Contemporary Clinical Trials 126 (2023) 107062

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Stepwise treatment of uncontrolled HyperTensioN (Stepwise-HTN): Study design of a cluster randomised controlled trial in primary care

Birsen Kiliç [a,*], Marion C.J. Biermans [b], Frans H. Rutten [a], Jaap Deinum [c], Wilko Spiering [d], Mark C. van der Wel [b], Wim J.C. de Grauw [b], Michiel L. Bots [a], Monika Hollander [a]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Department of Primary and Community Care, Radboud university medical Center, Nijmegen, the Netherlands
[c] Department of Internal Medicine, Radboud university medical Center, Nijmegen, the Netherlands
[d] Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Uncontrolled hypertension
General practice
Cluster randomised controlled trial

ABSTRACT

Background: Uncontrolled hypertension is a major health problem, and a key risk factor for cardiovascular disease. Most patients are detected and managed in primary care, but approximately 50% remains uncontrolled. Our aim is to assess whether a guided stepwise work-up management strategy for patients with uncontrolled hypertension in primary care would result in better blood pressure control in these patients compared to usual care.

Methods: A cluster randomised controlled trial aiming at randomizing 40 general practices to either "a protocolised stepwise work-up" or to "usual care".

Uncontrolled hypertension is defined as an office blood pressure (BP) >140/90 mmHg while being prescribed three or more antihypertensive drugs simultaneously from different therapeutic classes for three or more months in an adequate dose. In the intervention arm, patients with uncontrolled hypertension will receive the stepwise approach, consisting of (i) excluding a white coat effect, (ii) re-evaluation of lifestyle, (iii) re-evaluation of drug adherence, (iv) optimalisation of antihypertensive treatment and (v) referral if the office BP is still >140/90 mmHg. The control group receives usual care in a regular program for cardiovascular risk management.

The primary outcome is the absolute difference in the mean 24-h systolic BP between intervention and control arm after 8 months. Secondary outcomes include differences in the percentage of patients achieving a controlled BP, and time to reach a controlled BP.

Conclusion: If stepwise treatment of uncontrolled hypertension is proven effective, the strategy could be implemented by blending the approach to the cardiovascular risk management already applied in general practice.

Trial registration

NTR7304, https://www.trialregister.nl/trial/7099

1. Introduction

Cardiovascular diseases (CVD) are the number one cause of mortality, accounting for 17.9 million deaths worldwide [1]. As much as 54% of all strokes, 47% of all coronary heart diseases, and 20% of all heart failure cases are attributable to hypertension [2–4]. About 10% of the world's overall healthcare expenditure is related to poor blood pressure (BP) control, adding up to US$370 billion annually [5]. There is a wealth of evidence showing that BP lowering therapy combined with lifestyle changes is (cost)-effective in reducing CVD [6,7]. Nevertheless, European surveys showed that only around half of all patients managed for hypertension reach target levels (i.e., office systolic BP <140 mmHg), with similar data for the Netherlands [7]. It is well documented that patients with uncontrolled hypertension are at increased risk for CVD compared to those with controlled hypertension. [8]. Thus, a high prevalence in society coupled with an increased cardiovascular risk illustrates that there is an urgent need for better management of uncontrolled hypertension.

* Corresponding author at: Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
E-mail address: b.kilic@umcutrecht.nl (B. Kiliç).

https://doi.org/10.1016/j.cct.2022.107062
Received 5 August 2022; Received in revised form 18 December 2022; Accepted 20 December 2022
Available online 9 January 2023

General practitioners (GPs) in the Netherlands manage the vast majority of patients with hypertension. They use the most recent Dutch guidelines on cardiovascular risk management (CVRM) [9,10]. These guidelines recommend for patients who do not reach the targeted BP level to (i) use 24-h BP readings (or alternatively home BP measurements) to rule out white coat effects, (ii) re-evaluate the lifestyle, (iii) try to improve adherence to medication, and (iv) consider the possibility of secondary hypertension. Finally, it is recommended (v) to refer to a hospital specialist if uncontrolled hypertension persists (i.e. office systolic BP $>$ 140 mmHg, despite simultaneous use of 3 or more antihypertensive drugs). Yet, a practical work-up plan for implementation in daily practice, describing exactly how and in what order such steps should be taken, is not provided in the guideline.

A study showed that the vast majority of patients who were referred to the hospital specialist because of uncontrolled hypertension could reach control simply by adjusting antihypertensive treatment also available in primary care [11]. These findings may be a reflection of the lack of such a practical work-up approach.

An easy to follow and implementable stepwise work-up approach for uncontrolled hypertension in primary care could help GPs to improve the rates of hypertension control. and avoid unnecessary referral to hospital.

We aim to investigate the application of this stepwise work-up scheme which also includes a training programme for GPs and practice nurses (PNs) and compare blood pressure and other endpoints with usual primary care in a cluster-randomised trial.

2. Methods and analyses

2.1. Objective

To assess whether application of a stepwise work-up strategy in primary care patients with uncontrolled hypertension results in better BP control than usual care.

2.2. Study design

A cluster randomised controlled trial conducted among 40 Dutch general practices (20 in the intervention arm and 20 in the usual care arm).

By choosing for a cluster randomised trial instead of an controlled trial in which individuals are randomised, we avoid 'contamination' or lack of contrast (usual care becoming similar to intervention) [12]. Further, randomization on practice level has the practical advantage that all aspects of the implementation are organized within a group of closely cooperating caregivers within a practice.

2.3. Study population

In total, 120 + 120 community adults with uncontrolled hypertension. Eligible are i) people enlisted with the GP and aged between 18 and 80 years, with an office BP $>$140/90 mmHg while managed with simultaneously three or more antihypertensive drugs from different therapeutic classes for three or more months in an adequate dose (e.g. based on the current Dutch guideline on cardiovascular risk management). Additional inclusion and exclusion criteria are presented in Table 1.

2.4. Randomization, blinding and treatment allocation

Randomization is done at practice level, enabling uniform care (the so-called cluster). The randomization was 1:1, stratified by region (Utrecht/Nijmegen) and practice size (1 average practice, 2 average practices, 3 $\geq$ averaged practices) using a web-based randomization program (Julius Center, UMC Utrecht, Utrecht, the Netherlands). In the Netherlands, an average practice has 2350 enlisted patients. Since it is not deemed feasible to keep the GPs in the usual care arm unaware of the existence of an intervention arm, blinding of the participants to knowledge of an existing intervention group is considered necessary to minimize contamination in the intervention. Therefore, we apply different patient information sheets for the intervention group compared to the usual care group. The primary endpoint 'difference in mean 24-hour blood pressure' will be measured by an automated 24-h device, minimising observer bias in the end point measurement. The risk of observer bias for the other endpoints will be minimized because these are based on questionnaires that will be filled out by participants at home.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
A persisting office BP $>$140/90 mmHg, measured on at least two separate occasions in the last year despite simultaneous prescription of three or more BP lowering drugs of different classes at adequate dosage (based on current Dutch guideline on cardiovascular risk management), with for each antihypertensive drug at least 1 prescription of 3 months.
- During the inclusion consultation, the office BP should be twice $>$140/90 mmHg (measured according to the 'standardized office blood pressure measurement' in the Dutch CVRM guideline). Different classes of BP lowering drugs are defined as following with ATC codes: Direct and central anti hypertensives (C02*), diuretics (C03*), beta blocking agents (C07*), calcium channel blockers (C08*), agents acting on the renin-angiotensin system (C09*).
Aged $\geq$18 years and $\leq$ 80 years
Exclusion criteria
- A short life expectancy ($<$6 months) as judged by the GP.
- Inability to understand or conform to the stepwise-HTN protocol.
- Unwillingness to provide a written informed consent.
- In case of suspicion of a hypertensive crisis (a systolic blood pressure $\geq$ 200 mmHg and/or diastolic blood pressure $\geq$ 120 mmHg) the patient is referred for further evaluation. If a hypertensive crisis is excluded, the patient can be included in the study.
- Atrial fibrillation (because of difficulties to interpret 24-h BP measurements).
- Pregnancy or breast feeding.
Severe co-morbidity, which seriously interferes with diagnostic procedures or possible treatment.

2.5. Selection of eligible patients

All citizens in the Netherlands are registered with a GP, except those living in a nursing home or hospice and the homeless and undocumented migrants [13]. The GP registers data in the electronic health record (EHR). The Radboud Technology Center (RTC) Health Data [14] will extract data from the EHR of the participating practices, will advise on the linkage of EHR data to other study data, and will produce lists of eligible patients. The extractions (at the beginning and at the end of the study) include only de-identified coded data (no names or addresses) and will be used to collect data on demographics, diagnoses, contacts, measurements, and drug prescriptions. For drug prescriptions we use the Anatomical Therapeutic Chemical (ATC) codes [15] and for diagnoses we the International Primary Care codes ICPC) [16]. The included practices need to give permission for data extraction of the EHR for research purposes and will inform all their patients who can object to the use of their data (opt out procedure). This study will be performed according to the Code of Conduct for Health Research [17], and it has been approved by the Data Protection Authorities for conformity with the General Data Protection Regulation (GDPR).

The RTC Health Data centre will assign study numbers to these potential eligible patients.

The GP or PN will check this list against inclusion and exclusion criteria to determine if the patients are suitable for study participation. Subsequently, these patients are approached during routine care, by phone, or by letter to ask them if they want to participate in the study. If interested, the patient receives the detailed information letter and an appointment is made for a baseline visit. At baseline visit, patients sign

informed consent and blood and BP measurements are taken. If the patient has an elevated office BP (i.e., twice >140/90 mmHg), follow-up procedures can take place.

2.6. Study procedures

The flowchart of the Stepwise-HTN study is shown in Fig. 1.

GPs and PNs of both arms will receive an interactive training on study procedures, identification and recruitment of eligible patients and use of an online data collection system, called Research Online [18]. Intervention practices will receive additional training to execute the stepwise treatment.

2.6.1. Intervention group

The stepwise treatment of patients in the intervention group consists of 5 steps: i) excluding a white coat effect, ii) re-evaluation of lifestyle, iii) re-evaluation of adherence, iv) optimalisation of medication, and v) referral to a hospital specialist to rule out secondary hypertension.

At every step office BP will be measured, with at the first step also a 24-h BP measurement. When the BP is still "uncontrolled" patients will proceed to the following step. When the 24-h BP is ≤130/80 mmHg or the office BP ≤140/90 mmHg, patients will be considered to be "controlled" and will receive usual care from that point onward. However, they will be further scheduled for the endpoint visit at 8 months. In both arms, at the endpoint visit patients will undergo a 24-h BP measurement.

2.6.2. Step 1: excluding a white coat effect

The first step comprises a standardized 24-h BP to assess whether the BP is still above target level and to rule out a white coat effect.

When the mean 24-h BP is >130/80 mmHg patients will be considered "uncontrolled" and will proceed to step 2.

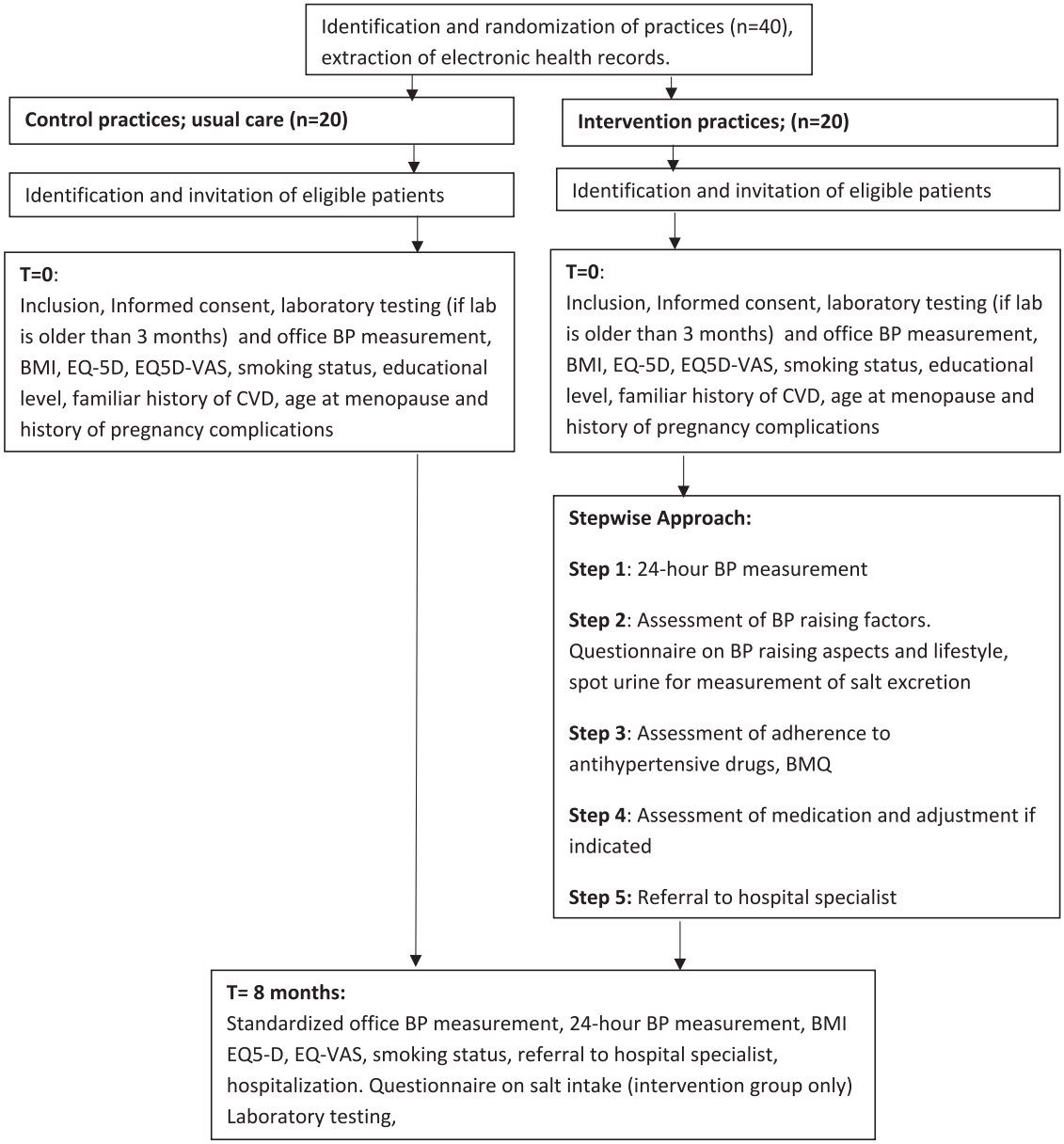

Fig. 1. Flowchart of the Stepwise-HTN study.
*BMI = Body Mass Index, BP = blood pressure, EQ-5D = EuroQuality of live on 5dimensions,
EQ5D-VAS = EQ5D –Visual Analogue Scale, CVD = cardiovascular diseases, BMQ = Believes about Medication Questionnaire.

2.6.3. Step 2: re-evaluation of lifestyle

This step consists of a comprehensive assessment of factors that increase BP and lifestyle. The patient's preparation consists of completing questionnaires about physical activity (number of days per week with activity of >30 min) using the SQUASH Questionnaire [19], and the use of factors that increase BP such as alcohol and licorice (see supplementary 1 for questionnaires used). A fasting spot urine sample will be collected prior to the visit for the second step to assess the sodium concentration according to the second morning urine method (SMU method) for estimating salt intake [20] [21]. Prior to the visit, the GP or PN checks the medical record for use of blood pressure elevating medication such as NSAIDs, beta-sympathicomimetics, oral anticonceptives, erythropoetin, and cyclosporine. During the visit in step 2, an office blood pressure measurement will be performed and the results of the questionnaires, measurements and blood pressure elevating factors emerging from the medical file will be shared with the participant. Furthermore, during the visit, patients will fill out a questionnaire on the intake of salt [22] together with the PN and will receive a flyer on salt intake (in Dutch: 'De ongezouten waarheid') [23]. If salt intake is above 6 g per day (i.e. 2,6 teaspons), the PNs will advise patients to reduce salt intake using illustrations from "the saltbook" (in Dutch: 'Het zoutboek') [24].

If the BP is still uncontrolled and no BP increasing factors are found then participants will receive advice on how to maintain a healthy lifestyle and proceed to step 3.

If the BP is still uncontrolled and one or more BP increasing factors are found then appropriate advice is given to change the concerning factors and re-evaluation of BP is planned after 2–4 weeks. If BP levels remain elevated during the re-evaluation visit, participants proceed to step 3 and are stimulated to continue the initiated lifestyle interventions.

2.6.4. Step 3: evaluation of drug adherence

This step implies the assessment of adherence to the antihypertensive drugs. Because adherence to medication is notoriously difficult to assess, we will use several approaches to map the possible problems with taking the antihypertensive medication. Prior to the visit the patient will fill out the Believes about Medication Questionnaire (BMQ) online or on paper [25]. The BMQ assesses both possible problems with taking the medication and beliefs about medication. The preparation of the PN consists of assessing the prescriptions of blood pressure lowering medication during the last year from the medical files along with the results of the BMQ questionnaire. During the visit, possible barriers for taking medication will be explored and discussed. In case of adherence problems, the GP or PN will further explore the reasons for non-adherence and options for improvement, including evaluation of psychosocial stress factors and alternatives in the way drugs are taken in shared decision with the patient. Simple but effective measures could be undertaken to improve the drug treatment by well-balancing a low as possible daily number of drugs with well-chosen long-acting antihypertensives adequately provided in combination pills and delivered in week boxes. In case of psycho-social problems, the patient will be referred to the GP or social worker for further counselling. At the end of the visit the GP or PN will indicate to what extent he/she thinks the patient is adherent to medication on a VAS scale (0−10).

When no adherence problems are found, participants will proceed to step 4. In cases of adherence problems, these are discussed, followed by a follow-up visit after 2–4 weeks. When the BP is still uncontrolled during the follow-up visit, participants proceed to step 4.

2.6.5. Step 4: optimalisation of antihypertensive treatment

This step consists of the assessment and adjustment of the medication, taking factors like preferences, side effects, contraindications, and interactions into account. For this step, several consultations may be needed. If possible, multiple long-acting, antihypertensive drugs will be prescribed acting on the different pathophysiological mechanisms (the renin-angiotensin aldosterone pathway, the sympathetic pathway, vasodilatation, and diuretics with salt clearance by the kidneys). The GP will keep in mind that 3 times half a dosage has more effect and often less adverse effects than twice the highest dosage [26]. Frequently used triple therapy contains a diuretic, a calcium channel antagonist combined with either an ACE inhibitor or an angiotensin receptor blocker. The preferred first, second and third type of antihypertensive drug depends on comorbidities. If the medication is already optimized, the patient proceeds to step 5. If this is not the case, as a guide, the medication may be changed according to the following steps.

1. If applicable: switch to long-acting drug types and, or fixed dose combination. E.g., first change 2 drug types into long-acting ones acting on the same pathophysiological pathway, and then switch the third other type.
2. Increase the dosage of the long-acting medication, one by one.
3. Add spironolactone (25 mg once daily) as fourth type to the medication (contra-indicated if potassium >5 mmol/l).
4. If BP levels are still elevated after all previous medication changes, the patient will proceed to step 5.

Each change is evaluated after 2 weeks by an office BP measurement and laboratory testing if indicated according to CVRM guideline. Prescriptions are changed after 2 or 4 weeks. Each change in medication is carried out only if applicable and considering (contra) indications and side effects. If necessary, the GP consults a pharmacist.

2.6.6. Step 5: referral

If the BP is still uncontrolled after the consultation(s) in this fourth step, the participant will be referred to a vascular internist for further diagnostic work-up and treatment.

2.6.7. Usual care group

Participants in the usual care are seen at least once yearly for cardiovascular risk management consultation in the general practice and are managed according to the Dutch guideline for cardiovascular risk management. In case of uncontrolled hypertension, the Dutch guideline on CVRM recommends to perform adequate BP readings, emphasizing that home blood pressure readings by the patients themselves, and 24-h BP readings better represent the 'true' blood pressure. The guideline further advices to address lifestyle (smoking, physical activity, diet, use of alcohol, salt, and licorice and stress) and adherence to medication. However, the guideline provides no practical guidance on how to address these factors in practice and in what order. Further, adjustment of medication is recommended if needed followed by a BP check after each change. Finally, referral to the specialist is recommended when the BP remains uncontrolled [9]. In the study, participants visit the GP 8 months after inclusion and will receive both a standardized office BP measurement and 24 h ambulatory BP measurement. Participants are not informed about the existence of the intervention group during the study, but after completion of the study after 8 months, they will be informed that they were enrolled in the control group. It will be explained to them why they had not been informed of the existence of the intervention group to prevent contamination and to achieve unbiased results. At baseline the participants will sign informed consent and undergo lab testing if this has not been done within the last 3 months. Further a standardized office BP measurement will be done and BMI, EQ-5D, EQ5D-VAS, smoking status, educational level, familiar history of CVD, age at menopause and history of pregnancy complications will be assessed using questionnaires. Finally, a follow-up visit after 8 months is scheduled (see Fig. 1).

2.7. Start and end visit

At baseline and end visit after 8 months, all participants in the intervention and control group will undergo a standardized office BP measurement and laboratory testing (if lab is not tested within the last 3

months) including fasting glucose, total cholesterol, LDL- and HDL cholesterol, TC/HDL ratio, triglycerides, serum creatinine and eGFR, serum potassium, and albumin to creatinine ratio in a urine sample.

Furthermore, every participant will fill out baseline questionnaires on educational level of him/herself and his/her parents, the length, weight, family history of cardiovascular disease, and for females age at menopause and history of pregnancy complications. Quality of life (EQ-5D and EQ5D-VAS), smoking status and weight will be asked during both the baseline and endpoint questionnaire. The EQ-5D is a generic quality of life questionnaire, consisting of a classification system (EQ5D-profile) and a Visual Analogue Scale (EQ5D-VAS) [27].

At the end visit, all participants will undergo a standardized office BP measurement and a 24-h ambulatory blood pressure measurement. Further, all participants fill out questionnaires on referrals to hospital specialists and hospitalisations. Patients in the intervention group who have completed step 2 will also fill out a questionnaire on salt intake [22] during the endpoint visit.

2.8. Outcome measures

2.8.1. Primary outcome

The primary outcome measure is the difference in the mean 24–hour systolic BP between the intervention and usual care group after 8 months follow up.

2.8.2. Secondary outcome

1. The percentage of patients achieving a controlled BP, that is, an office BP ≤140/90 mmHg or a mean 24-h BP ≤130/80 mmHg, measured after 8 months follow up.
2. The difference in the time window (time from baseline) to reach a controlled BP during the study, defined as twice an office BP of ≤140/90 mmHg, or a mean 24-h BP of ≤130/80 mmHg between both arms.
3. The difference in number and/or dosage needed of BP lowering drugs measured during the study time between both arms.
4. The difference in referral rates to the hospital specialist during the study time between both arms.
5. The difference in health care use and associated costs during the study period between both arms.
6. The difference in health-related quality of life as measured with the EQ5D and EQ-VAS at baseline and after 8 months between both arms.
7. The difference in self-reported BMI between both arms.

2.8.3. Sample size calculations

The sample size calculation for the primary endpoint is based on an estimated standard deviation (SD) of 16 mmHg around the group mean systolic blood pressure based on 24-h systolic blood pressure measurements. This is in line with renal denervation RCTs recently initiated by the UMC Utrecht [28]. We then need 233 individuals to detect a clinically relevant difference of 7.5 mmHg between the mean 24-h systolic blood pressure of both groups when we consider an intra-cluster correlation coefficient of 0.05 [29], and apply a 2-sided alpha of 5% and 90% power. The estimated prevalence of eligible patients is 15 per general practice. We checked for this assumption in routinely obtained data from 133 practices in the Nijmegen region. Anticipating a conservative 50% response for participation, and a drop-out rate of around 20%, we need to enrol 39 practices to be sure to end up with 583 participants who will be invited to participate (i.e., 233 * 2 * 1.25). Rounded up, we plan to include 40 general practices (20 in the intervention and 20 in the care as usual arm) and 120 patients per arm (40 * 15 * 0.50 * 0.80).

2.8.4. Data analyses

For the primary outcome - the difference in the mean 24-h systolic BP between both groups after 8 months follow-up- an intention-to-treat analysis will be performed. We will not be able to adjust for baseline 24 h results, since these were not assessed at baseline. The main reason for not assessing the 24 h blood pressure measurement at baseline because this measurement is included as the first step of the intervention approach. So, for the primary outcome we will not adjust for baseline 24 h blood pressure values. Furthermore, we will perform a sensitivity analysis in which we also adjust the primary outcome for baseline differences in office blood pressure. A multilevel approach will be used for analyses to adjust for clustering. The random part of the model will include a random intercept per practice and an unstructured correlation matrix for the correlation of measurements within patients. The fixed part of the model will include the variables treatment group. Potential difference of relevant parameters at baseline, in particular sex, age, and the office BP at baseline, will be considered when deemed appropriate.

For the secondary outcomes regression models will be applied, depending on the outcome variable and the intent (mean differences after 8 months follow up, or differences in change from baseline).

2.8.5. Patient and public involvement

Patients were not involved in the design and development of the protocol, however, the findings of our study will be disseminated to all study participants and their GPs and PNs.

2.8.6. Ethics and dissemination

The Stepwise-HTN study will be conducted according to the principles of the declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The protocol is approved by the Medical Research Ethics Committee of the UMC Utrecht, the Netherlands. This trial is registered with the Netherlands Trial Register (NTR7304 https://www.trialregister.nl/trial/7099). All patients will be asked written informed consent before inclusion. Patients' personal data will be saved separate from baseline and follow-up data at central hard drives ate the UMC Utrecht and their privacy will be guaranteed throughout the entire study by restriction of access to the data following the standard procedure at the UMC Utrecht. The data will be analysed by assigned researchers using a unique patient identification number and no identifiable information. Quality assurance is addressed using standard monitoring before, during and at the end of the trial. Changes to the study protocol are documented in amendments. Amendments are submitted for approval to the Medical Research Ethics Committee. Results of the trial are expected in 2022 and will be disseminated through peer-reviewed publications and presentations at (inter)national conferences.

3. Discussion

There is an urgent need for better management of uncontrolled hypertension, and primary care is the domain in which the vast majority of these patients are managed. In Stepwise-HTN we intend to investigate whether application of a comprehensive stepwise work-up strategy in primary care patients with uncontrolled hypertension results in a better blood pressure control. This may lead to a reduction of referral to hospital. The strategy is based on the wealth of evidence on modifiable risk factors in uncontrolled hypertension [30–34], and the importance of adherence [35–37]. Some issues need to be addressed. First, we anticipate a response rate of 50% for participants. Although this proportion is reasonable in general practice [38] the actual participation rate may be lower given the fact that participation in the study asks willingness of participants to visit the practice several times, especially in the intervention group. Participants need to be willing to undergo lab testing and 24 h BP measurement which may be more burdensome than anticipated. Further, the intervention is a complex process which asks dedicated attention of the practices. These factors challenge the feasibility of the study and the willingness of participants to participate in and to complete the study. However, implementing and investigating the study in

daily practice in primary care is the only option to investigate whether the stepwise program can be implemented on a wider scale.

We realize that the goal of 7.5 mmHg difference in mean 24 h systolic BP between both groups after 8 months is ambitious. Due to the limitations described above, we may not reach this goal. However, a lower difference (e.g. 5 mmHg difference) also will be clinically relevant in terms of effects on cardiovascular disease risk. We also realize that there is a risk of type 2 error.

If proven effective, the strategy could be implemented by blending the approach to the cardiovascular risk management already applied in general practice.

Contributors

MLB, MH and FR conceived the study idea and designed the study. All authors contributed to the study protocol. BK coordinated the study. BK, MH, and MCJB recruited the general practices. MCJB coordinated the data collection of the questionnaire on salt intake. BK and MH wrote the first draft of the manuscript. All authors contributed to revised versions of the manuscript and MH is guarantor of the study. All authors read and approved the final manuscript.

Funding

The study is conducted with an unrestricted research grant from The Netherlands Organization for Health Research and Development (ZonMw, project number: 839110013) and an additional grant from the Dutch Kidney foundation (project code: KF3P0lA).

Patient consent for publication

Not required.

Ethics approval

The medical Ethics Committee of the University Medical Center (UMC) Utrecht approved the study (NL61553.041.17).

Provenance and peer review

Not commisioned; externally peer reviewed.

Declaration of Competing Interest

None declared.

Data availability

No data was used for the research described in the article.

Acknowledgements

We thank all participating GPs and PNs for their willingness to participate in Stepwise-HTN. We also want to thank Prof. W.J.J. (Pim) Assendelft for his contribution to the design of Stepwise-HTN study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2022.107062.

References

[1] World Health Organization, Factsheet Cardiovascular Diseases 2021 [Internet]. [cited 2021 Feb 8]. Available from, https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
[2] S.S. Lim, T. Vos, A.D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, et al., A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet. 380 (9859) (2012) 2224–2260.
[3] S.M. Dunlay, S.A. Weston, S.J. Jacobsen, V.L. Roger, Risk factors for heart failure: a population-based case-control study, Am J Med [Internet] 122 (11) (2009) 1023–1028. Available from: https://doi.org/10.1016/j.amjmed.2009.04.022.
[4] G. Tocci, S. Sciarretta, M. Volpe, Development of heart failure in recent hypertension trials, J Hypertens 26 (7) (2008) 1477–1486.
[5] T.A. Gaziano, A. Bitton, S. Anand, M.C. Weinstein, The global cost of nonoptimal blood pressure, J Hypertens 27 (7) (2009) 1472–1477.
[6] J. Sundström, H. Arima, R. Jackson, F. Turnbull, K. Rahimi, J. Chalmers, et al., Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis, Ann Intern Med 162 (3) (2015) 184–191.
[7] K. Kotseva, D. Wood, G. de Backer, D. de Bacquer, K. Pyörälä, Z. Reiner, et al., EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries, Eur J Prev Cardiol 17 (5) (2010) 530–540.
[8] S.L. Daugherty, J.D. Powers, D.J. Magid, H.M. Tavel, F.A. Masoudi, K.L. Margolis, et al., Incidence and prognosis of resistant hypertension in hypertensive patients, Circulation. 125 (13) (2013) 1635–1642.
[9] Y.M. Smulders, J.S. Burgers, T. Scheltens, B.A. van Hout, T. Wiersma, M. L. Simoons, Clinical practice guideline for cardiovascular risk management in the Netherlands, Neth J Med 66 (4) (2008) 169–174.
[10] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, et al., 2016 European guidelines on cardiovascular disease prevention in clinical practice, Eur Heart J 37 (29) (2016) 2315–2381.
[11] W.L. Verloop, E.E. Vink, M. Voskuil, E.J. Vonken, M.B. Rookmaaker, M.L. Bots, et al., Eligibility for percutaneous renal denervation: the importance of a systematic screening, J Hypertens 31 (8) (2013) 1662–1668.
[12] D.J. Torgerson, Contamination in trials: is cluster randomisation the answer? Bmj. 322 (7282) (2001) 355.
[13] R. Gijsen, M.J.J.C. Poos, Using registries in general practice to estimate countrywide morbidity in the Netherlands, Public Health 120 (10) (2006) 923–936.
[14] Radboudumc Technology Center: Health data [Internet] [cited 2021 Nov 1]. Available from, https://www.radboudumc.nl/en/research/radboud-technology-centers/health-data.
[15] ATC/DDD Index 2021 [Internet] [cited 2021 Nov 1]. Available from: https://www.whocc.no/atc_ddd_index/.
[16] Wonca, World Organization of Family Doctors International Classification of Primary Care [Internet], Available from, www.globalfamilydoctor.com, 2016.
[17] A Code of Conduct for Health Research, 2022.
[18] Researsch Online [Internet], Available from, https://www.researchonline.info/en-us/.
[19] G.C.W. Wendel-Vos, A.J. Schuit, W.H.M. Saris, D. Kromhout, Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity, J Clin Epidemiol 56 (12) (2003) 1163–1169.
[20] M. Kawamura, T. Kawasaki, Clinical application of the second morning urine method for estimating salt intake in patients with hypertension, Clin Exp Hypertens 37 (2) (2015) 89–96.
[21] M. Kawamura, A. Ohmoto, T. Hashimoto, F. Yagami, M. Owada, T. Sugawara, Second morning urine method is superior to the casual urine method for estimating daily salt intake in patients with hypertension, Hypertens Res 35 (6) (2012) 611–616.
[22] De Zoutmeter [Internet] [cited 2021 Nov 1]. Available from: https://nierstichting.nl/zoutmeter.
[23] De ongezouten waarheid [Internet] [cited 2021 Nov 1]. Available from: https://nierstichting.nl/media/filer_public/80/07/8007b811-14ed-4dea-a113-6577e8809df2/spreekbeurt_de_ongezouten_waarheid_over_zout.pdf.
[24] Nierstichting voorlichtingsmaterialen: boeken [Internet] [cited 2021 Nov 1]. Available from: https://nierstichting.nl/voorlichtingsmaterialen/boeken/.
[25] B.L. Svarstad, B.A. Chewning, B.L. Sleath, C. Claesson, The brief medication questionnaire: a tool for screening patient adherence and barriers to adherence, Patient Educ Couns 37 (2) (1999) 113–124.
[26] M.R. Law, J.K. Morris, N.J. Wald, Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies, BMJ. 338 (7705) (2009) 1245.
[27] R. Rabin, F. De Charro, EQ-5D: a measure of health status from the EuroQol group, Ann Med 33 (5) (2001) 337–343.
[28] M. Azizi, H. Pereira, I. Hamdidouche, P. Gosse, M. Monge, G. Bobrie, et al., Adherence to antihypertensive treatment and the blood pressure-lowering effects

of renal denervation in the renal denervation for hypertension (DENERHTN) trial, Circulation. 134 (12) (2016) 847–857.
[29] M.K. Campbell, J. Mollison, N. Steen, J.M. Grimshaw, M. Eccles, Analysis of cluster randomized trials in primary care: a practical approach, Fam Pract 17 (2) (2000) 192–196.
[30] K.J. Low, M.A. Pelter, R.L.B.R. Deamer, Identification and evaluation of risk factors in patients with continuously uncontrolled hypertension, J Clin Hypertens 17 (4) (2015) 281–289.
[31] T. Semlitsch, C. Krenn, K. Jeitler, A. Berghold, K. Horvath, A. Siebenhofer, Long-term effects of weight-reducing diets in people with hypertension, Cochrane Database Syst Rev 2021 (2) (2021).
[32] F.J. He, J. Li, G.A. MacGregor, Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials, BMJ. 346 (7903) (2013) 1–15.
[33] A.R. Cooper, L.A.R. Moore, J. McKenna, C.J. Riddoch, What is the magnitude of blood pressure response to a programme of moderate intensity exercise? Randomised controlled trial among sedentary adults with unmedicated hypertension, Br J Gen Pract 50 (461) (2000) 958–962.
[34] C. Koliaki, N. Katsilambros, Dietary sodium, potassium, and alcohol: key players in the pathophysiology, prevention, and treatment of human hypertension, Nutr Rev 71 (6) (2013) 402–411.
[35] J. Meddings, E.A. Kerr, M. Heisler, T.P. Hofer, Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss, BMC Health Serv Res 12 (1) (2012) 1–11.
[36] R.L. De Jager, E. De Beus, M.M.A. Beeftink, M.F. Sanders, E.J. Vonken, M. Voskuil, et al., Impact of medication adherence on the effect of renal denervation: the SYMPATHY trial, Hypertension. 69 (4) (2017) 678–684.
[37] D.J. Steele, T.C. Jackson, M.C. Gutmann, Have you been taking your pills? The adherence-monitoring sequence in the medical interview, J Fam Pract 30 (3) (1990) 294–299.
[38] M.C. van der Wel, M. Biermans, R. Akkermans, J.W.M. Lenders, C. van Weel, J. Deinum, Patient characteristics do not predict the individual response to antihypertensive medication: a cross-over trial, Fam Pract 35 (1) (2018) 67–73.