | 3·9 | 3·1 | 3·3 | 2·5 | 2·9 | 1·8 | 3·3 | 3·1 |
| Urinary Mg (mmol/d)§ | 4·0 | 1·6 | 4·7 | 1·5 | 3·7 | 1·8 | 4·9 | 2·8 | 3·7 | 0·9 | 4·7* | 1·3 |
| Urinary Na:K | 2·1 | 0·9 | 1·2 | 0·7 | 2·5 | 0·7 | 1·0 | 0·4 | 2·3 | 1·1 | 1·3* | 0·6 |
| Wt (kg) | 81·6 | 13·0 | 81·7 | 13·0 | 91·1 | 16·9 | 90·7 | 17·2 | 82·4 | 8·5 | 82·1‡ | 9·1 |
| Pulse (bpm) | 66·8 | 8·6 | 66·8 | 8·2 | 67·2 | 8·8 | 68·1 | 9·3 | 65·6 | 6·4 | 67·3* | 6·7 |
| Systolic BP (mmHg) | 127·8 | 11·8 | 125·4 | 10·0 | 129·5 | 10·6 | 125·3 | 8·9 | 124·6 | 10·2 | 125·3*† | 9·6 |
| Diastolic BP (mmHg) | 80·6 | 8·1 | 79·9 | 7·8 | 78·2 | 10·9 | 76·8 | 9·7 | 77·6 | 8·3 | 78·3 | 8·9 |

RAS, renin–angiotensin system blockade; CD, control diet; bpm, beats per min; BP, blood pressure.

* Repeated measures ANOVA, between-group factor is antihypertensive medication groups within-group factor is diet (CD and OD) ($P<0{\cdot}05$).

† Repeated measures ANOVA, between-group factor is antihypertensive medication groups interaction (diet × medication group) ($P<0{\cdot}05$).

‡ Repeated measures ANOVA, between-group factor is antihypertensive medication groups ($P<0{\cdot}05$).

§ To convert mmol/d into mg/d, multiply by 23 for Na, 39 for $K^+$, 40 for $Ca^{2+}$ and 24·3 for Mg.

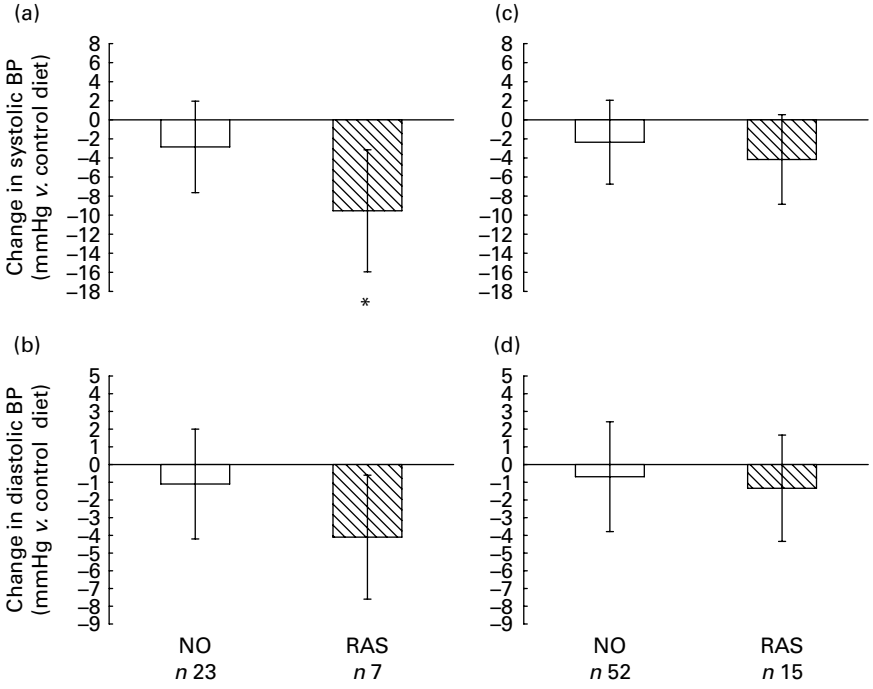


**Fig. 2.** Blood pressure (BP) response to test diets in those not on antihypertensive therapy and those on RAS monotherapy. Change in home measured BP relative to control diet phase during the low-sodium high-potassium diet (a) phase, systolic (b) diastolic BP, and the DASH-type diet (OD) phases (c) systolic BP and (d) diastolic BP. NO, not taking antihypertensive medication; RAS, renin–angiotensin system blockade as monotherapy. Data are means and standard deviations. * Mean values of RAS is significantly different to NO group ($P<0{\cdot}05$, ANOVA).

group (−4·2 (SD 4·7) mmHg, $P=0{\cdot}533$). The changes in DBP were not significantly different across the diet–medication groups (LNAHK $P=0{\cdot}199$; OD $P=0{\cdot}859$), although a similar pattern was followed to SBP (Fig. 2(b) and (d)).

## Discussion

The major finding of the present study was that in free-living persons on antihypertensive therapy, dietary advice to follow a LNAHK diet produced a greater fall in BP in those on antihypertensive therapy (regardless of medication type) than in those not on antihypertensive therapy. Furthermore, the LNAHK diet lowered BP more than the DASH-type dietary pattern (SBP −6·2 (SD 6·0) *v.* −1·1 (SD 6·1) mmHg) in those on antihypertensive therapy. Both the dietary patterns reduced systolic pressure to a greater degree in those on RAS blockers (compared with all others), and the fall in systolic pressure was 5 mmHg greater with the LNAHK diet than with the DASH-type diet. For those not on antihypertensive therapy, SBP was lowered by a similar extent under both the dietary patterns (approximately 2·6 mmHg). These findings are clinically relevant because it has been demonstrated that dietary advice to lower Na and K is feasible and effective in free-living persons on a range of different antihypertensive therapies.

In our earlier report[22], where we grouped all participants together, it was observed that the LNAHK diet produced a greater fall in SBP of 2·6 mmHg than the OD diet. In the present study, we found that for those not on therapy, the LNAHK and OD diets lowered BP by a similar degree (approximately −2·4 and −2·8 mmHg, respectively). The ratio of Na to K (Na:K) during both the test diet phases was close to 1:1 (OD 1·2:1 *v.* LNAHK 0·7:1), which was approximately half of the ratio during the CD period. Recently, it has been reported that Na:K may be a stronger predictor of CVD than either Na or K alone[23] and an important factor in BP regulation[23–25].

In the present study, 45 % of the cohort were on antihypertensive therapy. Compared with the OD diet, the LNAHK diet appeared to be a more favourable dietary pattern for BP reduction (SBP and DBP) for those on antihypertensive drug therapies. The LNAHK diet produced a marked potentiating effect on BP reduction across each of the medication groups, and the magnitude of this effect was greater in those on antihypertensive therapy than in those not on therapy. It has been reported that those with established hypertension are more likely to respond with a BP reduction on a reduced Na intake. This may in part explain the greater fall in BP, in those with established hypertension, when following the LNAHK diet. The mechanism(s) for heightened salt sensitivity remains undetermined[26], and despite controlling BP with antihypertensive medication, this hyperresponsiveness to salt persists.

An important finding of the present study was that those on OAH, which included those on diuretics and Ca channel blockers, exhibited a fall in BP with a LNAHK diet, and that the difference in the fall in BP was greater than the fall

British Journal of Nutrition

observed with the DASH-type diet (a difference of −7·6 mmHg). Previous studies have shown that Na restriction does not potentiate the BP-lowering effects of Ca channel blockers[16,17]. Chrysant *et al.*[8] demonstrated that in those taking a dihydropyridine Ca channel blocker (isradipine), the magnitude of BP reduction (relative to baseline) was greater during a high Na intake (200–250 mmol/d for 4 weeks) than during a low Na intake (50–80 mmol/d for 4 weeks). It is possible that the difference in the findings between the present study and previous studies is due to the context in which Na restriction occurs (e.g. when K levels are low), as this may be as crucial as the restriction itself. In the study of Chrysant *et al.*[8], the levels of K excretion were not reported, and therefore it is not known if the BP-lowering effect of isradipine occurred on the background of a high-K diet (or a Na:K of ≤ 1:1). Overall, our findings do suggest an important role for dietary modifications to lower Na and increase K to favourably lower BP in all those on antihypertensive drug therapies, although hypertension requiring multiple therapy may be less sensitive to the BP-lowering effects of diet.

It cannot be determined from the present study that whether the LNAHK diet is potentiating the BP effect of the antihypertensive medication via an increased effectiveness of the medication regime or via an independent mechanism that acts synergistically with the BP medication, or both. The interplay between Na, Ca and the RAS in the regulation of arterial BP remains unclear, and elucidation of the molecular mechanisms that cause hypertension continues to be an important area of research[27].

The OD diet was effective in lowering BP in those taking RAS blockade; however, this was not as marked as the LNAHK diet, and the OD diet did not lower BP in those taking combination therapies or monotherapies other than RAS blockade (e.g. Ca channel blockers or β-adrenoceptor blockers). This is an interesting observation that should be followed up in larger controlled studies, particularly given that the DASH-type diet is now recommended in hypertension management by the American Heart Association. To our knowledge, there has only been one other study that has examined the DASH-type dietary pattern in persons taking antihypertensive medication[28]. Kirpizidis *et al.*[28] reported no additive effect of a low Na DASH-type diet in combination with candesartan (angiotensin II receptor inhibitor) in hypertensives, than with candesartan alone, after 16 weeks of treatment. This contrasts with the present study and may be attributed to insufficient power to detect a difference in BP with their sample size. Moreover, it is not clear from the report of Kirpizidis *et al.*[28] that whether dietary compliance was achieved, as no defined measures of dietary compliance were reported.

The strengths of the present study were that dietary compliance was assessed by 24 h urine collection and home BP was measured. Home BP is becoming the BP measurement of choice as it is associated with less variability and therefore enhances the sensitivity to detect small changes in BP[22,29,30] with a smaller sample size. A limitation of the present study is that participants were classified *post hoc,* and therefore the sample size across the groups was unbalanced; however, the range of different medication regimens reflects the heterogeneity in treatment of hypertension in the real world. Although the present study had limited power (between 50 and 65 %) to detect a significant difference in SBP for each dietary regimen across all the medication groups, our findings do indicate that dietary modifications, particularly a LNAKH diet pattern is a useful adjunct treatment for hypertension.

In summary, a LNAHK diet reduced SBP in all the groups, particularly in those with established hypertension. The DASH-type diet selectively lowered BP in those not on therapy and those on RAS monotherapy, but the falls were less than with the LNAKH diet. The combination of RAS blockade (monotherapy) with either dietary pattern represents a more effective treatment regimen for BP reduction than RAS blockade alone. It is important that any dietary advice is applicable and sustainable for free-living individuals. Thus, a limitation of the present study is that participants were provided with a salt-free bread to achieve the low Na intake (and a Na:K ratio ≤ 1:1). The increased availability of bread with a lower Na content coupled with increased consumption of more fruits and vegetables to increase K intake would assist in controlling BP, particularly in those taking antihypertensive medication. The present study highlights that dietary modifications are an important part of all hypertension management regimens, and that reducing dietary Na and increasing dietary K enhances the BP-lowering effect of antihypertensive drug therapies.

## Acknowledgements

The authors have no conflicts of interest to declare. The present study was funded by the Dairy Research and Development Corporation, and they had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. The technical support of M. K. Jorna, S. J. Torres and S. J. Godfrey is acknowledged. C. E. H. conducted data analyses and writing of the manuscript. C. M. conducted the dietary counselling and participated in the data collection. A. W. and C. A. N. conceived the study, participated in the study design and coordinated the data collection. All the authors contributed to re-drafting, and read and approved the final manuscript.

## References

1. Lewington S, Clarke R, Qizilbash N, *et al.* (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360**, 1903–1913.

2. Chobanian AV, Bakris GL, Black HR, *et al.* (2003) Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* **42**, 1206–1252.
3. Vasan R, Larson M, Leip E, *et al.* (2001) Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* **345**, 1291–1297.
4. He FJ & Macgregor GA (2008) A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* **23**, 363–384.
5. MacGregor GA, Markandu ND, Singer DR, *et al.* (1987) Moderate sodium restriction with angiotensin converting enzyme inhibitor in essential hypertension: a double blind study. *Br Med J (Clin Res Ed)* **294**, 531–534.
6. Navis G, de Jong P, Donker AJ, *et al.* (1987) Diuretic effects of angiotensin-converting enzyme inhibition: comparison of low and liberal sodium diet in hypertensive patients. *J Cardiovasc Pharmacol* **9**, 743–748.
7. Navis G, de Jong PE, Donker AJ, *et al.* (1987) Moderate sodium restriction in hypertensive subjects: renal effects of ACE-inhibition. *Kidney Int* **31**, 815–819.
8. Chrysant SG, Weder AB, McCarron DA, *et al.* (2000) Effects of isradipine or enalapril on blood pressure in salt-sensitive hypertensives during low and high dietary salt intake. MIST II Trial Investigators. *Am J Hypertens* **13**, 1180–1188.
9. Anderson A & Morgan T (1990) Interaction of enalapril with sodium restriction, diuretics, and slow-channel calcium-blocking drugs. *Nephron* **55**, Suppl. 1, 70–72.
10. Weir MR, Smith DH, Neutel JM, *et al.* (2001) Valsartan alone or with a diuretic or ACE inhibitor as treatment for African American hypertensives: relation to salt intake. *Am J Hypertens* **14**, 665–671.
11. Morgan T, Anderson A, Wilson D, *et al.* (1987) The effect of perindopril on blood pressure in humans on different sodium intakes. *J Cardiovasc Pharmacol* **10**, Suppl. 7, S116–S118.
12. Wing LM, Arnolda LF, Harvey PJ, *et al.* (1998) Low-dose diuretic and/or dietary sodium restriction when blood pressure is resistant to ACE inhibitor. *Blood Press* **7**, 299–307.
13. MacGregor GA, Pevahouse JB, Cappuccio FP, *et al.* (1987) Nifedipine, sodium intake, diuretics, and sodium balance. *Am J Nephrol* **7**, Suppl. 1, 44–48.
14. Leonetti G, Rupoli L, Sangiorgio P, *et al.* (1987) Effects of different sodium intakes on the antihypertensive and renal effects of single oral doses of nifedipine in hypertensive patients. *J Cardiovasc Pharmacol* **10**, Suppl. 10, S138–S139.
15. Cappuccio FP, Markandu ND, Singer DR, *et al.* (1987) Does oral calcium supplementation lower high blood pressure? A double blind study. *J Hypertens* **5**, 67–71.
16. Campese VM, Wurgaft A, Safa M, *et al.* (1998) Dietary salt intake, blood pressure and the kidney in hypertensive patients with non-insulin dependent diabetes mellitus. *J Nephrol* **11**, 289–295.
17. Morgan T & Anderson A (1988) Interaction of slow-channel calcium blocking drugs with sodium restriction, diuretics and angiotensin converting enzyme inhibitors. *J Hypertens Suppl* **6**, S652–S654.
18. Kimura G, Deguchi F, Kojima S, *et al.* (1988) Antihypertensive drugs and sodium restriction. Analysis of their interaction based on pressure-natriuresis relationship. *Am J Hypertens* **1**, 372–379.
19. Owens CJ & Brackett NC (1978) Role of sodium intake in the antihypertensive effect of propranolol. *South Med J* **71**, 43–46.
20. Siani A, Strazzullo P, Giacco A, *et al.* (1991) Increasing the dietary potassium intake reduces the need for antihypertensive medication. *Ann Intern Med* **115**, 753–759.
21. Appel LJ, Moore TJ, Obarzanek E, *et al.* (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* **336**, 1117–1124.
22. Nowson CA, Worsley A, Margerison C, *et al.* (2004) Blood pressure response to dietary modifications in free-living individuals. *J Nutr* **134**, 2322–2329.
23. Cook NR, Obarzanek E, Cutler JA, *et al.* (2009) Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med* **169**, 32–40.
24. Nowson CA & Morgan TO (1988) Change in blood pressure in relation to change in nutrients effected by manipulation of dietary sodium and potassium. *Clin Exp Pharmacol Physiol* **15**, 225–242.
25. Elliott P, Stamler J, Nichols R, *et al.* (1996) Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ* **312**, 1249–1253.
26. Sanders PW (2009) Dietary salt intake, salt sensitivity, and cardiovascular health. *Hypertension* **53**, 442–445.
27. Franco M, Sanchez-Lozada LG, Bautista R, *et al.* (2008) Pathophysiology of salt-sensitive hypertension: a new scope of an old problem. *Blood Purif* **26**, 45–48.
28. Kirpizidis H, Stavrati A & Geleris P (2005) Assessment of quality of life in a randomized clinical trial of candesartan only or in combination with DASH diet for hypertensive patients. *J Cardiol* **46**, 177–182.
29. Mule G, Caimi G, Cottone S, *et al.* (2002) Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. *J Cardiovasc Risk* **9**, 123–129.
30. Nowson C, Morgan T & Gibbons C (2003) Decreasing dietary sodium whilst following a self-selected potassium-rich diet reduces blood pressure. *J Nutr* **133**, 4118–4123.


British Journal of Nutrition