Inorganic Nitrate and Beetroot Juice Supplementation Reduces Blood Pressure in Adults: A Systematic Review and Meta-Analysis

Mario Siervo,* Jose Lara, Ikponmwonsa Ogbonmwan, and John C. Mathers

Human Nutrition Research Centre, Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle on Tyne, UK

Abstract

Diets including food products rich in inorganic nitrate are associated with lower blood pressure (BP). The evidence for the BP-lowering effects of inorganic nitrate and beetroot in randomized clinical trials has not been systematically assessed. The objective was to conduct a systematic review and meta-analysis of randomized clinical trials that examined the effects of inorganic nitrate and beetroot supplementation on BP. Medline, EMBASE, and Scopus databases were searched from inception to February 2013. The specific inclusion criteria were: 1) randomized clinical trials; 2) trials reporting effects on systolic or diastolic BP or both; and 3) trials comparing inorganic nitrate or beetroot juice supplementation with placebo control groups. Random-effects models were used to assess the pooled BP effect sizes. Sixteen trials met the eligibility criteria for the systematic review. All studies had a crossover study design. The trials were conducted between 2006 and 2012 and included a total of 254 participants with 7–30 participants/study. The duration of each intervention ranged from 2 h to 15 d. Inorganic nitrate and beetroot juice consumption were associated with greater changes in systolic BP (−4.4 mm Hg [95% CI: −5.9, −2.8]; P < 0.001) than diastolic BP (−1.1 mm Hg [95% CI: −2.2, 0.1]; P > 0.06). The meta-regression showed an association between daily dose of inorganic nitrate and changes in systolic BP (P < 0.05). Inorganic nitrate and beetroot juice supplementation was associated with a significant reduction in systolic BP. These findings need to be tested in long-term trials and in individuals at greater cardiovascular risk.

Introduction

Hypertension exceeds smoking as a causal factor in total attributable mortality (1). Globally, two-thirds of stroke and one-half of ischemic heart disease events are linked to non-optimal blood pressure (BP) control, which contributes to 13% of all deaths and 4.5% of all disability-adjusted life years (1).

Antihypertensive drugs have attenuated the adverse effects of BP on cardiovascular health, but an adequate and sustained control of BP is achieved in only ~50% of hypertensive cases (2,3). Therefore, nutritional and lifestyle-based interventions are unanimously recognized as important strategies for the primary prevention of hypertension and as adjuvants in pharmacological therapies to reduce cardiovascular risk (4). The Dietary Approach to Stop Hypertension (DASH) is one of the most effective nutritional interventions for the prevention and nonpharmacological management of hypertension (5,6). The diet highlights the importance of an increased fruit and vegetable intake (7,8) and recent research has suggested that the beneficial effects of the DASH diet on BP are related to the high inorganic nitrate content of some of the food products included in the DASH dietary plan (e.g., green leafy and root vegetables) (9).

Larsen et al. (10) tested for the first time in a double-blind crossover study the effects of sodium nitrate on BP in healthy volunteers and reported a significant reduction in diastolic BP (−3.7 mm Hg). Beetroot is particularly rich in inorganic nitrate content (typically ranging from 110 to 3670 mg nitrate/kg [1]) and it has therefore been utilized in several studies as a nutritional strategy to test the effects of inorganic nitrate intake on BP. For example, Webb et al. (12) showed in healthy participants that 24 h after a single dose of 500 mL beetroot juice, systolic and diastolic BP were reduced by 10.4 and 8.0 mm Hg, respectively.

The BP-lowering effects of inorganic nitrate may derive from increased generation of nitric oxide (NO) (13,14), a pleiotropic molecule involved in the vasodilation of large arteries and resistance vessels (13,14). The endothelial isoform of the NO synthase uses arginine and molecular oxygen as precursors to...
Scopus databases was undertaken from inception to February 2013. The literature search of the PubMed, Embase, and reported, changes in nitrate and nitrite concentrations in biological fluids observed, which supports our analytical strategy to determine the pooled 110 6 14% for lettuce, and 15% for beetroot) compared with nitrate in aqueous solution was observed, which supports our analytical strategy to determine the pooled effect of the 2 interventions (24).

Outcome measures. The primary outcomes of the analyses were changes in diastolic and systolic BP after nitrate and/or beetroot supplementation. If reported, changes in nitrate and nitrite concentrations in biological fluids (plasma, urine, saliva) were also assessed.

Search strategy. A literature search of the PubMed, Embase, and Scopus databases was undertaken from inception to February 2013. The systematic review was restricted to articles published in English. The search was conducted based on predefined search terms (dietary, inorganic, nitrate, beetroot, beet root, BP, hypertension, vascular, NO, endothelial) and using specific building blocks (Boolean terms, truncation) to create the algorithms entered in each database. The full details of the algorithms are reported in the Supplemental Methods (Box 1).

Selection of studies. Two investigators (M.S., I.O.) assessed articles independently for eligibility. The first screening phase was based on the analysis of titles and abstracts. When full agreement had been reached, the article was either discarded or moved to the next phase. In case of disagreement, the article was moved to the next phase to increase the inclusiveness level. Reference lists of included papers and relevant reviews were searched for articles potentially missed during the electronic search. In the second phase, the full text of the selected articles was independently assessed by 2 investigators. When full agreement had been reached, the article was either discarded or moved to the next phase for full data extraction. In case of disagreement, the article was evaluated by a third investigator (J.L.) and a final decision was reached by consensus.

Data extraction and bias. Two investigators extracted the data using a standardized data collection form. A list of the extracted variables is provided in the Supplemental Methods (Box 2). When BP measurements were incomplete, the corresponding authors were contacted to request the missing data. The quality of each study was assessed using the Cochrane Risk of Bias Tool (25) to assess the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel to which intervention a participant received), detection bias (blinding of outcome assessment), attrition bias (completeness of outcome data, including attrition and exclusions from the analysis), and reporting bias (selective outcome reporting).

Measurement of treatment effect. The qualitative and quantitative interpretation of the data was based on the absolute mean differences in BP (in mm Hg) relative to baseline readings and SD of the mean differences (SDdiff). For matched study design (crossover studies), the effect of dietary supplementation (inorganic nitrate or beetroot juice) on BP was calculated as the difference between the supplementation and placebo groups at the end of each intervention. The SDdiff was calculated using the SDs for each intervention (SDE = intervention; SDc = control) and an imputed correlation coefficient (r) for the pre-post measurements (26). The formula used for the calculation of the SDdiff is:

\[ SD_{diff} = \sqrt{SD_E^2 + SD_C^2} - 2 \times r \times SD_E \times SD_C. \]

An imputed correlation value of 0.50 was used to provide a conservative estimate based on the assumption that this value would minimize the error of the effect size estimates. A sensitivity analysis was conducted to test the validity of the approach by entering a sequential range of low correlation coefficients (r = 0.10, r = 0.25) to evaluate changes in the effect size of the models.

Meta-analysis. A meta-analysis was conducted using Comprehensive Meta-Analysis software (Biostat). Data are presented as mean differences of systolic BP and diastolic BP (in mm Hg) and 95% CI. A random effect model was used to provide a more conservative estimate of the pooled effect size for diastolic and systolic BP. The BP differences were combined across studies using a weighted DerSimonian-Laird random effects model (27). Forest plots were generated for graphical presentations of the BP outcomes. Statistical heterogeneity across studies was assessed using the I² and the Q tests according to specific categories (low = 25%, moderate = 50%, high = 75%) and significance level (P < 0.10), respectively (28). Funnel plots and Egger’s regression test were used to evaluate potential publication bias and selective reporting bias. Additional analyses were conducted to evaluate the impact of publication bias on the effect size by removing studies with the largest effects. Sensitivity analyses were conducted to evaluate whether changes in diastolic and systolic BP were influenced by study duration (<3 vs. ≥3 d), type of intervention (beetroot juice vs. inorganic nitrate solution), and the removal of studies including highly trained participants. One study was published in abstract form only.

Inorganic nitrate, beetroot juice, and blood pressure 819


tonically release NO in the endothelium, which is important for the control of vascular tone, smooth muscle growth, platelet aggrega-

and inflammation (15,16). Reduced NO bioavailability has been associated with impairment of endothelial function and increased risk of hypertension and cardiovascular diseases (17–20).

A nonenzymatic pathway for the generation of NO in humans has been proposed (nitrate-nitrite-NO pathway), which may contribute to increased NO bioavailability (21). Dietary and endog-

enous inorganic nitrate molecules may be reduced by facultative anaerobic bacteria on the dorsal surface of the tongue to nitrite, which can be chemically (low pH) and enzymatically (xanthine oxidoreductase, myoglobin, cytochrome P450, complexes of the mitochondrial electron transport chain) further reduced to NO (21). This pathway may represent a plausible mechanism to explain the beneficial effects of dietary inorganic nitrate intake on BP (21). The main mechanistic pathways involved in the enzymatic and nonenzymatic generation of NO are described in Supplemental Figure 1.

Here, we conducted a systematic review of the evidence from randomized studies investigating the efficacy of inorganic nitrate and beetroot supplementation on BP in humans. The results will inform whether inorganic nitrate supplementation and nitrate-

enhanced diets could be considered as effective nutritional strategies for the prevention of hypertension and cardiovascular diseases.

Methods

The present systematic review was conducted according to established guidelines and is reported according to PRISMA guidelines (22).

Types of studies. Randomized clinical trials in human participants were included and the specific characteristics and designs of the trials (type of placebo, parallel or crossover design, blinding of the interventions, and duration) were assessed.

Subjects. Adult male and female participants (age >18 y) with or without health comorbidities (hypertension, diabetes, and peripheral arterial diseases) were included. Studies reporting data from participants with different BMIs, ethnic backgrounds, and physical activity levels were not excluded.

Types of interventions. Randomized clinical trials investigating the effects of inorganic nitrate or beetroot juice supplementation and providing information on the type of nitrate salt (potassium or sodium nitrate), volume, formulation, frequency, and route of administration were included. Studies that delivered the nitrate or beetroot supplementation alongside another intervention (e.g., exercise, pharmacological agent, or dietary supplement) were excluded if the interventions were different between groups. A combined meta-analysis model was derived for inorganic nitrate solutions and beetroot juice on BP. This approach was based on the evidence that inorganic nitrate is rapidly absorbed from the stomach and proximal small intestine with high bioavailability (23). A crossover study was specifically conducted to determine the oral bioavailability of nitrate from spinach, lettuce, and beetroot (24). A high bioavailability of the nitrate present in the 3 food products (98 ± 12% for spinach, 110 ± 14% for lettuce, and 110 ± 15% for beetroot) compared with nitrate in aqueous solution was observed, which supports our analytical strategy to determine the pooled effect of the 2 interventions (24).

Outcome measures. The primary outcomes of the analyses were changes in diastolic and systolic BP after nitrate and/or beetroot supplementation. If reported, changes in nitrate and nitrite concentrations in biological fluids (plasma, urine, saliva) were also assessed.

Search strategy. A literature search of the PubMed, Embase, and Scopus databases was undertaken from inception to February 2013. The
and reported a nonsignificant effect of inorganic nitrate on BP (29). This study was not included in the meta-analysis, because full data were not available after request. The potential influence of the nonsignificant results from the study on the pooled systolic BP and diastolic BP estimates was evaluated by entering into the model a null effect (mean difference = 0), the mean of the pooled SD, and the sample size of each study. A random effects meta-regression model was conducted to evaluate whether changes in plasma nitrite concentrations (in nmol/L), study duration (in hours), and daily dose of inorganic nitrate (in mmol) were associated with mean differences in diastolic and systolic BP.

Results

Main search. A total of 10,184 articles was identified by the primary search and, after the removal of duplicates (n = 6607), 3577 articles were screened for titles and abstracts. Then 41 articles were selected for a full-text review and 16 studies (10,12,29–42) were included in the systematic review (qualitative analysis) after the exclusion of 25 articles. One study was published as abstracts only (29). However, this study matched the inclusion and exclusion criteria and it was included in the systematic review (qualitative analysis) but excluded from the meta-analysis (quantitative analysis), because the full results on changes in BP were not available. A flow chart of the literature search is shown in Figure 1. All eligible studies used a crossover, double-blind, placebo-controlled, randomized study design. The trials were conducted between 2006 and 2012 and included a total of 254 participants, with 7–30 participants per individual study. The duration of the interventions ranged from 2 h to 15 d and the washout period from 6 to 28 d. One article reported the results of 3 individual trials from which 2 trials were eligible and were entered in the final analysis (33). The main characteristics of the studies included in the analysis are presented in Supplemental Table 1.

Participant characteristics. The majority of the studies recruited young, nonsmoking, healthy participants and 2 studies were conducted in older healthy participants (38) and overweight and obese older individuals with type 2 diabetes (40). In addition, most of the participants were men (~60%) and the male:female ratio was not reported in 2 studies (33,42). The mean BMI of the participants ranged between 22.3 and 30.8 kg m−2 and was not reported in 2 studies (10,36). Seven studies investigated the effects of inorganic nitrate and beetroot juice on exercise performance and recruited primarily young, physically active men (30–32,34,35,37,38).

Nitrate supplementation. Beetroot juice and nitrate salt (sodium nitrate/potassium nitrate) supplementation was tested in 12 (12,30–35,37–41) and 5 (10,29,33,36,42) studies, respectively. The daily amount of inorganic nitrate (sodium or potassium nitrate) consumed in these studies ranged from ~2.5 to 24 mmol/dose (157–1488 mg). Nitrate was dissolved either in distilled water or low-nitrate water. The daily amount of nitrate in the beetroot juice consumed varied between 5.1 and 500 mL/d and the beetroot juice was given as a concentrated solution in 2 studies (32,38). The choice of the placebo varied between studies and included equivalent volumes of water (3 studies) (12,33,41), isomolar potassium and sodium chloride solutions (5 studies) (10,29,33,36,42), blackcurrant juice (3 studies) (30,31,37), apple juice (1 study) (39), and nitrate-depleted beetroot juice (5 studies) (32,34,35,38,40). All solutions were given orally. Participants were asked to refrain from consuming nitrate-enriched foods in 9 studies (10,12,30,31,33,35,36,41–42), whereas participants were invited to maintain their prestudy dietary habits and physical activity level in 6 studies (32,34,37–40). The compliance with the dietary prescriptions (low-nitrate diet, habitual dietary habits)
was only evaluated in a few studies using diet diaries (37) of 24-h dietary recall (34,35). The assessment of the compliance to the nitrate supplementation was not reported, but the majority of the studies measured plasma or urinary concentrations of nitrate and/or nitrite, which could have provided information on the adherence to the nitrate supplementation. One study did not report the measurement of nitrate/nitrite concentrations (39).

**Study quality.** Resting BP was the primary outcome in 15 trials (10,12,29–38,42) and ambulatory 24-h BP was used in 3 studies (39–41). Three studies reported that the main aim of the study was concealed (30,31,37) to the study participants (30,31,40). All studies were double blind and reported information on the duration of washout periods and dropout rates. The order of the interventions in each trial was randomized. Three studies did not report data on diastolic BP (29,34,35). Therefore, a meta-analysis of the effects of inorganic nitrate and beetroot supplementation on systolic and diastolic BP was performed for 16 (10,12,30–42) and 13 (10,12,30–33,36–42) studies, respectively. Funding sources were disclosed in the majority of the studies, whereas 6 studies declared potential conflicts of interest (33,35,38–41). The majority of studies was rated high quality or low risk of bias. A small proportion of studies were rated as having high performance and detection bias (Supplemental Fig. 2).

**Adverse events.** Information on adverse events that occurred during the study was reported in 8 studies (12,30,31,33,37,40–42). Only one study reported a major adverse event (heartburn) requiring the exclusion of the participant from the trial (33). However, the unblinding of the study codes revealed that the participant was assigned to the placebo intervention, which excluded the link of nitrate with the onset of the event. The most common side effect reported in the beetroot juice trials was beeturia (red urine) and red stools (12,30,31,37,40–42). Only one study reported a major adverse event (heartburn) during the study was reported in 8 studies (12,30,31,33,37,40–42). A small proportion of studies were rated as having high performance and detection bias (Supplemental Fig. 2).

**BP qualitative results (systematic review).** Twelve studies showed a significant reduction in systolic BP (12,29–31,33–35,37,38,41,42), whereas a significant change in diastolic BP was observed in 6 studies (10,30,33,36–38). Beetroot juice supplementation had a greater effect than inorganic nitrate on both systolic and diastolic BP. The beneficial effects of beetroot juice supplementation on BP were not confirmed when ambulatory 24-h BP monitoring was used to measure changes in BP (39–41), including a group of older (>60 y) overweight and obese participants with type 2 diabetes (40) (Supplemental Table 2).

**BP quantitative results (meta-analysis).** Inorganic nitrate and beetroot juice consumption was associated with greater changes in systolic BP [−4.4 mm Hg (95% CI: −5.9, −2.8); P < 0.001] (Fig. 2) than diastolic BP [−1.1 mm Hg (95% CI: −2.2, 0.1); P = 0.06] (Fig. 3). The stratification of the analyses by duration (<3 and ≥3 d) and type of interventions (beetroot juice and inorganic nitrate salts) did not modify the effects on systolic BP, because the meta-analysis models were significant in studies of a shorter <3 d, −4.9 mm Hg (95% CI: −7.6, −2.2); P < 0.001] (12,33,34,36,39,41,42) and longer ≥3 d, −3.8 mm Hg (95% CI: −5.6, −2.1); P < 0.001] duration. Similarly, the stratification by study duration did not modify the effect on diastolic BP, because the model was not significant for both longer studies ≥3 d, −1.7 mm Hg (95% CI: −3.6, 0.1); P = 0.07] (10,30–32,35,37) and shorter <3 d, −0.2 mm Hg (95% CI: −1.3, 0.9); P = 0.71] interventions (12,33,34,36,39,41,42). The effects of beetroot juice supplementation [−4.5 mm Hg (95% CI: −6.4, −2.5); P < 0.001] (12,30–35,37–41) and inorganic nitrate [−4.2 mm Hg (95% CI: −6.1, −2.2); P < 0.001] (10,33,36,42) on systolic BP were both significant, whereas neither beetroot juice nor inorganic nitrate supplementation was associated with significant changes in diastolic BP (Table 1). The meta-regression showed that mean differences in systolic BP were directly associated with the daily dose of inorganic nitrate (P < 0.05) (Fig. 4A) but not with the study duration (P = 0.67) (Fig. 4B) or plasma nitrate concentrations (P = 0.40) (Fig. 4C). Changes in diastolic BP were not associated with the daily dose of inorganic nitrate, study duration or plasma nitrite concentrations (Fig. 5).

**Publication bias and heterogeneity.** Funnel plots for systolic BP revealed an overall symmetric distribution of the studies around the mean effect size, indicating the absence of publication bias (Supplemental Figs. 3 and 4). Egger’s regression test confirmed the nonsignificant association between the mean differences and

![Table 1: Meta-analysis of randomized clinical trials reporting the effects of beetroot juice and inorganic nitrate supplementation on systolic and diastolic BP](image)

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Studies</th>
<th>Effect size [mean difference (95% CI)]</th>
<th>P value</th>
<th>I²</th>
<th>Q value (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 d</td>
<td>8</td>
<td>−4.9 (−7.6, −2.2)</td>
<td>&lt;0.001</td>
<td>77.6</td>
<td>31.3 (&lt;0.001)</td>
</tr>
<tr>
<td>≥3 d</td>
<td>8</td>
<td>−3.8 (−5.6, −2.1)</td>
<td>&lt;0.001</td>
<td>46.2</td>
<td>13.0 (0.07)</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 d</td>
<td>7</td>
<td>−0.2 (−1.3, +0.9)</td>
<td>0.71</td>
<td>0</td>
<td>2.5 (0.86)</td>
</tr>
<tr>
<td>≥3 d</td>
<td>7</td>
<td>−1.7 (−3.6, +0.1)</td>
<td>0.07</td>
<td>69.1</td>
<td>19.4 (0.003)</td>
</tr>
</tbody>
</table>

1 The meta-analysis was stratified by study duration (<3 d, ≥3 d) and type of intervention (beetroot juice, inorganic nitrate). A random model was applied to each subgroup to obtain the pooled estimate of the mean difference. Variability of the estimates was reported as 95% CI.
the SEs of each study ($P = 0.47$). However, we advocate for a careful interpretation of the results in consideration of the small number of participants, the short duration of the interventions, and the over-representativeness of healthy participants. We observed a high heterogeneity for systolic ($I^2 = 66\%$, $Q = 44.3$, $P < 0.001$) and moderate heterogeneity for diastolic ($I^2 = 45\%$, $Q = 25.7$, $P < 0.01$) BP meta-analysis models. The stratification of the meta-analysis by study duration and type of intervention helped to identify potential sources of heterogeneity for systolic BP, because shorter duration (<3 d) and beetroot juice supplementation were associated with greater heterogeneity (Table 1). In addition, the exclusion of the study with the largest effect (12) and of studies including physical activity outcomes (30,31,34,35,37,38) did not modify the heterogeneity for both systolic (Supplemental Table 3) and diastolic (Supplemental Table 4) BP.

**Sensitivity analysis.** Imputation of different correlation coefficients ($r = 0.1$, $r = 0.25$ instead of $r = 0.5$) entered for the calculation of the effect size did not change the results for both systolic and diastolic BP (Supplemental Table 5). Similarly, the inclusion of a null mean difference in systolic and diastolic BP [to evaluate the potential effect of the study (29) reporting a nonsignificant effect on BP] reduced the mean difference in systolic BP by 0.6 mm Hg (from 4.4 to 3.8 mm Hg), but the pooled effect size remained significant ($P < 0.001$) (Supplemental Table 3). The inclusion of the study did not modify the results for diastolic BP ($P < 0.05$) (Supplemental Table 4). The removal of the studies investigating primarily the impact of inorganic nitrate and beetroot juice on exercise performance (30–32,34–38) did not change the results for systolic BP ($-3.9$ mm Hg; $P = 0.003$) (Supplemental Table 3) and diastolic BP ($0.2$ mm Hg; $P = 0.70$) (Supplemental Table 4).

**Discussion**

**Summary of main results.** Inorganic nitrate and beetroot juice supplementation were associated with a significant decrease in BP. The pooled effect for the 2 interventions showed a reduction in systolic BP of 4.4 mm Hg with a more modest decrease ($-1.1$ mm Hg) in diastolic BP. Beetroot juice was not associated with greater changes in systolic BP than inorganic nitrate solutions ($-4.5$ vs. $-4.2$ mm Hg, respectively). The meta-regression indicated that a higher daily amount of the dose of inorganic nitrate may be associated with greater reductions in systolic BP. Overall, studies

---

**FIGURE 2** Forest plot of randomized clinical trials investigating the effects of beetroot juice and inorganic nitrate supplementation on SBP. A random model was applied to obtain the pooled mean differences in SBP. Data for SBP are presented as mean differences and 95% CI. Two trials were reported in the same manuscript (33). BP, blood pressure; SBP, systolic blood pressure.

**FIGURE 3** Forest plot of randomized clinical trials investigating the effects of beetroot juice and inorganic nitrate supplementation on DBP. A random model was applied to obtain the pooled mean differences in DBP. Data for DBP are presented as mean differences and 95% CI. Two trials were reported in the same manuscript (33). BP, blood pressure; DBP, diastolic blood pressure.
were characterized by a small sample size, short duration, and over-representation of young, healthy men.

**Study quality, bias, and applicability of evidence.** The overall quality of the studies was high. All studies were randomized and double-blind and the crossover study design of the trials was justified by the type of interventions and outcomes. All studies reported the duration of washout periods, which was adequate to minimize the influence of carryover effects. The studies reported a high compliance with the interventions, which may be explained by the short duration of the trials. Participants recruited in the studies were mostly healthy, normal-weight men and therefore the results may not be applicable to a female population or to individuals with cardiovascular or metabolic diseases. Kapil et al. (33) have suggested a possible interaction with gender, as the BP-lowering effect of inorganic nitrate was more marked in men. However, we were unable to perform a sensitivity analysis to assess the interaction with gender, which needs to be tested in future studies. One study investigated the effects of beetroot juice supplementation in older (>60 y) overweight and obese individuals with type 2 diabetes and reported no significant effect of beetroot juice on 24-h ambulatory BP. A beneficial effect of a 3-d beetroot juice supplementation on resting systolic and diastolic BP was observed in older, healthy participants. In addition, the duration of the interventions was short and it is not known whether the observed BP-lowering effects will be maintained in the long term. These are critical factors to evaluate to understand if nitrate/beetroot interventions may represent effective strategies for the primary and/or secondary prevention of hypertension-related cardiovascular diseases.

**Potential biases in the review process.** This study has several potential limitations. The meta-analyses are based on retrospective analytical inference, which may be affected by several factors, such as...
as the quality of the studies included, inclusiveness of the search strategy to identify eligible studies to include in the meta-analysis, assumptions on consistency of methodologies applied across the different studies, inconsistency in reporting study results, limited accessibility to individual study data, and inability to ascertain the exact source of heterogeneity. In addition, we limited our search to articles published in English and in peer-reviewed journals, which may have increased the risk of publication bias. The clear delineation of a priori inclusion and exclusion criteria and the comprehensive search of 3 major electronic databases and reference lists are likely to have minimized bias and increased the representativeness of the results. A robust selection procedure was particularly important in the identification of studies exploring relationships among inorganic nitrate, beetroot juice, and BP control. However, all studies were characterized by a small sample size and short duration and most of the studies recruited young, healthy, nonsmoking men, making the representativeness of the results debatable. In addition, some of the studies included individuals with high physical activity levels (30–32,34,35,37), as the primary aim of the studies was to test the effect of inorganic nitrate on exercise performance. However, the exclusion of these studies did not modify the magnitude of the lowering effect on systolic BP. The analysis was also based on the imputation of pre- and post-intervention correlation of BP changes and the sensitivity analysis confirmed that the models for systolic BP and diastolic BP were not affected by the inclusion of different correlation values.

Agreements and disagreements with previous results. Our analyses showed that beetroot juice supplementation (−4.5 mm Hg) may not be associated with a greater reduction in systolic BP compared with inorganic nitrate supplementation (−4.2 mm Hg). However, a careful interpretation of the results is needed until the effects of the 2 interventions can be tested in a trial specifically designed to test this hypothesis. The results seem to indicate
that the similar effects on BP may be accounted for by comparable daily doses of inorganic nitrate, because the mean intake in the beetroot and nitrate studies was similar (beetroot, 12.0 ± 13.2 mmol/dose; inorganic nitrate, 15.5 ± 9.2 mmol/dose) and the presence in beetroot juice of other bioactive compounds (vitamin C, magnesium, betaine, and flavonoids) (43–46) influencing vascular physiology may provide minimal additive BP-lowering effects.

The results are comparable with other nutritional interventions modifying the NO pathway, such as oral arginine supplementation. A recent meta-analysis of the effects of oral l-arginine supplementation on BP reported a significant effect on systolic BP (−5.3 mm Hg) and diastolic BP (−2.6 mm Hg) (47), which are comparable with the effect sizes observed in our meta-analysis.

Plasma nitrite concentrations are a biomarker of NO bioavailability (13). However, our analyses showed a nonsignificant association of plasma nitrite with changes in BP, which could be related to the study heterogeneity (study duration, dosing schedule, and amount of nitrate). These factors may have influenced the pharmacokinetic profile of plasma nitrate and nitrite and altered the association with BP. Two studies found a significant association between changes in plasma nitrite concentrations and changes in systolic BP after oral inorganic nitrate supplementation (12,33), which supports our hypothesis on the lack of standardization of the measurement protocols. Cyclic GMP (cGMP) is the second messenger of the NO pathway and it represents a biomarker of NO bioactivity (13). Only 2 studies have tested the relationship between cGMP and changes in BP after oral inorganic nitrate and beetroot juice supplementation. Both studies showed a greater plasma cGMP concentration after ingestion of inorganic nitrate and beetroot juice (33).

**Implications for research practice and main conclusions.** Our results showed a significant decline in systolic BP after short-term inorganic nitrate and beetroot juice supplementation, which may potentially have important implications for the primary and secondary prevention of cardiovascular diseases. The seventh report of the Joint National Committee on BP estimated that a systolic BP reduction of at least 5 mm Hg (as observed here) could decrease the risk of mortality due to stroke by 14% and mortality from Cardiovascular diseases by 9% (48). However, before such nutritional approaches can be recommended, the long-term efficacy of inorganic nitrate needs to be tested in people at higher cardiovascular risk together with an assessment of the tolerance, safety, compliance, and cost-effectiveness of the interventions.

**Acknowledgments**

The authors are very grateful to Dr. Larsen, Professor Weitzberg, Dr. Kapil, Professor Ahluwalia, Professor Lovegrove, Dr. Cermak, and Professor Jones for providing the original data from their studies. The systematic review was conceived by J.C.M., J.L., and M.S; I.O. and M.S. searched, collected, and analyzed the data and co-wrote the manuscript; all authors contributed to subsequent analyses and interpretation; all authors contributed to the final revision of the manuscript; and M.S. is the guarantor for the manuscript and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

**Literature Cited**


Inorganic nitrate, beetroot juice, and blood pressure 825


