BMJ Open

Educational Intervention for improving control of blood pressure in patients with hypertension: A Systematic Review Protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006583
Article Type:	Protocol
Date Submitted by the Author:	10-Sep-2014
Complete List of Authors:	Ribeiro, Cibele; Federal University of Rio Grande do Norte, Department of Physical Therapy Resqueti, Vanessa; Federal University of Rio Grande do Norte, Department of Physical Therapy Lima, Íllia; Federal University of Rio Grande do Norte, Department of Physical Therapy Dias, Fernando; Federal University of Parana, Department of Physiology Glynn, Liam; National University of Ireland, Department of General Practice Fregonezi, Guilherme; Federal University of Rio Grande do Norte, Department of Physical Therapy
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Hypertension < CARDIOLOGY, EDUCATION & TRAINING (see Medical Education & Training), Rehabilitation medicine < INTERNAL MEDICINE, PREVENTIVE MEDICINE

EDUCATIONAL INTERVENTION FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW PROTOCOL

Corresponding Author: Guilherme Augusto de Freitas Fregonezi; Universidade Federal do Rio Grande do Norte – Departamento de Fisioterapia, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil; telephone number: +55 84 3342 2001; email: fregonezi.guilherme@gmail.com

Authors: Cibele D Ribeiro; Vanessa R Resqueti; Íllia Lima; Fernando A L Dias; Liam Glynn; Guilherme A F Fregonezi.

Authors affiliations:

1-Department of Physical Therapy – Federal University of Rio Grande do Norte, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil (Authors: Cibele; Vanessa; Íllia; Guilherme).

2-Department of Physiology – Federal University of Paraná, Centro Politécnico, Jardim das Américas, Caixa Postal 19031, 81531-980, Curitiba – Paraná – Brazil (Authors: Fernando)

3-College of Medicine – Nursing and Health Sciences – National University of Ireland Galway, University Road, Galway – Ireland (Authors: Liam).

Running Title: Educational intervention in hypertension - systematic review.

Key words: hypertension, blood pressure, educational interventions, randomized controlled trial, systematic review

Word Count: 2181

Abstract

Introduction: The aim of this review is to evaluate the effectiveness of educational interventions on improving the control of blood pressure in patients with hypertension.

Methods: Patients aged over eighteen years old regardless of sex, ethnicity with a diagnosis of hypertension (either treated or not treated with antihypertensive medications) will be included in our analysis. We will electronically search four databases: MEDLINE, CINAHL, PEDro, ScienceDirect. There will be no language restrictions in the search for studies. The data will be extracted independently by two authors using predefined criteria. Disagreements will be resolved between the authors. The risk of bias will be assessed using the Cochrane risk of bias tool. After searching and screening of the studies, we will run a meta-analysis of the included randomised controlled trials. We will summarise the results as risk ratio for dichotomous data and mean differences and weighted mean differences for continuous data.

Ethics and dissemination: The protocol for the systematic review has been registered in PROSPERO. The review will be published in a journal. The findings from the review will also be disseminated electronically and conferences presentations.

Trial registration number: Ribeiro C, Resqueti V, Lima I, Dias F, Glynn L, Fregonezi G. Educational interventions for improving control of blood pressure in patients with hypertension. PROSPERO: International prospective register of systematic reviews. 2014: CRD4201401071 Available from: http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=10171

Strenghts and limitations of this study:

- The trial screening and data extraction will be conducted independently by two authors.
- The results of this systematic review will help clinicians in making decisions in clinical practice, and help patients to better understand their conditions and also can heighten awareness about disease progression and complications.

INTRODUCTION

Description of the condition

Hypertension is a major health problem worldwide and is estimated to cause more than 13% of deaths annually,[1]. It is a multifactorial clinical condition characterized by high and sustained levels of blood pressure,[2]. It is one of the most important public health problems in the world and an important modifiable risk factor for the development of cardiovascular diseases. Adoption of healthy lifestyles by all individuals is critical for the prevention of high blood pressure and an indispensable part of the management of those with hypertension,[3].

A recent epidemiological worldwide study estimated that the high blood pressure causes approximately 7.6 million premature deaths (54% for stroke and 47% for ischaemic heart disease) and contributes to the functional disability of 92 million people in numbers adjusted for years of life in 2001,[4]. A recent systematic review reporting data performed in 35 different countries between the years 2003 and 2008 demonstrated an overall prevalence of 37.8% for men and 32.1% for women,[5].

Due to the fact that the prevalence of hypertension increases with age,[6] the management of hypertension and the prevention and treatment of major complications related to hypertension will continue to be a challenge for all health care professionals.

Description of the intervention

Hypertension is a condition almost entirely managed by the primary care team, composed by physicians, nurses, pharmacists and other health care professionals such as physiotherapists. All cited professional can play an important role on lowering the blood pressure. It is important to show patients that lowering a high blood pressure, has been showing in drug trials, and has been

associated with a reduction in many complications such as stroke (35-40%), heart attack (20-25%) and heart failure (over 50%)[3]. The majority of patients require a combination of antihypertensive drugs to reach target blood pressure.

A study had been showed that educational intervention led to an increase in the participants' levels of knowledge about hypertension and a positive influence on their beliefs about medicines,[7]. Educational interventions create opportunities for patients to better understand their conditions and the role of therapies and also can bring awareness about disease progression and complications. Through patient education, misconceptions that patients have about their therapy can be cleared. This can influence adherence to therapy,[8] and consequently blood pressure levels.

How the intervention might work

Different health professionals have become more involved in delivering interventions to the patients with the objective of preventing complications caused by high blood pressure. Patients expectations have a significant effect on the treatment they get from their doctor or any other health professional involved,[9]. Educational intervention is one of the proposed interventions applied to hypertensive patients.

Educational interventions can positively modify patients' beliefs which in turn can lead to a change in patient behavior, adherence to a therapy proposed by the responsible health care professional,[8] and a possible effect on variables related to the disease such as blood pressure levels. It may also affect in long term the progression of the disease and the prevalence of associated conditions related to hypertension such as heart attacks and cerebrovascular artery disease.

Why is important to do this review

Due to the high morbidity and mortality caused by hypertension and the global scale of this important public health, it is important to continue to investigate interventions that can improve blood pressure control. It is striking that blood pressure goals continue to be a achieved in only 25-40% of the patients who take antihypertensive drug treatment,[3,10], which is something that has remained unchanged for the last 40 years,[11].

A recent Cochrane review demonstrated that there are many categories of interventions that together reduce blood pressure in patients with hypertension,[12]. One of them was educational interventions directed to patient and physician. This kind of intervention demonstrated to be beneficial on lowering blood pressure; however, not alone and was recommended to be an adjunct additional therapy along other types of interventions such as antihypertensive drug therapy.

Due to the fact that there has been an increasing number of studies showing the importance of prevention in patients with hypertension,[13-15] this review will evaluate the current evidence of the effects of educational interventions on the control of blood pressure in patients with hypertension.

METHODS AND ANALYSIS

Criteria for considering studies for the review

Types of studies

We plan to include randomized clinical trials (RCTs) that have evaluated the effects of different models of educational interventions with the overall aim of improving blood pressure control in patients with hypertension, irrespective of language. The review will include RCTs where educational intervention used as the main or adjunct treatment was compared with no educational intervention or different types of educational strategies. We will exclude studies that use educational interventions not intended to improve blood pressure control.

Types of participants

We will include participants with age over 18 years regardless of sex, ethnicity with a diagnosis of hypertension either treated or not treated with antihypertensive medications in a primary care, outpatient or community setting.)

Types of interventions

The intervention of interest will include all educational interventions strategies designed to improve the control of blood pressure in patients with hypertension (e.g. educational interventions direct to the patient; educational interventions direct to the health professional). Comparators will be any educational intervention used as the main or adjunct treatment to improve the control of blood pressure compared with either no educational intervention or different types of educational strategies aimed to improve blood pressure control.

Types of outcomes assessments

The primary outcome of this review will be any changes in mean systolic blood pressure (SBP) and/or mean diastolic blood pressure (DBP) in any care setting as well as number of patients under control of blood pressure (BP) or proportion of controlled BP defined by each randomized trial´s investigators. The secondary outcomes will be: number of hospitalizations during treatment (e.g. increase of BP) or mortality from cardiovascular disease as an adverse events; the costs and cost effectiveness of interventions; the adherence to intervention (dropout rate) or adherence to medication and the outcome QOL will be measured using standardized generic questionnaire.

Search methods for identification of studies

Electronic searches

We will electronically search the following databases: MEDLINE, CINAHL, PEDro, ScienceDirect, WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. without any language restrictions. The search strategy will be developed after discussion among reviewers, according to the guidance of the Cochrane handbook (colocar ref.). The MEDLINE search strategy will be translated into the other databases using the appropriate controlled vocabulary as applicable for each database.

Other sources

The bibliographies of all retrieved and relevant publications identified by the above strategies will be searched for further studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will attempt to contact researchers to obtain additional information when needed.

Data collection and analysis

Selection of studies

Before the selection of studies, a procedure for screening will be developed by discussion among all the reviewers. We will extract data into Review Manager 5.3,[16] and summarize details using a standard data extraction sheet. Two reviewers (CR and VR) will independently assess the titles and abstracts of the studies identified from the search strategy against the inclusion criteria. Full versions of articles that appear to fulfil the inclusion criteria will be obtained for further assessment. Another review author (IL) will evaluate any discrepancies, if necessary, and will advise in case of disagreement. We will record all reasons for exclusion and we will exclude studies that not use the educational interventional to improve blood pressure control.

D*ata extraction and management*

Two review authors (CR and VR), working independently, will extract data and summarize details of trials using a standard data extraction sheet. According to methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[17] the extraction sheet includes information such as study design, methodology, participants, interventions, duration of treatment, outcomes, conclusions and potential sources of bias. We will resolve any discrepancies by discussion with a third review author (IL). If studies report more than one outcome time (e.g. 6 and 12 months), data concerning the longest follow up will be extracted. Where data are found to be missing, we will contact the corresponding author of studies to request the missing data or to clarify study details.

Assessment of risk of bias in included studies

For assessment of study quality and reporting bias two reviewers (CR and VR) will independently assess the risk of bias, using the Cochrane collaboration's tool for assessing risk of bias of the included trials,[18]which is composed of six domains of a trial, such as random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias. After assessing all the domains, the reviewers will summarize the assessments and categorize the included trials into three levels of bias: low, unclear and high risk of bias and high risk of bias. We will resolve any disagreements by discussion with a third author (IL).

Measures of treatment effect

We will present the effects on blood pressure between interventions at follow-up (systolic and diastolic blood pressure) according to the educational intervention proposed in each study. We will present the outcome results for each trial with 95% confidence intervals (CI). Continuous

outcomes (such as changes in systolic and diastolic blood pressure) will be expressed and calculated as mean difference (MD) and overall effect size between intervention and control groups. We will use Relative Risk (RR) or Odds Ratio (OR) depending on measurements indices in individual studies for other primary and secondary outcomes.

Unit of analysis issues

We will treat the number of individual participants as the unit of analysis in this review. We will include cluster-randomized trials in the analysis. For cluster-randomized trials, we will adjust results when the unit of analysis in the trial is presented as the total number of individual participants instead of number of clusters. Results will be adjusted using the mean cluster size and intracluster correlation coefficient,[19]. For meta-analysis, data will be combined to individually randomized trials using the generic inverse-variance method as described on Chapter 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions,[19].

Dealing with missing data

In the case of missing data, we will contact the original investigators to request missing data whenever possible. If trial does not specify participant group number prior to dropout, we will present only complete case analysis for primary and secondary outcomes.

Assessment of heterogeneity

Whenever studies appear to be similar in terms of level of participants, intervention type and duration and outcome type we will pool data using meta-analysis (using RevMan 5.3). We will test statistical heterogeneity using the Chi² test (considering a value of $P < 0.1$ to indicate heterogeneity) and estimate the amount of heterogeneity using the I^2 statistic,[20]. If I^2 is over

50% indicating a high level of heterogeneity data will not be pooled. In the absence of clinical and statistical heterogeneity we will use a fixed-effect model.

Assessment of reporting biases

We will present the overall risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting) in a risk of bias summary table per study. If sufficient studies (more than ten) are identified an attempt will be made to examine for publication bias using funnel plot as described in the Cochrane Handbook for Systematic Reviews of Interventions,[21]. If asymmetry is present we will explore possible causes including publication bias, poor methodological quality and true heterogeneity.

Data synthesis

We will present a narrative overview of the combined studies with meta-analysis of outcome data using the software Review Manager version 5.3 where appropriate. The decision to include studies in a meta-analysis will depend on the availability of treatment effect data and assessment of heterogeneity. Intervention effects will be calculated as relative risks with 95% confidence intervals for dichotomous data. For continuous data, we will calculate mean differences and weighted mean differences with 95% confidence intervals using a conservative fixed-effects meta-analysis model in the absence of significant heterogeneity ($p>0.05$ or $I^2 <50\%$). If there is high level of heterogeneity ($I^2 >50\%$) we will not pool data and we will perform sensitivity analysis of data.

Subgroup analysis

Subgroup analysis will be carried out according to the following variables: age and gender of participants, professional delivering intervention (e.g. nurse).

Sensitivity analysis

If sufficient trials are identified, we plan to conduct sensitivity analyses in order to explore the influence on the results of the following factors: assessor blinding (high risk of bias versus low risk of bias). We will restrict analyses to studies at low risk of bias.

Ethics and dissemination

This systematic review does not need ethical approval. Findings of this review will be disseminated via peer-reviewed journals and conference presentations.

DISCUSSION

This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in print. This review also will benefit patients with hypertension as they will better understand and accept the therapy and change their behavior about the treatment.

Author´s Contributions: The search strategy will be developed and run by IL. Copies of studies will be obtained by CR and VR. Selection of the studies to include will be performed by CR and VR. Extraction data from studies and entering data into RevMan will be conducted by CR and VR. The analysis will be carried out by CR, VR and IL. Interpretation of the analysis will be carried out by all authors. The final review will be drafted by all authors. The protocol was revised, and the final version was approved by all authors.

Funding Statement: The work was supported by the National Council for Scientific and Technological Development (CNPQ): 457357/2013-4 CTSaúde/Edital MCTI/CNPQ/MS – SCTIE – DECIT nº 57/2013 PEC-REBRATS - Brazilian Network for Health Technology Assessment in Health: Comparative Effectiveness Research.

Competing interests: None.

References

1- The world health report 2002—reducing risks, promoting healthy life. World Health Organization(WHO):www.who.int/whr/2002/en/. Accessed: August 01, 2014.

2- Williams B. The Year in Hypertension. Journal of American College of Cardiology 2008;51(18):1803-17.

3- Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection,Evaluation, and Treatment of High Blood Pressure - The JCN 7 Report. The Journal of American Medical Association 2003;289(19):2560-72.

4- Lopez AD, Mathers CD, Ezzati M et al. Measuring the Global Burden of Disease and Risk Factors, 1990- 2001. Global Burden of Disease and Risk Factors 2006: Available at: http://www.dcp2.org/pubs/GBD. Accessed September 18, 2012.

5- Pereira M, Lunet N, Azevedo A et al. Diferences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. Journal of Hypertension 2009;27(5):963-975.

6- Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.

7- Magadza C, Radloff SE, Srinivas SC. The effect of an educational intervention on patients' knowledge about hypertension, beliefs about medicines, and adherence. Research in Social and Administrative Pharmacy 2009;5:363-375.

8- Saounatsou M, Patsi O, Fasoi G et al. The Influence of the Hypertensive Patient´s in Compliance with their medication. Public Health Nursing 2001;18(6):436-442.

9- McKinstry B, Hanley J, Heaney D et al. Impact on hypertension control of a patient-held guideline: a randomised controlled trial. British Journal of General Practice 2006;56:842-847.

10- Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? Journal of Hypertension Supplement 2002;20:1251-3.

11- Wilber J, Barrow J. Hypertension: a community problem. The American Journal of Medicine 1972; 52: 653-63.

12- Glynn LG, Murphy AW, Smith SM et al. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005182 DOI: 10.1002/14651858.CD005182.pub4.

13- Aung MN, Yuasa M, Moolphate S et al. Reducing salt intake for prevention of cardiovascular diseases in high-risk patients by advanced health education intervention (RESIP-

CVD study), Northern Thailand: study protocol for a cluster randomized trial. Trial 2012;13:158. [10.1186/1745-6215-13-158]

14- Ng N, Carlberg B, Weinehall L, Norberg M. Trends of blood pressure levels and management in Vasterbotten County,Sweden, during 1990-2010. Glob Health Action 2012;5:18195.

15- Ribeiro AG, Ribeiro SMR, Dias CMGC, Ribeiro AQ, Castro FAF, Suarez-Varela MM, Cotta RMM. Non-pharmacological treatment of hypertension in primary health care: A comparative clinical trial of two education strategies in health and nutrition. BMC Public Health 2011;11:637.

16- Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

17- Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

18- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

19- Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

20- Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT. Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

21- Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

BMJ Open

Educational Intervention for improving control of blood pressure in patients with hypertension: A Systematic Review Protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006583.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Nov-2014
Complete List of Authors:	Ribeiro, Cibele; Federal University of Rio Grande do Norte, Department of Physical Therapy Resqueti, Vanessa; Federal University of Rio Grande do Norte, Department of Physical Therapy Lima, Íllia; Federal University of Rio Grande do Norte, Department of Physical Therapy Dias, Fernando; Federal University of Parana, Department of Physiology Glynn, Liam; National University of Ireland, Department of General Practice Fregonezi, Guilherme; Federal University of Rio Grande do Norte, Department of Physical Therapy
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Hypertension < CARDIOLOGY, EDUCATION & TRAINING (see Medical Education & Training), Rehabilitation medicine < INTERNAL MEDICINE, PREVENTIVE MEDICINE

EDUCATIONAL INTERVENTION FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW PROTOCOL

Corresponding Author: Guilherme Augusto de Freitas Fregonezi; Universidade Federal do Rio Grande do Norte – Departamento de Fisioterapia, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil; telephone number: +55 84 3342 2001; email: fregonezi.guilherme@gmail.com

Authors: Cibele D Ribeiro; Vanessa R Resqueti; Íllia Lima; Fernando A L Dias; Liam Glynn; Guilherme A F Fregonezi.

Authors affiliations:

1-Department of Physical Therapy – Federal University of Rio Grande do Norte, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil (Authors: Cibele; Vanessa; Íllia; Guilherme).

2-Department of Physiology – Federal University of Paraná, Centro Politécnico, Jardim das Américas, Caixa Postal 19031, 81531-980, Curitiba – Paraná – Brazil (Authors: Fernando)

3-College of Medicine – Nursing and Health Sciences – National University of Ireland Galway, University Road, Galway – Ireland (Authors: Liam).

Running Title: Educational intervention in hypertension - systematic review.

Key words: hypertension, blood pressure, educational interventions, randomized controlled trial, systematic review

Word Count: 2216

Abstract

Introduction: The aim of this review is to evaluate the effectiveness of educational interventions on improving the control of blood pressure in patients with hypertension.

Methods: Randomized controlled trials including patients aged over eighteen years old regardless of sex, ethnicity with a diagnosis of hypertension (either treated or not treated with antihypertensive medications) will be assessed in our analysis. We will electronically search four databases: MEDLINE, CINAHL, PEDro, ScienceDirect. There will be no language restrictions in the search for studies. The data will be extracted independently by two authors using predefined criteria. Disagreements will be resolved between the authors. The risk of bias will be assessed using the Cochrane risk of bias tool. After searching and screening of the studies, we will run a meta-analysis of the included randomised controlled trials. We will summarise the results as risk ratio for dichotomous data and mean differences for continuous data.

Ethics and dissemination: The protocol for the systematic review has been registered in PROSPERO. The review will be published in a journal. The findings from the review will also be disseminated electronically and conferences presentations.

Trial registration number: Ribeiro C, Resqueti V, Lima I, Dias F, Glynn L, Fregonezi G. Educational interventions for improving control of blood pressure in patients with hypertension. PROSPERO: International prospective register of systematic reviews. 2014: CRD4201401071 Available from: http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=10171

Strenghts and limitations of this study:

- The results of this systematic review will help clinicians in making decisions in clinical practice, and help patients to better understand their conditions and also can heighten awareness about disease progression and complications.

INTRODUCTION

Description of the condition

Hypertension is a major health problem worldwide and is estimated to cause more than 13% of deaths annually,[1]. It is a multifactorial clinical condition characterized by high and sustained levels of blood pressure,[2]. It is one of the most important public health problems in the world and an important modifiable risk factor for the development of cardiovascular diseases. Adoption of healthy lifestyles by all individuals is critical for the prevention of high blood pressure and an indispensable part of the management of those with hypertension,[3]. Uncontrolled hypertension is associated with high risk for development of heart disease, stroke, chronic kidney disease, retinopathy, peripheral vascular disease.

A recent epidemiological worldwide study estimated that the high blood pressure causes approximately 7.6 million premature deaths (54% for stroke and 47% for ischaemic heart disease),[4]. A recent systematic review reporting data from studies in 35 different countries between the years 2003 and 2008 demonstrated an overall prevalence of 37.8% for men and 32.1% for women,[5].

Due to the fact that the prevalence of hypertension increases with age,[6] the management of hypertension and the prevention and treatment of major complications related to hypertension will continue to be a global challenge for health care professionals.

Description of the intervention

Hypertension is a condition almost entirely managed by the primary care team by a variety of health professionals such as physicians, nurses, pharmacists and other allied health care professionals such as physiotherapists that frequently work in cardiac rehabilitation. All

professionals can potentially play an important role in lowering blood pressure. It is important that patients understand the benefits of blood pressure lowering which include a reduction in many complications such as stroke (35-40%), heart attack (20-25%) and heart failure (over 50%)[3]. The majority of patients will require a combination of antihypertensive drugs to reach target blood pressure.

A previous study demonstrated that educational interventions increased participants' levels of knowledge about hypertension and had a positive influence on their beliefs about medicines,[7]. Educational interventions can also create opportunities for patients to better understand their conditions and the role of therapies and also can heighten awareness about disease progression and complications. Through patient education, misconceptions that patients have about their therapy can be clarified. This can influence adherence to therapy,[8] and therefore potentially may lead to improve blood pressure control.

How the intervention might work

Different health professionals have become more involved in delivering interventions to the patients with the objective of preventing complications caused by high blood pressure. Patients expectations have a significant effect on the treatment they get from their doctor or any other health professional involved,[9]. Many previous trials in blood pressure control have used educational interventions on patients, physicians or both in an attempt to improve blood pressure control.

Educational interventions can positively modify patients' beliefs which in turn can lead to a change in patient behavior such as improvement in adherence to a therapy proposed by the health care professional,[8] and a possible effect on variables related to the disease such as blood

pressure levels. This may also affect in long term the progression of the disease and the prevalence of associated conditions related to hypertension such as heart attacks and stroke.

Why is important to do this review

Due to the high morbidity and mortality caused by hypertension and the global scale of this important public health issue, it is important to continue to investigate interventions that can improve blood pressure control. It is striking that blood pressure goals continue to be a achieved in only 25-40% of the patients who take antihypertensive drug treatment,[3,10], which is something that has remained unchanged for the last 40 years,[11].

A recent Cochrane review demonstrated that there are many categories of interventions that singly or in unison have the potential to reduce blood pressure in patients with hypertension,[12]. In this review educational interventions directed to patient and physician were examined; however, the focus of the review and protocol was not the educational intervention alone. Educational interventions either to health professionals or patients, did not appear to be associated with large net reductions in blood pressure but were recommended as an adjunct additional therapy along other types of interventions.

Due to the fact that there has been an increasing number of recent studies showing the importance of prevention in patients with hypertension,[13-15] this review will determine the current evidence of the effects of educational interventions to improve control of blood pressure in patients with hypertension, potentially updating the recommendation for clinical practice.

METHODS AND ANALYSIS

Criteria for considering studies for the review

Types of studies

We plan to include randomized clinical trials (RCTs) that have evaluated the effects of different models of educational interventions with the overall aim of improving blood pressure control in patients with hypertension, irrespective of language. The review will include RCTs where educational intervention used as the main or adjunct treatment was compared with no educational intervention or different types of educational strategies. We will exclude studies that use educational interventions not intended to improve blood pressure control.

Types of participants

We will include studies that participants have age over 18 years regardless of sex, ethnicity with a diagnosis of hypertension either treated or not treated with antihypertensive medications in a primary care, outpatient or community setting.)

Types of interventions

The intervention of interest will include all educational interventions strategies designed to improve the control of blood pressure in patients with hypertension (e.g. educational interventions direct to the patient; educational interventions direct to the health professional). Comparators will be any educational intervention used as the main or adjunct treatment to improve the control of blood pressure compared with either no educational intervention or different types of educational strategies aimed to improve blood pressure control.

Types of outcomes assessments

The primary outcome of this review will be any changes in mean systolic blood pressure (SBP) and/or mean diastolic blood pressure (DBP) in any care setting as well as number of patients under control of blood pressure (BP) or proportion of controlled BP defined by each randomized

trial´s investigators. The secondary outcomes will be: number of hospitalizations during treatment (e.g. increase of BP) or mortality from cardiovascular disease as an adverse events; the costs and cost effectiveness of interventions; the adherence to intervention (dropout rate) or adherence to medication and the outcome QOL will be measured using standardized generic questionnaire.

Search methods for identification of studies

Electronic searches

We will electronically search the following databases: MEDLINE, CINAHL, PEDro, ScienceDirect, WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. without any language restrictions. The search strategy will be developed after discussion among reviewers, according to the guidance of the Cochrane handbook[16].The MEDLINE search strategy will be translated into the other databases using the appropriate controlled vocabulary as applicable for each database.

Other sources

The bibliographies of all retrieved and relevant publications identified by the above strategies will be searched for further studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will attempt to contact researchers to obtain additional information when needed.

Data collection and analysis

Selection of studies

Before the selection of studies, a procedure for screening will be developed by discussion among all the reviewers. We will extract data into Review Manager 5.3,[17] and summarize details

using a standard data extraction sheet. Two reviewers (CR and VR) will independently assess the titles and abstracts of the studies identified from the search strategy against the inclusion criteria. Full versions of articles that appear to fulfil the inclusion criteria will be obtained for further assessment. Another review author (IL) will evaluate any discrepancies, if necessary, and will advise in case of disagreement. We will record all reasons for exclusion and we will exclude studies that not use the educational interventional to improve blood pressure control.

D*ata extraction and management*

Two review authors (CR and VR), working independently, will extract data and summarize details of trials using a standard data extraction sheet. According to methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[18] the extraction sheet includes information such as study design, methodology, participants, interventions, duration of treatment, outcomes, conclusions and potential sources of bias. We will resolve any discrepancies by discussion with a third review author (IL). If studies report more than one outcome time (e.g. 6 and 12 months), data concerning the longest follow up will be extracted. Where data are found to be missing, we will contact the corresponding author of studies to request the missing data or to clarify study details.

Assessment of risk of bias in included studies

For assessment of study quality and reporting bias two reviewers (CR and VR) will independently assess the risk of bias, using the Cochrane collaboration's tool for assessing risk of bias of the included trials,[19] which is composed of six domains of a trial, such as random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias. After assessing all the domains, the reviewers

will summarize the assessments and categorize the included trials into three levels of bias: low, unclear and high risk of bias and high risk of bias. We will resolve any disagreements by discussion with a third author (IL).

Measures of treatment effect

We will present the effects on blood pressure between interventions at follow-up (systolic and diastolic blood pressure) according to the educational intervention proposed in each study. We will present the outcome results for each trial with 95% confidence intervals (CI). Continuous outcomes (such as changes in systolic and diastolic blood pressure) will be expressed and calculated as mean difference (MD) and overall effect size between intervention and control groups. We will use Relative Risk (RR) or Odds Ratio (OR) depending on measurements indices in individual studies for other primary and secondary outcomes.

Dealing with missing data

In the case of missing data, we will contact the original investigators to request missing data whenever possible. If trial does not specify participant group number prior to dropout, we will present only complete case analysis for primary and secondary outcomes.

Assessment of heterogeneity

Whenever studies appear to be similar in terms of participants characteristics (established hypertensive, people with diabetes or other chronic disease), intervention type and duration and outcome type we will pool data using meta-analysis (using RevMan 5.3). We will test statistical heterogeneity using the Chi² test (considering a value of $P < 0.1$ to indicate heterogeneity) and estimate the amount of heterogeneity using the I^2 statistic,[20]. If I^2 is over 50% indicating a high

level of heterogeneity data will not be pooled. In the absence of clinical and statistical heterogeneity we will use a fixed-effect model.

Assessment of reporting biases

We will present the overall risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting) in a risk of bias summary table per study. If sufficient studies (more than ten) are identified an attempt will be made to examine for publication bias using funnel plot as described in the Cochrane Handbook for Systematic Reviews of Interventions,[21]. If asymmetry is present we will explore possible causes including publication bias, poor methodological quality and true heterogeneity.

Data synthesis

We will present a narrative overview of the combined studies with meta-analysis of outcome data using the software Review Manager version 5.3 where appropriate.

We will include cluster-randomized trials in the analysis. For cluster-randomized trials, we will adjust results when the unit of analysis in the trial is presented as the total number of individual participants instead of number of clusters. Results will be adjusted using the mean cluster size and intracluster correlation coefficient,[22]. For meta-analysis, data will be combined to individually randomized trials using the generic inverse-variance method as described on Chapter 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions,[22].

The decision to include studies in a meta-analysis will depend on the availability of treatment effect data and assessment of heterogeneity. Intervention effects will be calculated as relative risks with 95% confidence intervals for dichotomous data. For continuous data, we will calculate mean differences with 95% confidence intervals using a conservative fixed-effects meta-analysis

model in the absence of significant heterogeneity ($p>0.05$ or $I^2 <50\%$). If there is high level of heterogeneity ($I^2 >50\%$) we will not pool data and we will perform sensitivity analysis of data.

Subgroup analysis

Subgroup analysis will be carried out according to the following variables: age and gender of participants, professional delivering intervention (e.g. nurse).

Sensitivity analysis

If sufficient trials are identified, we plan to conduct sensitivity analyses in order to explore the influence on the results of the following factors: assessor blinding (high risk of bias versus low risk of bias). We will restrict analyses to studies at low risk of bias.

Ethics and dissemination

This systematic review does not need ethical approval. Findings of this review will be disseminated via peer-reviewed journals and conference presentations.

DISCUSSION

This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in print. This review also will benefit patients with hypertension as they will better understand and accept the therapy and change their behavior about the treatment.

Author´s Contributions: The search strategy will be developed and run by IL. Copies of studies will be obtained by CR and VR. Selection of the studies to include will be performed by CR and VR. Extraction data from studies and entering data into RevMan will be conducted by CR and VR. The analysis will be carried out by CR, VR and IL. Interpretation of the analysis will be carried out by all authors. The final review will be drafted by all authors. The protocol was revised, and the final version was approved by all authors.

Funding Statement: The work was supported by the National Council for Scientific and Technological Development (CNPQ): 457357/2013-4 CTSaúde/Edital MCTI/CNPQ/MS – SCTIE – DECIT nº 57/2013 PEC-REBRATS - Brazilian Network for Health Technology Assessment in Health: Comparative Effectiveness Research.

Competing interests: None.

References

1- The world health report 2002—reducing risks, promoting healthy life. World Health Organization(WHO):www.who.int/whr/2002/en/. Accessed: August 01, 2014.

2- Williams B. The Year in Hypertension. Journal of American College of Cardiology 2008;51(18):1803-17.

3- Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection,Evaluation, and Treatment of High Blood Pressure - The JCN 7 Report. The Journal of American Medical Association 2003;289(19):2560-72.

4- Lopez AD, Mathers CD, Ezzati M et al. Measuring the Global Burden of Disease and Risk Factors, 1990- 2001. Global Burden of Disease and Risk Factors 2006: Available at: http://www.dcp2.org/pubs/GBD. Accessed September 18, 2012.

5- Pereira M, Lunet N, Azevedo A et al. Diferences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. Journal of Hypertension 2009;27(5):963-975.

6- Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.

7- Magadza C, Radloff SE, Srinivas SC. The effect of an educational intervention on patients' knowledge about hypertension, beliefs about medicines, and adherence. Research in Social and Administrative Pharmacy 2009;5:363-375.

8- Saounatsou M, Patsi O, Fasoi G et al. The Influence of the Hypertensive Patient´s in Compliance with their medication. Public Health Nursing 2001;18(6):436-442.

9- McKinstry B, Hanley J, Heaney D et al. Impact on hypertension control of a patient-held guideline: a randomised controlled trial. British Journal of General Practice 2006;56:842-847.

10- Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? Journal of Hypertension Supplement 2002;20:1251-3.

11- Wilber J, Barrow J. Hypertension: a community problem. The American Journal of Medicine 1972; 52: 653-63.

12- Glynn LG, Murphy AW, Smith SM et al. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005182 DOI: 10.1002/14651858.CD005182.pub4.

13- Aung MN, Yuasa M, Moolphate S et al. Reducing salt intake for prevention of cardiovascular diseases in high-risk patients by advanced health education intervention (RESIP-

CVD study), Northern Thailand: study protocol for a cluster randomized trial. Trial 2012;13:158. [10.1186/1745-6215-13-158]

14- Ng N, Carlberg B, Weinehall L, Norberg M. Trends of blood pressure levels and management in Vasterbotten County,Sweden, during 1990-2010. Glob Health Action 2012;5:18195.

15- Ribeiro AG, Ribeiro SMR, Dias CMGC, Ribeiro AQ, Castro FAF, Suarez-Varela MM, Cotta RMM. Non-pharmacological treatment of hypertension in primary health care: A comparative clinical trial of two education strategies in health and nutrition. BMC Public Health 2011;11:637.

16- Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17- Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

18- Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

19- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

20- Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT. Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

21- Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

22- Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

EDUCATIONAL INTERVENTION FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW PROTOCOL

Corresponding Author: Guilherme Augusto de Freitas Fregonezi; Universidade Federal do Rio Grande do Norte – Departamento de Fisioterapia, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil; telephone number: +55 84 3342 2001; email: fregonezi.guilherme@gmail.com

Authors: Cibele D Ribeiro; Vanessa R Resqueti; Íllia Lima; Fernando A L Dias; Liam Glynn; Guilherme A F Fregonezi.

Authors affiliations:

1-Department of Physical Therapy – Federal University of Rio Grande do Norte, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil (Authors: Cibele; Vanessa; Íllia; Guilherme).

2-Department of Physiology – Federal University of Paraná, Centro Politécnico, Jardim das Américas, Caixa Postal 19031, 81531-980, Curitiba – Paraná – Brazil (Authors: Fernando)

3-College of Medicine – Nursing and Health Sciences – National University of Ireland Galway, University Road, Galway – Ireland (Authors: Liam).

Running Title: Educational intervention in hypertension - systematic review.

Key words: hypertension, blood pressure, educational interventions, randomized controlled trial, systematic review

Word Count: 2181

Abstract

Introduction: The aim of this review is to evaluate the effectiveness of educational interventions on improving the control of blood pressure in patients with hypertension.

Methods: Randomized controlled trials including patients aged over eighteen years old regardless of sex, ethnicity with a diagnosis of hypertension (either treated or not treated with antihypertensive medications) will be assessed in our analysis. We will electronically search four databases: MEDLINE, CINAHL, PEDro, ScienceDirect. There will be no language restrictions in the search for studies. The data will be extracted independently by two authors using predefined criteria. Disagreements will be resolved between the authors. The risk of bias will be assessed using the Cochrane risk of bias tool. After searching and screening of the studies, we will run a meta-analysis of the included randomised controlled trials. We will summarise the results as risk ratio for dichotomous data and mean differences ~~and weighted mean differences~~ for continuous data.

Ethics and dissemination: The protocol for the systematic review has been registered in PROSPERO. The review will be published in a journal. The findings from the review will also be disseminated electronically and conferences presentations.

Trial registration number: Ribeiro C, Resqueti V, Lima I, Dias F, Glynn L, Fregonezi G. Educational interventions for improving control of blood pressure in patients with hypertension. PROSPERO: International prospective register of systematic reviews. 2014: CRD4201401071 Available from: http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=10171

Strenghts and limitations of this study:

- ~~The trial screening and data extraction will be conducted independently by two authors~~.

- The results of this systematic review will help clinicians in making decisions in clinical practice, and help patients to better understand their conditions and also can heighten awareness about disease progression and complications.

INTRODUCTION

Description of the condition

Hypertension is a major health problem worldwide and is estimated to cause more than 13% of deaths annually,[1]. It is a multifactorial clinical condition characterized by high and sustained levels of blood pressure,[2]. It is one of the most important public health problems in the world and an important modifiable risk factor for the development of cardiovascular diseases. Adoption of healthy lifestyles by all individuals is critical for the prevention of high blood pressure and an indispensable part of the management of those with hypertension,[3]. Uncontrolled hypertension is associated with high risk for development of heart disease, stroke, chronic kidney disease, retinopathy, peripheral vascular disease.

A recent epidemiological worldwide study estimated that the high blood pressure causes approximately 7.6 million premature deaths (54% for stroke and 47% for ischaemic heart disease),[4]. A recent systematic review reporting data from studies ~~performed~~ in 35 different countries between the years 2003 and 2008 demonstrated an overall prevalence of 37.8% for men and 32.1% for women,[5].

Due to the fact that the prevalence of hypertension increases with age,[6] the management of hypertension and the prevention and treatment of major complications related to hypertension will continue to be a global challenge for health care professionals.

Description of the intervention

Hypertension is a condition almost entirely managed by the primary care team by a variety of health professionals such as physicians, nurses, pharmacists and other allied health care professionals such as physiotherapists that frequently work in cardiac rehabilitation. All professionals can potentially play an important role in lowering blood pressure. It is important that patients understand the benefits of blood pressure lowering which include a reduction in many complications such as stroke (35-40%), heart attack (20-25%) and heart failure (over 50%)[3]. The majority of patients will require a combination of antihypertensive drugs to reach target blood pressure.

A previous study demonstrated that educational interventions increased participants' levels of knowledge about hypertension and had a positive influence on their beliefs about medicines,[7]. Educational interventions can also create opportunities for patients to better understand their conditions and the role of therapies and also can heighten awareness about disease progression and complications. Through patient education, misconceptions that patients have about their therapy can be clarified. This can influence adherence to therapy,[8] and therefore potentially may lead to improve blood pressure control.

How the intervention might work

Different health professionals have become more involved in delivering interventions to the patients with the objective of preventing complications caused by high blood pressure. Patients expectations have a significant effect on the treatment they get from their doctor or any other health professional involved,[9]. Many previous trials in blood pressure control have used educational interventions on patients, physicians or both in an attempt to improve blood pressure control.

Educational interventions can positively modify patients' beliefs which in turn can lead to a change in patient behavior such as improvement in adherence to a therapy proposed by the health care professional,[8] and a possible effect on variables related to the disease such as blood pressure levels. This may also affect in long term the progression of the disease and the prevalence of associated conditions related to hypertension such as heart attacks and stroke.

Why is important to do this review

Due to the high morbidity and mortality caused by hypertension and the global scale of this important public health issue, it is important to continue to investigate interventions that can improve blood pressure control. It is striking that blood pressure goals continue to be a achieved in only 25-40% of the patients who take antihypertensive drug treatment,[3,10], which is something that has remained unchanged for the last 40 years,[11].

A recent Cochrane review demonstrated that there are many categories of interventions that singly or in unison have the potential to reduce blood pressure in patients with hypertension,[12]. In this review educational interventions directed to patient and physician were examined; however, the focus of the review and protocol was not the educational intervention alone. Educational interventions either to health professionals or patients, did not appear to be associated with large net reductions in blood pressure but were recommended as an adjunct additional therapy along other types of interventions.

Due to the fact that there has been an increasing number of recent studies showing the importance of prevention in patients with hypertension,[13-15] this review will determine the current evidence of the effects of educational interventions to improve control of blood pressure in patients with hypertension, potentially updating the recommendation for clinical practice.

METHODS AND ANALYSIS

Criteria for considering studies for the review

Types of studies

We plan to include randomized clinical trials (RCTs) that have evaluated the effects of different models of educational interventions with the overall aim of improving blood pressure control in patients with hypertension, irrespective of language. The review will include RCTs where educational intervention used as the main or adjunct treatment was compared with no educational intervention or different types of educational strategies. We will exclude studies that use educational interventions not intended to improve blood pressure control.

Types of participants

We will include studies that participants have age over 18 years regardless of sex, ethnicity with a diagnosis of hypertension either treated or not treated with antihypertensive medications in a primary care, outpatient or community setting.)

Types of interventions

The intervention of interest will include all educational interventions strategies designed to improve the control of blood pressure in patients with hypertension (e.g. educational interventions direct to the patient; educational interventions direct to the health professional). Comparators will be any educational intervention used as the main or adjunct treatment to improve the control of blood pressure compared with either no educational intervention or different types of educational strategies aimed to improve blood pressure control.

Types of outcomes assessments

The primary outcome of this review will be any changes in mean systolic blood pressure (SBP) and/or mean diastolic blood pressure (DBP) in any care setting as well as number of patients under control of blood pressure (BP) or proportion of controlled BP defined by each randomized trial´s investigators. The secondary outcomes will be: number of hospitalizations during

treatment (e.g. increase of BP) or mortality from cardiovascular disease as an adverse events; the costs and cost effectiveness of interventions; the adherence to intervention (dropout rate) or adherence to medication and the outcome QOL will be measured using standardized generic questionnaire.

Search methods for identification of studies

Electronic searches

We will electronically search the following databases: MEDLINE, CINAHL, PEDro, ScienceDirect, WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. without any language restrictions. The search strategy will be developed after discussion among reviewers, according to the guidance of the Cochrane handbook[16].The MEDLINE search strategy will be translated into the other databases using the appropriate controlled vocabulary as applicable for each database.

Other sources

The bibliographies of all retrieved and relevant publications identified by the above strategies will be searched for further studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will attempt to contact researchers to obtain additional information when needed.

Data collection and analysis

Selection of studies

Before the selection of studies, a procedure for screening will be developed by discussion among all the reviewers. We will extract data into Review Manager 5.3,[17] and summarize details using a standard data extraction sheet. Two reviewers (CR and VR) will independently assess the

titles and abstracts of the studies identified from the search strategy against the inclusion criteria. Full versions of articles that appear to fulfil the inclusion criteria will be obtained for further assessment. Another review author (IL) will evaluate any discrepancies, if necessary, and will advise in case of disagreement. We will record all reasons for exclusion and we will exclude studies that not use the educational interventional to improve blood pressure control.

D*ata extraction and management*

Two review authors (CR and VR), working independently, will extract data and summarize details of trials using a standard data extraction sheet. According to methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[18] the extraction sheet includes information such as study design, methodology, participants, interventions, duration of treatment, outcomes, conclusions and potential sources of bias. We will resolve any discrepancies by discussion with a third review author (IL). If studies report more than one outcome time (e.g. 6 and 12 months), data concerning the longest follow up will be extracted. Where data are found to be missing, we will contact the corresponding author of studies to request the missing data or to clarify study details.

Assessment of risk of bias in included studies

For assessment of study quality and reporting bias two reviewers (CR and VR) will independently assess the risk of bias, using the Cochrane collaboration's tool for assessing risk of bias of the included trials,[19]which is composed of six domains of a trial, such as random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias. After assessing all the domains, the reviewers will summarize the assessments and categorize the included trials into three levels of bias: low,

unclear and high risk of bias and high risk of bias. We will resolve any disagreements by discussion with a third author (IL).

Measures of treatment effect

We will present the effects on blood pressure between interventions at follow-up (systolic and diastolic blood pressure) according to the educational intervention proposed in each study. We will present the outcome results for each trial with 95% confidence intervals (CI). Continuous outcomes (such as changes in systolic and diastolic blood pressure) will be expressed and calculated as mean difference (MD) and overall effect size between intervention and control groups. We will use Relative Risk (RR) or Odds Ratio (OR) depending on measurements indices in individual studies for other primary and secondary outcomes.

~~*Unit of analysis issues*~~

~~We will treat the number of individual participants as the unit of analysis in this review. We will include cluster-randomized trials in the analysis. For cluster-randomized trials, we will adjust results when the unit of analysis in the trial is presented as the total number of individual participants instead of number of clusters. Results will be adjusted using the mean cluster size and intracluster correlation coefficient,[20]. For meta-analysis, data will be combined to individually randomized trials using the generic inverse variance method as described on Chapter 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions,[20].~~

Dealing with missing data

In the case of missing data, we will contact the original investigators to request missing data whenever possible. If trial does not specify participant group number prior to dropout, we will present only complete case analysis for primary and secondary outcomes.

Assessment of heterogeneity

Whenever studies appear to be similar in terms of ~~level of~~ participants characteristics (established hypertensive, people with diabetes or other chronic disease),OK intervention type and duration and outcome type we will pool data using meta-analysis (using RevMan 5.3). We will test statistical heterogeneity using the Chi² test (considering a value of $P < 0.1$ to indicate heterogeneity) and estimate the amount of heterogeneity using the I^2 statistic,[20]. If I^2 is over 50% indicating a high level of heterogeneity data will not be pooled. In the absence of clinical and statistical heterogeneity we will use a fixed-effect model.

Assessment of reporting biases

We will present the overall risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting) in a risk of bias summary table per study. If sufficient studies (more than ten) are identified an attempt will be made to examine for publication bias using funnel plot as described in the Cochrane Handbook for Systematic Reviews of Interventions,[21]. If asymmetry is present we will explore possible causes including publication bias, poor methodological quality and true heterogeneity.

Data synthesis

We will present a narrative overview of the combined studies with meta-analysis of outcome data using the software Review Manager version 5.3 where appropriate.

We will include cluster-randomized trials in the analysis. For cluster-randomized trials, we will adjust results when the unit of analysis in the trial is presented as the total number of individual participants instead of number of clusters. Results will be adjusted using the mean cluster size and intracluster correlation coefficient,[22]. For meta-analysis, data will be combined to

individually randomized trials using the generic inverse-variance method as described on Chapter 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions,[22].

The decision to include studies in a meta-analysis will depend on the availability of treatment effect data and assessment of heterogeneity. Intervention effects will be calculated as relative risks with 95% confidence intervals for dichotomous data. For continuous data, we will calculate mean differences with 95% confidence intervals using a conservative fixed-effects meta-analysis model in the absence of significant heterogeneity ($p>0.05$ or $I^2 <50\%$). If there is high level of heterogeneity ($I^2 >50\%$) we will not pool data and we will perform sensitivity analysis of data.

Subgroup analysis

Subgroup analysis will be carried out according to the following variables: age and gender of participants, professional delivering intervention (e.g. nurse).

Sensitivity analysis

If sufficient trials are identified, we plan to conduct sensitivity analyses in order to explore the influence on the results of the following factors: assessor blinding (high risk of bias versus low risk of bias). We will restrict analyses to studies at low risk of bias.

Ethics and dissemination

This systematic review does not need ethical approval. Findings of this review will be disseminated via peer-reviewed journals and conference presentations.

DISCUSSION

This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in print. This

review also will benefit patients with hypertension as they will better understand and accept the therapy and change their behavior about the treatment.

Author´s Contributions: The search strategy will be developed and run by IL. Copies of studies will be obtained by CR and VR. Selection of the studies to include will be performed by CR and VR. Extraction data from studies and entering data into RevMan will be conducted by CR and VR. The analysis will be carried out by CR, VR and IL. Interpretation of the analysis will be carried out by all authors. The final review will be drafted by all authors. The protocol was revised, and the final version was approved by all authors.

Funding Statement: The work was supported by the National Council for Scientific and Technological Development (CNPQ): 457357/2013-4 CTSaúde/Edital MCTI/CNPQ/MS – SCTIE – DECIT nº 57/2013 PEC-REBRATS - Brazilian Network for Health Technology Assessment in Health: Comparative Effectiveness Research.

Competing interests: None.

References

1- The world health report 2002—reducing risks, promoting healthy life. World Health Organization(WHO):www.who.int/whr/2002/en/. Accessed: August 01, 2014.

2- Williams B. The Year in Hypertension. Journal of American College of Cardiology 2008;51(18):1803-17.

3- Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection,Evaluation, and Treatment of High Blood Pressure - The JCN 7 Report. The Journal of American Medical Association 2003;289(19):2560-72.

4- Lopez AD, Mathers CD, Ezzati M et al. Measuring the Global Burden of Disease and Risk Factors, 1990- 2001. Global Burden of Disease and Risk Factors 2006: Available at: http://www.dcp2.org/pubs/GBD. Accessed September 18, 2012.

5- Pereira M, Lunet N, Azevedo A et al. Diferences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. Journal of Hypertension 2009;27(5):963-975.

6- Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.

7- Magadza C, Radloff SE, Srinivas SC. The effect of an educational intervention on patients' knowledge about hypertension, beliefs about medicines, and adherence. Research in Social and Administrative Pharmacy 2009;5:363-375.

8- Saounatsou M, Patsi O, Fasoi G et al. The Influence of the Hypertensive Patient´s in Compliance with their medication. Public Health Nursing 2001;18(6):436-442.

9- McKinstry B, Hanley J, Heaney D et al. Impact on hypertension control of a patient-held guideline: a randomised controlled trial. British Journal of General Practice 2006;56:842-847.

10- Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? Journal of Hypertension Supplement 2002;20:1251-3.

11- Wilber J, Barrow J. Hypertension: a community problem. The American Journal of Medicine 1972; 52: 653-63.

12- Glynn LG, Murphy AW, Smith SM et al. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005182 DOI: 10.1002/14651858.CD005182.pub4.

13- Aung MN, Yuasa M, Moolphate S et al. Reducing salt intake for prevention of cardiovascular diseases in high-risk patients by advanced health education intervention (RESIP-

CVD study), Northern Thailand: study protocol for a cluster randomized trial. Trial 2012;13:158. [10.1186/1745-6215-13-158]

14- Ng N, Carlberg B, Weinehall L, Norberg M. Trends of blood pressure levels and management in Vasterbotten County,Sweden, during 1990-2010. Glob Health Action 2012;5:18195.

15- Ribeiro AG, Ribeiro SMR, Dias CMGC, Ribeiro AQ, Castro FAF, Suarez-Varela MM, Cotta RMM. Non-pharmacological treatment of hypertension in primary health care: A comparative clinical trial of two education strategies in health and nutrition. BMC Public Health 2011;11:637.

16- Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17- Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

18- Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

19- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

20- Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT. Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

21- Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

22- Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE **(Federal University of Rio Grande do Norte)**
CENTRO DE CIÊNCIAS DA SÁUDE **(Health Science Center)**
DEPARTAMENTO DE FISIOTERAPIA **(Department of Physical Therapy)**

Guilherme Augusto de Freitas Fregonezi, PT, PhD
Universidade Federal do Rio Grande do Norte
Departamento de Fisioterapia
Campus Universitário Lagoa Nova, CEP 59072-970
Natal, RN, Brazil
Phone: +55 (84) 3342-2001 Fax: (84) 3342-2002
fregonezi.guilherme@gmail.com

September 05, 2014

Dear Editor

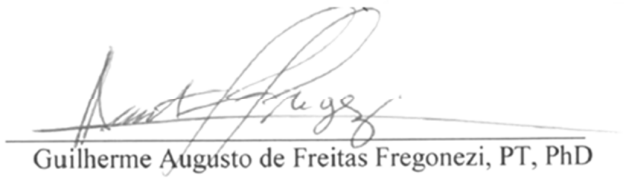
Please consider the manuscript "EDUCATIONAL INTERVENTION FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW PROTOCOL" for publication in *BMJ Open* as a study protocol. This protocol describes all the methodology to develop a systematic review that will evaluate the current evidence of the effects of educational interventions on the control of blood pressure on patients with hypertension.

All authors have contributed to the present work and have also read and approved the submission of the manuscript to this journal. This study protocol has not been published or is under consideration for publication elsewhere and the authors have no conflict of interest to report.

We appreciate your consideration and we hope we will be able to contribute to the journal.

Thank you.

Sincerely,



Guilherme Augusto de Freitas Fregonezi, PT, PhD

BMJ Open

Educational Interventions for improving control of blood pressure in patients with hypertension: A Systematic Review Protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006583.R2
Article Type:	Protocol
Date Submitted by the Author:	28-Nov-2014
Complete List of Authors:	Ribeiro, Cibele; Federal University of Rio Grande do Norte, Department of Physical Therapy Resqueti, Vanessa; Federal University of Rio Grande do Norte, Department of Physical Therapy Lima, Íllia; Federal University of Rio Grande do Norte, Department of Physical Therapy Dias, Fernando; Federal University of Parana, Department of Physiology Glynn, Liam; National University of Ireland, Department of General Practice Fregonezi, Guilherme; Federal University of Rio Grande do Norte, Department of Physical Therapy
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Hypertension < CARDIOLOGY, EDUCATION & TRAINING (see Medical Education & Training), Rehabilitation medicine < INTERNAL MEDICINE, PREVENTIVE MEDICINE

EDUCATIONAL INTERVENTIONS FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW PROTOCOL

Corresponding Author: Guilherme Augusto de Freitas Fregonezi; Universidade Federal do Rio Grande do Norte – Departamento de Fisioterapia, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil; telephone number: +55 84 3342 2001; email: fregonezi.guilherme@gmail.com

Authors: Cibele D Ribeiro; Vanessa R Resqueti; Íllia Lima; Fernando A L Dias; Liam Glynn; Guilherme A F Fregonezi.

Authors affiliations:

1-Department of Physical Therapy – Federal University of Rio Grande do Norte, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil (Authors: Cibele; Vanessa; Íllia; Guilherme).

2-Department of Physiology – Federal University of Paraná, Centro Politécnico, Jardim das Américas, Caixa Postal 19031, 81531-980, Curitiba – Paraná – Brazil (Authors: Fernando)

3-College of Medicine – Nursing and Health Sciences – National University of Ireland Galway, University Road, Galway – Ireland (Authors: Liam).

Running Title: Educational intervention in hypertension - systematic review.

Key words: hypertension, blood pressure, educational interventions, randomized controlled trial, systematic review

Word Count: 2216

Abstract

Introduction: The aim of this review is to evaluate the effectiveness of educational interventions on improving the control of blood pressure in patients with hypertension.

Methods: Randomized controlled trials including patients aged over eighteen years old regardless of sex, ethnicity with a diagnosis of hypertension (either treated or not treated with antihypertensive medications) will be assessed in our analysis. We will electronically search four databases: MEDLINE, CINAHL, PEDro, ScienceDirect. There will be no language restrictions in the search for studies. The data will be extracted independently by two authors using predefined criteria. Disagreements will be resolved between the authors. The risk of bias will be assessed using the Cochrane risk of bias tool. After searching and screening of the studies, we will run a meta-analysis of the included randomised controlled trials. We will summarise the results as risk ratio for dichotomous data and mean differences for continuous data.

Ethics and dissemination: The protocol for the systematic review has been registered in PROSPERO. The review will be published in a journal. The findings from the review will also be disseminated electronically and conferences presentations.

Registration: Ribeiro C, Resqueti V, Lima I, Dias F, Glynn L, Fregonezi G. Educational interventions for improving control of blood pressure in patients with hypertension. PROSPERO: International prospective register of systematic reviews. 2014: CRD4201401071 Available from: http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=10171

Strenghts and limitations of this study:

- The results of this systematic review will help clinicians in making decisions in clinical practice, and help patients to better understand their conditions and also can heighten awareness about disease progression and complications.

INTRODUCTION

Description of the condition

Hypertension is a major health problem worldwide and is estimated to cause more than 13% of deaths annually,[1]. It is a multifactorial clinical condition characterized by high and sustained levels of blood pressure,[2]. It is one of the most important public health problems in the world and an important modifiable risk factor for the development of cardiovascular diseases. Adoption of healthy lifestyles by all individuals is critical for the prevention of high blood pressure and an indispensable part of the management of those with hypertension,[3]. Uncontrolled hypertension is associated with high risk for development of heart disease, stroke, chronic kidney disease, retinopathy, peripheral vascular disease.

A recent epidemiological worldwide study estimated that the high blood pressure causes approximately 7.6 million premature deaths (54% for stroke and 47% for ischaemic heart disease),[4]. A recent systematic review reporting data from studies in 35 different countries between the years 2003 and 2008 demonstrated an overall prevalence of 37.8% for men and 32.1% for women,[5].

Due to the fact that the prevalence of hypertension increases with age,[6] the management of hypertension and the prevention and treatment of major complications related to hypertension will continue to be a global challenge for health care professionals.

Description of the intervention

Hypertension is a condition almost entirely managed by the primary care team by a variety of health professionals such as physicians, nurses, pharmacists and other allied health care professionals such as physiotherapists that frequently work in cardiac rehabilitation. All professionals can potentially play an important role in lowering blood pressure. It is important

that patients understand the benefits of blood pressure lowering which include a reduction in many complications such as stroke (35-40%), heart attack (20-25%) and heart failure (over 50%)[3]. The majority of patients will require a combination of antihypertensive drugs to reach target blood pressure.

A previous study demonstrated that educational interventions increased participants' levels of knowledge about hypertension and had a positive influence on their beliefs about medicines,[7]. Educational interventions can also create opportunities for patients to better understand their conditions and the role of therapies and also can heighten awareness about disease progression and complications. Through patient education, misconceptions that patients have about their therapy can be clarified. This can influence adherence to therapy,[8] and therefore potentially may lead to improve blood pressure control.

How the intervention might work

Different health professionals have become more involved in delivering interventions to the patients with the objective of preventing complications caused by high blood pressure. Patients expectations have a significant effect on the treatment they get from their doctor or any other health professional involved,[9]. Many previous trials in blood pressure control have used educational interventions on patients, physicians or both in an attempt to improve blood pressure control.

Educational interventions can positively modify patients' beliefs which in turn can lead to a change in patient behavior such as improvement in adherence to a therapy proposed by the health care professional,[8] and a possible effect on variables related to the disease such as blood

pressure levels. This may also affect in long term the progression of the disease and the prevalence of associated conditions related to hypertension such as heart attacks and stroke.

Why is important to do this review

Due to the high morbidity and mortality caused by hypertension and the global scale of this important public health issue, it is important to continue to investigate interventions that can improve blood pressure control. It is striking that blood pressure goals continue to be a achieved in only 25-40% of the patients who take antihypertensive drug treatment,[3,10], which is something that has remained unchanged for the last 40 years,[11].

A recent Cochrane review demonstrated that there are many categories of interventions that singly or in unison have the potential to reduce blood pressure in patients with hypertension,[12]. In this review educational interventions directed to patient and physician were examined; however, the focus of the review and protocol was not the educational intervention alone. Educational interventions either to health professionals or patients, did not appear to be associated with large net reductions in blood pressure but were recommended as an adjunct additional therapy along other types of interventions.

Due to the fact that there has been an increasing number of recent studies showing the importance of prevention in patients with hypertension,[13-15] this review will determine the current evidence of the effects of educational interventions to improve control of blood pressure in patients with hypertension, potentially updating the recommendation for clinical practice.

METHODS AND ANALYSIS

Criteria for considering studies for the review

Types of studies

We plan to include randomized clinical trials (RCTs) that have evaluated the effects of different models of educational interventions with the overall aim of improving blood pressure control in patients with hypertension, irrespective of language. The review will include RCTs where educational interventions used as the main or adjunct treatment was compared with no educational interventions or different types of educational strategies. We will exclude studies that use educational interventions not intended to improve blood pressure control.

Types of participants

We will include studies that participants have age over 18 years regardless of sex, ethnicity with a diagnosis of hypertension either treated or not treated with antihypertensive medications in a primary care, outpatient or community setting.)

Types of interventions

The intervention of interest will include all educational interventions strategies designed to improve the control of blood pressure in patients with hypertension (e.g. educational interventions direct to the patient; educational interventions direct to the health professional). Comparators will be any educational intervention used as the main or adjunct treatment to improve the control of blood pressure compared with either no educational interventions or different types of educational strategies aimed to improve blood pressure control.

Types of outcomes assessments

The primary outcome of this review will be any changes in mean systolic blood pressure (SBP) and/or mean diastolic blood pressure (DBP) in any care setting as well as number of patients under control of blood pressure (BP) or proportion of controlled BP defined by each randomized

trial´s investigators. The secondary outcomes will be: number of hospitalizations during treatment (e.g. increase of BP) or mortality from cardiovascular disease as an adverse events; the costs and cost effectiveness of interventions; the adherence to intervention (dropout rate) or adherence to medication and the outcome QOL will be measured using standardized generic questionnaire.

Search methods for identification of studies

Electronic searches

We will electronically search the following databases: MEDLINE, CINAHL, PEDro, ScienceDirect, without any language restrictions (in case of studies in another language, other than English, we will contact companies specialized in translation). The search strategy will be developed after discussion among reviewers, according to the guidance of the Cochrane handbook[16].The MEDLINE search strategy will be translated into the other databases using the appropriate controlled vocabulary as applicable for each database.

Other sources

The bibliographies of all retrieved and relevant publications identified by the above strategies will be searched for further studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will attempt to contact researchers to obtain additional information when needed.

Data collection and analysis

Selection of studies

Before the selection of studies, a procedure for screening will be developed by discussion among all the reviewers. We will extract data into Review Manager 5.3,[17] and summarize details

using a standard data extraction sheet. Two reviewers (CR and VR) will independently assess the titles and abstracts of the studies identified from the search strategy against the inclusion criteria. Full versions of articles that appear to fulfil the inclusion criteria will be obtained for further assessment. Another review author (IL) will evaluate any discrepancies, if necessary, and will advise in case of disagreement. We will record all reasons for exclusion and we will exclude studies that not use the educational interventional to improve blood pressure control.

D*ata extraction and management*

Two review authors (CR and VR), working independently, will extract data and summarize details of trials using a standard data extraction sheet. According to methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[18] the extraction sheet includes information such as study design, methodology, participants, interventions, duration of treatment, outcomes, conclusions and potential sources of bias. We will resolve any discrepancies by discussion with a third review author (IL). If studies report more than one outcome time (e.g. 6 and 12 months), data concerning the longest follow up will be extracted. Where data are found to be missing, we will contact the corresponding author of studies to request the missing data or to clarify study details.

Assessment of risk of bias in included studies

For assessment of study quality and reporting bias two reviewers (CR and VR) will independently assess the risk of bias, using the Cochrane collaboration's tool for assessing risk of bias of the included trials,[19] which is composed of six domains of a trial, such as random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias. After assessing all the domains, the reviewers

will summarize the assessments and categorize the included trials into three levels of bias: low, unclear and high risk of bias and high risk of bias. We will resolve any disagreements by discussion with a third author (IL).

Measures of treatment effect

We will present the effects on blood pressure between interventions at follow-up (systolic and diastolic blood pressure) according to the educational interventions proposed in each study. We will present the outcome results for each trial with 95% confidence intervals (CI). Continuous outcomes (such as changes in systolic and diastolic blood pressure) will be expressed and calculated as mean difference (MD) and overall effect size between intervention and control groups. We will use Relative Risk (RR) or Odds Ratio (OR) depending on measurements indices in individual studies for other primary and secondary outcomes.

Dealing with missing data

In the case of missing data, we will contact the original investigators to request missing data whenever possible. If trial does not specify participant group number prior to dropout, we will present only complete case analysis for primary and secondary outcomes.

Assessment of heterogeneity

Whenever studies appear to be similar in terms of participants characteristics (established hypertensive, people with diabetes or other chronic disease), intervention type and duration and outcome type we will pool data using meta-analysis (using RevMan 5.3). We will test statistical heterogeneity using the Chi² test (considering a value of $P < 0.1$ to indicate heterogeneity) and estimate the amount of heterogeneity using the I^2 statistic,[20]. If I^2 is over 50% indicating a high

level of heterogeneity data will not be pooled. In the absence of clinical and statistical heterogeneity we will use a fixed-effect model.

Assessment of reporting biases

We will present the overall risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting) in a risk of bias summary table per study. If sufficient studies (more than ten) are identified an attempt will be made to examine for publication bias using funnel plot as described in the Cochrane Handbook for Systematic Reviews of Interventions,[21]. If asymmetry is present we will explore possible causes including publication bias, poor methodological quality and true heterogeneity.

Data synthesis

We will present a narrative overview of the combined studies with meta-analysis of outcome data using the software Review Manager version 5.3 where appropriate.

We will include cluster-randomized trials in the analysis. For cluster-randomized trials, we will adjust results when the unit of analysis in the trial is presented as the total number of individual participants instead of number of clusters. Results will be adjusted using the mean cluster size and intracluster correlation coefficient,[22]. For meta-analysis, data will be combined to individually randomized trials using the generic inverse-variance method as described on Chapter 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions,[22].

The decision to include studies in a meta-analysis will depend on the availability of treatment effect data and assessment of heterogeneity. Intervention effects will be calculated as relative risks with 95% confidence intervals for dichotomous data. For continuous data, we will calculate mean differences with 95% confidence intervals using a conservative fixed-effects meta-analysis

model in the absence of significant heterogeneity ($p>0.05$ or $I^2 <50\%$). If there is high level of heterogeneity ($I^2 >50\%$) we will not pool data and we will perform sensitivity analysis of data.

Subgroup analysis

Subgroup analysis will be carried out according to the following variables: age and gender of participants, professional delivering intervention (e.g. nurse).

Sensitivity analysis

If sufficient trials are identified, we plan to conduct sensitivity analyses in order to explore the influence on the results of the following factors: assessor blinding (high risk of bias versus low risk of bias). We will restrict analyses to studies at low risk of bias.

Ethics and dissemination

This systematic review does not need ethical approval. Findings of this review will be disseminated via peer-reviewed journals and conference presentations.

DISCUSSION

This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in print. This review also will benefit patients with hypertension as they will better understand and accept the therapy and change their behavior about the treatment.

Author´s Contributions: The search strategy will be developed and run by IL. Copies of studies will be obtained by CR and VR. Selection of the studies to include will be performed by CR and VR. Extraction data from studies and entering data into RevMan will be conducted by CR and VR. The analysis will be carried out by CR, VR and IL. Interpretation of the analysis will be carried out by all authors. The final review will be drafted by all authors. The protocol was revised, and the final version was approved by all authors.

Funding Statement: The work was supported by the National Council for Scientific and Technological Development (CNPQ): 457357/2013-4 CTSaúde/Edital MCTI/CNPQ/MS – SCTIE – DECIT nº 57/2013 PEC-REBRATS - Brazilian Network for Health Technology Assessment in Health: Comparative Effectiveness Research.

Competing interests: None.

References

1- The world health report 2002—reducing risks, promoting healthy life. World Health Organization(WHO):www.who.int/whr/2002/en/. Accessed: August 01, 2014.

2- Williams B. The Year in Hypertension. Journal of American College of Cardiology 2008;51(18):1803-17.

3- Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection,Evaluation, and Treatment of High Blood Pressure - The JCN 7 Report. The Journal of American Medical Association 2003;289(19):2560-72.

4- Lopez AD, Mathers CD, Ezzati M et al. Measuring the Global Burden of Disease and Risk Factors, 1990- 2001. Global Burden of Disease and Risk Factors 2006: Available at: http://www.dcp2.org/pubs/GBD. Accessed September 18, 2012.

5- Pereira M, Lunet N, Azevedo A et al. Diferences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. Journal of Hypertension 2009;27(5):963-975.

6- Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.

7- Magadza C, Radloff SE, Srinivas SC. The effect of an educational intervention on patients' knowledge about hypertension, beliefs about medicines, and adherence. Research in Social and Administrative Pharmacy 2009;5:363-375.

8- Saounatsou M, Patsi O, Fasoi G et al. The Influence of the Hypertensive Patient´s in Compliance with their medication. Public Health Nursing 2001;18(6):436-442.

9- McKinstry B, Hanley J, Heaney D et al. Impact on hypertension control of a patient-held guideline: a randomised controlled trial. British Journal of General Practice 2006;56:842-847.

10- Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? Journal of Hypertension Supplement 2002;20:1251-3.

11- Wilber J, Barrow J. Hypertension: a community problem. The American Journal of Medicine 1972; 52: 653-63.

12- Glynn LG, Murphy AW, Smith SM et al. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005182 DOI: 10.1002/14651858.CD005182.pub4.

13- Aung MN, Yuasa M, Moolphate S et al. Reducing salt intake for prevention of cardiovascular diseases in high-risk patients by advanced health education intervention (RESIP-

CVD study), Northern Thailand: study protocol for a cluster randomized trial. Trial 2012;13:158. [10.1186/1745-6215-13-158]

14- Ng N, Carlberg B, Weinehall L, Norberg M. Trends of blood pressure levels and management in Vasterbotten County,Sweden, during 1990-2010. Glob Health Action 2012;5:18195.

15- Ribeiro AG, Ribeiro SMR, Dias CMGC, Ribeiro AQ, Castro FAF, Suarez-Varela MM, Cotta RMM. Non-pharmacological treatment of hypertension in primary health care: A comparative clinical trial of two education strategies in health and nutrition. BMC Public Health 2011;11:637.

16- Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17- Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

18- Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

19- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

20- Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT. Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

21- Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

22- Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

EDUCATIONAL INTERVENTIONS FOR IMPROVING CONTROL OF BLOOD PRESSURE IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW PROTOCOL

Corresponding Author: Guilherme Augusto de Freitas Fregonezi; Universidade Federal do Rio Grande do Norte – Departamento de Fisioterapia, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil; telephone number: +55 84 3342 2001; email: fregonezi.guilherme@gmail.com

Authors: Cibele D Ribeiro; Vanessa R Resqueti; Íllia Lima; Fernando A L Dias; Liam Glynn; Guilherme A F Fregonezi.

Authors affiliations:

1-Department of Physical Therapy – Federal University of Rio Grande do Norte, Av: Senador Salgado Filho, 3000, Lagoa Nova, 59072-970, Natal – Rio Grande do Norte – Brazil (Authors: Cibele; Vanessa; Íllia; Guilherme).

2-Department of Physiology – Federal University of Paraná, Centro Politécnico, Jardim das Américas, Caixa Postal 19031, 81531-980, Curitiba – Paraná – Brazil (Authors: Fernando)

3-College of Medicine – Nursing and Health Sciences – National University of Ireland Galway, University Road, Galway – Ireland (Authors: Liam).

Running Title: Educational intervention in hypertension - systematic review.

Key words: hypertension, blood pressure, educational interventions, randomized controlled trial, systematic review

Word Count: 2216

Abstract

Introduction: The aim of this review is to evaluate the effectiveness of educational interventions on improving the control of blood pressure in patients with hypertension.

Methods: Randomized controlled trials including patients aged over eighteen years old regardless of sex, ethnicity with a diagnosis of hypertension (either treated or not treated with antihypertensive medications) will be assessed in our analysis. We will electronically search four databases: MEDLINE, CINAHL, PEDro, ScienceDirect. There will be no language restrictions in the search for studies. The data will be extracted independently by two authors using predefined criteria. Disagreements will be resolved between the authors. The risk of bias will be assessed using the Cochrane risk of bias tool. After searching and screening of the studies, we will run a meta-analysis of the included randomised controlled trials. We will summarise the results as risk ratio for dichotomous data and mean differences for continuous data.

Ethics and dissemination: The protocol for the systematic review has been registered in PROSPERO. The review will be published in a journal. The findings from the review will also be disseminated electronically and conferences presentations.

~~**Trial registration number:**~~ **Registration:** Ribeiro C, Resqueti V, Lima I, Dias F, Glynn L, Fregonezi G. Educational interventions for improving control of blood pressure in patients with hypertension. PROSPERO: International prospective register of systematic reviews. 2014: CRD4201401071 Available from: http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=10171

Strenghts and limitations of this study:

- The results of this systematic review will help clinicians in making decisions in clinical practice, and help patients to better understand their conditions and also can heighten awareness about disease progression and complications.

INTRODUCTION

Description of the condition

Hypertension is a major health problem worldwide and is estimated to cause more than 13% of deaths annually,[1]. It is a multifactorial clinical condition characterized by high and sustained levels of blood pressure,[2]. It is one of the most important public health problems in the world and an important modifiable risk factor for the development of cardiovascular diseases. Adoption of healthy lifestyles by all individuals is critical for the prevention of high blood pressure and an indispensable part of the management of those with hypertension,[3]. Uncontrolled hypertension is associated with high risk for development of heart disease, stroke, chronic kidney disease, retinopathy, peripheral vascular disease.

A recent epidemiological worldwide study estimated that the high blood pressure causes approximately 7.6 million premature deaths (54% for stroke and 47% for ischaemic heart disease),[4]. A recent systematic review reporting data from studies in 35 different countries between the years 2003 and 2008 demonstrated an overall prevalence of 37.8% for men and 32.1% for women,[5].

Due to the fact that the prevalence of hypertension increases with age,[6] the management of hypertension and the prevention and treatment of major complications related to hypertension will continue to be a global challenge for health care professionals.

Description of the intervention

Hypertension is a condition almost entirely managed by the primary care team by a variety of health professionals such as physicians, nurses, pharmacists and other allied health care professionals such as physiotherapists that frequently work in cardiac rehabilitation. All

professionals can potentially play an important role in lowering blood pressure. It is important that patients understand the benefits of blood pressure lowering which include a reduction in many complications such as stroke (35-40%), heart attack (20-25%) and heart failure (over 50%)[3]. The majority of patients will require a combination of antihypertensive drugs to reach target blood pressure.

A previous study demonstrated that educational interventions increased participants' levels of knowledge about hypertension and had a positive influence on their beliefs about medicines,[7]. Educational interventions can also create opportunities for patients to better understand their conditions and the role of therapies and also can heighten awareness about disease progression and complications. Through patient education, misconceptions that patients have about their therapy can be clarified. This can influence adherence to therapy,[8] and therefore potentially may lead to improve blood pressure control.

How the intervention might work

Different health professionals have become more involved in delivering interventions to the patients with the objective of preventing complications caused by high blood pressure. Patients expectations have a significant effect on the treatment they get from their doctor or any other health professional involved,[9]. Many previous trials in blood pressure control have used educational interventions on patients, physicians or both in an attempt to improve blood pressure control.

Educational interventions can positively modify patients' beliefs which in turn can lead to a change in patient behavior such as improvement in adherence to a therapy proposed by the health care professional,[8] and a possible effect on variables related to the disease such as blood

pressure levels. This may also affect in long term the progression of the disease and the prevalence of associated conditions related to hypertension such as heart attacks and stroke.

Why is important to do this review

Due to the high morbidity and mortality caused by hypertension and the global scale of this important public health issue, it is important to continue to investigate interventions that can improve blood pressure control. It is striking that blood pressure goals continue to be a achieved in only 25-40% of the patients who take antihypertensive drug treatment,[3,10], which is something that has remained unchanged for the last 40 years,[11].

A recent Cochrane review demonstrated that there are many categories of interventions that singly or in unison have the potential to reduce blood pressure in patients with hypertension,[12]. In this review educational interventions directed to patient and physician were examined; however, the focus of the review and protocol was not the educational intervention alone. Educational interventions either to health professionals or patients, did not appear to be associated with large net reductions in blood pressure but were recommended as an adjunct additional therapy along other types of interventions.

Due to the fact that there has been an increasing number of recent studies showing the importance of prevention in patients with hypertension,[13-15] this review will determine the current evidence of the effects of educational interventions to improve control of blood pressure in patients with hypertension, potentially updating the recommendation for clinical practice.

METHODS AND ANALYSIS

Criteria for considering studies for the review

Types of studies

We plan to include randomized clinical trials (RCTs) that have evaluated the effects of different models of educational interventions with the overall aim of improving blood pressure control in patients with hypertension, irrespective of language. The review will include RCTs where educational interventions used as the main or adjunct treatment was compared with no educational interventions or different types of educational strategies. We will exclude studies that use educational interventions not intended to improve blood pressure control.

Types of participants

We will include studies that participants have age over 18 years regardless of sex, ethnicity with a diagnosis of hypertension either treated or not treated with antihypertensive medications in a primary care, outpatient or community setting.)

Types of interventions

The intervention of interest will include all educational interventions strategies designed to improve the control of blood pressure in patients with hypertension (e.g. educational interventions direct to the patient; educational interventions direct to the health professional). Comparators will be any educational intervention used as the main or adjunct treatment to improve the control of blood pressure compared with either no educational interventions or different types of educational strategies aimed to improve blood pressure control.

Types of outcomes assessments

The primary outcome of this review will be any changes in mean systolic blood pressure (SBP) and/or mean diastolic blood pressure (DBP) in any care setting as well as number of patients under control of blood pressure (BP) or proportion of controlled BP defined by each randomized

trial´s investigators. The secondary outcomes will be: number of hospitalizations during treatment (e.g. increase of BP) or mortality from cardiovascular disease as an adverse events; the costs and cost effectiveness of interventions; the adherence to intervention (dropout rate) or adherence to medication and the outcome QOL will be measured using standardized generic questionnaire.

Search methods for identification of studies

Electronic searches

We will electronically search the following databases: MEDLINE, CINAHL, PEDro, ScienceDirect, ~~WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov.~~ without any language restrictions (in case of studies in another language, other than English, we will contact companies specialized in translation). The search strategy will be developed after discussion among reviewers, according to the guidance of the Cochrane handbook[16].The MEDLINE search strategy will be translated into the other databases using the appropriate controlled vocabulary as applicable for each database.

Other sources

The bibliographies of all retrieved and relevant publications identified by the above strategies will be searched for further studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will attempt to contact researchers to obtain additional information when needed.

Data collection and analysis

Selection of studies

Before the selection of studies, a procedure for screening will be developed by discussion among all the reviewers. We will extract data into Review Manager 5.3,[17] and summarize details using a standard data extraction sheet. Two reviewers (CR and VR) will independently assess the titles and abstracts of the studies identified from the search strategy against the inclusion criteria. Full versions of articles that appear to fulfil the inclusion criteria will be obtained for further assessment. Another review author (IL) will evaluate any discrepancies, if necessary, and will advise in case of disagreement. We will record all reasons for exclusion and we will exclude studies that not use the educational interventional to improve blood pressure control.

D*ata extraction and management*

Two review authors (CR and VR), working independently, will extract data and summarize details of trials using a standard data extraction sheet. According to methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[18] the extraction sheet includes information such as study design, methodology, participants, interventions, duration of treatment, outcomes, conclusions and potential sources of bias. We will resolve any discrepancies by discussion with a third review author (IL). If studies report more than one outcome time (e.g. 6 and 12 months), data concerning the longest follow up will be extracted. Where data are found to be missing, we will contact the corresponding author of studies to request the missing data or to clarify study details.

Assessment of risk of bias in included studies

For assessment of study quality and reporting bias two reviewers (CR and VR) will independently assess the risk of bias, using the Cochrane collaboration's tool for assessing risk of bias of the included trials,[19] which is composed of six domains of a trial, such as random sequence generation (selection bias), allocation concealment (selection bias), blinding

(performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias. After assessing all the domains, the reviewers will summarize the assessments and categorize the included trials into three levels of bias: low, unclear and high risk of bias and high risk of bias. We will resolve any disagreements by discussion with a third author (IL).

Measures of treatment effect

We will present the effects on blood pressure between interventions at follow-up (systolic and diastolic blood pressure) according to the educational interventions proposed in each study. We will present the outcome results for each trial with 95% confidence intervals (CI). Continuous outcomes (such as changes in systolic and diastolic blood pressure) will be expressed and calculated as mean difference (MD) and overall effect size between intervention and control groups. We will use Relative Risk (RR) or Odds Ratio (OR) depending on measurements indices in individual studies for other primary and secondary outcomes.

Dealing with missing data

In the case of missing data, we will contact the original investigators to request missing data whenever possible. If trial does not specify participant group number prior to dropout, we will present only complete case analysis for primary and secondary outcomes.

Assessment of heterogeneity

Whenever studies appear to be similar in terms of participants characteristics (established hypertensive, people with diabetes or other chronic disease), intervention type and duration and outcome type we will pool data using meta-analysis (using RevMan 5.3). We will test statistical heterogeneity using the Chi² test (considering a value of $P < 0.1$ to indicate heterogeneity) and

estimate the amount of heterogeneity using the I^2 statistic,[20]. If I^2 is over 50% indicating a high level of heterogeneity data will not be pooled. In the absence of clinical and statistical heterogeneity we will use a fixed-effect model.

Assessment of reporting biases

We will present the overall risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting) in a risk of bias summary table per study. If sufficient studies (more than ten) are identified an attempt will be made to examine for publication bias using funnel plot as described in the Cochrane Handbook for Systematic Reviews of Interventions,[21]. If asymmetry is present we will explore possible causes including publication bias, poor methodological quality and true heterogeneity.

Data synthesis

We will present a narrative overview of the combined studies with meta-analysis of outcome data using the software Review Manager version 5.3 where appropriate.

We will include cluster-randomized trials in the analysis. For cluster-randomized trials, we will adjust results when the unit of analysis in the trial is presented as the total number of individual participants instead of number of clusters. Results will be adjusted using the mean cluster size and intracluster correlation coefficient,[22]. For meta-analysis, data will be combined to individually randomized trials using the generic inverse-variance method as described on Chapter 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions,[22].

The decision to include studies in a meta-analysis will depend on the availability of treatment effect data and assessment of heterogeneity. Intervention effects will be calculated as relative risks with 95% confidence intervals for dichotomous data. For continuous data, we will calculate

mean differences with 95% confidence intervals using a conservative fixed-effects meta-analysis model in the absence of significant heterogeneity ($p>0.05$ or $I^2 <50\%$). If there is high level of heterogeneity ($I^2 >50\%$) we will not pool data and we will perform sensitivity analysis of data.

Subgroup analysis

Subgroup analysis will be carried out according to the following variables: age and gender of participants, professional delivering intervention (e.g. nurse).

Sensitivity analysis

If sufficient trials are identified, we plan to conduct sensitivity analyses in order to explore the influence on the results of the following factors: assessor blinding (high risk of bias versus low risk of bias). We will restrict analyses to studies at low risk of bias.

Ethics and dissemination

This systematic review does not need ethical approval. Findings of this review will be disseminated via peer-reviewed journals and conference presentations.

DISCUSSION

This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in print. This review also will benefit patients with hypertension as they will better understand and accept the therapy and change their behavior about the treatment.

Author´s Contributions: The search strategy will be developed and run by IL. Copies of studies will be obtained by CR and VR. Selection of the studies to include will be performed by CR and VR. Extraction data from studies and entering data into RevMan will be conducted by CR and VR. The analysis will be carried out by CR, VR and IL. Interpretation of the analysis will be carried out by all authors. The final review will be drafted by all authors. The protocol was revised, and the final version was approved by all authors.

Funding Statement: The work was supported by the National Council for Scientific and Technological Development (CNPQ): 457357/2013-4 CTSaúde/Edital MCTI/CNPQ/MS – SCTIE – DECIT nº 57/2013 PEC-REBRATS - Brazilian Network for Health Technology Assessment in Health: Comparative Effectiveness Research.

Competing interests: None.

References

1- The world health report 2002—reducing risks, promoting healthy life. World Health Organization(WHO):www.who.int/whr/2002/en/. Accessed: August 01, 2014.

2- Williams B. The Year in Hypertension. Journal of American College of Cardiology 2008;51(18):1803-17.

3- Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection,Evaluation, and Treatment of High Blood Pressure - The JCN 7 Report. The Journal of American Medical Association 2003;289(19):2560-72.

4- Lopez AD, Mathers CD, Ezzati M et al. Measuring the Global Burden of Disease and Risk Factors, 1990- 2001. Global Burden of Disease and Risk Factors 2006: Available at: http://www.dcp2.org/pubs/GBD. Accessed September 18, 2012.

5- Pereira M, Lunet N, Azevedo A et al. Diferences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. Journal of Hypertension 2009;27(5):963-975.

6- Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.

7- Magadza C, Radloff SE, Srinivas SC. The effect of an educational intervention on patients' knowledge about hypertension, beliefs about medicines, and adherence. Research in Social and Administrative Pharmacy 2009;5:363-375.

8- Saounatsou M, Patsi O, Fasoi G et al. The Influence of the Hypertensive Patient´s in Compliance with their medication. Public Health Nursing 2001;18(6):436-442.

9- McKinstry B, Hanley J, Heaney D et al. Impact on hypertension control of a patient-held guideline: a randomised controlled trial. British Journal of General Practice 2006;56:842-847.

10- Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? Journal of Hypertension Supplement 2002;20:1251-3.

11- Wilber J, Barrow J. Hypertension: a community problem. The American Journal of Medicine 1972; 52: 653-63.

12- Glynn LG, Murphy AW, Smith SM et al. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005182 DOI: 10.1002/14651858.CD005182.pub4.

13- Aung MN, Yuasa M, Moolphate S et al. Reducing salt intake for prevention of cardiovascular diseases in high-risk patients by advanced health education intervention (RESIP-

CVD study), Northern Thailand: study protocol for a cluster randomized trial. Trial 2012;13:158. [10.1186/1745-6215-13-158]

14- Ng N, Carlberg B, Weinehall L, Norberg M. Trends of blood pressure levels and management in Vasterbotten County,Sweden, during 1990-2010. Glob Health Action 2012;5:18195.

15- Ribeiro AG, Ribeiro SMR, Dias CMGC, Ribeiro AQ, Castro FAF, Suarez-Varela MM, Cotta RMM. Non-pharmacological treatment of hypertension in primary health care: A comparative clinical trial of two education strategies in health and nutrition. BMC Public Health 2011;11:637.

16- Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17- Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

18- Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

19- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

20- Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT. Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

21- Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

22- Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org