Effectiveness of dietary inorganic nitrate in lowering blood pressure in hypertensive adults: a systematic review protocol

Jennifer Remington1,2 • Karen Winters1,2

1 School of Nursing, University of Mississippi Medical Center, Jackson, USA, 2 UMMC School of Nursing Evidence Based Practice and Research Team: a Joanna Briggs Institute Affiliated Group

**Review question:** The question of this review is: what is the effect of dietary inorganic nitrate on blood pressure in adults with blood pressure >120/80mmHg?

**Keywords** Blood pressure; dietary; hypertension; inorganic nitrate


**Background**

Cardiovascular disease (CVD) is a broad term that identifies many negative alterations of the cardiovascular system. Globally, cardiovascular diseases are responsible for being the number one cause of death, and more people die annually from CVDs than from any other cause. In the United States, heart disease is the leading cause of death, and the leading cause of heart disease is hypertension. Hypertension, also known as high blood pressure, is the heightened force of the flow of blood through the arteries. This heightened force causes stretching of the arteries and damage to surrounding tissues, and ultimately, whole organs. Damage from hypertension is manifested by vascular weakness, vascular scarring, increased risk of blood clots, increased plaque build-up, tissue and organ damage from narrowed and blocked arteries, and increased workload on the circulatory system. It is estimated that around 70 million American adults have hypertension. This means that almost one-third of the US adult population is affected by it. The prevalence of hypertension among US adults aged 18 and over was 29.1% in 2011–2012. This prevalence noticeably increases with age, to 65% among those aged 60 and over. The total cost associated with hypertension in 2011 in the US was US$46 billion in health care services, medications and missed days of work.

Nitric oxide (NO) is a molecule that performs various significant functions in many of the body’s systems, especially the cardiovascular system. It assists the cardiovascular system with anti-platelet, anti-proliferative and vasodilator functions. Nitric oxide can be found in either dietary sources or medications. The Food and Drug Administration has approved only three NO products on the market: organic nitrates, inhaled NO therapy and phosphodiesterase inhibitors. Nitroglycerin is an example of an organic nitrate and a light anesthesia, analgesia is an example of inhaled NO, and sildenafil is an example of a phosphodiesterase inhibitor. Dietary sources that contain a high nitrate concentration include certain vegetables and supplements. Vegetables that have been found to have the highest nitrate content of greater than 250 mg/100 g include celery, cress, chervil, lettuce, red beetroot, spinach, and rocket (rucola). Red beetroot that is consumed in the form of beetroot juice or via a beetroot supplement has been studied in relation to blood pressure, particularly because of the vegetable’s ability to generate high concentrations of nitrate.

The reduced concentrations of NO in the body, caused by either decreased production or increased utilization, subjects the circulatory system to endothelial dysfunction, possibly leading to CVD. However, it is possible that the consumption of certain vegetables or supplements high in inorganic nitrate content could establish a protective effect on the cardiovascular system. Nitric oxide derived from dietary inorganic nitrate has been proven to...
have vasodilating effects.\textsuperscript{7,14} The possible blood pressure-lowering effect of inorganic nitrate is acquired from the increased production of NO when these high-nitrate sources are consumed. The dietary approach of inorganic nitrate consumption is currently under evaluation for treating hypertension, pulmonary artery disease and cardiac events, and for reducing the risk of cardiovascular disease.\textsuperscript{13}

There is an overwhelming amount of research conducted on the proper management of hypertension, both organically and inorganically.\textsuperscript{10-15} An appraisal of the evidence concerning the effect of dietary inorganic nitrate on blood pressure in hypertensive adults would help providers make informed decisions regarding interventions to address one of the nation’s biggest killers. Generally, dietary interventions are one of the least invasive components of a management strategy. The literature reveals that there are several studies concerning dietary inorganic nitrate intake and its effectiveness in reducing blood pressure in normotensive, healthy individuals.\textsuperscript{15-18} One systematic review exists concerning the effect of dietary inorganic nitrate on blood pressure. However, this review evaluates studies that are over-represented by healthy, normotensive participants. At the time of the previous review, there were no studies that specifically included participants with blood pressure greater than 120/80 mmHg. Therefore, it would be impossible to understand if blood pressure would be affected by inorganic nitrate in individuals with pre-hypertension or hypertension without the most current evidence. In the results section of the review it was also mentioned that more evidence and studies were needed that involved patients at greater cardiac risk.\textsuperscript{18} Furthermore, there is currently no systematic review concerning the effectiveness of inorganic nitrate on blood pressure in adults with blood pressure greater than 120/80 mmHg.

As previously mentioned, the burden of hypertension on the United States population is enormous. Although methods have been developed to control the disease, cardiovascular disease still remains the number one cause of death.\textsuperscript{1} Furthermore, because hypertension is such a pronounced issue in our nation, systematic reviews are needed for evaluation and pooling of research concerning methods of blood pressure control. The purpose of this systematic review is to synthesize the evidence regarding consumption of dietary inorganic nitrate and blood pressure in adults with blood pressure greater than 120/80 mmHg. The results of this review will contribute towards more effective methods in the prevention and treatment of hypertension. Therefore, this would sequentially result in less morbidity and mortality from cardiovascular diseases. A search of Cochrane Library of Systematic Reviews, JBI Database of Systematic Reviews and Implementation Reports and MEDLINE was performed, and no systematic review was found pertaining to the effects of dietary inorganic nitrate on blood pressure in adults with blood pressure greater than 120/80 mmHg. A preliminary search identified that systematic reviews of topics regarding inorganic nitrate and blood pressure exist, but none has specifically investigated the topic described in this review protocol.

**Inclusion criteria**

**Participants**

This review will consider studies that include adult subjects aged 18 years and over with blood pressure greater than 120/80 mmHg. Participants with lone elevated systolic or diastolic blood pressure will also be included. Healthy, normotensive adults will be excluded.

**Intervention(s)**

This review will consider studies that examine the effects of inorganic nitrate intake on blood pressure. All durations of the applied intervention will be considered. This review will consider studies that include inorganic nitrate intake via dietary modification, in the form of a dietary supplement, and/or beetroot juice. All dosages and frequencies of inorganic nitrates will be considered.

**Comparator(s)**

This review will consider studies that compare the intervention with the following: no intervention; different dosage, frequency, duration of intervention; and other interventions that are administered to reduce and manage blood pressure.

**Outcomes**

The review will consider studies that measure systolic and diastolic blood pressure pre- and post-intervention. The outcomes will be measured by the following: systolic blood pressure, diastolic...
blood pressure, pulse wave velocity, pulse wave analysis, and/or flow mediated dilatation by Doppler ultrasound. The duration of studies will vary with no limitations for inclusion to evaluate the short-term and prolonged effects post-intervention.

**Study types**

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, and case-control studies will be considered for inclusion. The review will also consider pilot studies.

This review will include studies published in English. Studies published since 2013 will be included.

**Search strategy**

The search strategy will aim to find both published and unpublished studies. An initial limited search of MEDLINE and CINAHL has been undertaken to identify articles on this topic, followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe these articles. This informed the development of a search strategy including identified keywords and index terms, which will be tailored for each information source. A full search strategy for each database is detailed in Appendix I. The reference list of all studies selected for critical appraisal will be screened for additional studies.

**Information sources**

The databases to be searched include: MEDLINE, CINAHL, Embase, Scopus and Natural Medicines. The trial registers to be searched include: Cochrane Central Register of Controlled Trials and ClinicalTrials.gov.

The search for unpublished studies will include: MedNar, Google Scholar and ProQuest Dissertations and Theses.

**Study selection**

Following the search, all identified citations will be collated and uploaded into Endnote (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI-SUMARI). The full text of selected citations will be retrieved and assessed in detail against the inclusion criteria by two independent reviewers. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

**Critical appraisal**

Selected studies will be critically appraised by two independent reviewers using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental and quasi-experimental studies. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

All studies, regardless of their methodological quality, will undergo data extraction and synthesis (where possible).

**Data extraction**

Data will be extracted by two independent reviewers from papers included in the review using pilot data extraction forms along with the standardized data extraction tool available in JBI SUMARI. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

**Data synthesis**

Papers will, where possible, be pooled in statistical meta-analysis using JBI-SUMARI. Effect sizes will be
expressed as either odds ratios (for dichotomous data) and weighted (or standardized) mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared and I² tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance provided by Tufanaru et al.20 Subgroup analyses will be conducted where there is sufficient data to investigate diet versus supplements, aging and gender differences, other cardiovascular health issues or chronic conditions, hypertensive medication compliance, and type of medication. Sensitivity analyses will be conducted to test if the results of an individual study appears to be heterogeneous with the results of other included studies, or when the methodology of included studies may present an element of bias in the context of this review, for example, when studies exclude subjects who should otherwise be included if this was an original research study of normotensive subjects. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

A funnel plot will be generated within JBI-SUMARI to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Assessing confidence
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing confidence in the quality of evidence will be used for this review, with the results presented in a summary of findings table created using GRADEPro.

Acknowledgements
This review will contribute to a doctor of nursing practice degree from the School of Nursing, University of Mississippi Medical Center.

References
4. American Heart Association [Internet]. American Heart Association; 2016 [cited 2016 Nov]; Available from: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressureWhat-is-High-Blood-Pressure_UCM_301759_Article.jsp.V9n_r5MrLMU.


Appendix I: Search strategy

MEDLINE (PubMed)


CINAHL

(MH hypertension+ OR TI hypertension OR AB hypertension OR TI “high blood pressure” OR AB “high blood pressure” OR TI “vascular resistance” OR AB “vascular resistance”)) AND (MH nitrates+ OR TI nitrate’ OR AB nitrate” OR TI “nitric oxide” OR AB “nitric oxide” OR TI “inorganic nitrate” OR AB “inorganic nitrate”” OR TI “inorganic nitrate” OR AB “dietary nitrate” OR TX “dietary nitrate” OR AB “dietary nitrate” OR TX “dietary nitrate” OR AB “nitrate rich” OR TX “nitrate rich” OR AB “nitrate supplement” OR TX “nitrate supplement” OR AB “nitrate diet” OR TX “nitrate diet” OR AB “oral nitrate” OR TX “oral nitrate” OR AB “oral nitrate” OR TX “oral nitrate” OR AB “nitrate/nitrite” OR TX “nitrate/nitrite” OR AB “nitrate/nitrite” OR TX “nitrate/nitrite” OR AB “beetroot juice” OR TX “beetroot juice” OR AB “beetroot juice” OR TX “beetroot juice” OR AB NO3- OR TX NO3-) AND (MH diet+ OR TI “western diet” OR AB “beetroot juice” OR TX “beetroot juice” OR AB placebo OR TX placebo OR AB “placebo diet” OR TX “placebo diet” OR AB “placebo diet” OR TX “placebo diet” OR TX control OR AB control OR TX control) AND (MH “blood pressure” OR TI “blood pressure control” OR AB “blood pressure control” OR TX “blood pressure control” OR TI “endothelial function” OR AB “endothelial function” OR TX “endothelial function” OR TI “vascular resistance” OR AB “vascular resistance” OR TX “vascular resistance” OR TI vascul OR AB vascul’ OR AB “pressure” OR TX “pressure” OR AB “pressure”).

Embase

(‘hypertension’/exp OR hypertension:ti,ab OR ‘hypertension’/syn OR ‘high blood pressure’:ti,ab OR ‘blood pressure’/exp OR ‘blood pressure’:ti,ab OR ‘prehypertension’/exp OR ‘prehypertension’/syn OR ‘vascular resistance’:ti,ab OR ‘cardiovascular risk factors’:ti,ab OR ‘older adults’:ti,ab OR obesity:ti,ab OR overweight:ti,ab OR ‘heart failure’:ti,ab OR cardiovascular:ti,ab) AND (nitrates:ti,ab OR nitrate:ti,ab OR ‘inorganic nitrate’:de,ti,ab OR ‘inorganic nitrates’:ti,ab OR ‘inorganic nitrites’:ti,ab OR ‘inorganic nitrites’/ti,ab OR ‘dietary nitrate’:ti,ab OR ‘dietary nitrates’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab OR ‘beetroot juice’:ti,ab) AND (‘decreased blood pressure’:ti,ab OR ‘increased blood pressure’:ti,ab OR ‘no change in blood pressure’:ti,ab OR ‘decreased vascular resistance’:ti,ab OR ‘increased vascular resistance’:ti,ab OR ‘blood pressure control’:ti,ab OR ‘blood pressure’:ti,ab OR ‘vascular effects’:ti,ab).
Scopus
(TITLE-ABS-KEY(Hypertension OR “high blood pressure” OR “blood pressure” OR prehypertension OR “vascular resistance” OR “cardiovascular risk factors” OR “older adults” OR obesity OR overweight OR “heart failure” OR cardiovascular)) AND (TITLE-ABS-KEY(Diet OR “nitrate deficient” OR “western diet” OR “control diet” OR placebo OR “beetroot juice”)) AND (TITLE-ABS-KEY(“decreased blood pressure” OR “increased blood pressure” OR “no change in blood pressure” OR “decreased vascular resistance” OR “increased vascular resistance” OR “blood pressure control” OR “blood pressure” OR “vascular effects”)) AND (TITLE(Nitrate OR “inorganic nitrate” OR “inorganic nitrite” OR “dietary nitrate” OR “beetroot juice” OR beetroot OR “dietary inorganic nitrate” OR “high nitrate” OR “nitrate rich” OR “nitrate supplement” OR “nitric oxide” OR vegetables)) AND (LIMIT-TO(PUBYEAR,2016) OR LIMIT-TO(PUBYEAR,2015) OR LIMIT-TO(PUBYEAR,2014) OR LIMIT-TO(PUBYEAR,2013) OR LIMIT-TO(PUBYEAR,2012) OR LIMIT-TO(PUBYEAR,2011) OR LIMIT-TO(PUBYEAR,2010) OR LIMIT-TO(PUBYEAR,2009) OR LIMIT-TO(PUBYEAR,2008) OR LIMIT-TO(PUBYEAR,2007) OR LIMIT-TO(PUBYEAR,2006)).

Natural Medicine
(beet), (“blood pressure”), (vegetables)
Cochrane Central Register of Controlled Trials
(MH hypertension+ OR TI hypertension OR AB hypertension OR TI “high blood pressure” OR AB “high blood pressure” OR TI “vascular resistance” OR AB “vascular resistance”) AND (MH nitrates+ OR TI nitrate+ OR AB nitrate+ OR TI “nitric oxide” OR AB “nitric oxide” OR TI “inorganic nitrate” OR AB “inorganic nitrate” OR TX “inorganic nitrate” OR TI “dietary nitrate” OR AB “dietary nitrate”) OR TX “dietary nitrate” OR TI “nitrate rich” OR AB “nitrate rich” OR TX “nitrate rich” OR TI “nitrate supplement” OR AB “nitrate supplement” OR TX “nitrate supplement” OR TI “nitrate diet” OR AB “nitrate diet” OR TX “nitrate diet” OR TI “oral nitrate” OR AB “oral nitrate” OR TX “oral nitrate” OR TI “nitrate/ nitrite” OR AB “nitrate/nitrite” OR TX “nitrate/nitrite” OR TI “beetroot juice” OR AB “beetroot juice” OR TX “beetroot juice” OR TI NO3- OR AB NO3- OR TX NO3-) AND (MH diet+ OR TI “western diet” OR AB “western diet” OR AB “dietary nitrate” OR TX “dietary nitrate” OR TI “vascular resistance” OR AB “vascular resistance” OR TX “vascular resistance” OR TI vascul OR AB vascul’ OR TI “pressure, blood” OR AB “pressure, blood”)

ClinicalTrials.gov
Hypertension OR “high blood pressure” OR “blood pressure” OR prehypertension OR “vascular resistance” OR “cardiovascular risk factors” OR “older adults” OR obesity OR overweight OR “heart failure” OR cardiovascular | Nitrate OR “inorganic nitrate” OR “inorganic nitrite” OR “dietary nitrate” OR “beetroot juice” OR beetroot OR “dietary inorganic nitrate” OR “high nitrate” OR “nitrate rich” OR “nitrate supplement” OR “nitric oxide” OR vegetables

MedNar
Title: (hypertension OR “high blood pressure” OR “blood pressure” OR cardiovascular OR “vascular resistance”) AND (nitrate OR “inorganic nitrate” OR “inorganic nitrite” OR “dietary nitrate” OR “dietary inorganic nitrate” OR “nitrate supplement” OR “nitrate rich” OR “beetroot juice”) AND (“decreased blood pressure” OR “increased blood pressure” OR “no change in blood pressure” OR “decreased vascular resistance” OR “increased vascular resistance” OR “blood pressure control” OR “vascular effects”)/ From: 2006 / To: 2016
Google Scholar
allintitle: dietary hypertension OR inorganic OR nitrate OR beetroot OR nitrates “blood pressure”

ProQuest Dissertations and Theses
all[Hypertension OR “high blood pressure” OR “blood pressure” OR hypertension OR “vascular resistance” OR “cardiovascular risk factors” OR “older adults” OR obesity OR overweight OR “heart failure” OR cardiovascular] AND all[Nitrate OR “inorganic nitrate”” OR “inorganic nitrite”” OR “dietary nitrate”” OR “beetroot juice” OR beetroot OR “dietary inorganic nitrate”” OR “high nitrate” OR “nitrate rich” OR “nitrate supplement”” OR “nitric oxide” OR vegetables] AND all[Diet OR “nitrate deficient” OR “western diet” OR “control diet” OR placebo OR “beetroot juice”] AND all[“decreased blood pressure” OR “increased blood pressure” OR “no change in blood pressure” OR “decreased vascular resistance” OR “increased vascular resistance” OR “blood pressure control” OR “blood pressure” OR “vascular effects”).