Faculty of Medicine at the Martin Luther University of Halle-Wittenberg

Randomized Controlled Trials on Prevention, Diagnosis and Treatment of Hypertension in Africa, a Systematic Review

Thesis
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Abstract

Background: The high burden of undiagnosed and untreated hypertension cases in Africa signals the need to increase detection rates of existing hypertension and provide resources for adequate treatment. The primary aim of this systematic review was to evaluate the number of existing randomized controlled trials (RCTs) on hypertension in Africa and to describe all examined interventions and their reported effects on blood pressure.

Methods: We performed a systematic review of publications (PROSPERO registration number CRD42018075062) retrieved by a systematic literature search in online databases and registers of ongoing and completed studies, to identify all relevant RCTs on hypertension conducted in African countries. Outcomes were systolic blood pressure, diastolic blood pressure, mean arterial pressure or its change to baseline values within the longest follow-up period.

Results: 90 RCTs on hypertension in Africa were identified as eligible up to January 2020 with all together 23 562 participants. We noted a concentration in urban settings with 94% of included trials, more female participants and an underrepresentation of RCTs conducted in Central and Northern Africa. We found eligible RCTs with different pharmacological and non-pharmacological interventions. On the basis of 4 RCTs the results indicated a convincing blood pressure control by improving physical activity in African countries. The results in RCTs included on standardized treatment, education and adherence strategies and comparisons of different drug classes were heterogeneous. A total of 15 RCTs, 22% of drug intervention RCTs included compared active drug to placebo and showed better effects for the intervention. All RCTs showed a risk of bias in at least one of the assessed topics.

Conclusion: An improvement in the prognosis of patients with high blood pressure in Africa requires the implementation of comprehensive diagnostics, medical treatment and subsequent regular checks. The identified studies offer effective approaches that have been tested in African countries. Yet, the number of RCTs on treatment of hypertension is still not representive for all Africans. Research on interventions to treat hypertension needs to be expanded to the rural areas of Africa. Pharmacotherapy should be given special attention in these patients regarding these special genetic disposition. Furthermore, it is crucial to plan and implement more campaigns to increase awareness and diagnosis of hypertension. Particularities of African population with cultural and social particularities, such as distance to facilities, traditional beliefs, decision making in the families, special genetic backgrounds between African populations has to be taken into account. Local guidelines are needed based on local evidence-based data to do justice to the particularities of African population.

Cernota, Monique, Randomized controlled trials on hypertension in Africa, a systematic review, Halle (Saale), Martin Luther University, Institute of General Medicine, Dissertation, 66 pages, 16/03/2020

Referat

Hintergrund: Die hohe Zahl nicht diagnostizierter und unbehandelter Fälle von Hypertonie in Afrika signalisiert die Notwendigkeit die Erkennungsrate und Diagnostik der Erkrankung zu verbessern und mehr Ressourcen für eine angemessene Behandlung bereitzustellen. Das Hauptziel dieser systematischen Arbeit war es, die Anzahl der vorhandenen randomisierten kontrollierten Studien (RCTs) zur Hypertonie in Afrika zu bewerten und alle untersuchten Interventionen und ihre berichteten Auswirkungen auf den Blutdruck zu beschreiben.

Methoden: Für die systematische Übersicht der Veröffentlichungen (PROSPERO-Registrierungsnummer CRD42018075062) führten wir eine systematische Literaturrecherche in Online-Datenbanken und Registern laufender und abgeschlossener Studien durch, um alle relevanten RCTs zur Hypertonie in afrikanischen Ländern zu identifizieren.

Ergebnisse: Bis Januar 2020 wurden 90 geeignete RCTs zum Thema Bluthochdruck in Afrika mit insgesamt 23 562 Teilnehmern identifiziert. 94% der eingeschlossenen Studien fanden in städtischen Gebieten statt, es gab mehr weibliche Studienteilnehmer und eine Unterrepräsentation von RCTs in Zentral- und Nordafrika. Wir fanden RCTs mit unterschiedlichen pharmakologischen und nicht-pharmakologischen Interventionen. Die Ergebnisse der Studien mit standardisierten Behandlungs-, Aufklärungs- und Adhärenzstrategien sowie nach Vergleichen verschiedener Arzneimittelklassen waren heterogen. Durch Steigerung der körperlichen Aktivität (4 RCTs) konnte eine überzeugende Blutdruckkontrolle erreicht werden. Insgesamt 15 RCTs, 22% der Arzneimittel-RCTs, verglichen aktive Wirkstoffe mit Placebo und wiesen bessere Wirkungen der aktiven Substanzen bei afrikanischen Patienten nach. Alle RCTs zeigten in mindestens einem der bewerteten Themen ein erhöhtes Verzerrungspotenzial.

Schlussfolgerung: Eine Verbesserung der Prognose von Hypertoniepatienten in Afrika erfordert die Etablierung einer umfassenden Diagnostik, medizinischen Behandlung und anschließender regelmäßiger Kontrollen. Die identifizierten Studien bieten für die Umsetzung effektive Ansätze, die in afrikanischen Ländern getestet wurden. Die Anzahl und Verteilung der RCTs zur Behandlung von Bluthochdruck ist jedoch immer noch nicht für alle Afrikaner repräsentativ. Die Forschung zu Interventionen muss dafür auf die ländlichen Gebiete Afrikas ausgedehnt werden. Dabei sollte der Pharmakotherapie besondere Aufmerksamkeit hinsichtlich dieser besonderen genetischen Disposition gewidmet werden. Darüber hinaus ist es wichtig, mehr Kampagnen durchzuführen, um das Bewusstsein für die Erkrankung in der Bevölkerung und die Identifikation der Erkrankten zu verbessern. Vor allem kulturelle und soziale Besonderheiten der afrikanischen Bevölkerung wie Entfernung zu Einrichtungen, traditionelle Überzeugungen und Entscheidungsfindung in den Familien müssen berücksichtigt werden. Lokale Leitlinien, die auf lokalen evidenzbasierten Daten basieren, sind erforderlich, um den Besonderheiten der afrikanischen Bevölkerung gerecht zu werden.

Cernota, Monique, Randomisierte kontrollierte Studien zu Hypertonie in Afrika, eine systematische Übersichtsarbeit, Halle (Saale), Martin Luther Universität, Institut für Allgemeinmedizin, Dissertation, 66 Seiten, 16/03/2020

Inhaltsverzeichnis

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme-inhibitor
ADL	Activities of daily living
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
BB	Beta-blocker
bid	Twice a day
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
CAD	Coronary artery disease
CBPM	Clinic blood pressure measurement
CCB	Calcium channel blocker
CG	Control group
CI/95% CI	Confidence interval/95% confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HCT	Hydrochlorothiazide
HIC	High income country
HR	Heart rate
HAT	Hypertension/Hypertensive
IG	Intervention group
LIC	Low income countries
LMIC	Low-middle income country
MAP	Mean arterial pressure
MD	Mean difference
n	Number of participants
N	Number of trials
NCD	Noncommunicable disease
n.r.	Not reported
NYHA	New York Heart Association
QOL	Quality of life
RR	Relative risk
RCT	Randomized controlled trial
SD	Standard deviation
SBP	Systolic blood pressure
SPC	Single pill combination
SSA	Sub-Saharan Africa
TOD	Target organ damage
UMIC	Upper-middle income countries
US	United States
WHO	World Health Organisation

1 Introduction

Hypertension is becoming a major public health problem with an estimated 1 billion people living with it and causing 9.4 million hypertension related annual deaths worldwide (Poulter NR, 2015). The World Health Organization (WHO) estimates that the prevalence of hypertension is highest in the African region, with about 46% of adults aged 25 years and older being hypertensive (WHO, A global brief on hypertension, 2015). Hypertension prevalence ranged from 15% in West Africa to 25% in East Africa. As reported by the Global Ageing and Adult Health report, the prevalence of hypertension in South Africa was over 77% (Lloyd-Sherlock, 2014).

Incidence of hypertension has increased by 67% since 1990 and was projected to have caused more than 500,000 deaths and 10 million years of life lost in 2010 in SSA (Mensah, 2015). Hypertension is one of the major contributors to devastating health events and may result in stroke and myocardial infarction, which can be catastrophic to both individuals and the resource scarce health systems that provide their care (Thorogood, 2007).

The high burden of undiagnosed and untreated hypertension cases in Africa signals the need to increase detection rates of existing hypertension and provide resources for adequate treatment. A study conducted in multiple countries in sub-Saharan Africa stated that fifty percent of persons with hypertension are unaware of their hypertension (Guwatudde, 2015). According to another study conducted in Kenya, of those who were aware of being hypertensive, 87% were being treated but only 51% had it controlled (Gómez-Olivé, 2018). The Study of Global Ageing (SAGE) reported that in South Africa the hypertensive treatment coverage was only 27.5% and factors like advanced age, greater contact with primary care, and female sex were identified as determinants for treatment and control of hypertension (Morris-Paxton, 2018). This shows the need for urgent interventions to increase the treatment coverage.

Also the group of African Americans have a higher prevalence of hypertension than other groups with a higher risk of coronary heart disease, stroke, renal disease, and BP-related mortality (Ferdinand, 2006). The incidence of end-stage renal disease for example even has been reported to be as much as 17 times more common in African American patients than in whites (Richardson, 2000).

This once more indicates that there is a genetic predisposition for hypertension and its complications in African patients and patients with African ancestry, making not only the inadequate access to health care services and missing accurate health-related information responsible for poor BP control in African hypertensives. In addition to the socioeconomic and health systems-related concerns, pharmacotherapy should be given special attention in these patients regarding these specicial genetic dispositions.

There have been several pathophysiologic factors postulated which may also contribute to the increased risk of hypertension in blacks and its consequences in this population, such as cellular sodium transport defects and lower levels of natriuretic vasodilator prostaglandins and kinins

(Ferdinand, 2006; Richardson, 2000). On the other hand, Bewster 2013 found out that there are no biomarkers that may adequately predict responses of individual persons of African ancestry to different types of antihypertensive drugs. Self-identified ethno-geographic ancestry remains the best available predictor of blood pressure lowering responses to antihypertensive drugs (Bewster, 2013). Contrary to that, the meta-analysis by Sehgal 2004 found that race has little value in predicting antihypertensive drug response, because whites and blacks overlap greatly in their response to all categories of drugs (Sehgal, 2004). In their conclusion, the majority of whites and blacks have similar responses to commonly used antihypertensive drugs. They suggest that clinical decisions to use a specific drug should be based on efficacy in individual patients, compelling indications, and cost and stated that race is a poor predictor of drug-metabolizing enzymes (Sehgal, 2004).

The pan African society of Cardiology (PASCAR) identified several factors hindering the control of hypertension. First they stated a lack of established policies for controlling hypertension with poor universal health insurance coverage and poor political willingness to implement policies on screening, proper referral systems and on antihypertensive medication procurement and distribution for patients with noncommunicable diseases (NCDs) which results in a lack of quality and affordable antihypertensive medications. This is followed by a lack of appropriate evidence-based guidelines for healthcare professionals in individual countries with, if available, poorly applied hypertension treatment guidelines due to lack of quality health education on NCD for professionals and a scarcity of healthcare professionals at primary health care level. Poor awareness about hypertension and its consequences, poor drug adherence because of limited access to medication, difficulty in changing lifestyles, and false health beliefs that hypertension is curable, all due to poor patient education is described by PASCAR as further reasons that hinder effective treatment of hypertension in the continent (Dzudie, 2017).

Improved strategies are required for diagnosing and managing NCDs in this sector (Folb, 2015). Ten action points were identified that need to be undertaken by the African Ministries of health to control 25% of the hypertension in the continent by 2025. The ten point action plan comprises:

1. including hypertension in all NCD programs
2. allocate funding
3. write or adopt clinical guidelines for hypertension
4. monitor and report the clear target
5. integrate hypertension with existing policies
6. promote task sharing
7. ensure availability of resources
8. provide universal coverage for hypertension
9. invest in quality research and
10. invest in community interventions (Dzudie, 2017).

Only 25.8% of the African countries have developed or adopted guidelines for the management of hypertension (Dzudie, 2017), for example Egypt and South Africa.

For the Egyptian guideline they focused the problem on limited financial resources and the limited government spending on health in Egypt. The total annual/capita expenditure on health in Egypt is 124 USD compared with 3925 USD in USA. They stated that guidelines should give priority to cost of care. Therefore, countries with limited resources can not treat everyone with BP beyond the defined threshold stated in the international guidelines. They stated that low risk patients with BP 150-159/95-99 mmHg can be followed while on lifestyle modification without drug therapy. For low or intermediate risk groups it is recommended to initiate drug therapy with a BP >160/100 mmHg. That means they recommend a higher threshold of >150/95 mmHg for initiation of therapy should be considered and priority should be given to high risk patients. Furthermore, drugs of first choice should be the least expensive such as thiazide diuretics, beta adrenergic blockers and generic forms because patients will not adhere to drugs that they can not afford (Ibrahim, 2014). The members of the Egyptian working group reviewed available evidence from world literature and other national and international guidelines.

The South African Hypertension practice guideline 2014 recommends lifestyle modification for patients with BP 140-159/90-99 and if BP is not at target level after 3-6 months commence drug monotherapy. Drug therapy should start with either a low-dose diuretic, calcium channel blocker or an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Combination therapy should be considered initially if the BP is ≥ 160/100 mmHg. In black patients, either a diuretic and/or a calcium channel blocker (CCB) is recommended initially because the response rate is better compared to an ACEi. In resistant hypertension, an alpha-blocker, spironolactone, vasodilator or beta-blocker (BB) should be added (Seedat, 2014). These recommendation based on references from South Africa, Europe and North America, including national guidelines and trials that took into account the specifics of blood pressure therapy and complications in black patients, for example Bewster 2013. In the end they adopted the evidence-based guidelines of Europe and America for the African setting.

The European Society of Cardiology Guidelines 2018 recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients, and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. It is recommended to initiate an antihypertensive treatment with lifestyle interventions and a two-drug combination, preferably in a single-pill combination (SPC) for most hypertensive patients as initial therapy. The core treatment strategy simplified drug treatment algorithms preferred use of an ACEi or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, with BB used for specific indications (Williams, 2018). These recommendations are based on references from

Europe and worldwide multicenter trials, especially systematic reviews and meta analyses. Hypertension epidemiology, diagnosis and treatment database available for European black population is much scarcer in contrast to data studied in black US patients. Therefore, ESC extrapolated recommendations for the European black population from US data (Williams, 2018). There were no African trials or data mentioned.

In the clinical practice guideline for the management of high BP in adults the American Heart Association (AHA) recommended the use of BP-lowering medication for primary prevention of cardiovascular diseases (CVD) in adults with no history of CVD and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. For secondary prevention of recurrent CVD events in patients with clinical CVD and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher, the use of BP-lowering medications is recommended for patients with an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACEis or ARBs. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension. In blacks, thiazide diuretics or CCBs are more effective in lowering BP than are RAS inhibitors or beta blockers and more effective in reducing CVD events than are RAS inhibitors or alpha blockers. Furthermore, the combination of an ACE inhibitor or ARB with a CCB or thiazide diuretic produces similar BP lowering in blacks as in other racial or ethnic groups (Whelton, 2017). These recommendations are based on references from North-America and worldwide multicenter trials, especially systematic reviews and meta analyses, including Sprint 2017.

Considering guideline recommendations from America, Europe, Egypt and South Africa, the PASCAR published in 2017 a simple and practical treatment algorithm as a Road Map to achieve 25% hypertension control in Africa by 2025. The schedule should consider patient costs (including transport and loss of wages because of time off to attend clinic visits), which affect treatment adherence and burden to the healthcare system (Dzudie, 2017). For classification of raised blood pressure they used the common definitions as we can find for example in the European guidelines by ESC/ESH (ESC/ESH Guideline, 2018): grade 1 (140-159/90-99 mmHg), grade 2 (160-179/100-109 mmHg), grade 3 (≥180/≥110) and isolated systolic hypertension (≥140/<90 mmHg).

The recommendations by PASCAR can be used as a guideline for the African continent, as it exists for several countries. This guideline includes the following recommendations: The goal of treating hypertensive patients is keeping the blood pressure (BP) of patients to less than 140/90 mmHg. Screening can take place in health centers, clinics, hospitals, pharmacies, on markets or in churches. Lifestyle modification is the first recommendation for 3–6 months. If this fails, adding a thiazide or thiazide like diuretic or long-acting calcium channel blockers as monotherapy will be the next step. If blood pressure still cannot be controlled, combination of two medications is preferred along with lifestyle modifications. If patient has got three medications, secondary causes are suspected and BP not at goal referral to a specialist are recommended (Dzudie, 2017).

On the other hand, newer recommendations by the SPRINT research group stated that among patients at high risk for cardiovascular events but without diabetes a systolic blood pressure (SBP) of less than 120 mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause compared with a systolic BP less than 140 mmHg (SPRINT, 2017). These data are already counted by the AHA for the American guideline. But some adverse events occurred significantly more frequently with the lower target like hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure, but not injurious falls or bradycardia (SPRINT, 2017). The authors admitted that their observations suggested that achieving a systolic blood-pressure (SBP) goal of less than 120 mmHg in the overal population of patients with hypertension would be more demanding and time-consuming for both providers and patients than achieving a goal of 140 mm Hg, and would require increased medication costs and clinic visits (SPRINT, 2015).

Considering all specified guideline recommendations about hypertension, included the new recommendations after the publications of the SPRINT results, in this review blood pressure control is defined as a BP under 140/90 mmHg. In the African context problems with a more demanding and time consuming and additionally with increased medication costs and clinic visits do not seem to be feasible.

Especially if we take into account the low awareness of the disease with high prevalence of severe forms of hypertension with greater risk of target organ damage (TOD) among the African people (Bosu, 2015; Oladapo, 2012; Ferdinand, 2006). Nonetheless, there is evidence suggesting the awareness of hypertension among people living with the disease has been increasing since 1990; however, the overall awareness rate still remains relatively low in many parts of Africa (Adeloye, 2014).

2 Objective

The primary aim of this systematic review was to evaluate the number of existing randomized controlled trials (RCTs) on hypertension in Africa as there is to our knowledge no specific systematic review of RCTs on hypertension in Africa available yet. We wanted to describe all examined interventions to control hypertension in Africa and their reported effects on blood pressure.

Moreover, we wanted to report about the geographical distribution of the study centers and to what extent the results of studies included can be applied to all African people.

Results of this review should underline the importance of diagnosis and treatment of hypertension and therefore will have implications on research and clinical practice in African countries. One big target, not only by this review, should be the implementation of general evidence-based guidelines for hypertension in Africa and its different regions.

3 Methods

3.1 Literature search and study selection

The protocol of this systematic review was prospectivelly registered on 17/07/2017 (PROSPERO registration number (CRD42018075062). As registered in PROSPERO protocol we planed a narrative synthesis but changed to a systematic synthesis with the beginning of literature search. We searched in online databases (Medline Ovid, Central, CINHAL) and registers of ongoing and completed studies (http://apps.who.int/trialsearch/AdvSearch.aspx) to identify all relevant RCTs on hypertension conducted in African countries. The main keywords for the search strategy included: hypertension, high blood pressure, blood pressure control, Africa, a list of all African countries and randomized controlled trials (see Appendix, 9.5 Search Strategies). The first search was conducted in July 2017 and updated in October 2019. The last search was conducted in January 2020. The study selection process was described in a flow chart according to the PRISMA statement (Moher, 2009).

Titles and abstracts of all articles retrieved from literature search were independently screened by the same two authors. Full texts of potentially eligible articles were obtained and further assessed for final inclusion. Disagreements were resolved through consensus. All these steps were conducted by the author of this thesis and a second author.

3.2 Inclusion and exclusion criteria

We included all full-text publications on RCT including cross-over RCT and cluster RCT which reported results on blood pressure as a result of secondary or tertiary prevention of hypertension. We only included RCTs, because they lead to greater efficiency of research and supply of care. Lange 2017 stated that RCTs are the only way to ensure the required significance necessary for clinical guidelines (Lange, 2017).

RCTs on primary prevention were excluded due to the high variety of interventions and broad objectives of these RCTs. For detailed inclusion criteria see figure 1.

	Inclusion criteria
Design	Randomized controled trials initiated and conducted in African countries
Population	African patients in secondary and tertiary prevention, diagnosis and treatment of hypertension
Intervention	all preventive, diagnostic and curative interventions on CVD
Outcome	primary: hospital admission and death, secondary: blood pressure (SBP, DBP, MAP), heart rate (HR), adherence to therapy within longest follow-up
Publication	Full-text publication according to CONSORT in English or German
CONSORT: Consolidated Standards of Reporting Trials (Moher 2010, Boutron 2017); CVD: cardiovascular disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: Heart rate	

Figure 1 Inclusion criteria

3.3 Outcome

The primary outcomes of the systematic review on CVD were hospital admission and death. Secondary outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) or its change to baseline values within the longest follow-up period and grade of cardiac insufficiency classified by the New York Heart Association (NYHA). We added heart rate (HR) and adherence to therapy for this systematic review on hypertension.

3.4 Data extraction and management

Information about

- ⇒ study data (authors name, study name, year of publication, other publications)
- ⇒ study characteristics (study design, prevention level, grade of disease, inclusion/exclusion criteria, study duration, country and region in which the study was conducted, outcomes)
- ⇒ characteristics of included participants (sample size enrolled, mean age, baseline values according to our defined outcomes, mean weight/Body mass index (BMI))
- ⇒ a description of the intervention and control groups and
- ⇒ the main results of our pre-planned outcomes

were abstracted and entered into an Excel sheet. Study name consists of name of first author and the year of the first puclication of final results. Grade of hypertension described according to the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines: mild hypertension corresponds to grade 1 (140-159/90-99 mmHg), moderate to grade 2 (160-179/100-

109 mmHg) and severe to grade 3 ≥180/≥110 mmHg) hypertension (ESC/ESH guidelines 2007, Tran 2014). Concerning our RCTs included resistant, severe, malignant or uncontrolled hypertension can be classified as severe, therefore grade 3 hypertension. We included all records in this review with participants who had a BP higher than 140/90 mmHg.
Main results are presented for intervention group (IG) and control group (CG). Intervention groups are defined as groups with the treatment to be investigated. That means in case of drug treatment RCTs: defined medication (IG) compared to placebo (CG), or new medication or specified combination of different drugs (IG) compared to established medication or single therapy (CG). In the case of non-pharmacological RCTs: intervention group got special treatment strategies (IG), while control group got usual care (CG). There are RCTs with more than two intervention groups. Here we present first the group with the strongest effect (IG).

In the case of reported BP and HR measured in standing, supine or lying position we extracted results for supine position. In the case of reported BP and HR mean resulting from 24h-ambulatory blood pressure monitoring we additionally extracted these results. In the case of presented mean change of SBP, DBP, MAP to baseline values, we extracted these results.
Effect sizes were calculated on the basis of mean and standard deviation for metrically captured values or by comparing the frequencies of better BP control. They are based on the precision of reported values.
We present the mean differences (MD) with their 95 % confidence intervals (CI) in forest plots. MD describe the difference of results between mean values in the intervention and control groups. Negative MD describe a positive treatment effect with lower BP or higher decrease of BP at end of longest follow up. Furthermore, we calculated relative risks (RRs) to compare the frequency of BP control in the intervention and control group. A RR greater than 1 describes a better control in the intervention compared with the control group.

3.5 Quality assessment and risk of bias

Quality and risk of bias of all studies was evaluated using the Cochrane risk of bias assessment tool (Higgins, 2011). The quality was assessed by two independent investigators (the author of this thesis and another author) in the following domains:

- ⇒ sequence generation
- ⇒ allocation concealment
- ⇒ blinding of personal and participants
- ⇒ blinding of outcome assessors
- ⇒ incomplete outcome data
- ⇒ selective outcome reporting and
- ⇒ other sources of bias.

Selective outcome reporting was defined as low, when the study protocol was available and high if any result of pre-planned outcomes was missing. Incomplete outcome data was high when there were more than 10 percent of randomized participants dropped out from analyses. Other sources of bias was reported to be high if sample size calculation was missing, no primary endpoint was defined or study had other problems such as no reporting of baseline values.

3.6 Data synthesis

We summarized results of different RCTs on strategies and substances in forest plots (Higgins, 2011), but did not estimate pooled treatment effects due to the high clinical heterogeneity between included RCTs due to different settings, interventions, control groups, included participants and lengths of follow-up. These forest plots should give a visualization of different investigated interventions and observed treatment effects on SBP and DBP.

Results will be categorized as statistically significant or clinically relevant. Clinically relevant results are statistically significant and the mean differences at the end of follow up are at least 5 mmHg.

4 Results

We originally planned to include RCTs on all CVDs, but we restricted this systematic review to hypertension as one of the main risk factors of other CVDs due to the high number of eligible studies and restricted time resources. Therefore, no RCT reported results on our pre-planned primary endpoints. So we added adherence and heart rate as additional endpoints.

We identified a total of 4994 references (Medline: 2960, CENTRAL: 2008, CINHAL: 26) from electronical databases and 18 references from the International Clinical Trials registry platform. A total of 330 articles were thought to be potentially eligible and full texts were assessed against the inclusion and exclusion criteria. No new potentially eligible studies were identified by the latest search in CINAHL. A total of 198 + 20 articles were excluded. Causes of their exclusion are described in the appendix (see Excluded studies with causes (N=218)). A total of 90 trials, described in 112 publications on treatment of patients with hypertension fulfilled the inclusion criteria and were considered as eligible for this systematic review (Fig. 2).

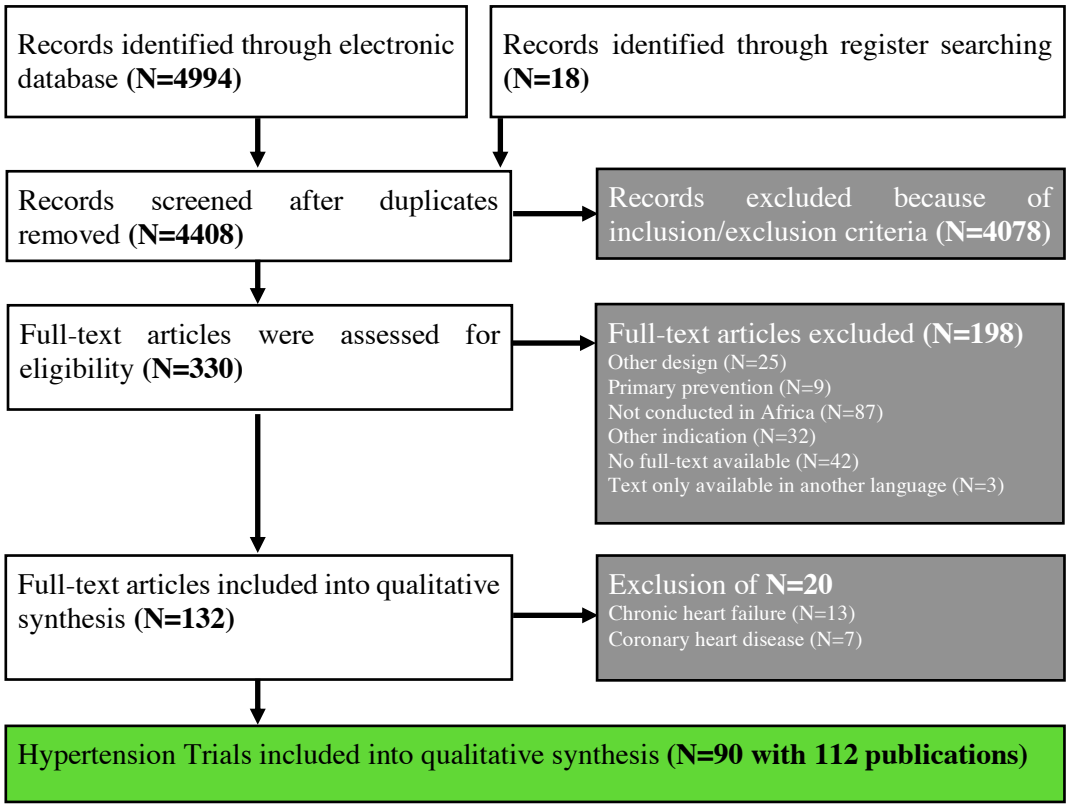

Figure 2 PRISMA flow diagram describing the process of study selection

4.1 Study characteristics

We included 63 RCTs with two or more independent parallel groups and individual randomisation of patients, 13 cluster-RCTs with randomisation of different observation units, such as two or more independent villages, clinics or different geographical regions and 14 cross-over RCTs, where each study participant receives both medications "A" and "B" in a randomized order (i.e., either AB or BA). The two treatment periods in a cross-over RCT are usually separated by a wash-out period, to avoid overlap of the medication effects or side-effects (Lange 2017).

Most of the included RCTs were conducted in South Africa (N=36) and West Africa (N=27; Nigeria N=25, Ghana N= 2), nearly all of them in urban (94%) setting. Concerning the distribution of conducted RCTs on the African continent see figure 3.

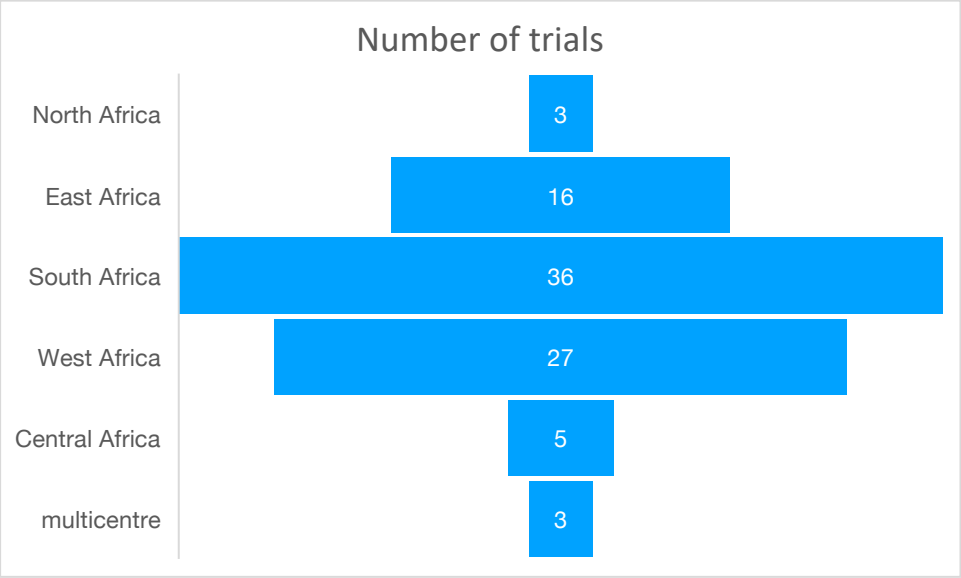

Figure 3 Distribution of conducted RCTs on the African continent (North Africa: Libya, Egypt; East Africa: Ethiopia, Kenya, Zambia, Zimbabwe; South Africa: South Africa; West Africa: Ghana, Nigeria; Central Africa: Cameroon, DR Kongo; multicentre: Subsaharan Africa)

RCTs reviewed in this article were conducted in 3 upper-middle income countries (South Africa, Libya, Gabon), in 9 low-middle income countries (Nigeria, Kenya, Zimbabwe, Zambia, Cameroon, Egypt, Ghana, Senegal, Côte d´Ivoire) and in 4 low income countries (Ethiopia, D.R. Congo, Mozambique, Uganda). Mozambique, Uganda, Senegal, Côte d'Ivoire and Gabon only occur in multicenter studies (figure 4). The classification of income level was taken from New country classifications by income level: 2019-2020, WORLD BANK DATA TEAM|JULY 01, 2019.

Furthermore, figure 4 shows the number of generally available essential NCD medication and the number of generally available essential NCD technologies in the African counties included in this review according to Noncommunicable diseases country profiles (WHO, 2018).

The 10 essential NCD medicines include aspirins, statins, angiotensin-converting enzyme inhibitors, thiazide diuretics, long-acting calcium channel blockers, beta-blockers, insulin, metformin, bronchodilators, and steroid inhalants. The six basic technologies include blood

pressure measurement device, weighting scales, height measuring equipment, blood sugar and blood cholesterol measurement devices with strips, and urine strips for albumin assay (WHO, 2018).

In South Africa, Kenya and Ghana there is a good access to essential medication. In Egypt, South Africa, Ghana and Libya most if the NCD technologies are generally available.

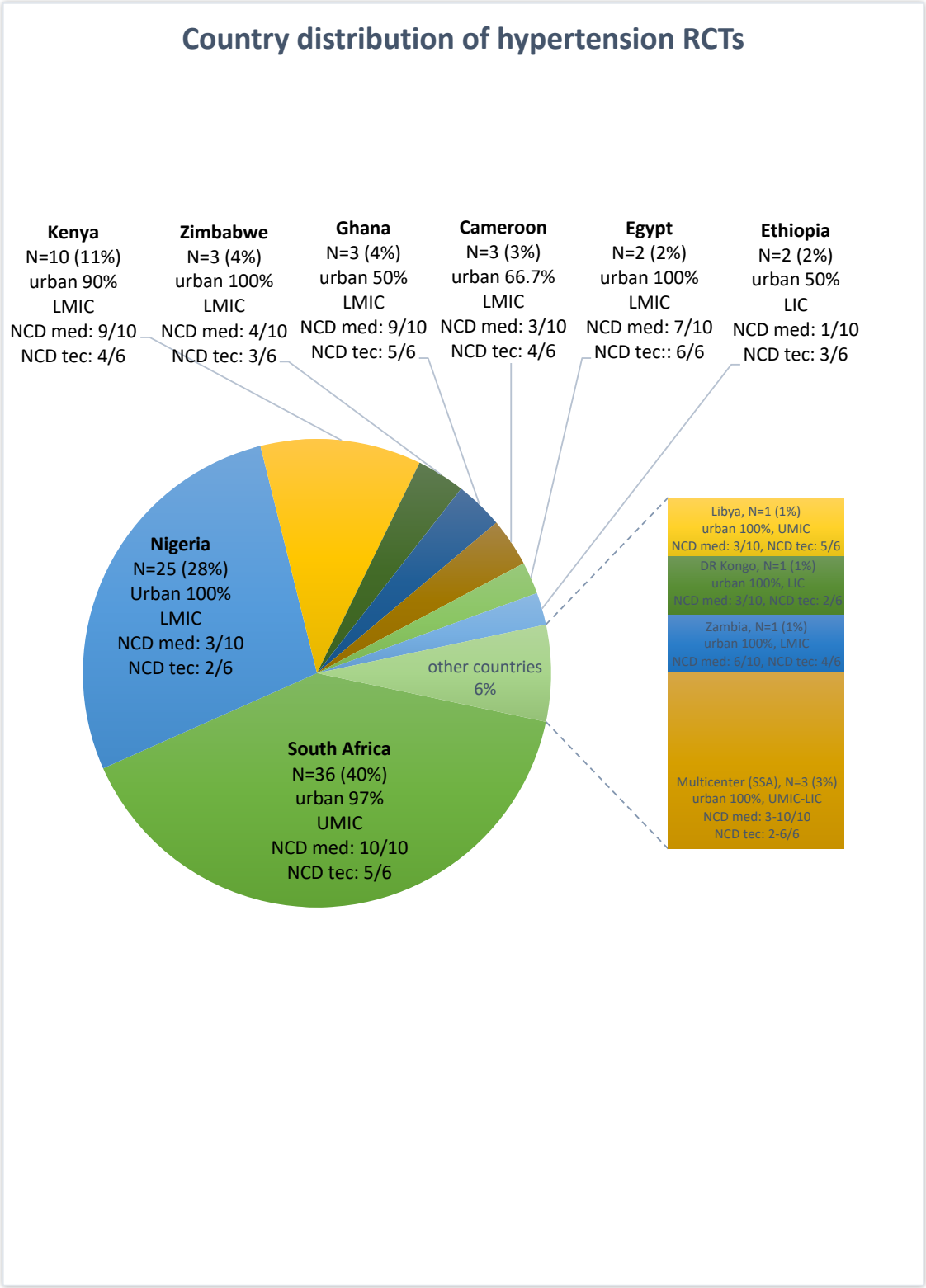

Figure 4 LIC: low income country, LMIC: low-middle income country, UMIC: upper-middle income country, **New country classifications by income level: 2019-2020, WORLD BANK DATA TEAM|JULY 01, 2019, NCD med: number of essential NCD medication generally available***, NCD tec: number of essential NCD technologies generally available***; ***Noncommunicable diseases country profiles, 2018; SSA: Sub-Saharan-Africa (Nigeria, South Africa, Kenya, Cameroon, Mozambique, Uganda, Senegal, Côte d`Ivoire, Gabon)

We had no time constriction on year of publication so we included RCTs published from 1971 to 2019. From 1971 to1979 there were eight RCTs (5 of them in South Africa, 3 of them in Nigeria), from 1980 to 1989 twenty (such as 7 of them in South Africa, 5 of them in Kenya, 4 of them in Nigeria), 1990 to 1999 twenty-six (such as 14 of them in South Africa, 4 of them in Nigeria, 4 of them in Kenya), 2000 to 2009 seven (5 of them in South Africa, 2 of them in Nigeria) and from 2010 to January 2020 there were twenty-nine (12 of them Nigeria, 5 of them in South Africa, 3 of them in Cameroon, 3 of them in Ghana, 2 of them in Egypt, 2 of them in SSA) RCTs on treatment of hypertension (Figure 5).

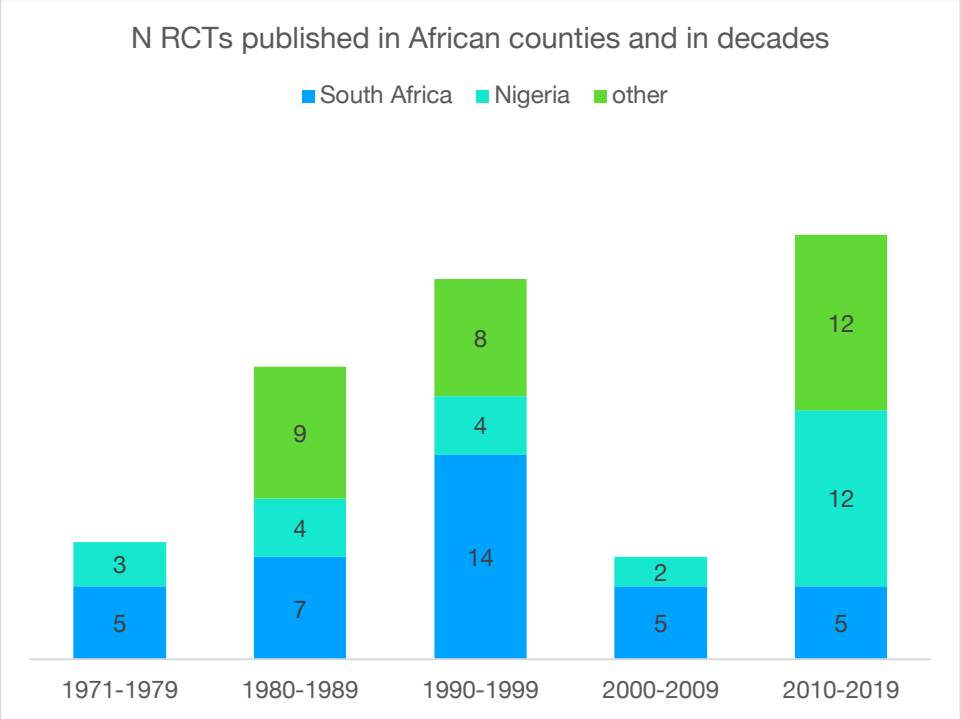

Figure 5 Time distribution of hypertension randomized controlled trials in Africa

4.2 Participants

The total number of participants was 23 562. A total of 72 of the 90 RCTs (80%) include participants with mild to moderate hypertension, 7 (7.8% of 90 trials) (422 participants) with resistant, severe, malignant or uncontrolled hypertension, 3 (3.3% of 90 trials) (3640 participants) with mild to severe hypertension, 2 (2.2% of 90 trials) (88 participants) with mild and 1 (1.1% of 90 trials) (45 participants) with moderate hypertension. 5 trials (5.6% of 90 trials)(1396 participiants) did not differentiate grade of hypertension.

Although there were 6 RCTs (696 participants) conducted only with men, more women took part in hypertension RCTs, of those who reported sex distribution (men 38%, women 62%). In 9 RCTs sex distribution was not mentioned, that concerns 394 participants.

Except for 1 RCT (Mabadeje 1989, n=20, 40% female, mean age 37 ± 6), in all trials of those who reported age, mean age of participants was higher than 40 years.

Corresponding to the ESC/ESH guidelines we included RCTs with following distribution of grades of hypertension:

grade 1 hypertension	2.2%
grade 2 hypertension	1.1%
grade 3 hypertension	7.8%
grade 1 to 2 hypertension	80%
grade 1 to 3 hypertension	3.3%
unknown grade of hypertension	5.6%.

4.3 Interventions

RCTs investigate the efficacy of pharmacological (N=67, 74.44%) and non-pharmacological (N=23, 25.56%) interventions.

4.3.1 Pharmacological Interventions

A total of 67 RCTs compared different drug regimes. 11 trials with pharmacological intervention randomized more than 100 participants. That means there were 56 RCTs with less than 100 participants, the smallest RCT was conducted by Salako 1979a with 9 participants. The biggest RCT was conducted by Ojii, 2019 with 728 randomized participants. 18 (27%) of 67 RCTs were conducted as cross-over RCTs. There was no cluster RCT among the pharmacological intervention RCTs.

These RCTs examined mainly the effect of 6 different antihypertensive drug classes (diuretics, beta-blockers, calcium-channel blocker (CCB), angiotensin-converting-enzyme inhibitors (ACEi), alpha-receptor-blockers, angiotensin-receptor blockers (ARB)) and a few other drugs (sympathomimetics, indolalkaloid, serotoninantagonist, vasopeptidaseinhibitor, phosphodiesteraseinhibitor, benzodiazepine, fatty acids, plants, electrolytes), with in total 48 different drugs.

Diuretics

Table 1 shows baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for pharmacological intervention RCTs with diuretics.

Table 1 Study characteristics of RCTs on intervention with Diuretics in secondary prevention of hypertension

Study		Patients						Intervention	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
Diuretics vs. placebo									
Dean 1971 #	South Africa	120	n.r.	n.r.	white: 179, Batu: 173	White:104, Bantu: 114		Baycaron (mefruside) 25 mg vs. hydrochlorothiazide (HCT) 50 mg vs. placebo 2xtgl	3
Mngola EN. 1980 **	Kenya	22	n.r.	n.r.	154.7±5	101.4±4.6		spironolactone 25 mg + althiazide 15 mg vs. placebo	4.5
Stein 1992 **	Zimbabwe	25	49.2 ± 8.8	47 %	174±22.2	104.3±7.1		HCT 50 vs. 25 vs. 12.5 vs. 6.25 mg vs. placebo	1.5
Diuretics vs. other diuretic									
Iyalomhe 2007 #	Nigeria	80	57.6 ± 9.9	50 %	n.r.	n.r.	MAP: 127.2±26.6	furosemide 40 mg vs. HCT 25 mg	<1
Obel 1984	Kenya	50	18-65	47 %	158.3±16.9	104.8±9.1		bendrofluazide 10 mg vs. furosemide 60 mg	8
Radevski 2002	South Africa	42	57 ± 11	67 %	157±15	96.5±8.5	24h SBP 148±15, DBP 94 ±7	indapamide 2.5 mg vs. HCT 12.5 mg	3
Wadhawan 1981	Zambia	40	41.5	30 %	162.5	105.2	MAP: 124.4± 5.1	furosemide 40 mg vs. HCT 50 mg	6
Diuretics vs. CCB									
Ajayi 1995	Nigeria	20	54.6 ± 8	53 %	185.3± 15.8	103.5± 12.6		HCT 25 (50) mg vs. amlodipine 5 (10) mg	1.5
Daniels 1987 **	South Africa	47	49 ± 1	84 %	165± 17	107.7± 6.5		HCT-amiloride 1x1 vs. HCT-amiloride 2x1 vs. nisoldipine 1x1 vs. nisoldipine 2x1	6
Iyalomhe 2013	Nigeria	90	64.3 ± 11.4	50 %	166.7±30.8	105.2±16.9		HCT 25 mg (+amlodipine 5 mg or 10 mg) vs. amlodipine 5 mg (10 mg) (+HCT 25 mg) vs. amlodipine +HCT 5+25 (10+25)	12
Leary 1990	South Africa	45	41.5 (22-60)	2 %	157.8± 13	107.5± 5.5		HCT 12,5 (25) mg 2x/d vs. felodipine 2,5 (5) mg 2x/d, at week 4 dosage doubled if DBP >90 mmHg, after week 8 Metoprolol 100mg 2x/d added if DBP >90 mg	3
Nwachukwu 2017	Nigeria	50	48.3 ± 11.3	44 %	157 vs. 154	101 vs. 99	MAP: 129 vs. 128	HCT 25 mg 1x/d vs. amlodipine 5 mg 1x/d	5
Salako 1998	Nigeria	62	52.8 ± 15.8	68 %	157.2± 16.8	100.6± 5.2		HCT 25 (50) mg vs. lacidipine 4 (6) mg	3
Sobngwi 2019	Cameroon	30	median: 57 (IQR 53-60) vs. 60 (IQR 52-64)	53 %	143 (IQR 140-150) vs. 147 (IOR 141-151)	91 (IQR 85-93) vs. 89 (IQR 84-96)	24h SBP: 144 (IQR 138-152) vs. 145 (IQR137-155), 24h DBP: 85(IQR 75-89) vs.89 (IQR 82-93),	perindopril-indapamide (Bipreterax 5/1.25 mg) vs. perindopril-amlodipine (Coveram 5/5 mg) 1x/d	1.5
Ahaneku 1995 #	Nigeria	81	n.r.	n.r.	n.r.	n.r.	n.r.	HCT 50 mg + amiloride 5 mg vs. amlodipine 5-10 mg vs. doxazosin 2-16 mg	3

Study		Patients						Intervention	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
Mengesha 2018	Ethiopia	141	46 ± 10	60 %	172 ± 18.1	104 ± 6		nifedipine 20 (40) mg po bid vs. enalapril 5 (15) mg bid vs. HCT 12.5 (25) mg po daily mg	3
Sareli 2001	South Africa	409	53.3 ± 10.1	77 %	164.7 ± 18.5	99.4 ± 8		nifedipine 30 (60, 90) mg vs. verapamil 240 (360, 480) mg vs. HCT 12,5 (25) mg vs. enalapril 10 (20) mg	13
Diuretics vs. BB									
Habte 1992	Ethiopia	67	42,47 ± 13,14	50 %	160.85± 21.97	103.83± 6.66		HCT 25 (50, 100) vs. timolol 10 (20, 40) mg vs. enalapril 10 (20, 40) mg	2
Obel 1981 **	Kenya	34	22-65	59 %	141± 14.2	98± 12		butizide 2.5 mg vs. metipranolol 20 mg vs. fixed combination metipranolol/butizide 20/2.5 mg	4
Obel AO. 1990	Kenya	62	44 ± 9	56 %	150.5± 13	104.5± 4		chlorthalidone (25 mg) 50 mg vs. oxprenolol (160 mg) 320 mg vs. oxprenolol/chlorthalidone (160/20 mg) 320/40 mg	6
Ogola 1993	Kenya	60	42 ± 9	50 %	156.1± 11.2	102.1± 8.6		hydroflumethiazide 50 mg vs. propranolol 80 mg (160 mg)	3
Salako 1990 **	Nigeria	24	29-70	71 %	182.6± 23.8	107.8± 9.1		chlorthalidone 25 mg vs. atenolol 100 mg vs. atenolol+ chlorthalidone 100/25 mg separate vs. atenolol+ chlorthalidone 100/25 mg combined	4
Seedat 1980 **	South Africa	24	n.r.	n.r.	159± 22.5	102.5± 15.2		chlorthalidone 25 mg + placebo vs. atenolol 100 mg + placebo vs. atenolol/chlorthalidone 100/25 mg vs. placebo	5
Diuretics vs. ACEi									
Ajayi 1989	Nigeria	20	54.58 ± 8	55 %	169.5 ±23.5	111.5 ±16.5		HCT 50 mg + placebo vs. enalapril 20 mg + placebo vs.	1
Diuretics vs. others									
Djoumessi 2016	Cameroon	17	62.9 ± 8.3	53 %	158±13.6	89.8 ±9.7		spironolactone 25 mg daily vs. alternative antihypertensive regime (8 mg candesartan, 100 mg atenolol or 750 mg alpha methyldopa)	4
Leary 1987	South Africa	32	48 ± 6.4	0 %	161.9 ± 15.3	104.1 ± 3.3	MAP: 124.4± 5.1	HCT + ketanserin 40 mg vs. ketanserin 40 mg, both once daily	12
Obel 1991	Kenya	84	44.5 ± 3.4	48 %	164± 13	110± 2.5		bendrofluazide 10 mg vs. potassium supplements 64 mmol	8

No sign= RCT, *cluster-RCTs, **cross-over RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure ; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk, HCT: Hydrochlorothiazide;

In 34 RCTs the effect of diuretics was examined, mostly thiazide and thiazid-like diuretics, such as hydrochlorothiazide (HCT) (N=22), chlorthalidone (N=4), bendrofluazide (N=2), hydroflumethiazide (N=2), indapamide (N=2), althiazide (N=1), butizide (N=1),

cyclopenthiazide (N=1). But also the effects of furosemide (N=3), as a loop diuretic and other diuretics (amiloride N=3, spironolacton N=2 and mefruside N=1) were examined. The results of RCTs with diuretics are summarized in figure 5 for SBP, figure 6 for DBP and figure 7 for MAP.

A total of 3 RCTs (Dean, 1971; Mngola, 1980; Stein, 1992) with 167 participants compared the effect of antihypertensive therapy by diuretics against placebo. Mean age was 49 years (Stein, 1992) or not reported (Dean, 1971; Mngola, 1980) and 47% were females (Stein, 1992, sex not reported: Dean, 1971; Mngola, 1980).
Dean 1971 (n=120) and Mngola 1980 (n=22) reported results which favours the medication for SBP and DBP compared to placebo without reporting SD. Stein 1992 (n=25) reported a significant higher effect on DBP for diuretics compared to placebo (MD -10.9 mmHG; 95 % CI -17.2 to -4.5).

A total of 4 RCTs (Iyalomhe, 2007; Obel, 1984; Radevski, 2002; Wadhawan 1981) with 354 participants investigated the effects of different subgroups of diuretics. Mean age was between 42 (Wadhawan, 1981) and 58 years (Iyalomhe, 2007) and between 30% (Wadhawan, 1981) and 67% (Radevski, 2002) were females.
Three RCTs (Iyalomhe, 2007; Wadhawan, 1981; Obel 1984) compared the effect of thiazide and loop diuretics and one RCT (Radevski, 2002) compared the effect of two different thiazid-like diuretics (see table 1). Radevski 2002 reported a non-significant lower SBP (see figure 6) a significant lower DBP (see figure 7) with indapamide compared to HCT (MD -10 mmHg; CI (-21.83 to 1.83). Obel 1984 reported a non-significant lower SBP (see figure 6) with the thiazide diuretic compared to the loop diuretic.
Comparisons between furosemide to HCT showed significant but clinically not relevant improvements for the loop diuretic in one RCT (Iyalomhe, 2007: MD -3.7 mmHg; CI -6.92 to -0.48) (see figure 8).

A total of 10 RCTs (Ajayi, 1995; Daniels, 1987; Iyalomhe, 2013; Leary, 1990; Nwachukwu, 2017; Salako, 1998; Sobngwi, 2019; Ahaneku, 1995; Ojii, 2019; Mengesha, 2018; Sareli, 2001) with a total of 1703 participants compared effects between diuretics (HCT) and different CCBs. Mean age was between 42 (Leary, 1990) and 64 years (Iyalomhe, 2013) and between 2% (Leary, 1990) and 84 % (Daniels, 1987) were females.
In the RCTs by Ahaneku 1995, Ojii 2019, Mengesha 2018 and Sareli 2001 this investigation was part of a comparison of more different drugs, for example beside the diuretic and CCB subgroup also a ACEi subgroup was part of the trial by Mengesha and Sareli. We decided to concentrate our report on the effects comparing diuretics versus CCBs.
Ahaneku 1995, Ojii 2019, Sareli 2001 and Sobngwi 2019 did not report mean outcome and SD of SBP, DBP or MAP. Daniels 1987 (n=47), Leary 1990 (n=45) and Salako 1998 (n=62) showed

a better effect for the therapy with diuretics compared to CCBs for both, SBP and DBP. The results were not statistically significant.
Ajayi 1995 (n=20) favoured the therapy with diuretics compared to CCBs for SBP, without being statistically significant.
Nwachukwu 2017 (n=80) favoured the therapy with diuretics compared to CCBs for change in DBP (MD -7.2 mmHg; CI -8.29 to -6.11) and MAP (MD -7.2 mmHg; CI -8.42 to -5.98), with statistically significant and clinically relevant results. However, Nwachukwu 2017 showed also statistically significant and clinically relevant better effects for the therapy with CCB compared to diuretics for SBP change (MD 9.1 mmHg; CI 7.73 to 10.47). Same did Mengesha 2018 (n= 141) with statistically significant and clinically relevant results for SBP change (MD 5.3 mmHg; CI 1.25 to 9.35).
Iyalomhe 2013 (n= 90) favoured the therapy with CCBs for SBP and DBP compared to diuretics. The results were not statistically significant.

A total of 6 RCTs (Habte, 1992; Obel, 1981; Obel, 1990; Ogola, 1993; Salako, 1990; Seedat 1980) with a total of 271 participants compared the effect of different diuretics with different beta-blockers. Mean age was between 42 (Ogola, 1993) and 44 years (Obel, 1990) and between 50% (Habte, 1992; Ogola, 1993) and 71 % (Salako, 1990) were females.
All showed a better SBP for the therapy with diuretics compared to the therapy with beta-blockers, Salako 1990 (n=24) with the smallest (MD -2.6 mmHg; CI -10.84 to 5.64) and Obel 1990 (n=62) with the strongest effect (MD -20 mmHg; CI -26.02 to -13.98). Obel 1981 and 1990 and Hapte 1992 showed statistically significant and clinically relevant results.
Obel 1981 and 1990, Ogola 1993, Salako 1990 and Seedat 1980 showed similar effects on DBP with statistically significant and clinically relevant results in Obel 1981 and 1990 and Ogola 1993.

One RCT, Ajayi 1989 (n= 20 participants, 55% female, mean age 55 years) compared the effect of diuretics with ACEi (HCT vs. enalapril). They reported better effects to treatment with HCT for SBP (MD -6.00 mmHg; CI -30.30 to 18.30, not statistically significant) and DBP (MD -13.00 mmHg; CI -24.91 to -1.09, statistically significant).

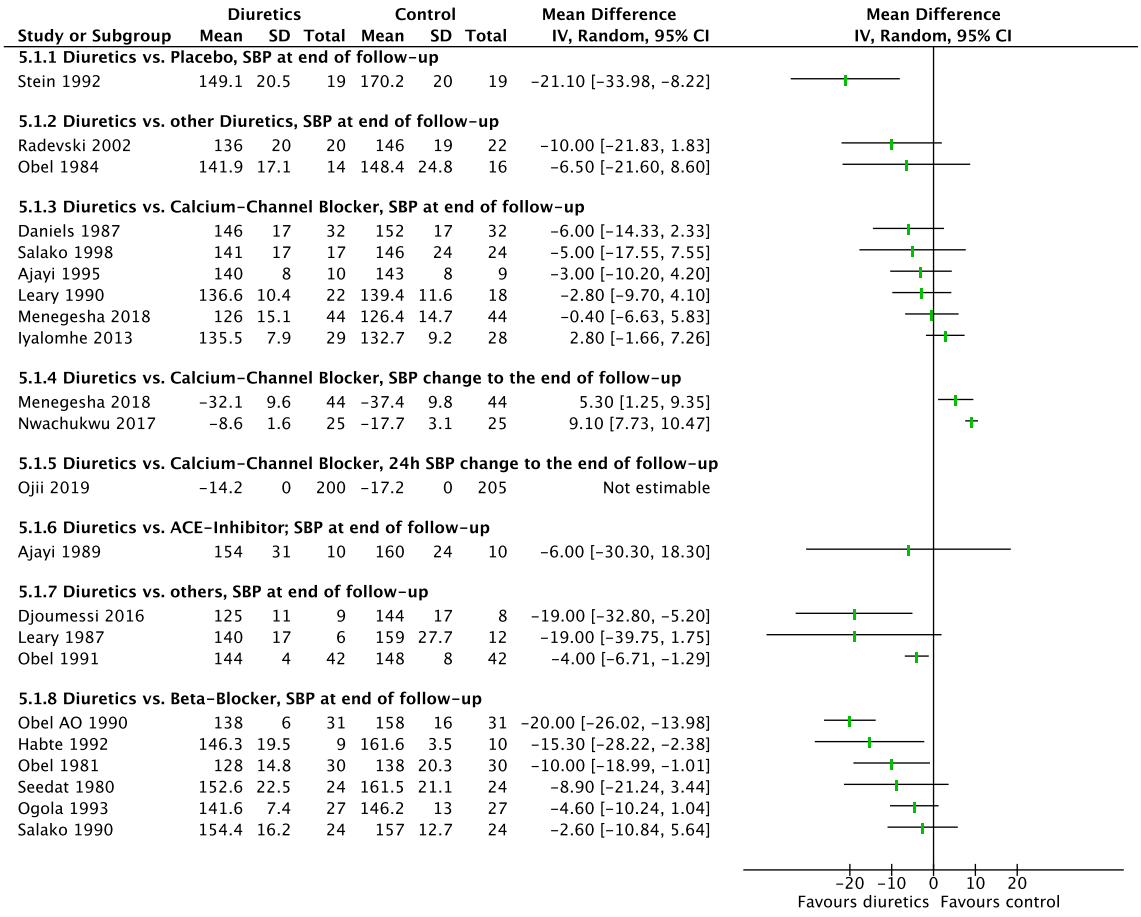

Figure 6 Forest plot of comparison: diuretics, outcome: systolic blood pressure

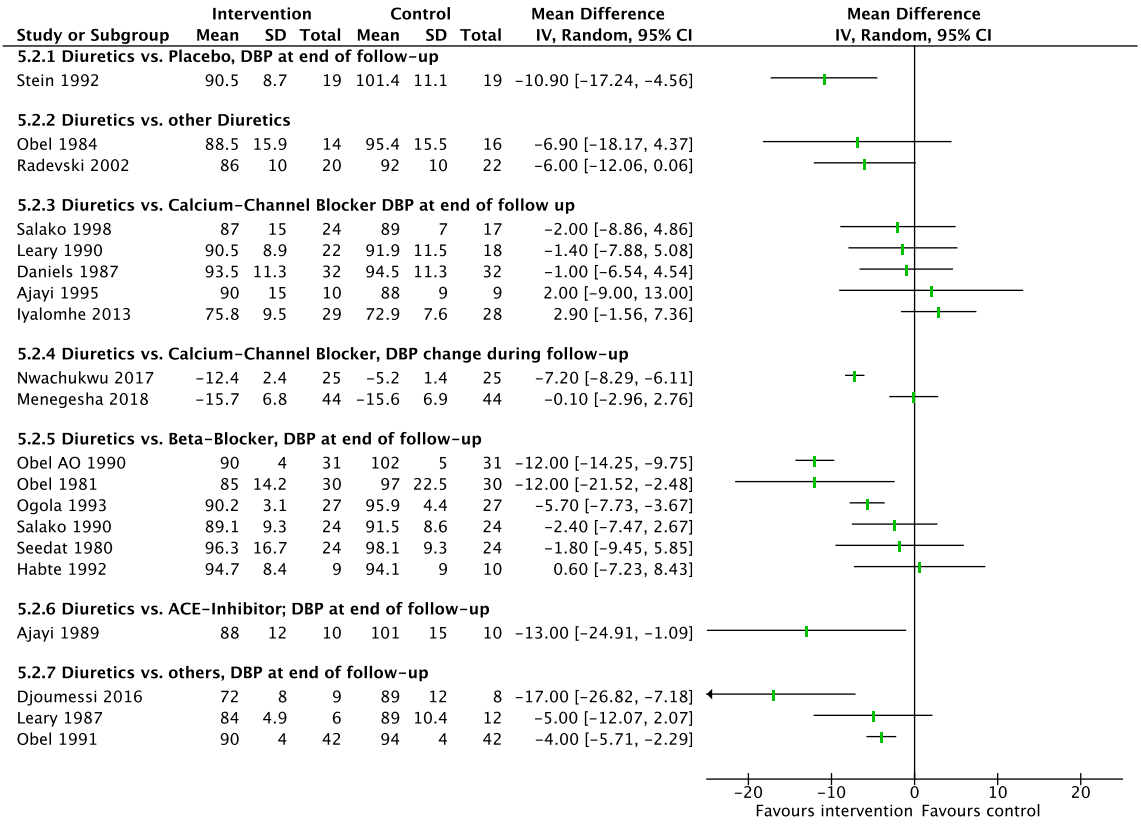

Figure 7 Forest plot of comparison: diuretics, outcome: diastolic blood pressure

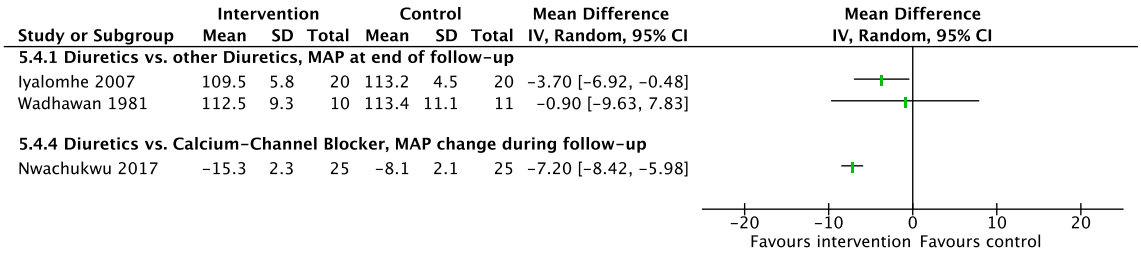

Figure 8 Forest plot of comparison: diuretics, outcome: mean arterial blood pressure

Calcium-channel blocker (CCB)

Table 2 shows baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for pharmacological intervention trials with CCB.

Table 2 Study characteristics of RCTs on intervention with calcium-channel-blocker in secondary prevention of hypertension

Study		Patients						Intervention	
Name (design)	**Country**	**N**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
Calcium-channel-blocker vs. placebo									
Fadayomi 1986	Nigeria	32	37-59	44 %	180.4± 3.9	114.4± 2.4		nifedipine 20 mg 2x1 (16) vs. placebo	1.5
Opie 1997	South Africa	206	52 (20-75)	55 %	164.1	104.3		nisoldipine 30 mg vs. 20 mg vs. 10 mg vs. placebo	1.5
Calcium-channel-blocker vs. other dosages or other calcium-channel-blocker									
Leary 1991	South Africa	45	48.2 ± 7.7	0 %	121.7± 9.7			isradipine 1.25 vs. 2.5 vs. 5 mg twice daily	3
Maharaj 1992	South Africa	30	49.1 (19-60)	0 %	198.1	129.1		nifedipine 10 mg vs. 5 mg	4hrs
Onwubere 2001	Nigeria	121	50.5 ± 11.8	47 %	153.1± 17.9	98.5± 9.1		nifedipine 10 mg2x/d vs. felodipine 5 mg 1x/d	1.5
Calcium-channel-blocker vs. BB									
Farag 2018 #	Egypt	160	56.38 ± 10.74	68 %	n.r.	n.r.		amlodipine 10 mg/valsartan 160 mg (single pill) vs. nebivolol 5 mg/valsartan 160 mg (1 tablet each)	12
Isles 1986	South Africa	20	57 ± 11	50 %	229.5 (233/226)	141.5 (142/141)	MAP: 171.5 ± 8.6	slow release nifedipine 40mg at 0 and 12h vs. atenolol 100mg at 0h only	1d!
M'Buyamba-Kabangu 1988	Zaire (DR Kongo)	34	52 (20-75)	47 %	161± 8.3	101.5± 4.1		nitrendipine 20 mg vs. atenolol 100 mg	1.5
Poulter 1993 **	Kenya	37	30-69	n.r.	180 ± 30.2	114± 14		nifedipine 2x20 mg + HCT 25 mg vs. propanolol 2x80 mg +HCT 25 mg	3
Calcium-channel-blocker vs. ACEi									
Maharaj 1993a	South Africa	52	n.r.	0 %	155.9±18.79	102.2± 9.35	MAP: 120.1± 11.19	isradipine 2,5 mg vs. enalapril 10 mg once daily,	2
Radevski 1999	South Africa	143	47.5 ± 9	52 %	180± 13.6	117.6± 6.2		nisoldipine 10/20/40 mg vs. enalapril 10/20/40 mg	6
Skoularigis 1994	South Africa	45	47.5 ± 10	49 %	n.r.	n.r.	24h: SBD:156 ± 13.6, DBD: 101± 6	nifedipine 2x20 (2x40) mg vs. captopril 2x25 (2x50) mg	3
Calcium-channel-blocker vs. others									
Manyemba 1997 **	Zimbabwe	32	21-65	81 %	181.5± 15.5	113.1± 8.9		nifidipine 20 mg + HCT 25 mg vs. reserpine 0,25 mg + HCT 25 mg vs.	2
Seedat 1990 **	South Africa	47	49 ± 9.7	63 %	173.1± 21.7	103± 4.9		nitrendipin 10/20/40 mg vs. methyldopa 250 mg	3

No sign= RCT, *cluster-RCTs, **cross-over RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure ; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk, HCT: Hydrochlorothiazide

In 27 RCTs the efficacy of calcium-channel-antagonists (CCB) was studied, such as nifedipine (N=10), amlodipine (N=8), nisoldipine (N=2), felodipine (N=2), isradipine (N=2), nitrendipine (N=2), lacidipine (N=1) and verapamil (N=1) (see figure 8 for SBP and figure 9 for DBP).

Two RCTs (Fadayomi, 1986; Opie, 1997) compared the effect of antihypertensive therapy by calcium-channel blocker against a placebo. Fadayomi 1986 (n= 32, age between 37 and 59 years) compared the effect of nifedipine against a placebo. Opie 1997 (n= 206, 55% female, mean age 52 years) compared the effect of nisoldipine against placebo. They reported a statistically significant and clinically relevant effect for the intervention with the calcium-channel blocker on SBP (Fadayomi, 1986: MD -56.5 mmHg; CI -65.45, -47.55), DBP (Fadayomi, 1986: MD -32.3 mmHg; CI -37.07 to -27.53) and DBD change from baseline to the end of follow up (Opie, 1997: MD -4.8 mmHg; CI -8.45 to -1.15).

A total of 3 RCTs with a total of 196 participants examined the effect of different dosages of the same active substance, isradipine (Leary, 1991) or nifedipine (Maharaj, 1992), respectively, or of two different CCB (Onwubere, 2001). Mean age was between 48 (Leary, 1991) and 51 years (Onwubere, 2001) with 0% (Leary, 1991; Maharaj, 1992) to 47% (Onwubere, 2001) females.
Leary 1991 and Maharaj 1992 showed a better effect on SBP (for MD and 95%CI see figure 8) and DBP (for MD and 95%CI see figure 9) for the higher dose. Onwubere 2001 (n=121) showed a slightly better but not statistically significant effect on SBP for felodipine once daily compared to nifedipine twice daily (MD -1.8 mmHg; CI -6.85 to 3.25).

A total of 4 RCTs (Farag, 2018; Isles, 1986; M'Buyamba-Kabangu, 1988; Poulter, 1993) with in total 251 participants compared the therapeutic effect of different CCBs with different BB. Mean age was between 52 (M'Buyamba-Kabangu, 1988) and 57 years (Isles, 1986) with between 47% (M'Buyamba-Kabangu, 1988) and 68% (Farag, 2018) females.
Farag 2018, (n=160) and M'Buyamba-Kabangu 1988 (n= 34) showed better effects for CCB compared to BB on SBP change (figure 9) and DBP change (figure 10), M'Buyamba-Kabangu 1988 with statisticall significant and clinically relevant results for both and Farag 2018 with statisticall significant and clinically relevant only for DBP change. Poulter 1993 (n= 37) reported a better effect for CCB (nifedipine) than beta-blocker (propanolol) on SBP and DBP, but not statistically significant. Isles 1986 (n= 20) showed a slightly better but not significant effect for BB (atenolol) on MAP (MD 2 mmHg; CI -8.55 to 12.55) in acute situation with malignant hypertension compared to CCB slow release nifedipine.

A total of 3 RCTs (Maharaj, 1993a; Radevski, 1999; Skoularigis, 1994) with in total 240 participants compared the therapeutic effect of different CCBs with different ACEis on blood pressure, all in South Africa. Mean age was 47 years with 0% (Maharaj, 1993a) to 52 % (Radevski, 1999) females. All showed a better effect for the therapy with CCB compared to ACEi

on SBP (figure 9) and DBP (figure 10), with statistically significant and clinically relevant results for Radevski 1999 and Skoularigis 1994.

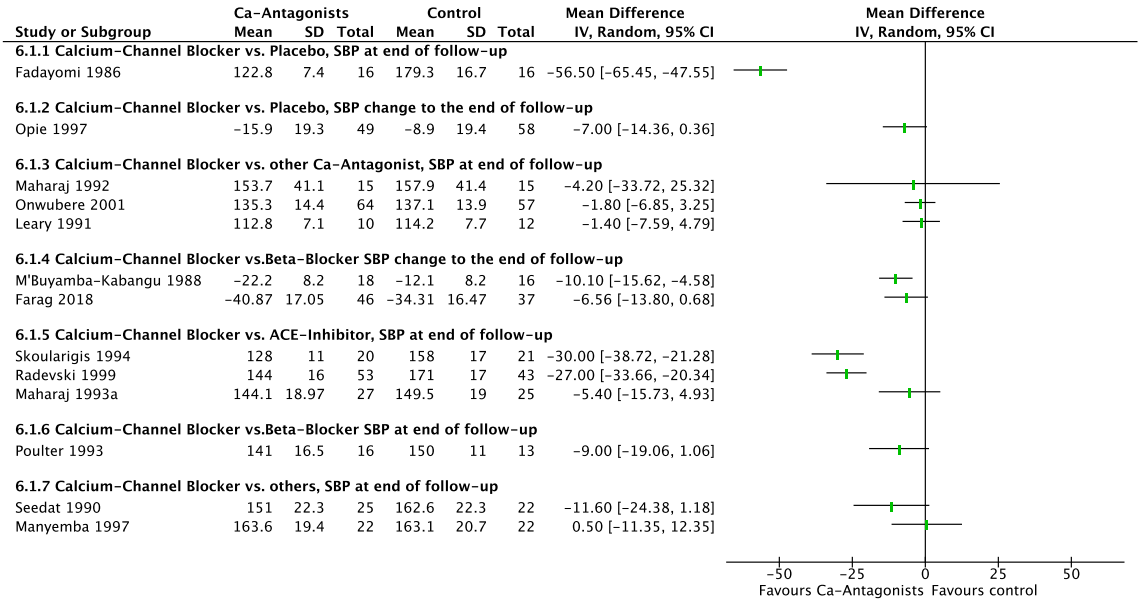

Figure 9 Forest plot of comparison: calcium-channel blocker, outcome: systolic blood pressure

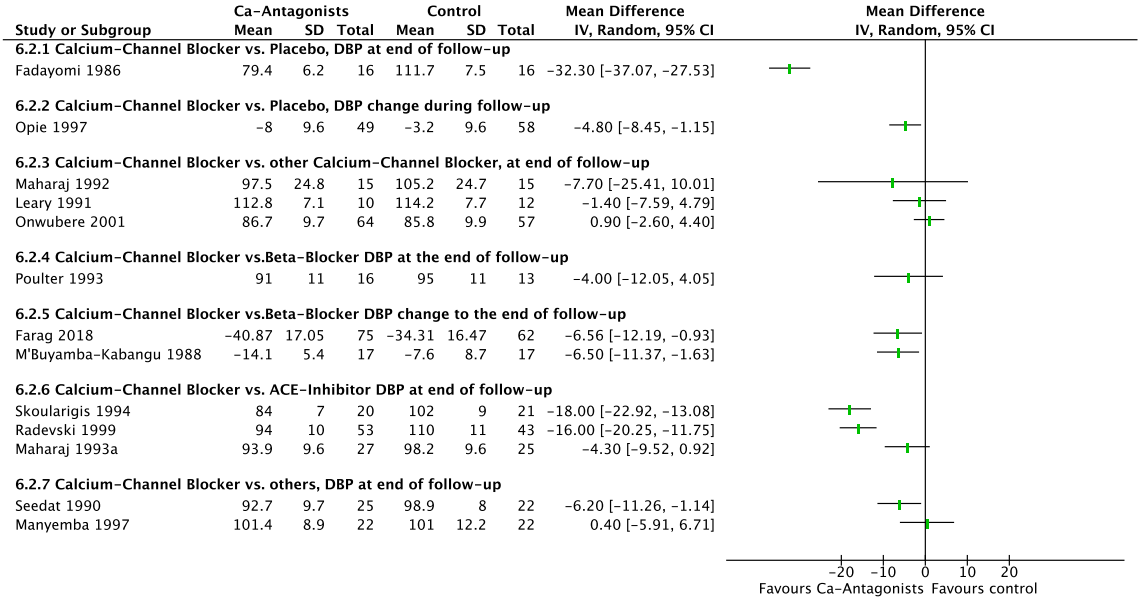

Figure 10 Forest plot of comparison: calcium-channel blocker, outcome: diastolic blood pressure

Beta-Blocker (BB)

Table 3 shows baseline characteristics including sex information, mean age, blood pressure as well as a short description of the intervention with longest follow up for pharmacological intervention RCT with beta-blocker.

Table 3 Study characteristics of RCTs on intervention with BB in secondary prevention of hypertension

Study		Patients						Intervention	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
Beta-blocker vs. placebo									
Abson 1981 **	Zimbabwe	36	23-65	61 %	169.8±18.7	110± 9.6		atenolol 200 mg vs. atenolol 100 mg vs. placebo	3
Cilliers AJ. 1979 **	South Africa	110	49.5 ± 12.1	46 %	A: 165.8± 18.5; B: 175.8± 18.2	A: 107.7± 6.5; B: 107.1± 5.9		atenolol 100 mg vs. placebo	1
Mabadeje1989 **	Nigeria	20	37 ± 6	40 %	177.5±46.2	100.8± 5		bromazepam 1,5/d vs. labetalol 100mg 2x/d vs. placebo	0.5
Salako 1979 **	Nigeria	20	46.1 (37-60)	73 %	172.8 (R 140-220)	109.1 (R 97-118)		alprenolol 200 mg vs. placebo	4
Salako 1979a **	Nigeria	9	40.9 ± 6.3	n.r.	Rest: 176.4± 20.7; a.ex.: 190.6± 24.9	Rest: 110.9± 9.7; a.ex.: 114.8± 9.3		pindolol 20 mg vs. propanolol 100 mg vs. placebo	6hrs
Venter 1991 **	South Africa	50	25-65	n.r.	164± 17	103± 7		penbutolol 40 mg (80 mg) vs. placebo	3
Beta-blocker vs. other beta-blocker									
Abengowe 1985 #	Nigeria	45	48.6 ±	60 %	191	102.2		acebutol 400 mg (800 mg)1x/d vs. propanolol 160 mg (320mg) 2x/d	5
Bosman 1977	South Africa	93	49 ± 2.6	54 %	172.9± 45.9	106.8± 17.1		metoprolol 40 mg 3x/d vs. 70 mg 3x/d vs. propanolol 80 mg 3x/d vs. propanolol 120 mg 3x/d	2.5
Beta-blocker vs. ACEi									
Goodman 1985	South Africa	26	48.8 (32-60)	38 %	156 ±3.5	97.5 ±3		propanolol 40mg 2x1 vs. enalapril 5 mg 2x1	12
Mangoush 1990 **	Libya	67	48.3 ± 2.34	51 %	175.8± 23.7	109.5± 10.6	MAP: 120.1± 15.6	atenolol (50 mg up to 100 mg) vs enalapril 10- 20 mg up to 80 mg)	3
Rogers 1988	South Africa	26	62	65 %	180.2± 23.5 after 50W: 208.8 ± 37.4	114± 8.8, after 50W: 114 ± 8.8		atenolol 50-200 mg vs. lisinopril 20-80 mg vs.	3
Seedat 1987	South Africa	36	48.8	75 %	162.7 ± 22.1	102±6.5		atenolol 50/100/200 mg (+12,5/25 mg HCT) vs. lisinopril 20/40/80 mg (+12,5/25 mg HCT)	6
Beta-blocker vs. others									
Mabadeje1977	Nigeria	24	44.9 ± 11	n.r.	189.6±20.3	111.8± 11.2	MAP: 137.7± 8.8	oxprenolol 80 (160) mg 3x/d vs. methyldopa 250 (500) mg 3x/d	3
Maharaj 1993	South Africa	52	n.r.	0 %	155.4±17	102.6± 11.9	MAP: 120.3± 11.37	atenolol 50 mg + chlortalidone 12.5 mg once daily vs. hydroflumethiazide 50 mg + reserpine 0.125 mg	2
Beta-blocker +diuretic vs. others									
Levenstein 1978	South Africa	249	50 ± 9.8	51 %	168.9 ± 18.2	105.4.1 ± 7		oxprenolol +cyclopenthiazideKCl 160 mg/600 mg (1x/s) vs. methyldopa 250 mg (3x/d)	3

Study		Patients						Intervention	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
Obel 1983	Kenya	32	41 ± 10	66 %	160± 17.6	106.9± 8.9		Fixed combination: timolol 10 mg+ HCT 25 mg + amiloride 2,5 mg 1x/d vs. methyldopa 500 mg 3x/d up to 3g/d	4

No sign= RCT, *cluster-RCTs, **cross-over RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure ; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk, HCT: hydrochlorothiazide;

In 27 RCTs the effect of BB was studied, mostly cardioselective substances as atenolol (N=10), propanolol (N=6), metoprolol (N=1), bisoprolol (N=1), acebutol (N=1), nebivolol (N=1). But also effectiveness of non-cardioselective BB (oxprenolol N=3, timolol N=2, alprenolol N=1, labetalol N=1, metipranolol N=1, penbutolol N=1, pindolol N=1) was surveyed (see figures 11 and 12).
A total of 6 RCTs, all cross-over RCTs, (Abson, 1981; Cillers, 1979; Mabadeje, 1989; Salako, 1979; Salako 1979a, Venter, 1991) with in total 245 participants examined the effect of antihypertensive therapy by beta-blocker against a placebo. Mean age was between 37 (Mabadeje, 1989) and 50 years (Cillers, 1979) with 40% (Mabadeje, 1989) to 73% (Salako, 1979) females.
All showed a statistically significant and clinically relevant better effect for the medication, for example Mabadeje 1989 (n=20) for SBP with a MD -30.4 mmHg; CI -36.20 to -24.60 and for DBP with a MD -19 mmHg; CI -21.96 to -16.04.

Two RCTs (Abengowe, 1985, n=45; Bosman, 1977, n=93) compared the effect of different cardioselective BB. Mean age was 49 years with 54 % to 60% females. Abengowe 1985 did not report on SD for BP in outcome. Boseman showed a better effect for metoprolol on SBP (MD -8.4 mmHg; CI -25.52 to 8.71) and on (MD -7.4 mmHg; CI 15.59 to 0.79), but not statistically significant.

A total of 4 RCTs (Mangoush, 1990; Rogers, 1988; Seedat, 1987; Goodman, 1985) compared the effect of antihypertensive therapy by beta-blocker against ACEi. Mean age was 48 (Mangoush, 1990) to 62 years (Rogers, 1988) with 38 % (Goodman, 1985) to 75 % (Seedat, 1987) females. Goodman 1985 (n=26) did not report on SD in outcome. Mangoush 1990, Rogers 1988 and Seedat 1987 favoured for lowering SBP more or less the therapy with ACEi, for example Mangoush 1990 (n=67) (MD 7.8 mmHg; CI 0.32 to 15.28) (figure 11). For DBP only Seedat 1987 (n=36) showed a statistically significant and clinically relevant results for the therapy with ACEi (MD: 7 mmHg; CI 0.65 to 13.35). Mangoush 1990 (n=67) and Rogers 1988 (n=62) reported a better effect on DBP for the therapy with beta-blocker compared to ACEi (figure 12), but not stastically significant or clinically relevant.

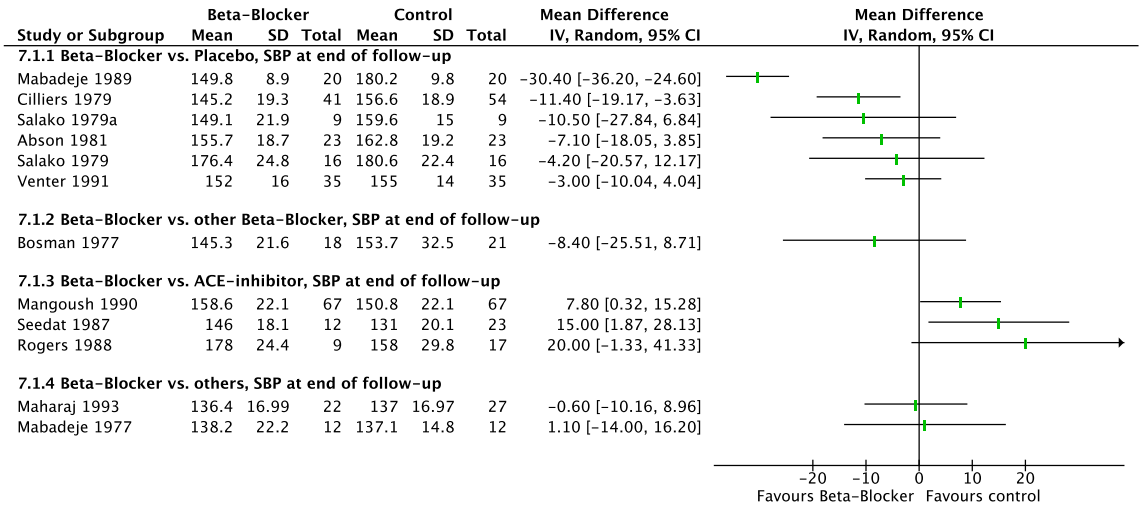

Figure 11 Forest plot of comparison: beta-blocker, outcome: systolic blood pressure

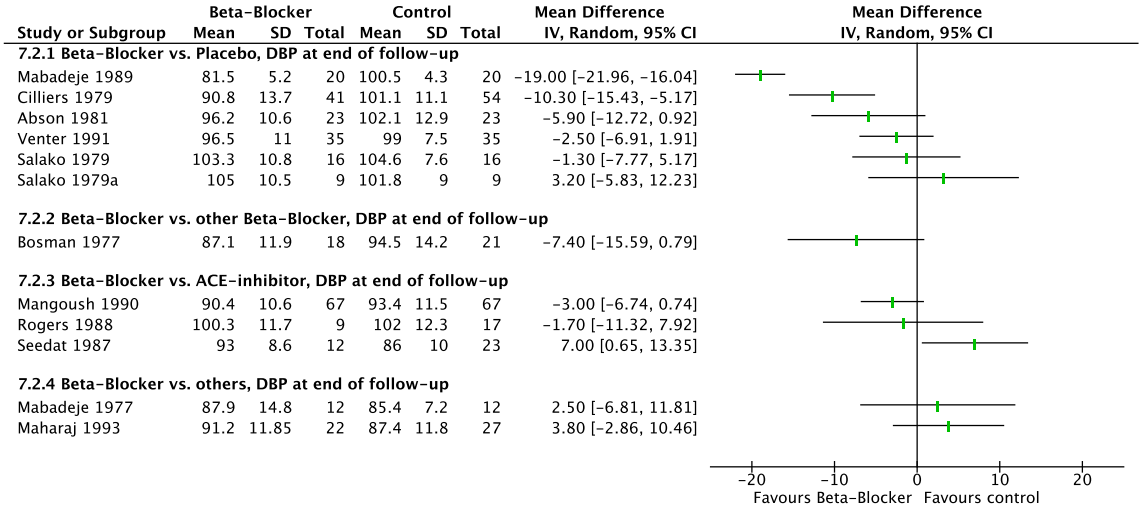

Figure 12 Forest plot of comparison: beta-blocker, outcome: diastolic blood pressure

Angiotensin-converting-enzyme-inhibitors (ACEi)

Table 4 shows baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for pharmacological intervention RCTs with ACEi.

Table 4 Study characteristics of RCTs on intervention with ACEi in secondary prevention of hypertension

Study		Patients						Intervention	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
ACEi vs. Placebo									
Opie 2002	South Africa	40	50	20 %	n.r.	n.r.	24h: SBD:136.3± 21.1, DBD: 86.8± 5.3	lisinopril 20 mg (40 mg) vs. placebo	48
ACEi vs. other ACEi									
Middlemost 1994	South Africa	38	46± 10	53 %	172± 18.1	104± 6		enalapril 20 mg+HCT 12,5 mg vs. enalapril 20 mg	3
Skoularigis 1996	South Africa	47	47.5 ± 10.5	55 %	n.r.	n.r.	24h: SBD:154.4 ± 13.1, DBD: 99.5± 6	enalapril +HCT (20/12,5 mg) vs. captopril + HCT (50/25 mg)	3
ACEi vs. others									
Norton 1999	South Africa	64	50 (36-70)	63 %	162.5	102		lisinopril 10 mg/20 mg vs. sampatrilat 50 mg/100 mg	2

No sign= RCT, *cluster-RCTs, **cross-over RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure ; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk, HCT: hydrochlorothiazide;

In 16 RCTs the effect of angiotensin-converting-enzyme-inhibitors (enalapril N=10, lisinopril N=5, captopril N=2 and perinopril N=2) was studied (see figures 13 and 14).

A total of 3 RCTs (Opie, 2002; Middlemost, 1994; Skoularigis, 1996; Norton, 1999) with in total 189 participants compared the effect of ACEi against a placebo (Opie, 2002, n=40), ACEi against other ACEi (Skoularigis, 1996, n=47), ACEi alone against ACEi plus a diuretic (Middlemost, 1994, n=38) and ACEi against alternative substance (Norton, 1999, n=64). Mean age was 46 (Middlemost, 1994) to 50 years (Norton, 1999) with 20% (Opie, 2002) to 63% (Norton, 1999) females. Opie 2002 showed a statistically significant and clinically relevant effect for the therapy with lisinopril compared to placebo for 24h SBP (MD -11 mmHg; CI -19.69 to -2.31). Middlemost 1994 reported a statistically significant and clinically relevant effect for the combination therapy of enalapril and HCT versus enalapril alone for SBP (MD -22 mmHg; CI -36.40 to -7.60). Enalapril alone was not able to lower the blood pressure compared to the baseline values. Skoularigis showed a better effect for the combination therapy of captopril plus HCT versus the combination of enalapril plus HCT, which means a a better but not statistically significant effect for captopril on SBP (MD 8 mmHg; CI -1.01 to 17.01). Norton 1999 reported a better effect for the alternative substance (Sampatrilat, vasopeptidase inhibitor) on change in SBP and DBP compared to ACEi.

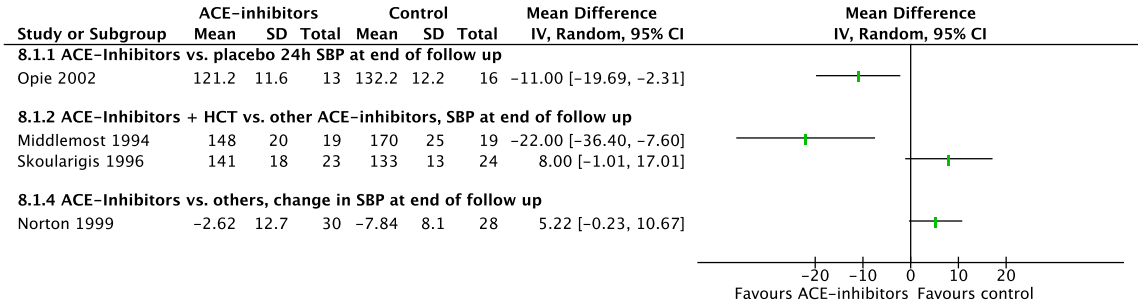

Figure 13 Forest plot of comparison: ACE-inhibitors, outcome: systolic blood pressure

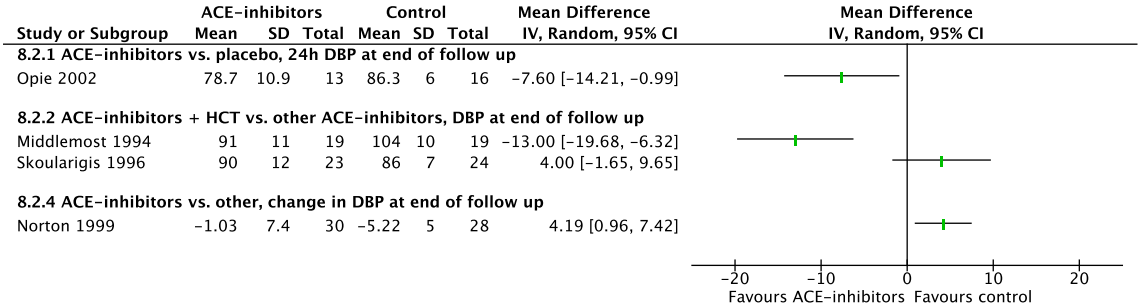

Figure 14 Forest plot of comparison: ACE-inhibitors, outcome: diastolic blood pressure

Other medication

Table 5 shows baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for pharmacological intervention RCTs with other drugs than described in previous sections.

Table 5 Study characteristics of RCTs on intervention with other medication in secondary prevention of hypertension

Study		Patients						Intervention	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Other BP (mmHg)**	**Description**	**Follow-up (mon)**
Others									
Lubbe 1974 **	South Africa	25	34-68	68 %	210	125		clonidine vs. placebo	2
M'Buyamba-Kabangu 2013	Sub-Saharan Africa	183	51.3 ± 9	52 %	156± 11.7	92.7± 10		valsartan 160 mg plus amlodipine 5mg (uptitrated to 160/10 mg) vs. 6.25mg hydrochlorothiazide plus 5 mg bisoprolol (uptitrated to 6.25/10 mg)	6
Nwachukwu 2015+2017	Nigeria	80	50.1 ± 36//50-7 ± 19.9	42 %	152.5 ± 25.6	99.9± 23.9	117.6 ± 15.8	hibiscus sabdariffa-infusion 150 mg/kg) vs. 25 mg HCT vs. placebo///hibiscus sabdariffa-infusion 150 mg/kg) vs. lisinopril 10 mg vs. placebo	1
Obel 1989	Kenya	48	40 ± 8.5	56 %	174± 9	100± 3.5		potassium supplements vs. placebo	4
Ojii, 2019	Sub-Saharan Africa	728	51.1 ± 10.6	63 %	158 ± 11.7	97.6± 10.3		amlodipine 5 (10) mg+ HCT 12.5 (25) mg (A) vs. amlodipine 5 (10) mg + perindopril 4 (8) mg (B) vs. perindopril 4 (8) mg+ 12.5 (25) mg HCT (C), (AML vs. HCT)	6
Venter 1988 **	Cameroon	25	40-65	n.r.	157	102		efamolmarine vs. sunflower seed and linseed oil capsules	8

No sign= RCT, *cluster-RCTs, **cross-over RCTs, # no reported BP, n.r. = not reported, BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure ; MD: mean difference; n: number of randomized participants; RR: relative risk, HCT: hydrochlorothiazide; AML: amlodipine

We found single RCTs on other antihypertensive drugs like alpha-receptor-blockers (methyldopa N=4, doxazosin N=1), renin-angiotensin-inhibitors (valsartan N=1), Sympathomimetics (clonidine N=1) and few others. The results are varying and are summarized in table 11 in appendix.

Nwachukwu 2015 (n=80, 42% female, mean age 50.1 years) compared the effect of hibiscus sabdariffa-infusion vs. HCT vs. lisinopril vs. a placebo. For sabdariffa-infusion they showed a decline in SBP (MD -15 mmHg; CI -20.64 to -9.26), DBP (MD -8.4 mmHg; CI -11.65 to -5.15) and MAP. The effect compared to a placebo you can find in figure 15 and 16.

Obel 1989 (n=48, 56% female, mean age 48 years) compared the effect of potassium supplements with placebo and showed a clear favour to therapy with potassium supplements for SBP (MD -39 mmHg; CI -43.88 to -34.12) and for DBP (MD -17 mmHg; CI -19.26 to -14.74).

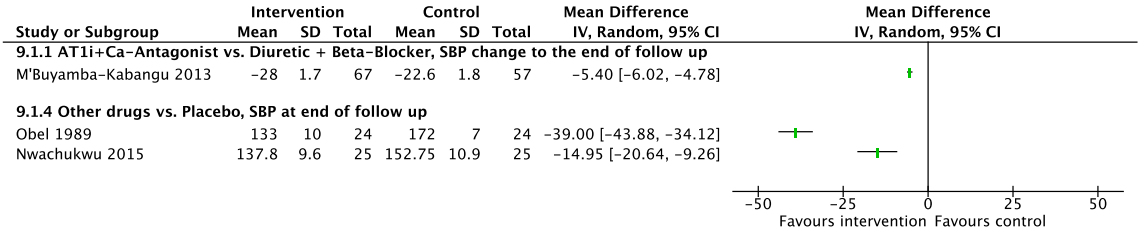

Figure 15 Forest plot of comparison: other drugs, outcome: systolic blood pressure

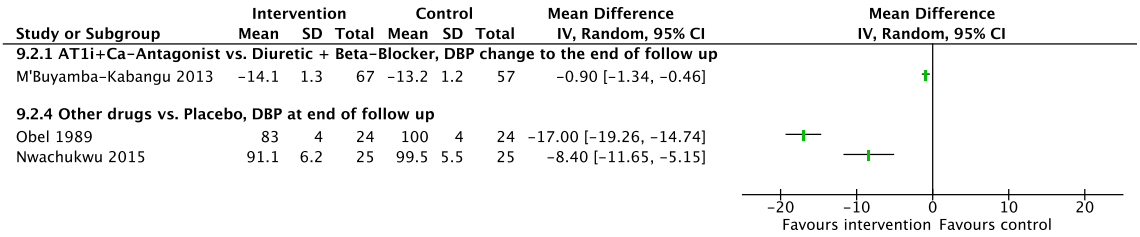

Figure 16 Forest plot of comparison: other drugs, outcome: diastolic blood pressure

Different combination therapies

There were few RCTs examining differences in antihypertensive efficacy between all those different drug classes.

Obel 1983 (n=32, 66% female, mean age 41years) and Levenstein 1978 (n=249, 51% female, mean age 50 years) compared the combination of beta-bocker and diuretics with methyldopa. Both showed better effects on SBP and DBP for the combination therapy (see figure 17 and 18).

M´Buyamba-Kabangu 2013 (n=183, 52% female, mean age 51.3 years) compared the effect of a combination of angiotensin-receptor-blocker and CAA with combination of diuretic and beta-blocker. They showed a better effect for ARB+CAA on SBP (MD -5.4 mmHg; CI -6.02 to -4.78) and DBP (MD -0.9 mmHg; CI -1.34 to -0.46) (see figure 15 and 16).

In general combination therapy in African patients was more effective than monotherapy (Iyalomhe, 2013; Middlemost, 1994; Obel, 1990; Seedat, 1980). Also different combination regimes were examined for example by Ojii 2019 in their trial involving black patients in Sub-Saharan Africa. They found that among three commonly recommended drug combinations, amlodipine (CCB) combined with either perindopril (ACEi) or a thiazide diuretic (hydrochlorothiazide) was superior to perindopril plus hydrochlorothiazide in lowering both ambulatory and office blood pressures (Ojii, 2019). Additionally, single-pill combination formulas were more effective than free combination of substances in separate pills (Farag, 2018; Obel, 1983, Obel, 1981; Salako, 1990).

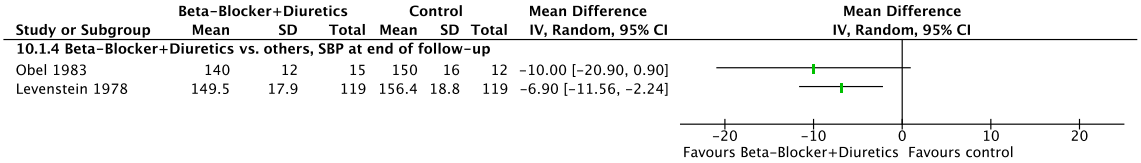

Figure 17 Forest plot of comparison: beta-blocker+diuretics, outcome: systolic blood pressure

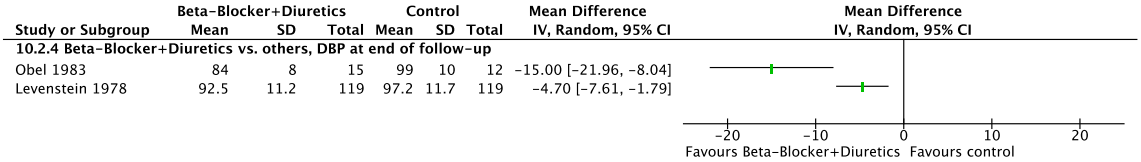

Figure 18 Forest plot of comparison: beta-blocker+diuretics, outcome: diastolic blood pressure

4.3.2 Non-pharmacological intervention

A total of 23 RCTs compared different non-pharmacological intervention strategies. Of them 17 non-pharmacological trials randomized more than 100 participants. That means there are 6 RCTs with less than 100 participants, the biggest RCT was conducted by Goudge 2018 with 4722 participants, the smallest by Turky 2013 with 30 participants. From these 23 non-pharmacological RCTs 8 were cluster RCTs (35%). There was no cross-over RCT.

The non-pharmalogical intervention RCTs compared strategies on standardized treatment strategies (N=3), education strategies to improve adherence (N=15), physical activity (N=4) and modified nutrition strategies (N=1).

Standardized treatment strategies

Baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for standardized treatment intervention RCTs is summarized in table 6.

Table 6 characteristics of RCTs on standardized treatment strategies in secondary prevention of hypertension trials

Study		**Patients**					**Intervention**	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Description**	**Follow-up (mon)**
Standardized treatment (3 RCTs)								
Akintunde 2017	Nigeria	105	56.6±14.3	53 %	170.9 ± 19.2	85.6 ± 21.8	physiologically individualized therapy	12
Okeahialam 2011	Nigeria	181	49.7 ± 14.2	61%	150.3 ± 14.8	93.7 ± 9.6	chronotherapy (night-time dosing)	3
Steyn 2013*	South Africa	920	60.3±11.1	79%	151.2 ±26.7	87.1 ± 12.4	multi-faced intervention to implement national guidelines	12
*cluster-RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk; SBP: systolic blood pressure								

3 RCTs (Akintunde, 2017; Okeahialam, 2011; Steyn, 2013) investigated the effect of special treatment strategies on blood pressure and other parameters. They were laid out for a duration from 3 up to 12 months. Two of them (Akintunde, 2017; Okeahialam, 2011) were able to produce a significantly decrease in systolic and diastolic blood pressure (figures 19 and 20).

Akintunde 2017 conducted a RCT in Nigeria (n=105, 53% females, mean age 56.6 years) with a mean baseline BP of 170.9/85.6 (± 19.2/21.8). They defined a physiologically individualized therapy, oriented to blood values of plasma renin activity and aldosterone and compared the effect after 1 year to a group with usual care. The control of SBP (MD -13.2 mmHg; CI -19.43, -6.97) and DBP (MD -5.6 mmHg; CI -9.43, -1.77) was significantly higher in intervention group (IG) after 12 months follow up.

In 2011 Okeahialam 2011 (n=181, mean age 49.7 years) compared in Nigeria an ingestion strategy of medication. They found out, night-time dosing had significantly greater SBP change (MD -4 mmHg; CI -8.99 to 0.99) and DBP change (MD -6.9 mmHg; CI -10.36 to -3.44) and MAP change after 3 months follow up.

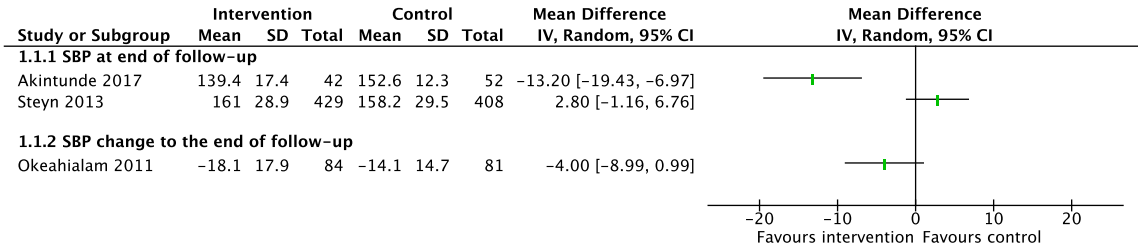

Figure 19 Forest plot of comparison: intervention: standardized treatment strategies, outcome: systolic blood pressure

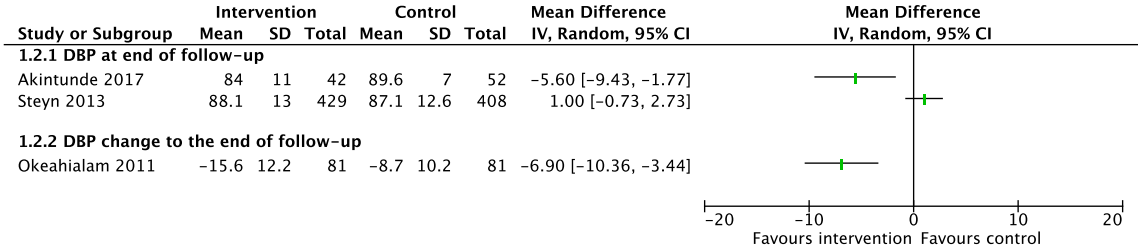

Figure 20 Forest plot of comparison: intervention: standardized treatment strategies, outcome: diastolic blood pressure

Education and adherence strategies

Baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for education and adherence intervention RCTs is summarized in table 7.

Table 7 characteristics of RCTs on education and adherence strategies in secondary prevention of hypertension trials

Study		**Patients**					**Intervention**	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Description**	**Follow-up (mon)**
Education and adherence (15 RCTs)								
Adeyemo 2013	Nigeria	668	62.7±10.0	66%	167.4±19.2	91.8 ±12.3	nurse-led intervention with home visits	6
Bobrow 2016	South Africa	1372	54.3±11.5	72%	135.4 ±17.5	83.4 ±12.1	mobile phone text messages (interactive or only information)	12
Bolarinwa 2019	Nigeria	299	61.1±10.8	77 %	140.0 ± 22.9	86.9 ±11.9	home-based follow-up care	12
Cappuccio 2016*	Ghana	1013	54.5±11.0	62%	128.1 ± 25	76.5 ±13	health education to reduce salt intake	6
Fairall 2016*	South Africa	4393	52	73%	139±23.6[a]	90±13.2[a]	nurse training on NCD care	14
Goudge 2018*	South Africa	4722	56.6±19.4	56 %	Hypertension: 46.6 %		management by lay health workers	18
Gyamfi + Ogedegbe 2017*	Ghana	757	58.0±12.4	60 %	155.9 ± 12.1	89.6 ± 10.8	nurse training in task shifting for hypertension control +health insurance	12
Hacking 2016 #	South Africa	223	54.3, 26.8-92.2	80%	n.r.	n.r.	SMS text messages to improve knowledge	4
Labhardt 2011* #	Cameroon	187	59.9± 12.5	64%	175.8	100.7	financial incentive (1 month free treatment for regular attenders)	12
Mendis 2010*	Nigeria	2397	55 ± 4.7	58 %	153.2 ±12.4	94 ± 9.7	WHO CVD risk management package	12
Sarfo 2019	Ghana	60	55 ± 13	35 %	143.8 ± 26.7	90.5 ± 15.7	phone-based intervention	9
Saunders 1991 #	South Africa	224	65 % between 40-50	73%	n.r.	116.6	compliance improving strategies (reminders)	6
Stewart 2005	South Africa	83	late middle aged	n.r.	146.4±18.5	93.5±11.1	risk factor modification (telephonic intervention)	6
Vedanthan 2019*	Kenya	1460	54.2±16.4	58 %	159.4±19.5	89.7 ±12	tailored behavioral communication (smartphone or paper-based)	12
Wahab 2017	Nigeria	35	58.1 ±10.5	34%	138.3 ± 24.2	85.0 ±12.4	nurse-led Intervention (education and skill-building)	0.5

*cluster-RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk; SBP: systolic blood pressure

We found 15 RCTs with subject to improve knowledge about blood pressure and health related behavior concerning hypertension. They were conducted for a duration from 6 up to 18 months with the exception of Wahab 2017 and Hacking 2016 which lasted over weeks (2 weeks and 17 weeks, respectively).

Five of these education and adherence RCTs investigated the efficacy of phone or letter based interventions with SMS for information, improved knowledge of hypertension, interactive and adherence support, reminder letters for follow ups (Bobrow, 2016; Hacking, 2016; Sarfo, 2019; Stewart, 2005; Vedanthan, 2019).
Bobrow 2016 (n=1372, 72% female, mean age 54.3 years) and Steward 2005 (n=83, late middle aged) reported non significant changes in SBP at the end of 1 year (Bobrow, 2016) and at the end of 24 weeks (Steward, 2005) follow up time. Both results on SBP are not clinically relevant. But Steward 2005 showed strong preferences to the intervention in knowledge and self-reported behaviour changes. Additionally, Bobrow 2016 showed statistically significant better blood pressure control in the intervention group (RR 1.12; CI 1.02 to 1.23). Hacking 2016 (n=223, 80% female, mean age 54.3 years) did not report on blood pressure but knowledge and self-reported behaviour changes was related with strong preferences to the intervention after 17 weeks follow up. These 3 studies were all conducted in South Africa. Vedanthan 2019 (n=1460, 58% female, mean age 54.2 years) showed small preference to the intervention for the decline of SBP compared to baseline values.

Six of the 15 education and adherence RCTs investigated the efficacy of nurse-led interventions with home visits, patient education and nurse training/education (Adeyemo, 2013; Bolarinwa, 2019; Cappuccio, 2016; Fairall, 2016; Mendis, 2010; Wahab, 2017). The effect on SBP, DBP and BP control is shown in figure 21, figure 22 and figure 23.
The duration of these 6 trials was between 6 and 14 months, except Wahab 2017. They published a feasibility study without a statistically significant better effect for the intervention after a follow up time off 14 days.
Cappuccio 2016 (n=1013, 62% female, mean age 54.5 years), a cluster RCT, reported significant, but clinically not relevant changes in DBP (MD -2.7 mmHg; CI -4.67 to -0.73) with a better effect for the intervention at the end of 6 months follow up. Mendis 2010 (n=2397, 58% female, mean age 55 years), a cluster RCT, reported statistically significant, but not clinically relevant changes in SBP (MD -4.4 mmHg; CI -5.94 to -2.86) and DBP (MD -3.4 mmHg, CI -4.39 to -2.41) with a better effect for the intervention. Bolarinwa 2019 showed statistically significant better blood pressure control in the intervention group (RR 1.12; CI 1 to 1.25).

Two of the 15 education and adherence RCTs investigated the efficacy of combined phone/letter based intervention with nurse and health worker led interventions, respectively (Goudge, 2018; Saunders, 1991).

None of these RCTs showed clinically relevant changes in BP or knowledge and self-reported behavior changes.

Two of the 15 education and adherence RCTs investigated the efficacy of availability of health insurance/financial incentive or not (Gyamfi, 2017; Labhardt, 2011).

Gyamfi 2017 (n=757, 60% female, mean age 58 years), a cluster RCT, reported non-significant changes in SBP (MD -1.3 mmHg; CI -5.54 to 2.94), but small significant change in SBP change (MD -2.9 mmHg; CI -5.68 to -0.12) (figure 20). The effect in DBP and DBP change at the end of 1 year follow up was not significant (figure 21). Labhardt 2011 (n=187, 64% female, mean age 59.9 years), a cluster RCT in rural Cameroon, reported patient retention rates as primary outcome. After 1-year follow up they showed significant higher retention rates in CVD disease management than in patient group without financial incentive.

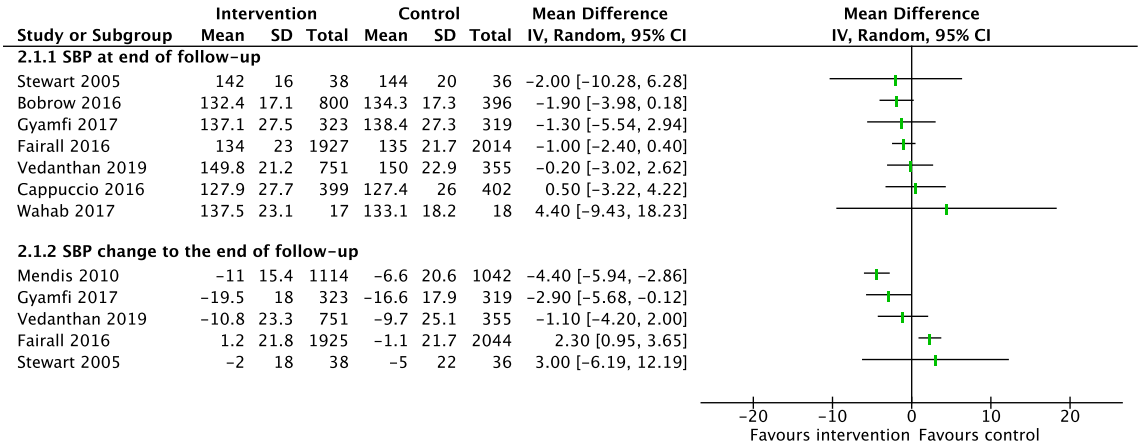

Figure 21 Forest plot of comparison: intervention: education and adherence strategies, outcome: systolic blood pressure

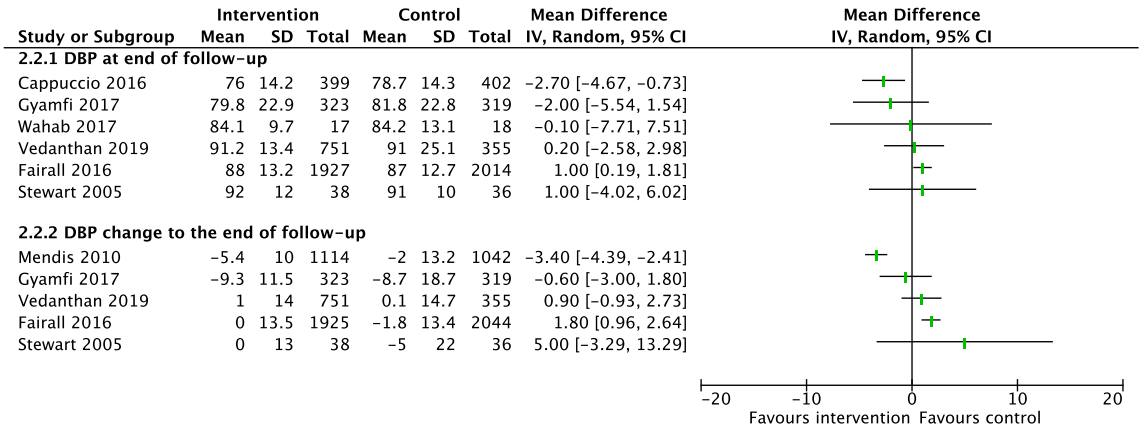

Figure 22 Forest plot of comparison: intervention: education and adherence strategies, outcome: diastolic blood pressure

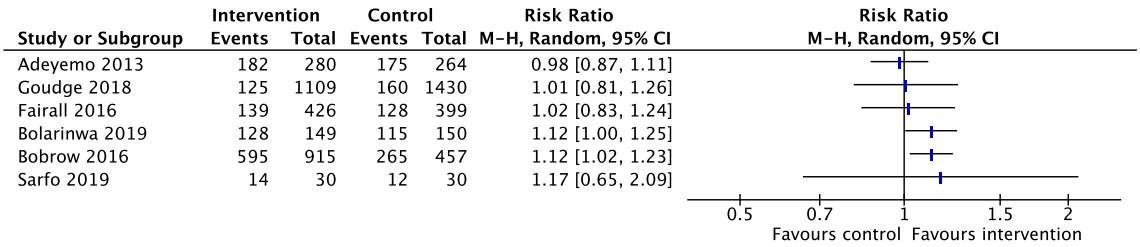

Figure 23 Forest plot of comparison: intervention: education and adherence strategies, outcome: blood pressure control

Strategies with physical activity

Baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for physical activity intervention RCTs is summarized in table 8.

Table 8 characteristics of RCTs on physical activity strategies in secondary prevention of hypertension trials

Study		**Patients**					**Intervention**	
Name (design)	**Country**	**n**	**Age (years)**	**females**	**SBP (mmHg)**	**DBP (mmHg)**	**Description**	**Follow-up (mon)**
Physical activity (4 RCTs)								
Aweto 2012	Nigeria	50	45±12.3	58 %	138.7±10.9	79.9±9.3	dance movement therapy	1
Lamina 2010	Nigeria	485	58.5 ±6.8	0 %	165.4±13.2	98.1 ± 4.6	training program (interval or continuous)	2
Maruf 2016	Nigeria	120	52.8±8.4, 38-65	71 %	155.7±11.4	93±10	aerobic dance training	3
Turky 2013	Egypt	30	52.8±2.4, 40-50	100 %	151±6.2	94.5±4.2	moderate exercise training	2

*cluster-RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk; SBP: systolic blood pressure

We found 4 RCTs who investigated the effect of physical activity on blood pressure and other parameters (Aweto, 2012; Lamina, 2010; Maruf, 2016; Turky, 2013). They were laid out for a duration from 1 up to 3 months with all together 685 participants. We found two general interventions on antihypertensive effects of physical activity strategies: dance training (Aweto, 2012; Maruf, 2016) and exercise training on ergometer (Lamina, 2010) or treadmill (Turky, 2013). A total of 3 trials (Aweto, 2012; Maruf, 2016; Lamina, 2010) were conducted in Nigeria (western Africa) and 1 trial (Turkey, 2013) in Egypt.

Lamina 2010 (n=485, only males, mean age 58.5 years) published 12 papers of 1 trial on exercise training on ergometer with different outcomes. They examined the effect of interval training on several metabolic and inflammation markers (uric acid, white blood cell count, lipid profile, CRP). Additionally, they investigated the effects of continuous and interval training compared to usual drug therapy on hypertension and hypertension control. As a result, Lamina 2010 concluded

that continuous and interval training programs are effective adjunct non-pharmacological management of chronic essential hypertension. The study revealed a significant and clinical relevant decrease in SBP and DBP in the experimental groups compared to placebo group after 8 weeks follow up (SBP: MD -11.1 mmHg; 95%CI -14.8 to -7.4, DBP: -1.4; 95%CI -2.6 to -0.2).

Turky 2013 (n=30, 100% female, mean age 52.8 years) showed a significant and clinical relevant decrease on SBP (MD -21.00 mmHg; 95% CI -25.83 to -16.17) and DBP (MD -10.00 mmHg, 95% CI -13.66 to -6.34), also on body mass index after 8 weeks follow up.

Maruf 2016 (n=120, 71% female, mean age 52.8 years) showed improvements in the physical health, psychological health and exercise capacity in individuals with essential hypertension after 12 weeks follow up. They also proved that combination of aerobic dance and antihypertensive drugs reduces number of antihypertensive drugs needed to achieve BP control and enhances BP control in individuals with hypertension on two antihypertensive drugs.

Aweto 2012 (n=50, 58% female, mean age 45 years) showed the effectiveness of dance movement therapy in improving cardiovascular parameters and estimated maximum oxygen consumption in hypertensive patients after 4 weeks follow up (SBP: MD -15.60 mmHg; 95% CI -22.38 to -8.82, DBP: MD -3.20 mmHg; 95%CI -8.08 to 1.68).

All in all, the 4 RCTs we found with physical activity improvement in hypertensive patients in African setting had significant positive impact on blood pressure, but also on general condition, no matter what kind of physical activity they examined.

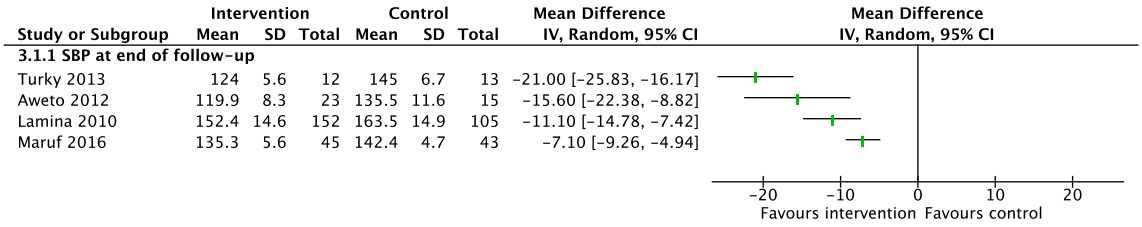

Figure 24 Forest plot of comparison: intervention: physical activity strategies, outcome: systolic blood pressure

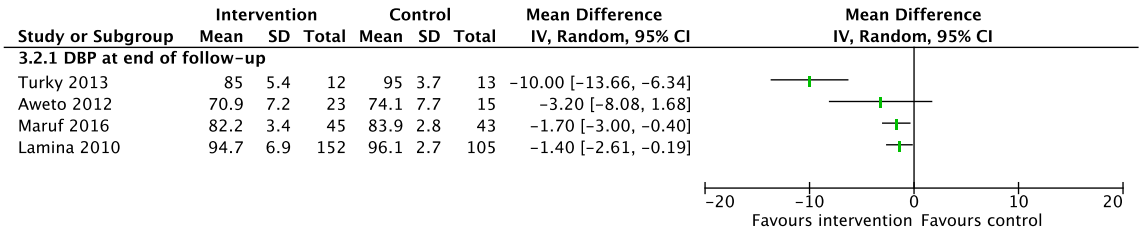

Figure 25 Forest plot of comparison: intervention: physical activity strategies, outcome: diastolic blood pressure

Modified nutrition strategies

Baseline characteristics including sex, mean age, blood pressure as well as a short description of the intervention with longest follow up for modified nutrition intervention RCTs is summarized in table 9.

Table 9 characteristics of RCTs on modified nutrition strategies in secondary prevention of hypertension trials

Study		Patients					Intervention	
Name (design)	Country	n	Age (years)	females	SBP (mmHg)	DBP (mmHg)	Description	Follow-up (mon)
Modified nutrition (1 RCT)								
Charlton 2008	South Africa	92	61.1±7	84 %	134.6±15.7	81.1±8.1	food based dietary strategy	2

*cluster-RCTs, # no reported BP, BP: blood pressure; DBP: diastolic blood pressure; MD: mean difference; n: number of randomized participants; n.r. not reported; RR: relative risk; SBP: systolic blood pressure

We found one RCT examining modified nutrition strategies (Charlton, 2008) which was conducted in South Africa (n=92, 84% female, mean age 61.1 years), who modified salt consumption. Reducing salt consumption they showed a small, but statistically not significant decrease in blood pressure after 2 months follow up (SBP: MD -5.00 mmHg; 95%CI -11.92 to 1.92, DBP: MD -3.00 mmHg; 95% CI -7.60 to 1.60).

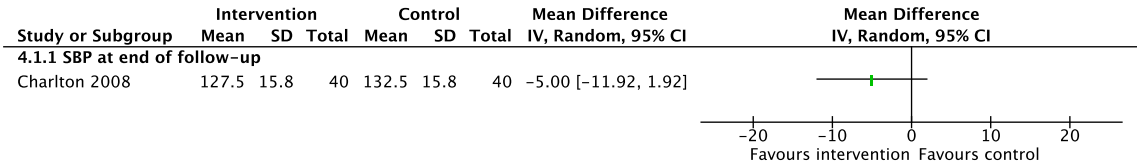

Figure 26 Forest plot of comparison: intervention: modified nutrition strategies, outcome: systolic blood pressure

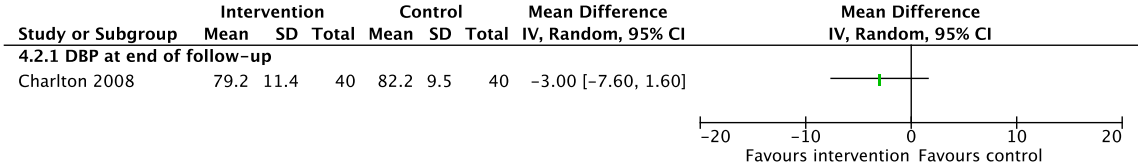

Figure 27 Forest plot of comparison: intervention: modified nutrition strategies, outcome: diastolic blood pressure

4.4 Potential biases

Quality and risk of bias of all RCTs were summarized in figures 28 and 29 and in table 11 in Appendix.

The greatest restriction to study quality was a high risk of bias in blinding due to unfeasibility and and incomplete outcome data in most of the non-pharmacological intervention RCTs. However, pharmacological intervention instead were frequently rated to have high risk of bias concerning other risk of bias, mostly because of missing sample size calculation, missing reporting of baseline values and missing reporting of wash out between different intervention phases in cross-over RCTs. Further pharmacological RCTs had, all in all, high quality due to double blinding of patients and physicians.

Potential biases in pharmacological trials

In pharmacological RCTs (N=67) adequate information to judge risk of bias on sequence generation and allocation concealment (N=56, 84%, respectivly N=44, 66%) were rarely reported. Problems in blinding could be excluded in 49 (blinding of participants and staff) and 35 (blinding of outcome assessors) RCTs. In 27 RCTs incomplete outcome data with more than 10 percent of randomized participants dropped out from analyses restricted study quality. For 52 phamacological RCTs study protocol was not available, therefore reporting bias was judged as unclear. Reporting bias could not be excluded in 8 RCTs. 52 trials other sources of bias could not be excluded because of missing sample size calculation, missing primary endpoint definition or missing baseline values. For relative distribution of assessed bias on pharmacological RCTs see figure 28.

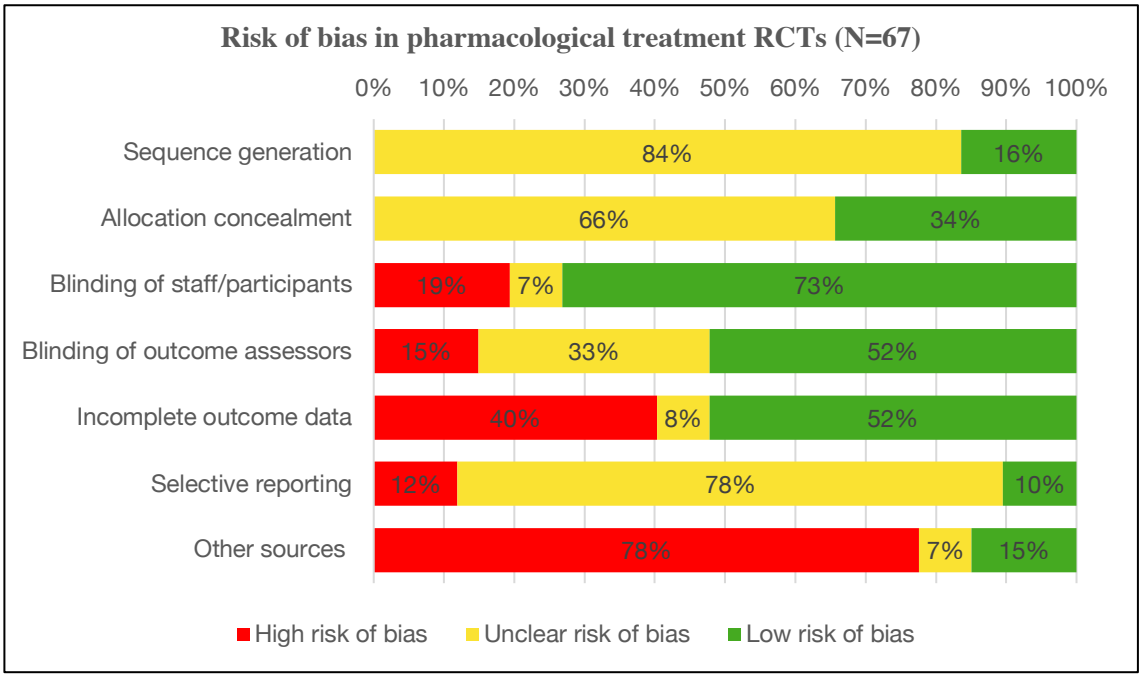

Figure 28 Risk of bias of st udies on pharmacological treatment in secondary prevention of hypertension, rounded

Potential biases in non-pharmacological trials

Biases in pharmacological RCTs (N=23) for sequence generation and allocation concealment could be excluded for 12, respectivly 13 RCTs. Problems in blinding could not be excluded in 17 (blinding of participants and staff) and 13 (blinding of outcome assessors) RCTs. In 13 RCTs incomplete outcome data with more than 10 percent of randomized participants dropped out from analyses restricted study quality. In 9 non-phamacological RCTs study protocol was not available, therefore reporting bias was judged as unclear. In 6 RCTs reporting bias could not be excluded. In 14 RCTs other sources of bias could be excluded. 7 RCTs had a high risk of other sources of bias because of missing sample size calculation, missing primary endpoint definition or missing baseline values.

For relative distribution of assessed bias on pharmacological RCTs see figure 29.

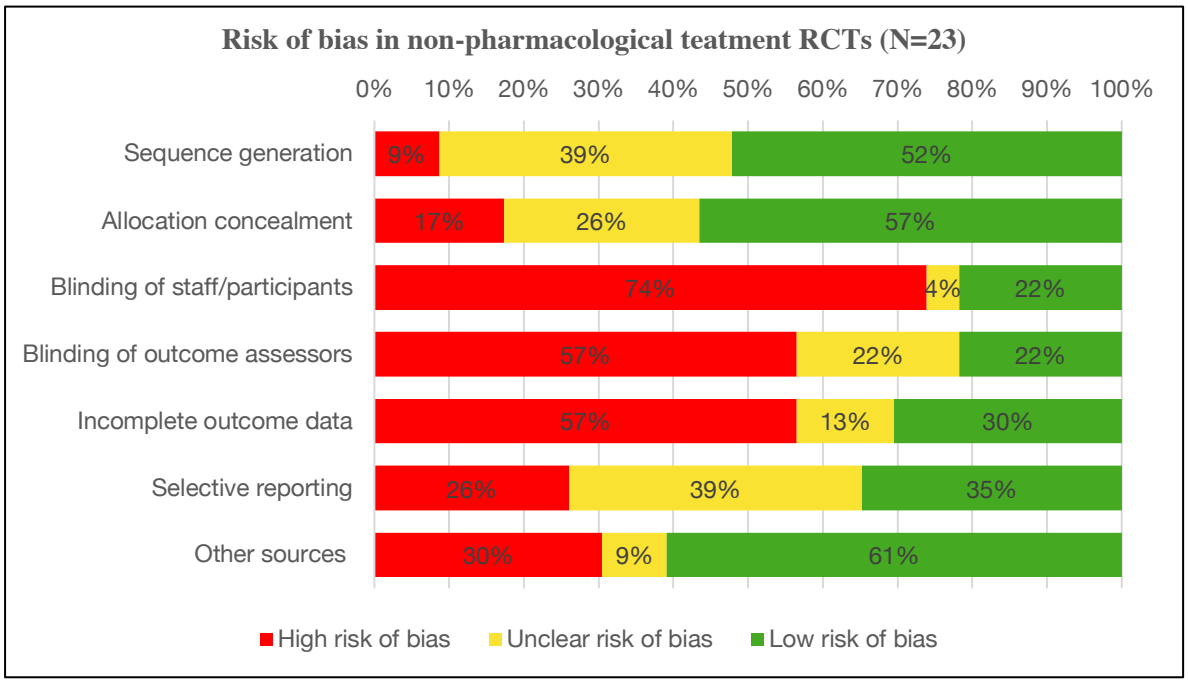

Figure 29 Risk of bias of studies on non-pharmacological treatment in secondary prevention of hypertension, rounded, (Blinding of outcome assessors: high 56.52%, unclear 21.74%, low 21.74%)

5 Discussion

This systematic review described 90 eligible RCTs on hypertension in Africa published without time constriction until november 2019. The number of included RCTs was smaller than the number of related articles, because results from some RCTs were published in more than one article (Bobrow, 2016; Fairall, 2016; Gyamfi, 2017; Iyalomhe, 2007; Iyalomhe 2013; Lamina, 2010; M'Buyamba-Kabangu, 2013; Maruf, 2016; Nwachukwu, 2015; Obel, 1990; Ogola, 1993; Okeahialam, 2011).

The total sample size ranged from 9 to 4722 participants with in total 23 562 participants.

We noted a concentration in urban settings with 94% of included RCTs, more female participants (62%) and a underrepresentation of RCTs conducted in Central and Northern Africa.

We found eligible RCTs with different pharmacological and non-pharmacological interventions. All in all the results indicated a convincing and clinically relevant blood pressure control by improving physical activity in African countries. The results in RCTs included on standardized treatment, education and adherence strategies and comparisons of different drug classes were heterogeneous. Included drug intervention RCTs with active drugs compared to placebo showed a clear favour to the intervention.

As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting (Moher, 2009). All RCTs showed a risk of bias in at least one of the assessed domains.

5.1 Study characteristics, sites and participants

5.1.1 Periods

We found the period with the smallest number of published RCTs on treatment of hypertension to be between 2000 and 2009 (N=7), with only 3 published RCTs from 2005 to 2009. This low frequency is comparable to another systematic review with the aim to summarize results on prevalence of hypertension in older adults living in Africa (Bosu, 2019). Similar to our findings, Bosu 2019 reported the lowest number of all designs of RCTs on prevalence of hypertension was in the 2005–2009 period (Bosu, 2019). For the decade before 2000, 1990 to 1999, considering only RCTs conducted in South Africa and Nigeria, we found 14 RCTs and 4 RCTs, respectively. After 2010 the number of RCTs rose again especially in Nigeria (South Africa 5, Nigeria 12), but still low with 29 randomized controlled trials between 2010 and October 2019, especially between 2015 and October 2019 (N=19). Non-pharmocological interventions are predominant in the 2010 to 2019 period (N=20) with 12 publications between 2015 and 2019 compared to publications on pharmacological interventions (N=9). On the other hand, pharmacological RCTs predominate the period between 1971 and 2009 (N=59) over nonpharmacological interventions (N=3). Because

all included cross-over RCTs (N=18) were pharmacological RCTs, they were conducted in the same period (1971-1979: N=4, 1980-1989: N=7, 1990-1999: N=7). Whereas all included cluster RCTs (N=8) were conducted in the 2010 to 2019 period.

5.1.2 Sites

The NCD Risk Factor collaboration conducted a pooled analysis of population-based measurement studies to give an overview of worldwide trends in BP from 1975 to 2015. They found out that the highest worldwide blood pressure levels have shifted from high-income countries to low-income countries in south Asia and SSA during the past four decades (NCD-RisC, 2017).

Currently there are 54 known states in Africa but only in 16 different countries RCTs have been conducted until January 2020. The inhabitants of these 16 countries (approximately 800 million) represent more than half of all African people not nearly all (1.3 billion) (Noncommunicable Disease. Progress Monitor, WHO, 2017).

Additionally to that most of the trials were conducted in Southern Africa (N=36) and Western Africa (N=27). Moreover, the international African multicenter RCTs also concentrate in the Western part with few additional sites in Eastern Africa and South Africa. In total we see lower numbers of RCTs in Eastern Africa (N=16) and a striking underrepresentation of RCTs in Northern Africa (N=3) and central Africa (N=1).

Gomez 2014 concluded in their publication what is currently known about genetic variation in Africa and that there are high levels of genetic diversity within and between African populations. Important genetic variants may are geographically restricted within Africa because of local adaptation to a particular lifestyle or environment. Further, many common variants that are adaptive because of protection from an infectious disease may also result in susceptibility to a different, possibly noninfectious, disease in populations of recent African origin (Gomez, 2014). Because of this stated genetic diversity, which depends on the geographic site, it is uncertain whether datas of our conclusions can be extrapolated to black patients in northern and central Africa.

This becomes even more important because Adeloye 2014 described in their systematic analyses of population-based studies on hypertentension a higher pooled crude prevalence of hypertension in Northern Africa than in sub-Saharan Africa (SSA), with hypertension prevalence of 33.3% in Northern Africa and 27.8% in SSA. (Adeloye, 2014). Opposite to that findings the NCD Risk Factor collaboration stated SSA as one of four regions at the highest risk for hypertension, even though some countries in SSA had no or few data sources (NCD-RisC, 2017).

Gomez-Olive 2017 concluded after their cross-sectional trial at six African sites from their data highly sex-specific and region-specific differences. They stated that further detailed understanding is required to inform effective intervention strategies (Gomez-Olive, 2017).
Systematic reviews on prevalences with inclusion of mainly observational studies included trials conducted in more African countries. For example, Adeloye 2014 included 92 cross-sectional population or community based observational studies conducted in 31 African countries (Adeloye, 2014).
Other systematic reviews, also without concentration on RCTs, had a similar concentration of trials in SSA (Ataklte, F 2015) or in South Africa (Brennan, 2018; Seedat, 1999) as in our review. Bosu 2019 systematically reviewed population based studies with different designs and found less trials in Southern and Northern Africa, with the lowest number of participants observed in studies from Eastern Africa (Bosu, 2019). This is partly in line with our results, except concerning the Southern Africa region.

Furthermore, Bosu 2019 showed the lowest number of participants in urban populations with a higher number of studies with mixed populations (Bosu, 2019). This is opposite to that we found where nearly all (94%) studies were conducted in urban setting. The possible reason for that could be that RCTs are interventional studies with more effort in standardization and monitoring of procedures. Therfore, they were frequently conducted in university hospitals which are situated in cities. With resulting high internal but lower external validity because a high percentage of the African population lives in rural areas. Taking data from the world data atlas in 2019, for example, 21.3% of the Ethiopian population lives in urban areas (worldometer, 2019).

This means that for a comprehensive care for hypertension, and NCDs in general, it is crucial to be as close as possible to the environment of the people. That means research on interventions to treat hypertension expanded to the rural areas is required. This includes all services like promotion and prevention to treatment, rehabilitation and palliative care and ensures that the quality of those services is good enough to improve the health of the people who receive them (WHO, UHC, 2019).

5.1.3 Participants

We expected to see a higher number of male participants because we excluded RCTs on pregnant and nursing women and the birth rate is still high in African countries. Futhermore, a higher prevalence of hypertension in males was described (Adeloye, 2014; Bosu, 2015). This may be a consequence of the overall mean age from all selected studies by Adeloye 2014 at an age 47.4 years, which is similar to the reported mean age of menopause 49.4 years among African women, and there is established evidence of a steeper blood pressure rise in men than women before the age of menopause (Adeloye, 2014).

Indeed, there were more RCTs only with men (N=6) than only with women (N=1). Opposite to that there were in total more female participants (62%). This is in line with Franconi 2019 who reported that females are well-represented in RCTs, especially for arterial hypertension and pulmonary arterial hypertension in the United States of America (Franconi, 2019; Scott, 2018). Bosu 2019 showed a similar distribution in their systematic review on hypertension in older adults in Africa in 2019. They reviewed studies with a female proportion of 54.2% of the total number of enrolled subjects (Bosu, 2019).

Except for one RCT, in all RCTs of those that reported age, mean age of participants was higher than 40 years with a range from 23 to 84 years. The only restriction on age was that partcipants had to be older than 18 years, as there were reported higher prevalence rates of hypertension with increasing age of subjects (Bosu, 2015; Gomez-Olive, 2017), with a relevant increase especially in people aged more than 60 years (Bosu, 2015).

It is possible that this review underrepresents severe hypertension and its treatment corresponding to prevalence of severe hypertension in Africa.
In contrast to findings of Bosu 2015, Oladapo 2012 and Ferdinand 2006, in our review, most RCTs (83.3%) included participiants with grade 1 hypertension (2.2%), grade 2 hypertension (1.1%) and grade 1 to 2 hypertension (80%). Together 11.1% of included RCTs (grade 3 hypertension: 7.8%, grade 1 to 3 hypertension: 3.3%) had severe forms of hypertension with potentially TOD. In 5.6% grade of hypertension was not mentioned.
The reason for that underrepresentation can be found in our inclusion criteria. We included only interventions RCTs on hypertensives with outcomes on SBP, DBP or MAP. We did not include RCTs on patients with stroke or other TOD. These RCTs did not fulfill our inclusion criteria because hypertension therapy is an important, but not the only part of the specific therapy regime and objectives of those RCTs are different.

Blacks have been shown to have more severe forms of hypertension with greater risk of target organ damage (TOD) (Bosu, 2015; Oladapo, 2012; Ferdinand, 2006) characterized by enhanced vascular contractility and salt retaining capacity, therapy resistance, and higher morbidity and mortality of the condition and its complications (Bewster, 2013). One reason for more severe forms could be the fact that many hypertensives are diagnosed for the first time when they present with complications such as stroke or heart failure (Bosu, 2015; Oladapo, 2012; Ferdinand, 2006). That means mild and moderate forms remain undetected.
In African patients, TOD was associated to the presence of newly diagnosed hypertension with an incidence rate of 43.1% in rural Nigerian hypertensives (Oladapo, 2012). This is probably caused or exacerbated by the prevailing low awareness (Bosu, 2015).

Patients are mostly unwilling to take drugs that may have side effects, especially when they do not have any symptoms. Even if African patients are on treatment, if BP remains uncontrolled due to inadequate treatment or a lack of follow up contol by a clinician or primary health care, patients are likely to have worse outcomes with TOD and cardiovascular disease (CVD) (Oladapo, 2012).

5.2 Pharmacological intervention

The prevalence of hypertension among black African patients is high, and these patients usually need two or more medications for blood-pressure control (Ojii, 2019). Furthermore, hypertension in persons of African ethnicity is associated with more therapy failure and more severe and earlier end organ damage. Therfore, persons of African ethnicity need to be screened at a younger age and treatment should potentially start at lower thresholds with early use of combination therapy and intensive treatment monitoring (Bewster, 2016).

The WHO Hearts Technical Package lists the essential medicines for the management of hypertension:

- thiazide or thiazide-like diuretic,
- calcium channel blocker (CCB) (long acting) (amlodipine),
- angiotensin converting enzyme inhibitor (ACEi) (long acting) and angiotensin receptor blocker (ARB) and
- beta-blocker (HEARTS, 2018).

Black hypertensive patients respond best to diuretics and vasodilators, like prazosin, doxazosin or calcium channel blockers. However, responses to antihypertensive monotherapy with beta-blockers and ACEi are poor compared to whites unless these agents are combined with a thiazide diuretic (Sedat, 1999; Seedat, 2014).

This corresponds to the fact that we found several RCTs on antihypertensive therapy with diuretics (N=32) and CCA (N=27) in African setting but also on beta-blocker (N=29). There are comparisons between subgroups of thiazide diuretics and loop diuretics and comparisions to placebo, as well as comparisons between other antihypertensive drug groups. RCTs on the effect of Methyldopa (N=4) as another vasodilator are few and on doxazosin (N=1) or prazosin (N=0) are rare.

5.2.1 Diuretics and Calcium Channel Blockers

Thiazide and thiazide-like diuretics are the mainstay of antihypertensive treatment and are unsurpassed at preventing cardiovascular complications of hypertension in black patients (Ferdinand, 2006; ALLHAT, 2002). According to our pre-determined outcomes the results of eligible trials in our review showed significant better effects in lowering BP for all diuretics

compared to placebo (Dean, 1971; Mngola, 1980; Stein, 1992). Comparing thiazide diuretics with loop diuretics thiazide diuretics showed a stronger effect on SBP and DBP (Obel, 1984; Radevski, 2002). As ALLHAT 2002 was conducted with African Americans over a period of eight years in our review the longest follow up time of pharmacological RCTs was 13 months. So we need trials in African setting with the aim to investigate that effect with a longer follow up time to give information on prevention of cardiovascular complications of hypertension in black patients by lowering BP.

In ALLHAT, the diuretic chlorthalidone was also superior to the dihydropyridine CCB amlodipine for the prevention of heart failure although the two agents had similar overall benefits in cardiovascular disease prevention (Ferdinand, 2006; ALLHAT, 2002). Regarding the decline of blood pressure in African setting, we found trials with varying results. Some trials showed a better effect for the therapy with diuretics (Ajayi, 1995; Daniels, 1987; Leary, 1990; Nwachukwu, 2015; Salako, 1998) and some trials reported a better effect for the therapy with CCBs (Mengesha, 2018; Nwachukwu, 2015; Iyalomhe, 2013). A number of other studies, including ALLHAT, have shown that in addition to their BP- lowering efficacy, CCBs reduce the probability of stroke and cardiovascular events to a similar extent as diuretics and beta-blockers (Ferdinand, 2006). Main morbidity and mortality outcomes did not differ significantly between treatment groups when drugs were combined to reach blood pressure goals (Brewster, 2004).

Therfore, we are not able to conclude a clear priorisation to diuretics or CCBs on the basis of African RCTs. A therapy with CCBs seems to be as effective in lowering BP as the therapy with diuretics in black patients. Seghal 2004 postulated in their review that diuretics and calcium-channel blockers resulted in a larger decrease among blacks than in whites. By contrast, among whites beta-blockers and angiotensin-converting enzyme inhibitors resulted in a larger decrease compared with blacks (Sehgal, 2004). Bewster 2013 summarized in their review that in all subgroups of sex, age and blood pressure strata, including high baseline DBP CCBs are effective (Bester, 2013). In all guidelines CCBs and Diuretics are suggested as one of the first choice drugs if starting a medication therapy is nessesary, in monotherapy and in their combination (ESC/ESH Guideline, 2018, James, 2014).

5.2.2 Beta-Blocker

Beta-blockers have little or no effect on all-cause mortality when used as initial treatment for hypertension. Furthermore, higher declines in cardiovascular events are produced by starting therapy with CCB or ARB than with beta-blockers (Wiysonge, 2018). On the other hand, agents of this class are especially effective in patients with stable and unstable angina and they have been shown to be beneficial in reducing mortality in African-American patients following myocardial infarction (Ferdinand, 2006).

The antihypertensive effect of beta-blocker compared to placebo was confirmed in African patients by Abson 1981, Cillers 1979, Mabadeje 1989, Salako 1979 and 1979a and Venter 1991.

Compared to other drugs we found two trials that showed the inferiority of beta-blockers compared to ACEi-therapy (Mangoush, 1990; Seedat, 1987). We found two trials that showed the inferiority of beta-blockers compared to CCB (Farag, 2018; M'Buyamba-Kabangu, 1988). In all RCTs included comparing beta-blockers with diuretics, beta-blocker therapy was inferior (Habte, 1992; Obel, 1981; Obel, 1990; Ogola, 1993; Salako, 1990; Seedat, 1980). In the end the results confirm the known and established effect on blood pressure for African patients but also show the inferiority compared to other antihypertensive medication for hypertension without complications or related organ damage. These findings are comparable to the recomendations of American and European treatment guidelines (James, 2014; Whelton, 2017; Williams, 2017). Agents of this class are especially effective in patients with stable and unstable angina and they have been shown to be beneficial in reducing mortality in African-American patients following myocardial infarction (Ferdinand, 2006).

5.2.3 ACE Inhibitors

ACE inhibitors were found to reduce cardiac events in patients with congestive heart failure and the high prevalence of heart failure among African Americans and are therefore especially recommended in this patient group (Ferdinand, 2006).

Among elderly patients in Europe with isolated systolic hypertension, nitrendipine (CCB), enalapril (ACEi) and HCT (thiazide diuretic) reduced the risk of stroke and the occurrence of various other cardiovascular complications (Staessen, 1997).

On the other hand, Helmer 2018 found no evidence for a reduced risk of cardiovascular or cerebrovascular outcomes for the antihypertensive therapy with ACEi in black hypertensives in their review of international guidelines and its references. They even stated that although there are no published data assessing clinical outcomes specifically in black patients using ACE inhibitor or ARB monotherapy, evidence from subgroup analyses and cohort studies suggests that these patients may have higher rates of cardiovascular and cerebrovascular outcomes compared with those taking other antihypertensives. Furthermore, they found no evidence that adding an ACE inhibitor or ARB as a second-line agent increases or decreases cardiovascular or cerebrovascular outcomes so ACE inhibitors or ARBs should not routinely be initiated as monotherapy in black patients with hypertension (Helmer, 2018).

Only one RCT from this systematic review compared ACEi-therapy to placebo (Opie, 2002). This RCT stated the efficacy of ACEi-therapy reducing BP as recommended in the American and European guidelines.

But this small and old RCT in Africa included a very small sample size of 40 participants from South Africa. More trials in other regions of Africa with more participants should be conducted to confirm or refute this recommendation.

Maharaj 1993a, Radevski 1999, Sareli 2001 and Skoularigis 1994 compared the therapeutic effect of different CCBs with different ACEis on blood pressure, all in South Africa. Radevski 1999 and Skoularigis 1994 showed significant and clinically relevant better effects for the therapy with CCB (nisoldipine and nifedipine, respectively) compared to ACEi (enalapril and captopril, respectively). The follow up time ranged from 3 months to 6 months. Sareli 2001 showed, however, a better effect for the therapy with ACEi (enalapril) against nifedipine after a follow up time of 13 months. YK Sedat 1999 reported that responses to therapy with ACEi get better when these agents are combined with a thiazide diuretic. In the RCTs of Sareli 2001 and Skoulariges 1994 HCT 12,5 mg could be added if BP remained uncontrolled.

So we could assume, that the full effect of ACEi on blood pressure in black hypertensives depends on time of consequent ingestion and on the fact if a second drug (for example a thiazide diuretic) was added. Due to the heterogeneity of results of different reviews, there is still a need of high quality RCTs on effectiveness of ACEi in black hypertensives under consideration of the different regions of the African continent.

5.2.4 Combination therapy of different drugs

There were few trials examining differences in antihypertensive efficacy between all those different drug classes. Overall, combination therapy in African patients was more effective than monotherapy (Iyalomhe, 2013; Middlemost, 1994; Obel, 1990; Seedat, 1980) in African patients. Some more trials should be conducted with the aim to compare different combination therapy options in African hypertensives, especially in North and Central Africa to verify recommandations from African guidelines. Five RCTs included found out that these drug combinations in a single pill were more effective than free combination of substances in separate pills. One of them concluded that although there is no biological difference between taking the two drugs separately and taking them in a combined formulation, compliance is easier with the fixed dosage combination and so this formulation should be preferred in the African context (Salako, 1990).

5.2.5 Evidenced-based guidelines

Drugs differ in their efficacy for reducing blood pressure in black patients, but there is no solid evidence that efficacy for reducing morbidity and mortality outcomes differs once patients achieve the blood pressure goal (Bewster, 2004). In our review, diuretics (Dean, 1971; Mngola, 1980; Stein, 1992), calcium-channel blockers (Fadayomi, 1986; Opie, 1997), beta-blockers (Abson, 1981; Cillers, 1979; Mabadeje, 1989; Salako, 1979; Salako, 1979a; Venter, 1991), ACEi (Opie, 2002) and α-blockers (Lubbe, 1974) were more effective than a placebo in reducing blood pressure in African hypertensives.

However, despite missing RCTs which compared the effect of Angiotensin II receptor blockers against placebo in African setting, our findings correspond to the established guidelines of Europe and America (Williams, 2018; James, 2014). The editors of the PASCAR roadmap 2017 considered the recommendations from these guidelines. Furthermore, they considered the recommendations based on references from WHO, South Africa, Europe, North America, and of trials that took into account the specifics of blood pressure therapy and complications in black patients, for example Bewster 2013, to adopt a guideline for the African continent for the management of hypertension. If the treatment strategy after lifestyle modification failed the use of a thiazide or thiazide-like diuretic or long-acting calcium-channel blockers as monotherapy is recommended and, if blood pressure still cannot be controlled, the combination of two medications is recommended. It is also possible to start with a combination therapy of two drugs in severe hypertension by initial diagnosis (Dzudie, 2017). This considers our previously discussed point of the frequently severe forms with TOD in patients of African ancestry (Bosu, 2015; Oladapo, 2012; Ferdinand, 2006).

According to European Society of Cardiology Guidelines 2018, it is recommended to initiate an antihypertensive treatment at all grades with a two-drug combination, preferably in a single-pill combination (SPC). The core treatment strategy requires the use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, with beta-blockers used for specific indications (Williams, 2018). According to the American guideline, the pharmacological therapy is recommended to be started in black patients with thiazide-like diuretics or CCB, alone or in combination and for non-black hypertensives with thiazide-like diuretics or ACEi or ARB or CCB alone or in combination (James, 2014). In all guidelines, the combination therapy is optional but the European one tends to start with the combination therapy more often, no matter what grade of hypertension is present. This is in our opinion preferable for the African guideline considering the frequently severe hypertension at initial diagnosis with TOD in patients with African ancestry (Bosu, 2015; Oladapo, 2012; Ferdinand, 2006). Additionally, we found combination therapy was more effective than monotherapy in African patients (Iyalomhe, 2013; Middlemost, 1994; Obel, 1990; Seedat, 1980).

In the Egyptian guideline they focused on the problem of Egypt's limited financial resources. Drugs of first choice should be the least expensive such as thiazide diuretics, beta adrenergic blockers and generic forms (Ibrahim, 2014). Nevertheless, a combination therapy of least expensive drugs should be possible if available.

So is it useful and practicable to import guidelines to general treatment? Our results affirm that. Gimshaw 1993 concluded after their systematic review that explicit guidelines do improve clinical practice, when introduced in the context of rigorous evaluations (Gimshaw, 1993).

5.2.6 Availability of medicine

Addressing availability of the essential medicine (chapter 5.2) within countries and at all levels of care and sectors is critically important. An analysis by Cameron and colleagues across 40 countries showed that chronic disease medicines were significantly less available than those for acute conditions, in both the public and private sectors, with this lack of availability even more evident in the public sector (HEARTS, 2018).

A large proportion of communities in low-income and middle-income countries do not have access to more than one blood pressure-lowering medicine and, when available, they are often not affordable. These factors are associated with poor blood pressure control. Ensuring access to affordable blood pressure-lowering medicines is essential for control of hypertension in low-income and middle-income countries (Attaei, 2017).

Macquart de Terline 2019 investigated relevant factors associated with poor adherence to medication among hypertensive patients in twelve low and middle-income SSA countries. They reported 26.5% of the patients admitted having stopped their treatment due to financial reasons and this proportion was 4 fold higher in the lowest compared to the highest wealth group (47.8% vs 11.4%). In low-income countries, the proportion of low adherence increased progressively and considerably with decreasing level of individual patient wealth. In contrast, in middle-income countries, they observed a minor and non-significant increase of the proportion of low adherence between individual wealth categories. However, these data derived from specific urban clinics so they likely represent the best-case scenario and the magnitude of the problem in the general population with hypertension could be underestimated (Macquart de Terline, 2019).

Transferred to the studies we included (see figure 4), only South Africa, Kenya and Ghana have a good access to essential medication. As Ghana and Kenya are low-middle income countries the affordability might stay difficult for most of the hypertensives.

Estimates by Attaei 2017 for affordability and use of blood pressure-lowering medicines and blood pressure control are consistent with their findings from studies showing that adherence to medicines declines as out-of-pocket expenditure increases, whereas improvements in insurance coverage for medicine costs and low out-of- pocket expenditure improves adherence (Attaei, 2017). HICs have achieved huge reductions in mortality by making medical treatment widely available. This progress must be extended to LMICs in order for global goals to be achieved (p.17, Prabhakaran, 2017).

5.3 Non pharmacological intervention

Pharmacotherapy is the mainstay of hypertension management because the efficacy of antihypertensive medications is well-established (Noone, 2019; Williams, 2018).

Strategies to increase awareness and adherence to therapy and lifestyle modification are important as non-pharmalogical interventions to treat hypertension because of evidence for BP lowering effects (Noone, 2019).

Starting therapy of hypertension in low risk patients with grade 1 hypertension first lifestyle modification is recommended. For patients with higher cardiovascular risk and/or higher grades of hypertension lifstyle modification remains an important part besides pharmacotherapy (Williams, 2018; Whelton, 2017; Seedat, 2014; Ibrahim, 2014). Healthy lifestyle choices, including regular physical activity, sodium restriction, weight reduction, smoking cessation, moderation of alcohol consumption and other dietary changes have been shown to reduce BP and may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 hypertension. They can also augment the effects of BP- lowering therapy (Noone, 2019; Williams, 2018).

High and upper-middle income countries have reduced the age-standardized mortality resulting from CVD by more than 25 percent since 2000 (WHO, 2012), largely by using policy interventions to reduce risk-factor levels, strengthening the health system at the primary-care level, and improving acute care with attention to early initiation of treatment. Policies aimed at reducing population-wide risk factors, such as reduction of salt in processed foods, or bans on fatty acids (trans fats), are effective but have not been widely adopted in LMICs (p.3, Prabhakaran, 2017).

We found two randomized controlled trials in African setting (Ghana, Cameroon) who investigated the effect of financial incentive on the hypertension control (Gyamfi, 2017) and patient retention rates for CVD therapy (Labhardt, 2011) favouring the intervention in each trial. Even though evidence for cost-effective CVD treatment approaches with non-pharmacological interventions has increased since 2006, evidence gaps still remain. The need still exists to generalize many findings from middle and high-income countries to estimate the potential cost-effectiveness of highly effective individual-level treatments for which coverage is low and technologies are not available in many low-income countries (p.4, Prabhakaran, 2017). In our review we found not only one example for insufficient or unavailable equipment or medication shortage. For instance in one trial, conducted by Goudge 2017, all clinics faced numerous challenges, including rapidly increasing number of users of chronic care, unreliable BP machines and cuffs, intermittent drug shortages and insufficient space. They first had to provide sufficient BP-monitors before trial enrollment was possible. This seems to be a general challenge in blood pressure, and other NCDs, management (Goudge, 2017).

Another challenge was faced in a multi-faced intervention in South Africa to implement national guidelines with training doctors in their use was exposed to a lack of acceptance by staff (Steyn, 2013). There was no impact on hypertension control in that trial. Poor implementation of hypertension treatment guidelines because of a lack of continuing medical education was reported to be one roadblock among others, such as the already mentioned lack of affordable antihypertension medication or the poor universal health insurance coverage (Dzudie, 2017).

Improvements in health promotion and system strengthening could help to improve awareness, treatment and control of hypertension among African rural and urban populations. It is crucial to plan and implement more active campaigns aiming to increase awareness and diagnosis of hypertension (Gomez-Olive, 2017). Several methods were examined with subject to improve knowledge of the general population about blood pressure and health related behavior concerning hypertension with some convincing results. We identified five RCTs that investigated the efficacy of phone or letter-based interventions with SMS for information, improved knowledge of hypertension, interactive and adherence support, reminder letters for follow ups (Bobrow, 2016; Hacking, 2016; Sarfo, 2019; Stewart, 2005; Vedanthan, 2019). Some of them showed strong preferences to the intervention in knowledge and self-reported behavior changes (Hacking, 2016; Steward, 2005) and, if reported, relevant declines in BP at the end of follow up (Bobrow, 2016; Steward, 2005; Vendanthan, 2019). But Sarfo 2019 showed no better effect for the intervention as it was an RCT with the aim to demonstrate feasibility of implementing an intervention special BP device in an app for monitoring BP and medication intake under nurse guidance. Therefore, the RCT was not designed to control BP. A possible cause might be that the longest follow up time of 12 month seems to be too short considering the aim of reaching a sufficient BP control by improving knowledge and awarenss of the disease with enormous difficulties of attempting to change a lifetime of poor health habits in these patients (Stewart, 2005). But also realizing the limitations of implementing such interventions in the developing world, concerning infrastructure, such as high SMS delivery failure (Hacking, 2016) access to data provided by clinicians (medication prescribing data) (Vedanthan, 2019).
Three RCTs with follow up periods between 6 and 14 months reported a decline in BP after nurse-led interventions to improve the management of hypertension. With home visits and/or patient education by a trained nurse and/or training and education of nurses, positive effects could be seen even after a relatively short follow up time. But we also found RCTs without a significant decline in BP that combined phone/letter based intervention with nurse or health worker led interventions, respectively (Goudge, 2018; Saunders, 1991).

We know about the posive effects on BP control by improving physical activity and reducing salt consumption as it is one lifstyle recommendation to achieve BP control in common guidelines (Williams, 2018; James, 2014). These recomendations were supported by a clear decline on BP

by improving physical activity and a statstistically not significant decline on BP by lowering salt consumption in 5 RCTs in African countries, Nigeria, Egypt and South Africa, respectively (Turky, 2013; Aweto, 2012; Maruf, 2016; Lamina, 2010; Charlton, 2008).

There was no RCT eligible to this review on other lifestyle interventions such as other dietary changes, smoking cessation or weight reduction.

5.4 Strengths and Limitations of this Review

This review was restricted to studies with the highest level of evidence to investigate the benefits and harm of medical interventions. The randomized allocation of patients to the treatment and control groups will adequately ensure that characteristics of participants are evenly distributed across intervention groups. But lack of equipment and insufficient space complicated the carrying out of some studies. This might have caused the unclear or high risk of bias in some domains of all included studies and might restrict the internal validity of these RCTs.

External validity is restricted by several points. First, we restricted this review to RCTs published in English. Therefore, it may have missed studies published in languages other than English, such as French or local languages. Secondly, there is a focus on Western and Southern African countries. Other regions are underrepresented in this review. Moreover, nearly all trials were conducted in urban setting and not all studies reported details on the local settings.

Considering that urban Africans have a better access to health care, more RCTs should be investigated in rural settings. Especially low cost-interventions such as nurse-led or task-shifting interventions as well as secure providing of essential medication should be taken into account. Furthermore, these intervention studies seem to have too short follow-up times to be able to show effects by the intervention on the management of hypertension.

We had to exclude RCTs on primary prevention of hypertension due to the high variety of interventions and broad objectives of these studies. These studies should be summarized in another systematic review.

Finally, there is still the need to conduct RCTs in all regions of the African continent to be aware of intercultural differences in hypertension management and treatment.

The local context, the unique environment, cultural and social particularities, such as distance to facilities, traditional beliefs, and decision making in the families have to be taken into account for research on hypertension as well as the special genetic backgrounds with high levels of genetic diversity within and between African populations (Gomez, 2014). Therefore, evidence-based information from this systematic review might be used to improve the implementation of strategies on hypertension under consideration of the special African conditions.

6 Conclusion

This study shows that even though hypertension is a critical health problem in different regions and settings in Africa, the number of randomized controlled trials on treatment of hypertension is still low. Furthermore, the distribution of RCTs on treatment of hypertension across the African continent is still not representive for all Africans. The concentration of previous RCTs in urban SSA with a underrepresentation of RCTs on hypertension in Northern and Central Africa considering the known high levels of genetic diversitiy all over the continent, make the present data untransferable to all African countries.
Research on interventions to treat hypertension needs to be expanded to the rural areas of Africa and to all African regions.

Pharmacotherapy should be given special attention regarding high levels of genetic diversity and the inadequate access to health care services.
Furthermore, it is crucial to plan and implement more campaigns to increase awareness and diagnosis of hypertension due to missing accurate health-related information.
Particularities of African population with cultural and social particularities, such as distance to facilities, traditional beliefs, decision making in the families within African populations has to be taken into account for research on hypertension.
Low availibility of resources on the African continent, such as basic NCD technologies for diagnostic, medication and health care proffessionals trained on NCD, form another challenge for implementation of hypertension prevention and management.
The identified studies offer effective approaches that have been tested in African countries.

The need for guidelines for screening and diagnosis, treatment, treatment control and screening for related organ effects for all regions in Africa as there are high levels of genetic diversity within and between African populations is undisputed. There is the PASCAL Roadmap 2017 as a guideline for the African continent based on international data. Only few of the African countries have developed or adopted guidelines for the management of hypertension by taking available evidence from world literature and other international guidelines. Local guidelines are needed based on local data with strong evidence taking into account local specifics to do justice to the particularities of African population.
Following evidence-based local data will advance the implementation of hypertension prevention and management and those guidelines with its special needs in the African context.
An improvement in the prognosis of patients with high blood pressure in Africa requires the implementation of comprehensive diagnistics, medical treatment and subsequent regular checks.

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8 Theses

1. A total of 90 RCTs on treatment of hypertension with all together 23 562 participants in Africa indicated a lack of evidence in different settings.

2. We stated an underrepresentation of RCTs in Central and Northern Africa and rural settings.

3. A total of 67 RCTs on pharmacological interventions showed a clear advantage of treatment with anti-hypertensive drugs compared to placebo, and a clear benefit for diuretics, (whereas comparisons of different drug classes were heterogeneous). There was no RCT eligible to this review with angiotensin-rezeptor blockers compared to placebo.

4. A total of 23 RCTs on non-pharmacological indicated convincing better blood pressure control by improving physical activity (and heterogeneous results on standardized treatment, education and adherence strategies) in African countries. There was no RCT eligible to this review on other dietary changes than salt restriction, smoking cessation or weight reduction.

5. Risk of bias could not be excluded in all of the assessed topics with the most important problems in sequence generation and allocation concealment in pharmacological intervention RCTs and blinding staff, participants and outcome assessors as well as incomplete outcome data in non-pharmacological intervention RCTs.

6. Research on interventions to treat hypertension should be expanded to the rural areas and include all services like promotion, prevention, diagnosis, treatment and regular checks.

7. Low awareness, low availability and big intercultural differences on the African continent form another challenge to implement interventions to manage hypertension.

8. The number of randomized controlled trials on treatment of hypertension and the concentration of previous RCTs in urban Sub-Saharan Africa considering the known high levels of genetic diversitiy all over the continent make the present data untransferable to all African countries.

9. An improvement in the prognosis of patients with high blood pressure in Africa requires the implementation of comprehensive diagnistics, medical treatment and subsequent regular checks.

9 Appendix

9.1 Included Hypertension studies (N=90)

1. Abengowe CU (1985) A double-blind comparison of acebutolol (Sectral) and propranolol (Inderal) in the treatment of hypertension in black Nigerian patients. Journal of International Medical Research. 13(2):116-21
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9.2 Excluded studies with causes (N=218)

9.2.1 Other design (N=25)

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9.2.4 Other indication (N=32)

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9.2.8 Coronary heart disease (N=7)

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9.3 More than one publication of same trial (N=22)

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9.4 Full text available after second screening (N=6)

(In first stepp no full text available, in second screening full text available-thats why removed from part „no full text available“)

1. Bobrow K, Brennan T, Springer D, Levitt NS, Rayner B, Namane M, et al. (2014) Efficacy of a text messaging (SMS) based intervention for adults with hypertension: protocol for the StAR (SMS Text-message Adherence suppoRt trial) randomised controlled trial. BMC Public Health, 14:28.
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9.5 Search strategies

9.5.1 Medline (Ovid)

Nr.	Searches 24/07/2017	Results
Search after Indikation (Buckley 2010, Hooper 2011)		
1	exp heart diseases/	1045178
2	exp vascular diseases/	1545526
3	cerebrovascular disorders/	45731
4	exp brain ischemia/	96444
5	exp carotid artery diseases/	44085
6	exp dementia, vascular/	6133
7	exp intracranial arterial diseases/	56391
8	exp intracranial embolism/ and thrombosis/	1116
9	exp intracranial hemorrhages/	64404
10	exp stroke/	110795
11	exp hyperlipidemias/	63208
12	Exp hypercholesteremia/	24922
13	exp Myocardial Ischemia/	407994

14	angina.tw	50026
15	(heart adj3 disease$).tw.	157850
16	(coronary adj3 disease$).tw.	131594
17	(peripheral adj3 disease$).tw.	26278
18	(cerebrovascular disease).tw	13408
19	Renal artery stenosis.tw	5139
20	(Aortic aneurism or Aneurysm$).tw	106967
21	myocardial infarct$.tw.	173836
22	exp Myocardial Revascularization/	88171
23	(coronary adj3 bypass$).tw.	44015
24	(coronary adj3 angioplast$).tw.	14432
25	(heart adj3 infarct$).tw.	7597
26	postmyocardial infarct$.tw.	964
27	cardiovascular diseases/	129106
28	Hypertens$.tw	382295
29	(high adj2 blood pressure).tw	14704
30	(blood pressure control).tw	8967
31	Hypertensive heart disease.tw.	1411
32	Cardiomyopath$.tw.	59962
33	Heart failure.tw.	137172
34	(Pulmonary heart disease).tw	580
35	Cardiac dysrhythmia*.tw.	1039
36	Inflammatory heart disease.tw.	153
37	Endocarditis.tw.	30531
38	Cardiomegaly.tw	3108
39	Valvular heart disease.tw.	4473
40	Rheumatic heart disease.tw	3956
41	Myocarditis.tw	13206
42	Arrhythmi$.tw	80102
43	Vasculitis.tw	28301
44	or/1-40	2498192
45	Africa.tw	188711
46	Exp Africa/	231956
47	Algeria$.tw or exp Algeria/	4028
48	Angol$.tw or exp Angola/	1568
49	Benin$.tw or exp Benin/	3313
50	Botswan$.tw or exp Botswana/	2156

51	Burkina Faso.tw or exp Burkina Faso/	3753
52	Burund$.tw or exp Burundi/	856
53	Cameroon$.tw or exp Cameroon/	6705
54	Cape Verde.tw or exp Cape Verde/	468
55	Central African Republic$.tw or exp Central African Republic/	1063
56	Chad$.tw or exp Chad/	2867
57	Comoros$.tw or exp Comoros/	407
58	Cote d'Ivoire.tw or exp Cote d'Ivoire/	3399
59	Democratic Republic of Congo.tw or exp Democratic Republic of Congo	1275
60	Djibout$.tw or exp Djibouti/	362
61	Egypt$.tw or exp Egypt/	21294
62	Equatorial Guinea$.tw or exp Equatorial Guinea/	400
63	Eritrea$.tw or exp Eritrea/	515
64	Ethiop$.tw or exp Ethiopia/	13487
65	Gabon$.tw or exp Gabon/	2141
66	Gambia$.tw or exp Gambia/	7552
67	Ghana$.tw or exp Ghana/	9091
68	Guinea$.tw or exp Guinea/	105830
69	Guinea-Bissau.tw or exp Guinea-Bissau/	1140
70	Kenya$.tw or exp Kenya/	18692
71	Lesoth$.tw or exp Lesotho/	605
72	Liberia$.tw or exp Liberia/	1665
73	Libya$.tw or exp Libya/	1710
74	Madagascar$.tw or exp Madagascar/	6489
75	Malawi$.tw or exp Malawi/	6144
76	Mali.tw or exp Mali/	3359
77	Mauritania$.tw or exp Mauritania/	647
78	Mauritius$.tw or exp Mauritius/	897
79	Morocc$.tw or exp Morocco/	7666
80	Mozambique$.tw or exp Mozambique/	3040
81	Namibia$.tw or exp Namibia/	1419
82	Niger.tw or exp Niger/	10659
83	Nigeria$.tw or exp Nigeria/	33785
84	Rwanda$.tw or exp Rwanda/	2712
85	(Sao Tome and Principe).tw	119
86	Senegal$.tw or exp Senegal/	8140

87	Seychell$.tw	634
88	Sierra Leone.tw or exp Sierra Leone/	1956
89	Somalia$.tw or exp Somalia/	1896
90	South Africa$.tw or exp South Africa.de	48624
91	South Sudan.tw or exp South Sudan/	337
92	Sudan$.tw or exp Sudan/	9205
93	Swaziland$.tw or exp Swaziland/	747
94	Tanzania$.tw or exp Tanzania/	12657
95	Togo$.tw or exp Togo/	1590
96	Tunisia$.tw or exp Tunisia/	9812
97	Uganda$.tw or exp Uganda/	13717
98	Zambia$.tw or exp Zambia/	5339
99	Zimbabwe$.tw or exp Zimbabwe/	6813
100	Somaliland$.tw or exp Somaliland/	319
101	#1.tw	1
102	or/45-101	436084
103	44 and 102	19017
Study design (Lefebvre 2011)		
104	randomized controlled trial.pt.	469079
105	controlled clinical trial.pt.	94421
106	randomized.ab.	402209
107	placebo.ab.	188717
108	randomly.ab.	279685
109	trial.ab.	422040
110	groups.ab.	1721011
111	or/104-110	2535560
112	exp animals/ not humans.sh.	4438699
113	111 not 112	2133129
114	103 and 113	2643

New search in 10/2019: 317 records

9.5.2 CENTRAL

14/08/2017

1	Africa, explode all trees	381
2	Algeria* or Angol* or Benin* or Botswan*	746
3	(Burkina Faso) or Burund* or Cameroon* or (Cape Verde) or (Central African Republic)	939
4	Chad* or Comoros* or Cote d'Ivoire or Congo*	1728
5	Djibout* or Egypt* or (Equatorial Guinea*) or Eritrea*	4540
6	Ethiop* or Gabon* or Gambia* or Ghana* or Guinea* or Guinea-Bissau	2580
7	Kenya* or Lesoth* or Liberia* or Libya* or Madagascar* or Malawi*	2326
8	Mali* or Mauritania* or Mauritius* or Morocc* or Mozambique* or Namibia* or Niger*	20804
9	Nigeria* or Rwanda* or (Sao Tome and Principe) or Senegal* or Seychell*	2179
10	Sierra Leone or Somalia* or (South Africa) or (South Sudan*) or Sudan* or Swasiland	5877
11	Tanzania* or Togo* or Tunisia* or Uganda* or Zambia* or Zimbabwe* or Somaliland or (Sahrawi Arab Democratic Republic)	3790
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	39610
13	MeSH descriptor Cardiovascular Diseases, this term only	680
14	MeSH descriptor Heart Diseases explode all trees	795
15	MeSH descriptor Vascular Diseases explode all trees	632
16	MeSH descriptor Cerebrovascular Disorders, this term only	297
17	MeSH descriptor Brain Ischemia explode all trees	70
18	MeSH descriptor Carotid Artery Diseases explode all trees	108
19	MeSH descriptor Dementia, Vascular explode all trees	133
20	MeSH descriptor Intracranial Arterial Diseases explode all trees	95
21	MeSH descriptor Intracranial Embolism and Thrombosis explode all trees	76
22	MeSH descriptor Intracranial Hemorrhages explode all trees	29
23	MeSH descriptor Stroke explode all trees	669
24	MeSH descriptor Hyperlipidemias explode all trees (4197)	27
25	(coronar* or heart or peripheral* or cerebrovascular* or myocardial) near 3 (disease or infarct*)	5799
26	myocardi* near 3 (infarct* or revascular* or ischaem* or ischem*)	1600
27	vascular* near 3 (peripheral* or disease* or complication*))	1217
28	hypertensi* or (high near 2 blood pressure)	50221

29	(heart near 2 failure) or stroke	50245
30	Endocarditis or myocarditis or Cardiomegaly or arrythmi*	2038
31	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30	101472
32	#12 and #31	4139

2008 of 4139 were RCTs and were exportet to endnote

9.5.3 CINAHL

01/2020

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswan$ or (Burkina Faso) or Burund$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$ or Ethiop$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocc$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychell$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zambia$ or Zimbabwe$ or Somaliland or (Sahrawi Arab Democratic Republic)) in Abstract

AND

hypertension or high blood pressure or elevated blood pressure or htn or hypertensive in Abstract

AND

randomized or rct or randomized in Abstract

AND

In English

AND

Peer-reviewed

And

Humans

9.5.4 WHO international clinical trials registry platform search portal

28/10/2019

Condition: hypertension or (blood pressure control) or (high blood pressure)

Recruitment status: all

Countries of recruitment: all African Countries

9.6 Risk of bias assesment

Table 10 Risk of bias on different intervention RCTs in secondary prevention of hypertension

Study	Sequence generation	Allocation concealment	Blinding of		Incomplete outcome data	Selective reporting	Other sources
			personnel / participants	outcome assessors			
Standardized treatment							
Akintunde 2017	☹	😐	😐	😐	☹	☺	☹
Okeahialam 2011	☺	☺	☹	😐	☹	😐	☹
Steyn 2013	☺	☺	☹	☹	☺	☺	☺
Education and adherence							
Wahab 2017	☺	☺	☹	☹	☺	😐	☹
Adeyemo 2013	😐	😐	☹	😐	☹	😐	☹
Bobrow 2016	☺	☺	☺	☺	☹	☺	☺
Bolarinwa 2019	☺	☺	☹	☹	☹	☹	☹
Cappuccio 2016	😐	☺	☹	☹	☹	😐	☹
Fairall 2016	☺	☺	☹	😐	☺	☺	☺
Goudge 2018	☺	☺	☹	☺	☹	☺	☺
Gyamfi 2017	☺	☺	☹	😐	☹	☹	☺
Hacking 2016	😐	😐	☹	☹	☺	😐	☺
Labhardt 2011	☺	☺	☹	☹	☹	☹	☺
Mendis 2010	☹	☹	☹	☹	☹	😐	☺
Sarfo 2019	☺	☺	☹	☺	☺	☺	☺
Saunders 1991	😐	😐	☹	☹	☺	😐	☺
Stewart 2005	😐	😐	☹	☹	☹	😐	☺
Vedanthan 2019	😐	☺	☹	☹	☹	☺	☹

Study	Sequence generation	Allocation concealment	Blinding of		Incomplete outcome data	Selective reporting	Other sources
			personnel / participants	outcome assessors			
Physical activity							
Aweto 2012	😐	☹	☹	☹	😐	☹	😐
Lamina 2010	😐	☺	☺	☹	😐	☺	😐
Maruf 2016	☺	☹	☺	☺	☹	☹	☺
Turky 2013	☺	☹	☹	☹	😐	☹	☺
Modified nutrition							
Charlton 2008	😐	😐	☺	☺	☺	😐	☺
Diuretica							
Dean 1971	😐	☺	☺	☺	☹	😐	☹
Iyalomhe 2013	☺	😐	😐	😐	☺	😐	☺
Iyalomhe 2007	😐	😐	☹	☹	😐	😐	😐
Mngola EN. 1980	😐	☺	☺	😐	☺	☹	☹
Obel 1984	☺	😐	☺	😐	☹	😐	😐
Radevski 2002	😐	😐	😐	☺	☺	😐	☹
Stein 1992	😐	😐	☺	☺	☹	😐	☹
Wadhawan 1981	😐	😐	☺	☺	☹	😐	☹
Beta-Blocker							
Abengowe 1985	😐	😐	☺	☺	☺	😐	😐
Abson 1981	☺	😐	☺	☺	☹	☹	☹
Bosman 1977	😐	😐	☺	😐	☹	😐	☺
Cilliers AJ. 1979	😐	☺	☺	☺	☹	😐	☹
Salako 1979	😐	😐	☺	☺	☹	😐	☹
Salako 1979a	😐	😐	☺	☺	☺	😐	☹

Study	Sequence generation	Allocation concealment	Blinding of		Incomplete outcome data	Selective reporting	Other sources
			personnel / participants	outcome assessors			
Venter 1991	😐	😐	☺	☺	☹	😐	☹
Ca-Antagonists							
Fadayomi 1986	😐	😐	☺	☺	☺	☹	☹
Leary 1991	😐	☺	☺	😐	☹	😐	☹
Maharaj 1992	😐	☺	☺	😐	☺	😐	☹
Onwubere 2001	☺	😐	☹	😐	☹	😐	☹
Opie 1997	😐	😐	☺	☺	☺	😐	☺
Betablocker vs. Diuretika							
Obel 1981	☺	☺	☺	☺	☺	😐	☹
Obel AO.	😐	☺	☺	☺	☺	☹	☹
Ogola 1993	😐	😐	😐	😐	☺	😐	☹
Salako 1990	☺	☺	☺	☺	☺	😐	☹
Seedat 1980	😐	😐	☺	☺	☺	😐	☹
Ca Antagonists vs. Diuretika							
Ajayi 1995	😐	😐	☹	☹	☹	😐	☹
Daniels 1987	😐	☺	☺	☹	☹	😐	☹
Leary 1990	😐	☺	☺	😐	☹	😐	☹
Nwachukwu 2017	😐	😐	☺	😐	☺	😐	☹
Salako 1998	😐	😐	☺	☺	☹	😐	☹
Sobngwi 2019	☺	😐	☺	☺	☺	☺	☺
Other drug combinations							
Ahaneku 1995	😐	😐	☹	☹	😐	☹	😐
Ajayi 1989	😐	😐	☺	☺	☺	☺	😐

Study	Sequence generation	Allocation concealment	Blinding of		Incomplete outcome data	Selective reporting	Other sources
			personnel / participants	outcome assessors			
Djoumessi 2016	😐	☺	☹	😐	☺	☺	☺
Farag 2018	😐	😐	☹	😐	☹	😐	☹
Goodman 1985	😐	😐	☺	☺	☹	😐	☺
Habte 1992	😐	☺	☺	☺	☹	😐	☹
Isles 1986	😐	😐	☹	☹	☺	☹	☺
Leary 1987	😐	☺	☺	😐	☹	😐	☹
Levenstein 1978	😐	☺	☺	☺	☺	😐	☹
Lubbe 1974	😐	☺	☺	☺	☹	😐	☹
Mabadeje1989	😐	😐	😐	😐	😐	😐	☹
Mabadeje 1977	😐	😐	☺	😐	☺	☺	☹
Maharaj 1993	😐	😐	☺	😐	☺	😐	☹
Maharaj 1993a	😐	😐	☺	😐	☺	😐	☺
Mangoush 1990	😐	😐	☹	😐	😐	😐	☹
Manyemba 1997	😐	😐	☹	☹	☹	☺	☹
M'Buyamba-Kabangu 2013	☺	☺	😐	😐	☹	☺	☺
M'Buyamba-Kabangu 1988	😐	☺	☺	😐	☺	😐	☹
Mengesha 2018	☺	😐	☹	☹	☺	😐	☺
Middlemost 1994	😐	☺	☺	😐	☺	😐	☹
Norton 1999	😐	☺	☺	☺	☺	😐	☹
Nwachukwu 2015+2017	😐	☺	☺	☺	☺	😐	☹
Obel 1983	☺	😐	☹	😐	☹	😐	☹

Study	Sequence generation	Allocation concealment	Blinding of		Incomplete outcome data	Selective reporting	Other sources
			personnel / participants	outcome assessors			
Obel 1989	😐	☺	☺	☺	☺	😐	☹
Obel 1991	😐	☺	☺	☺	☺	☹	☹
Ojii, 2019	☺	☺	☹	☹	☹	☺	☺
Opie 2002	😐	😐	☺	☺	☹	😐	☹
Poulter 1993	😐	😐	☺	☺	☹	😐	☹
Radevski 1999	😐	😐	☺	☺	☺	😐	☹
Rogers 1988	😐	😐	☺	☺	😐	😐	☹
Sareli 2001	😐	😐	☹	☹	☹	😐	☹
Seedat 1987	😐	😐	☺	☺	☺	😐	☹
Seedat 1990	😐	😐	☺	☺	☺	😐	☹
Skoularigis 1994	😐	😐	☹	☹	☺	☹	☹
Skoularigis 1996	😐	😐	☺	☺	☺	😐	☹
Venter 1988	😐	😐	☺	☺	☹	😐	☹
☺: low; 😐: unclear; ☹: high risk of bias							

9.7 Extracted data of all included RCTs

Table 11 Exel sheet with data extraction of all included RCTs (original format table available on request)

Study	Study name	Year of publication	Other publications	Design	Prevention	Grade	inclusion/exclusion criteria	Duration	Intervention	outcome	amount/groups	male/female %	Age	Baseline values (pooled mean, pooled sd)	Weight /BMI	Country	Region	Results (pooled mean, pooled sd)
Abengowe CU	Abengowe 1985	1985		RCT	Secondary prevention	Mild to moderate	DBP 95-120 after wash out//cardiovascular or cerebrovasc. Complications, renal or hepatical impairment, malignant/secondary hypertension, d.m., cold, psychosis, pregnancy, no other medication	20 weeks	**Drugs:** Acebutol (initiated 400 mg, maximum 800 mg) 1x/d vs. Propanolol 2x/d (initiated 160 mg, maximum 320 mg), titrated until DBP<90 mmHg	BP, HR: Change from baseline to end of medication	r/a: 45; 2 (27 vs. 18)	40%; 60%, 18, 27	48.6 (25-66)	SBP:191, DBP:110.2, HR:81.8	77.3 (50-109)	Nigeria	Urban (Kaduna)	Change from baseline to end of medication: HR: -17% vs. -24%; SBP: -22% vs. -17%; DBP: -16% vs. -14%
Abson CP, Levy LM, Eyherabide G.	Abson 1981	1981		Cross over RCT	Secondary prevention	Mild to moderate	Newly diagnosed hypertension, DBP 100-120 after run in//cardiac failure, myocardial infarction within 6 months, bronchial asthma, renal or hepatic impairment, d.m., gout, pregnancy	12 weeks	**Drugs:** Atenolol 200 mg vs. Atenolol 100 mg vs. placebo	Not specified: BP, HR reported as other outcomes	r: 36, a: 23	39%; 61%, 14, 22	23-65	SBP: 169.8 (18.7), DBP:110 (9.6), HR:77.3 (10.1)		Zimbabwe	Urban (Salisbury)	SBP: 155.7 (18.7) vs. 159.7 (19.7) vs. 162.8 (19.2), DBP: 96.2 (10.6) vs. 100.6 (10.6) vs. 102.1 (12.9) HR: 71.0 (11.5) vs. 70, 3 (11) vs. 76.0 (13.4)
Adeyemo A, Tayo BO, Luke A,	Adeyemo 2013	2013		RCT	Secondary prevention	Mild to moderate	40 years and older, BP 140/90 on three consecutive occasions 1 week apart or BP at least 160/ 90 mmHg on two consecutive occasions 1 week apart; not on any antihypertensive medication, no known comorbidity or complications of hypertension; no plans to move from the community for at least 1 year//Pregnant	6 months	**Adherence strategies:** IG: clinic management and home visits (Clinic +HmV) vs. CG: Clinic management (Clinic only), (clinic management: clinic-based treatment, free medication (HCT, Atenolol), free transp. costs), nurse-led	primary: Adherence (Pill count), other: BP, HR,	r: 668, a: 544// 2 (280 vs. 264); rural: 119 vs. 122; urban: 161 vs. 142	34%; 66%, 227, 441	62.74 (9.95)	SBP:167.4 (19.2); DBP: 91.8 (12.3); HR: 77.3 (13.7)	//23.8 (4.9)	Nigeria	Urban (Idikan)/rural (Igboora), South west, Ibadan/ Igbo-ora and Idere	Over 6 months intervention: excellent adherence (pill count <= 2/month): 72.5% vs. 79.0% (OR 0.586 (SE 0.122); (rural: 76.5,% vs. 89.3 %, urban: 69.6 % vs. 75.4 %); BP controlled at 6 months: 65.0 vs. 66.3% (rural: 68.1 vs. 71.3%, urban: 62.7 vs. 62.0%)
Ahaneku JE, Agbedana OE, Taylor OG	Ahaneku 1995	1995		RCT	Secondary prevention	Mild to moderate	Hypertension// alcohol, smoke, contraceptives, pregnant, lactating	3 months	**Drugs:** Doxazosin 2-16 mg vs. HCT 50 mg + Amlorid 5 mg vs. Amlodipine 5-10 mg, in each group obese (BMI>25) vs. non-obese, Diet: high carb+veg., low fat+prot.	HDL, total Cholesterol (TC), BMI after 3 and 6 months,	r/a: 81; 3 (27 vs. 34 vs. 20)	43%, 57% , 35, 46	39-65	**(no mean/SD reported)**	//24.3 (0.7) (Obese: 29 (0.9)//non-obese: 22.1 (0.7))	Nigeria	Urban (Ibadan)	**(no mean/SD reported)**
Ajayi AA, Oyewo EA, Ladipo GO, Akinsola A	Ajayi 1989	1989		RCT	Secondary prevention	Mild to moderate	DBP =/>95 mmHg, aged 30-75//malignant hypertension, renal impairment (ser.-creatinine >/=150 micromol/L, congestive heart failure, hepatic dysfunction, d.m., other medication, smoking, alcohol, non-non-compliance during placebo run-in	4 weeks	**Drugs:** Enalapril 20 mg + placebo vs. placebo HCT 50 mg	BP	r/a: 20;2 (10 vs. 10)	45%, 55%, 9, 11	53 (11.5) (35-75)	SBP: 169.5 (23.5); DBP: 111.5 (16.5)	66.5 (13.7)	Nigeria	Urban (ife-Ife)	Ena: SBP: 160 (24); DBP: 101 (15) vs. HCT: SBP: 154 (31); DBP 88 (12)
Ajayi AA, Akintomide AO	Ajayi 1995	1995		RCT	Secondary prevention	Mild to moderate	DBP =/>95 mmHg//malignant hypertension, renal impairment (ser.-creatinine >/=150micromol/L, d.m., other medication, smoking, alcohol	6 weeks	**Drugs:** Amlodipine 5 (4 Prob.)-10 mg vs. HCT 25 (3 Prob.)-50 mg	BP, HR	r: 20; 2 (10 vs 10), a: 19;2 (10 vs. 9	47%, 53%, 9, 11	54.58 (8)	SBP: 185.3 (15.8), DBP: 103.5 (12.6)	Unclear	Nigeria	Urban (Ife-Ife)	reduction in SBP and DBP (p<0.001), to SBP: 143 (8) vs. 140 (8), DBP: 90 (15) vs. 88 (9)
Akintunde, A., Nondi, J., Gogo, K., Jones, E. S. W., Rayner, B. L., Hackam, D. G., Spence, J. D.	Akintunde 2017	2017	ISRCTN69440037	RCT, multicenter	Secondary prevention	Uncontrolled	systolic blood pressure >140 or diastolic blood pressure >90 despite usual treatment,	1 year	standardized treatment strategies: physiologically individualized care guided by their physiological phenotype, based on plasma renin and aldosterone (PhysRx) vs. usual care (UC)	primary: BP control after 1 year, secondary: baseline sodium/creatinine ratio, medications at baseline and end of study, number of visits	r: 105, a: 94, 2 (42 vs. 52)	47%, 53%, 49, 56	56.55 (14.31)	SBP: 170.86 (19.25), DBP: 85.62 (21.82)	n.r.	Nigeria, Kenia, South Africa	Urban	After 1 year: SBP: 139.38 (17.35) vs. 152.58 (12.33), DBP: 84.03 (10.99) vs. 89.56 (7.02)
Aweto HA, Owoeye OB, Akinbo SR, Onabajo AA.	Aweto 2012	2012		RCT	Secondary prevention	Mild to moderate	Prehypertension, Hypertension Stage I, II, all on antihypertensive drugs//stage III hypertension, diabetes mellitus, osteoporosis, mental illness, physical disability, transient ischeamic attack, stroke, those who were on Beta – blockers,	4 weeks	**Physical activity strategies:** IG: Dance movement therapy vs. CG: educational sessions, both 2x/week	BP, HR, Vo2 max, (cardiopulmonary effects on hypertension)	r: 50, a: 38; 2 (23 vs. 15)	42%, 58%, 21, 29	45 (12,28)	SBP: 138.7 (10.9), DBP: 79.9 (9.3), HR: 76.5 (9.6), *VO2max: 24.6 (3.0)*	Unclear	Nigeria	Urban (Lagos, University)	SBP: 119.9 (8.3) vs. 135.5 (11.6), DBP: 70.9 (7.2) vs. 74.1 (7.7), HR: 70.9 (6.8) vs. 73.1 (5.4) with significant improvements in IG, *VO2max: 25.5 (2.6) vs. 25.9 (2.7)*
Bobrow K, Farmer AJ, Springer D, Shanyinde M, Yu LM, Brennan T, et al.	Bobrow 2016	2016	Leon N, Surender R, Bobrow K, Muller J, Farmer A. Improving treatment adherence for blood pressure lowering via mobile phone SMS-messages in South Africa: a qualitative evaluation of the SMS-text Adherence SuppoRt (StAR) trial. 2015, BMC Family Practice., PACTR201411000724141	RCT	Secondary prevention	Mild to moderate	Hypertension, >/=21 years old, on medication, SBP<220mmHg, DBP<120mmHg, access to a mobile phone, 1 member per household//those requiring specialist care for their hypertension at a hospital, being pregnant or within 3 months postpartum, very high blood pressures (SBP >220 mm Hg or diastolic blood pressure >120 mm Hg), who had symptoms suggestive of a hypertensive emergency, were otherwise acutely unwell	1 year (between June 26, 2012 and November 23, 2012)	**Adherence strategies:** Sms messages (in week intervals), IG1: information-only adherence support vs. IG2: interactive adherence support vs. CG: usual care	primary: SBP, secondary: treatment adherence, BP control, health status, scheduled clinic appointments attended, retention in clinical care, satisfaction with clinic services and care, hospital admissions, self-reported adherence to medication, basic hypertension knowledge	r: 1372;3 (457 vs. 458 vs.457), a: 1196 (406 vs.394 vs. 396)	28%, 72%, 384, 988	54.3 (11.5)	SBP: 135.4 (17.5), DBP: 83.4 (12.1)	83.3 (19.1)// 32.8 (7.7)	South Africa	Urban (Cape Town)	SBP 132.1 (16.6) vs. 132.7 (17.5) vs. 134.3 (17.3), IG1 vs. CG: -2.2 (95%CI -4.4; -0.04) ; IG2 vs. CG: -1.6 (95%CI -3.7; 0.6) Controlled BP < 140/90 mmHg: IG1 vs. CG: OR 1.42 (1.03; 1.95); IG2 vs. CG: OR 1.41 (95%CI 1.02; 1.95)
Bolarinwa, O. A., Juni, M. H., Nor Afiah, M. Z., Salmiah, M. S., Akande, T. M.	Bolarinwa 2019	2019	PACTR201606001671335.	RCT	Secondary prevention	?	Hypertensive patients attending medical and general outpatient's clinics of the University of Ilorin, ≥ 40 years, newly diagnosed or on treatment for hypertension//clinically established target organ damage or established CVD	12 months, mid-term impact of the intervention is reported	**standardized treatment strategies**: IG (home-based follow-up care (HBFC)*) vs. CG, * Wilson and Cleary causal model of HRQoL, hypertension education and counseling session, assessing adherence level of the patients and then offering adherence counseling, increase in access to healthcare, reduce waste of time and bureaucratic bottlenecks usually experienced at the health facility, rained and professionally competent nurses in the form of task-shifting strategy, monthly follow-up visits involving home-based blood pressure and body mass index (BMI) monitoring by nurses with a view to give medical advice and counseling to the patients at home,	primary: BP, BMI, medication adherence, blood lipids, blood glucose secondary: HRQoL (Health-related quality of life)	r: 299, 2 (149 vs. 150), a: 239 (120 vs. 119)	23%, 77%, 68, 231	61.15 (10.85)	SBP: 139.98 (22.86), DBP: 86.93 (11.87),	//28.15 (6.16)	Nigeria	Urban (Ilorin)	BP control: controlled: 85.9% vs. 76.7%, uncontrolled: 14.1% vs. 23.3%, medical adherence: low: 4% vs. 16.6%, medium: 17.5% vs. 34.7%, high: 78.5% vs. 48.7%
Bosman AR, Goldberg B, McKechnie JK, Offermeier J, Oosthuizen OJ	Bosman 1977	1977		RCT	Secondary prevention	Mild to moderate	>21 years old, hypertension WHO tage I or II//history of angina, myocardial infarction, heart failure, stroke, chronic obstructive respiratory disease, asthma or severe renal, hepatic or haematological disease	10 weeks	**Drugs:** Metoprolol 40 mg 3x/d vs. 70 mg 3x/d vs. Propanolol 80 mg 3x/d vs. Propanolol 120 mg 3x/d	HR, BP,	r: 93, 1, a: 81; 4 (18 vs. 20 vs. 21 vs. 21)	46%, 54%, 43, 50	49 (2.6)	SBP: 172.9 (45.9), DBP: 106.8 (17.1), HR: 80.3 (29.7)	74.9 (27.9)	South Africa	Urban (Cape Town, Durban, Johannesburg, Port Elizabeth)	SBP: 145.3 (21.6) vs. 149.3 (28.6) vs. 162.4 (31.6) vs. 153.7 (32.5); DBP: 87.1 (11.9) vs. 91.9 (13.9) vs. 96 (14.7) vs. 94.5 (14.2); HR: 64.2 (11.9) vs. 65.8 (10.3) vs. 62.7 (10.1) vs. 59.9 (8.2), therapeutic effectiveness: 89.5 vs. 70.0 vs. 75.0 vs. 75.0%
Cappuccio FP, Kerry SM, Micah FB, Plange-Rhule J, Eastwood JB.	Cappuccio 2016	2016		Cluster RCT	Primary and Secondary prevention	Hypertensives and healthy	rural and semi-urban communities, rural: lack electricity and piped water, have a small population and are some distance from Kumasi, semi-urban: closer to Kumasi and usually have electricity and piped water, aged 40 to 75, agreement	6 months (Between January and March 2001 randomization, between June 2001 and June 2002 data collection)	**Education strategies:** IG: Health education program with advice to reduce salt intake vs. CG: health education program without dietary prevention of hypertension	primary: urinary sodium excretion, BP	r: 12 communities (6r, 6su), 1013 (522 vs. 491), a: 801 (399 vs. 402), 12 villages, (6r, 6su)	38%, 62%, 385, 628	54.5 (11)	r: SBP: 128.1 (25), DBP: 76.5 (13), HR: 73.1 (12), a: SBP 127.4 (25.6), DBP 76.1 (13.2)	54 (11)// 21 (4)	Ghana	rural, semi-urban, (Ashanti)	SBP: 127.9 (27.7) vs. 127.4 (26), MDa: -2.54 (-6.54; 1.45); DBP: 76 (14.2) vs. 78.7 (14.3), MDa: -3.95 (-7.11; -0.78) favours intervention; HR n.r.
Charlton KE, Steyn K, Levitt NS, Peer N, Jonathan D, Gogela T, et al.	Charlton 2008	2008		RCT	Secondary prevention	Mild to moderate	blacks, 50-75 years, drug-treated, systolic BP </= 160 mmHg and diastolic BP </= 95 mmHg// taking two or more diuretics; taking furosemide for cardiac failure; cerebral infarction or haemorrhage; renal impairment, three or more alcoholic drinks per day; type 1 diabetes mellitus; impaired cognitive function; incontinence; and BMI > 45 kg/m2	8 weeks, 2 phases: May–December 2004 and January–July 2005	**Modified nutrition strategies:** (Modified food + salt replacement + 500 ml of maas (less Na, more K, Ca, Mg)) = intervention foods vs. control foods	BP	r: 92 (47 vs. 45), a: 80 //2, (40 vs 40)	16%, 84%, 15, 77	61.1 (7)	SBP: 134.6 (15.7), DBP: 81.1 (8.1)	86.1 (14.6)// 34.1 (5.9)	South Africa	Urban (Cape Town, Township (Langa))	SBP: 132.5 (15.8) vs. 127.5 (15.8); DBP: 82.2 (9.5) vs. 79.2 (11.4); mean net difference: SBP:-6.194 (17.1); (p=0.021), DBP: -0.595 (7.6) (p=0.626)
Cilliers AJ.	Cilliers 1979	1979		cross over RCT	Secondary prevention	Mild to moderate	previously untreated (A) or on antihypertensive therapy (B) other than non.beta-adrenergic receptor blocking drugs, DPB between 100 and 120 mmHg// history, signs or symptoms of congestive cardiac failure, myocardial infarction and angina pectoris, or whose blood urea exceeded 50 mg/100 ml (8,0 mmol/l), Asthma, pregnancy	2x 4 weeks (+ 8 weeks with atenolol)	**Drugs:** atenolol 100 mg vs. placebo tablets, (taken once daily in the morning, after study completed, all patients were given a further 8 weeks' treatment with the agent)	primary: BP	110//4 (A/B; Intervention vs. control); A/B: r: 50/60, a: 41/54	54%, 46%, 59, 51	49.5 (12.1)	**A**: SBP 165.8 (18.5), DBP 107.7 (6.5), HR 83.6 (13); **B**: SBP: 175.8 (18.2), DBP: 107.1 (5.9), HR 78.1 (10.4)	78.2 (16.5)	South Africa	Urban (Johannesburg)	After 4 weeks treatment: **A**: significant falls in both groups (p<0.001): SBP 145.24 (19.30) vs. 156.58 (18.88), DBP 90.84 (13.72) vs. 101.08 (11.10), HR 70.57 (12.52) vs. 83.02 (17.45) (8W: SBS: 133.10 (14.85), DBP 86.18 (10.39), HR 67.75 (12.52)), significant falls in both groups (p<0.001): **B**: SBP 155.26 (20.8) vs. 163.29 (19.67), DBP: 93.95 (12.32) vs. 97.70 (10.929, HR: 66.78 (8.37) vs. 77.95 (11.77)(8W: SBP: 152.85 (26.18), DBP: 91.13 (13.56), HR 66.63 (8.91))
Daniels AR, Opie LH.	Daniels 1987	1987		Cross over RCT	Secondary prevention	Mild to moderate	DBP 90-114 on any therapy//Secondary hypertension, diabetes mellitus, coronary artery disease, cerebral vascular disease, renal failure or hypokalemia	6 week treatment (3 weeks single dose, 3 week twice daily), 6 week washout between treatment	**Drugs:** HCT-Amilorid 1x1 vs. HCT-Amilorid 2x1 vs. Nisoldipin 1x1 vs. Nisoldipin 2x1	BP, Adverse events	r: 47, a: 32	16%, 84%, 8, 39	49 (1)	SBP: 165 (17), DBP: 102 (5.7), HR 74 (5.7)	70 (11.3)	South Africa	urban, Cape Town	After 6 weeks of treatment: SBP: 150 (17) vs. 142 (17) vs. 154 (17) vs. 150 (17), DBP: 95 (11.3) vs. 92 (11.3) vs. 95 (11.3) vs. 94 (11.3), HR: 74 (11.3) vs. 73 (11.3) vs. 74 (11.3) vs. 78 (5.7)
Dean G, Louw S, Hersch C, Kirsten HO, Brereton DN, Finnemore L, et al.	Dean 1971	1971		RCT	Secondary prevention	Mild to moderate	medium to severe grade II hypertension, white and Bantu patients	White patients 12 weeks/bantu patients 2 weeks	**Drugs:** Baycaron (Mefruside) 25 mg vs. Hydrochlorothiazide 50 mg vs. Placebo 2xtgl.	BP, weight, serum sodium, potassium and urea concentrations	r: 120/2, 60 white, 60 bantu, a: 49 white/ 57 Bantu; treatment groups 3 (20 each)	(120)		white: SBP: 179, DBP:104, Bantu: SBP: 173, DBP: 114		South Africa	urban, Port Elisabeth	Before to after treatment: white: BP 179/105 to 159/97 vs. 176/103 to 161/97 vs. 180/104 to 168/94/ LoW: 1.5 vs. 1.7 vs. 0.5, Bantu: white: BP 173/114 to 151/98 vs. 172/116 to 143/96 vs. 174/113 to 166/103, Weight loss: 0.5 vs. 0.9 vs. 0.2
Djoumessi RN,. Noubiap JJN, Kaze FF, Essouma M, Menanga AP, Kengne AP, Mbanya JC, Sobngwi E	Djoumessi 2016	2016	NCT02426099	RCT	Secondary prevention	Resistent	diabetic patients, <75 years, resistant hypertension (office BP value ≥140/90 mmHg) and those participating in an ongoing study on HbA1c, unknown etiology, outpatient clinics, under at least three antihypertensive drugs at optimal dosages for at least two months, including a diuretic//T2DM with overt acute/chronic complications, serum potassium ≥5.5 mmol/l, eGFR ≤30 ml/min/1.73 m2, absolute contraindication to any of the drug regimen of the trial, current aldosterone antagonist treatment or cessation within the last 15 months	4 weeks, October 2011 to March 2012	**Drugs:** spironolactone 25 mg daily vs. alternative antihypertensive regime (8 mg candesartan, 100 mg atenolol or 750 mg alpha methyldopa)	primary: BP secondary: serum potassium, sodium, and creatinine levels	r+a: 17, 2 (9 vs. 8)	47%, 53%, 8, 9	62.9 (8.3)	SBP: 158 (13.6), DBP: 89.8 (9.7), HR 75.5 (14)	//30.4 /6..6)	Cameroon	Urban	SBP: 125 (11) vs. 144 (17), DBP: 72 (8) vs. 89 (12)
Fadayomi MO, Akinroye KK, Ajao RO, Awosika LA.	Fadayomi 1986	1986		RCT	Secondary prevention	Mild to moderate	newly diagnosed or inadequately controlled hypertension//patients with therapy, that might interfere with nifedipine	2 weeks placebo run in, 6 week treatment,	**Drugs:** nifedipine 20 mg 2x1 (16) vs. placebo	BP	32, 2 (16 vs. 16)	56%, 44%, 18, 14	av. 48 (37-59)	SBP: 180.4 (3.9), DBP: 114.4 (2.4), ((HR(without Placebogroup) : 75.9 (1.9)))	Only nifedipine-group) 71.9 (3.1)//	Nigeria	urban, Lagos	SBP: 122.8 (7.4) vs. 179.3 (16.7) , DBP: 79.4 (6.2) vs. 111.7 (7.5) mmHg

Study	Study name	Year of publication	Other publications	Design	Prevention	Grade	inclusion/exclusion criteria	Duration	Intervention	outcome	amount/groups	male/female %	Age	Baseline values (pooled mean, pooled sd)	Weight /BMI	Country	Region	Results (pooled mean, pooled sd)
Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, et al.	Fairall 2016	2016	Folb 2015	Cluster RCT	Primary prevention	Mild to moderate	public sector clinics and patients with at least one condition: hypertension (Self-reported antihypertensive medication), diabetes, chronic respiratory disease or who screened positive for depression, 18 y or older, likely to reside in the area for the next year	enrollement: between 28 March 2011 and 10 November 2011, 14 month follow up, (between 21 May 2012 and 13 December 2012.	**Education strategies for nurses:** nurse training in educational outreach sessions with a primary care program to expand their role in NCD care + authorization to prescribe an expanded range of drugs on NCDs vs. no change + usual training	primary: Treatment intensification secondary: disaggregation of primary outcomes by type of medication, cardiovascular risk factors (BP, BMI, smoking), health-related quality of life, mortality, healthcare utilization	38 clinics, 2 (19 vs. 19); r: 4393 (2166 vs. 2227) a: 4280, 2 (2110 vs. 2170), hypertension: r.:1555 vs. 1672 (hypertension alone: 304 vs. 326), a.: 1512 vs. 1626	27%, 73%, 1186, 3207	52	for patients with hypertension: SBP 139 (23.6), DBP: 90 (13.2), BP>140/90 mmHg: 59.4%: BP>180/110 mmHg: 10.4% (Folb 2015)	for patients with hypertension: 31.1 (7.5)	South Africa	rural, Western cape	**All patients**: SBP: 134 (23) vs. 135 (21,7), MD 2.00 (95%CI -0.87; 4.87), p=0.172; DBP: 88 (13,2) vs. 87 (12,7), MD 1.58 (95%CI -0,56-3.72), p=0.148; Mortality: 64/2166 (3%) vs. 64/2227 (3%), RR 1.11 (95%CI 0.79; 1.56), p=0.564 **for patients with hypertension:** BP controlled: 139/426 (33%) vs. 128/399 (32%); effect estimate: RiskRatio 1,01 (0,76-1,33)
Farag, S. M., Rabea, H. M., Mahmoud, H. B.	Farag 2018	2018		RCT	Secondary prevention	Mild to severe	essential hypertension, Grade 2 or more (defined as SBP≥ 160 mmHg or DBP ≥ 100), seated pulse rate ≥ 55 bpm, uncontrolled on their hypertension treatment; not achieving peripheral BP goal (BP < 140/90 mm Hg) or having uncontrolled central blood pressure//secondary hypertension, women of childbearing period not using effective contraception, lactating women, Second- or third-degree heart block, sick sinus syndrome, Atrial fibrillation, Ischemic heart disease, heart failure, known hypersensitivity or contraindications to Valsartan, Amlodipine or Nebivolol	12 weeks, October 2016 to January 2018	**Drugs:** Amlodipine 10 mg/Valsartan 160 mg (single pill) vs. Nebivolol 5 mg/Valsartan 160 mg (1 tablet each)	BP, MAP,	r: 160, 2 (80 vs. 80), a: 137, 2 (75 vs. 62)	32%, 68%, 44, 93	25-84 (range) , 56.38 (10.74)	n.r.	86.25 (13.96) //31.62 (5.84)	Egypt	Urban (Beni-Suef)	After 6 weeks: pSBP: -39.49 (17.32) vs. -31.26 (13.57), pDBP: -17.43 (11.54) vs. -15.28 (10.79), MAP: -24.78 (11.55) vs. -20.60 (9.57); after 12 weeks (46 vs. 37): pSBP: – 40.87 (17.05) vs. – 34.31 (16.47), pDBP: – 16.31 (11.77) vs. – 15.16 (11.32), MAP: – 24.50 (11.74) vs. – 21.54 (11.15)
Goodman C, Rosendorff C, Coull A.	Goodman 1985	1985		RCT	Secondary prevention	Mild to moderate	Hypertension, aged 18 - 60 years, average untreated supine DBP 90 - 120 mmHg at the end of placebo period//secondary hypertension, signs of congestive cardiac failure, papilloedema, recent (6 months) myocardial infarction, recent (1 year) cerebrovascular accident or hypertensive encephalopathy, heart block or resting heart rate less than 54/min, bronchial asthma, chronic obstructive pulmonary disease, treatment with monoamine oxidase inhibitors, appetite suppressants, oral contraceptives or any other drug known to affect blood pressure, renal failure (blood urea level > 10 mm0111) or hepatic disease, history of drug allergies	1 year: (4 weeks placebo washout, 1.) 2 weeks (0-12) treatment titrated every 4 weeks to max. doses (2x20 mg vs. 2x 120 mg), 2.) 12 weeks (14-26) continuation of current therapy or the addition of 25 mg or (after 4 weeks) 50 mg hydrochlorothiazide to achieve a supine diastolic pressure of less than 90 mmHg, 3.) 28-48: patients were maintained on the therapy assigned during part 2)	**Drugs:** Enalapril 5 mg 2x1 vs. Propanolol 40mg 2x1	BP	r: 26, 2 (13 vs. 13); a:19 (lost to follow up during part 1	62%, 38%, 16, 10	48.8 (32-60) (48,9 vs. 48,6)	SBP: 156 (3.5), DBP: 97.5 (3)	77.3	South Africa	urban, Johannesburg	changes; SBP: -15 vs. -12; DBP: -10 vs. - 10 (p>0.05)
Goudge J, Chirwa T, Eldridge S, *et al*.	Goudge 2018	2018	ISRCTN12128227	Cluster RCT		All	Clinics: if they were located in the site, rather than on the periphery, if the clinic manager consented to participate, people > 18 years//individuals who had recently been randomly selected to participate in another research study	18 months	**standardized treatment strategies:** hypertension management of lay health workers (LHW) vs. usual care (UC)	primary: population who have uncontrolled hypertension and moderate risk of CVD , secondary: population with different levels of BP-related CVD risk, undiagnosed hypertension, BP measured, attenders of a clinic in the last year, appointments kept during the study period, clinic visits due to hypertension	Clinics: r+a: 8, 2 (4 vs. 4), r: 4722, (3413) a: 2539	44%, 56%, 1516, 1897	56.6 (19.4)	No HT: 53.4%, on treatment and controlled HT: 8.6%, on treatment and uncontrolled HT 9%, not on treatment 29%	n.r.	South Africa	Rural (Bushbuckridge subdistrict, Mpumalanga Province)	No HT: 52.9% vs. 50.9%, on treatment and controlled HT: 11.2% vs. 11.3%, on treatment and uncontrolled HT 13.2% vs. 13%, not on treatment 22.7% vs. 24.9%,
Gyamfi, J., Plange-Rhule, J., Iwelunmor, J., Lee, D., Blackstone, S. R., Mitchell, A., Ntim, M., Apusiga, K., Tayo, B., Yeboah-Awudzi, K., Cooper, R., Ogedegbe, G.	Gyamfi 2017	2017	NCT01802372, Ogedegbe, G., Plange-Rhule, J., Gyamfi, J., et al., 2018, Health insurance coverage with or without a nurse-led task shifting strategy for hypertension control: A pragmatic cluster randomized trial in Ghana. PLoS Med	Cluster RCT	Secondary prevention	Mild to moderate	community health centers and district hospitals in the Ashanti region of Ghana; patients: uncomplicated hypertension: SBP 140–179 mm Hg or DBP 90–99 mm Hg, absence of target organ damage, >= 40 years old, not received prior treatment//prior history of diabetes, coronary artery disease, stroke, heart failure, or proteinuria	1 year/2 years, 28/11/2012 - 7/10/16	**standardized treatment strategies**: nurse-led task shifting strategy for hypertension control + health insurance coverage vs. health insurance coverage alone	primary: mean change in SBP from baseline to 12 months, s.o.: rate of BP control and lifestyle behaviors, at 12 months and the sustainability of SBP reduction at 24 months	32 health centers (16 vs. 16); 757 (368 vs. 389) (follow up: 12m: 323 vs. 319, 24m: 304 vs. 296, ITT a: 368 vs. 389), nurses: 64,	40%; 60%, nurses: female: 87,5%	58.03 (12.37) , nurses: 30.6 (6.68)	SBP: 155.9 (12.1), DBP: 89.6 (10.8)	n=412: underweight (<18.5 kg/m2) : 10.7%, Normal (18.5 to 24.9 kg/m2) : 51.9%, Overweight (25.0 to 29.9 kg/m2) : 26.2%, Obese (30 kg/m2) : 11.2%	Ghana	Rural and urban 50 vs. 50% (Ashanti)	After 12 months: SBP: 137.1 (27.5) vs. 138.4 (27.3), DBP: 79.8 (22.9) vs. 81.8 (22.8); change in SBP -19.5 (17.97) vs. -16.6 (17.86), change in DBP: -9,3 (11.46) vs. -8,7 (18.68)
Habte B.		1992		RCT	Secondary prevention	Mild to moderate	>=18 years, DBP 95-120 mmHg//severe target organ damage /grade III Retinoparthy, cardiac failure, renal failure, secondary hypertension, bronchial asthma, cardiac, neurologic, renal or hepatic diseases, d.m	September 1987-November 1990, 8 weeks,	**Drugs:** HCT 25 (50, 100) vs. timolol 10 (20, 40) mg vs. Enalapril 10 (20, 40) mg, (dose change: if DBP remained >95 mmHg: (after 4 weeks, after 8 weeks), 2 weeks run in (sodium restriction, no medication))	BP	r: 67, a: 26, (17 after 12 weeks)//3 (9 vs. 10 vs. 7)	50%, 50%, 13, 13	42,47 (13,14)	SBP: 160,85 (21,97), DBP: 103,83 (6,66),	-	Ethiopia	Addis Abeba	8 weeks: SBP: 146.3 (19.5) vs. 161.6 (3.5) vs. 150.4 (22.1); DBP: 94.7 (8.4) vs. 97.6 (17) vs. 94.1 (9)
Hacking D, Haricharan HJ, Brittain K, Lau YK, Cassidy T, Heap M.	Hacking 2016	2016		RCT	Secondary prevention	Mild to moderate	Hypertension	17 weeks, 2012	**Education strategies:** Standard care + 90 SMS to improve knowledge of hypertension + healthy lifestyle recommendations vs. standard care without SMS	health knowledge and self-reported health-related behaviors	r: 223//2 (109 vs. 114);74%f, a: 146//2 (76 vs. 70)	20%, 80%, 29, 117	54.3 (26.8-92.2)	*No BP; (HKS: 8.8 (1-15) vs. 8.5 (2-16), HSBS: 8 (2-10) vs. 8 (4-11), OS: 17 (3-24) vs. 16 (8-22))*	-	South Africa	Cape Town	after intervention: no significant change **(no mean/SD reported), no BP**
Isles CG, Johnson AO, Milne FJ.	Isles 1986	1986		RCT	Secondary prevention	Malignant hypertension	untreated hypertension, DBP greater than 120mmHg // heart failure, hypertensive encephalopathy	1day	**Drugs:** slow release nifedipine 40mg at 0 and 12h vs. atenolol 100mg at 0h only	MAP	r/a: 20//2 (10 vs. 10)	50 %, 10, 10	47 (8)	SBP: 229.5 (233/226) DBP: 141.5 (142/141) MAP: 171.5 (8.6)	-	South Africa	Johannesburg	max fall MAP: 56 (13) vs. 58 (11), *188/114 mmHg vs. 173/112 mmHg at the end of the study*
Iyalomhe GB, Omogbai EK, Isah AO, Iyalomhe OO, Dada FL, Iyalomhe SI.	Iyalomhe 2013	2013	Iyalomhe GBSOEKIIOOBISI. Long-term effects of amlodipine and hydrochlorothiazide combination therapy on creatinine clearance in hypertensive Nigerians. 2013, Global journal of pharmacology	RCT	Secondary prevention	Mild to moderate	BP>160/90 and </=180/120 mmmHg//secondary hypertension, bronchial asthma, cardiac, cerebrovascular, gastrointestinal, endocrinologic, renal or hepatic diseases, history of drug allergies, smoking, alkohol, substance abuse, mental illness, pregnancy, lactating women, digitalis, NSAR, MOAinhibitors, psychotropic drugs, oral contraceptives	march 2008-march 2009, 48 weeks treatment	**Drugs:** AML (5 mg, after 6 weeks doubled if BP not controlled, after 12 weeks + HCZ 25 mg) vs. HCZ (25 mg, after 6 weeks +AML 5mg, after 12 weeks: +AML 10 mg) vs. AML-HCZ (5+25, after 6 weeks: 10+25)	BP	r/a: 90/87; 3 (30 vs. 30 vs. 30)/(28 vs. 30 vs. 29) (male:	50 %, 45, 45	64,29 (11,44)	SBP: 166,67 (30.8) DPB: 105,17 (16.9)	76,15 (7,77)// 26,42 (0,5)	Nigeria	Auchi, Edo state	After 48 weeks of treatment: SBP: 132.73 (9.2) vs. 133.67 (6.9) vs. 135.5 (7.9); DBP: 72.86 (7.6) vs. 76.67 (9.5) vs. 75.84 (9.5) (**male**: SBP: 131.79 (8) vs. 132.67 (4.2) vs. 135 (6.3), DBP: 72.14 (4.4), 76 (6.3) vs. 75.67 (6.2); **female**: SBP: 133.92 (5) vs. 134.67 (4.8) vs. 136 (5), DBP: 73.57 (6.5) vs. 77.33 (7) vs. 76 (7.4))
Iyalomhe GBS, Omogbai EKI, Ozolua RI.	Iyalomhe 2007	2007	Iyalomhe GBS, Omogbai EKI, Ozolua RI, Iyalomhe OOB., Effects of hydrochlorothiazide and furosemide on creatinine clearance in some hypertensive Nigerians. 2008, African journal of biotechnology [Internet].	RCT	Primary + Secondary prevention	Mild to moderate	untreated hypertension, BP>160/95 and </=180/110 mmmHg//pregnancy, cardiac, gastrointestinal, endocrinologic, renal or hepatic diseases, history of drug allergies, smoking, alkohol, substance abuse, mental illness, patients with therapy, that might interfere with BP or renal function + normotensives (age, sex-matched, healthy)	january-june 2004, 21 days	**Drugs:** HCT 25 mg (20 hypertensives+ 20 healthy) vs. Furosemide 40 mg (20 hypertensives+ 20 healthy)	BP, (Urine and serum electrolytes)	80 (40 hypertensives, 40 normotensives), 2 subgroups à 20	50 %, 40, 40	57.6 (9.9)	MAP: hypertensives: 127.2 (26.6)//normotensives: 92.3 (39.8)	70.1 (8)//26.1 (3.6)	Nigeria	Auchi, Edo state	HCT vs. Furosemid: hypertensives: MAP: 113.2 (4.5) vs.109.5 (5.8); normotensives: 86 (6.3) vs. 85.3 (5.3)
Labhardt ND, Balo JR, Ndam M, Manga E, Stoll B.	Labhardt 2011	2011		Cluster RCT	Secondary prevention	Mild to moderate	nurse-led health centres, staffed, equipped and trained to care for hypertension and type 2 diabetes at study initiation, Adult, newly diagnosed with uncomplicated hypertension and / or type 2 diabetes in nurse-led facilities, completing 12 follow-up visits within 12 months, the last recorded consultation 1 year after the start of the treatment	1 year, recruitment phase August 2008 to January 2009	**Adherence strategies:** incentive group (financial incentive of 1 month of free treatment for patients who regularly attended follow-up visits) vs. letter group (received reminder letters in case of a missed follow-up visit) vs. Control group	primary: patient retention secondary: adherence to follow-up schemes, BP, blood glucose levels, additional endpoint: costs	r: 33 facilities (11 vs. 11 vs. 11), a: 30 (8 vs. 11 vs. 11), patients: 221 (55 vs. 77 vs. 89), hypertensives: r:187 (45 vs. 63 vs. 79), a: 104	36%, 64%, 67, 120	59.9 (12.5)	SBP: 175.8, DBP: 100.7, (of 104 hypertensives patients retained at 1 year)	overweight: 28.5% obese: 20.4%	Cameroon	Rural	104 hypertensive patients retained at 1 year: MD: 40.2 (27); MD 20.6 mmHg (17.1); 109 (49.3%) of the 221 patients remained, retention rate: 60% vs. 65% vs. 29%, adherence (attendance at >/=80%): 10% vs. 38% vs. 35%, average monthly cost to patient for antihypertensive medication: 1.1 (0.9) €, transport: 1.1 (1.0) €
Lamina S.	Lamina 2010	2010	Journal of Strength & Conditioning Research. /Nigerian journal of medicine/Journal of the Association of Physicians of India/Nigerian Medical Journal [Internet]/JPMA - Journal of the Pakistan Medical Association./Nigerian Postgraduate Medical Journal./Nigerian journal of clinical practice [Internet]./Annals of Medical & Health Sciences Research. /African journal of medicine and medical sciences/African Health Sciences./Ghana medical journal [Internet]	RCT	Secondary prevention	Mild to moderate + stable	Male, stable hypertension (>1 year, BP 140-179/90-109 mmHg), 50-70 years, who had stoped medication or only on single medication, no psycholog./psychiatr. Disorders, BMi 20-30 kg/m2//smokers, alcoholic, diabetes, other cardiac, renal, respiratory disease, above average physically fit people	8 weeks, 24.10.2007-24.2.2009	**Physical activity:** Interval training (max. HR 60-79%, bicycle ergo, 3x/week) vs continuous training (max. HR 60% first two weeks, then 79%,) vs control (no viragos physical activity); 45min 2 weeks, rest: 60 min., wash out (Placebo): 1 week, then pretest (ergo), all on methyldopa, end: wash out again (placebo), posttest	BP, HR, MAP, VO2max (uric acid, CRP, white blood cells, TG, LDL, HDLWHR, BMI)	r: 485, 3 (162 vs. 162 vs. 161) a: 357, 3, (140 vs. 112 vs. 105),	100% male. 357, 0	58.5 (6.8)	SBP: 165.4 (13.2), DBP: 98.1 (4.6), HR: 83.5 (14.9), MAP 119.8 (6.8), *VO2max: 22 (9.6)*	68,62 (12,91) //23,75 (3,88)	Nigeria	urban, Kano	SBP: 150.4 (16.7) vs. 154.4 (12.6) vs.163.5 (14.9); DBP: 95 (5) vs. 94.4 (8.8) vs. 96.1 (2.7),; HR: 76.8 (8.5) vs. 70.8 (9.8) vs. 80.5 (22); MAP: 113.3 (7.7) vs. 115.6 (10.9) vs. 118.3 (5.8), *VO2max: 37.5 (7.5) vs. 28.7 (13.6) vs. 22.8 (7.4)*
Leary WP, Maharaj B.	Leary 1990	1990		RCT	Secondary prevention	Mild to moderate	Supine DBP 96-116 mmHg, uncomplicated essential hypertension//other significant disease	4 weeks placebo (any anti-hypertensive medication stopped), 12 weeks of therapy	**Drugs**: Felodipine 2,5 mg twice daily vs. HCT 12,5 mg twice daily, after 3 weeks doubled dosage in all cases, at week 4 dosage doubled if DBP >90 mmHg, after week 8 Metoprolol 100mg twice daily added if DBP >90 mg	BP	r: 45, 2 (21 vs. 24), a: 40 (18 vs. 22)	98%, 2%, 39, 1	41.5 (22-60)	SBP: 157.8 (13), DBP: 107.5 (5.5), HR 79.9 (11.3)	n.r.	South Africa	Natal	After 12 weeks: Adherence: 85%, SBP: 139.4 (11.6) vs. 136.6 (10.4), DBP: 91.9 (11.5) vs. 90.5 (8.9), changes from baseline: -21.1/-15.8 vs. -19.6/-16.2
Leary WP, Reyes AJ, Byl K, Maharaj B.	Leary 1987	1987		RCT	Secondary prevention	Mild to moderate	Resting supine DBP >100 mmHg on two occasions, employers at a adjacent factory, no other medication,	4 weeks placebo, 12 weeks	**Drugs:** ketanserin 40 mg + HCT vs. Ketanserin 40 mg, both once daily	BP	r: 32, a. 21 (9 vs.12), at week 12: 18 (6 vs. 12)	100% male, 32, 0	48 (6.4)	SBP: 161.9 (15.3), DBP: 104.1 (3.3), HR: 78.3 (9.4)	78.7 (15.1)	South Africa	Urban	After 12 weeks: SBP: 140 (7.4) vs. 159 (27.71), DBP: 84 (4.9) vs. 89 (10.4), HR: 77 (12.2) vs. 74 (10.4)

Study	Study name	Year of publication	Other publications	Design	Prevention	Grade	inclusion/exclusion criteria	Duration	Intervention	outcome	amount/groups	male/female %	Age	Baseline values (pooled mean, pooled sd)	Weight /BMI	Country	Region	Results (pooled mean, pooled sd)
Leary WP, Reyes AJ, Maharaj B, Byl K.	Leary 1991	1991		RCT	Secondary prevention	Mild to moderate	Supine DBP 95-115 mmHg//history of cardiac disease requiring medication, diabetes mellitus, or gastrointestinal disease involving frequent or copious bowel actions; need for chronically taken concomitant medication other than antihypertensive agents; history of alcohol and/or drug abuse; any situation or condition which could interfere with optimal participation in the study; female gender	4 weeks placebo (any anti-hypertensive medication stopped), 12 weeks of therapy	**Drugs**: isradipine 1.25 vs. 2.5 vs. 5 mg twice daily	BP	r:45, a: 33 (12 vs. 11 vs. 10) (a : 5 vs. 9 vs. 5)	100% male, 45, 0	28-62, 48.2 (7.7)	SBP 121.7 (9.7)	n.r.	South Africa	Durban /Natal	After 10 or 12 weeks: SBP: 114.2 (7.7) vs. 112.8 (7.1) vs. 112.4 (9.1)
Levenstein JH.		1978		RCT	Secondary prevention	Mild to moderate	basal DBP of 95 - 110 mmHg in previously treated or basal DBP 100-120 in previously untreated patients//initial serum creatinine more than 124 micromol/l, myocardial infarction, av-block, congestive cardiac failure, bradycardia (<50bpm), diabetes mellitus, asthma bronchiale, obstructive lung disease, severe liver disease	2 weeks placebo wash out, 10 weeks active treatment	**Drugs:** Oxprenolol with cyclopenthiazideKCl 160 mg/600 mg (1x/s) vs. Methyldopa 250 mg (3x/d)	BP, HR, response to treatment	r: 249, a: 238 (119, 119), 39 centers,	49%, 51 %, 7 unspecified, 117, 121	21-65 years, 50 (9.8)	SBP 168.9 (18.2), DBP 105.4 (7), HR 78 (10.4)	74 (13.2)	South Africa	n.r. (urban)	SBP 149.5 (17.9) vs. 156.4 (18.8), DBP 92.5 (11.2) vs. 97.2 (11.7), HR 71.3 (10.7) vs. 76.5 (11.4)
Lubbe WF.		1974		Cross over RCT	Secondary prevention	Severe hypertension	BP inadequately controlled on large doses of several other antihypertensive drugs, or reasonable control was obtained with existing regimens but at the price of significant side-effects	2 months (2x 1 month)	**Drugs:** Clonidine vs. Placebo	BP, (side effects, renal function)	r: 25, a: 21	32%, 68%, 7, 14	34-68 years	SBP 210, DBP 125	n.r.	South Africa	Cape Town	After 1 month: SBP 160 vs. 190, DBP 100 vs. 120 (from fig. 2, SD is missing)
Mabadeje AF, Adebayo GI.		1989		Cross over RCT	Secondary prevention	n.r.	labile hypertension or fixed hypertension with emotional overlay	1 week placebo run in, 2 week active therapy (1 wk per drug)	**Drugs:** bromazepam 1,5/d vs. Labetalol 100mg 2x/d vs. placebo	BP, HR (avarage and maximum)	r: 20	60%, 40%, 12, 8	(19-53) 37 (6)	After 1 week: SBP: 177.5 (46.2), DBS 100.8 (5), HR 95.4 (8.5)	n.r.	Nigeria	Lagos	SBP: 165.7 (11.6) vs. 149.8 (8.9) vs. 180.2 (9.8), DBP: 91.4 (5.3) vs. 81.5 (5.2) vs. 100.5 (4.3), HR: 85.1 (7.2) vs. 79.8 (5.4) vs. 96.2 (7.3)
Mabadeje AFB.	Mabadeje 1977	1977		RCT	Secondary prevention	n.r.	Essential hypertension,	4-9/1974, 12 weeks (4 weeks placebo+chlorthalidone 25 mg, 8 weeks treatment)	**Drugs:** Oxprenolol 80 (160) mg 3x/d vs. Methyldopa 250 (500) mg 3x/d	BP, HR, (MAP)	r: 24 (12 vs. 12)	n.r., (24)	(28-72), 44.9 (11)	SBP 189.6 (20.3), DBP 11.8 (11.2), HR 80.8 (11.6), MAP: 137.7 (8.8)	n.r.	Nigeria	Lagos	SBP: 138.2 (22.2) vs. 137.1 (14.8), DBP 87.9 (14.8) vs. 85.4 (7.2), HR 68.1 (6) vs. 68.8 (6.7), MAP: 104.7 (16.7) vs. 102.6 (7.4)
Maharaj B, Byl K.	Maharaj 1993	1993		RCT	Secondary prevention	Mild to moderate	male black outpatients, 18-65 yrs, Supine DBP 95-115 mmHg after 2 week placebo period//any co-existent disease	2 weeks placebo run in, 8 weeks active therapy	**Drugs**: hydroflumethiazide 50 mg + reserpine 0.125 mg vs. chlortalidone 12.5 mg + atenolol 50 mg once daily, doubled dosage after 4 weeks if DBP not <90 mmHg	BP, MAP, HR	r: 52, a.: 49 (27 vs. 22)	100% male, 52, 0	n.r.	SBP: 155.4 (17), DBP: 102.6 (11.9), MAP: 120.2 (11.37), HR: 71.5 (10.18)	n.r.	South Africa	n.r. (urban)	After 8 weeks of treatment: SBP: 137 (16.97) vs.: 136.4 (16.99), DBP: 87.4 (11.8) vs. 91.2 (11.85), MAP: 104. (11.38) vs. 106.3 (11.35), HR: 64.4 (10.18) vs. 60.5 (10.18)
Maharaj B, Byl K.	Maharaj 1993a	1993		RCT	Secondary prevention	Mild to moderate	Supine DBP 95-115 mmHg after 2 week placebo period//any co-existent disease	2 weeks placebo run in, 8 weeks active therapy	**Drugs:** isradipine 2,5 mg vs. enalapril 10 mg once daily, doubled dosage after 4 weeks if DBP not <90 mmHg	BP, MAP, HR	r: 52, a: 52 (27 vs. 25)	100% male, 52, 0	18-65	SBP: 155.9 (18.79), DBP: 102.2 (9.35), MAP: 120.1 (11.19), HR: 72.3	n.r.	South Africa	n.r. (urban)	SBP:144.1 (18.97) vs.: 149.5 (19), DBP: 93.9 (99.6) vs. 98.2 (9.6), MAP: 110.7 (11.28) vs. 115.3 (11.35), HR: 73 () vs. 72.9 ()
Maharaj, B., Byl, K.,	Maharaj 1992	1992		RCT	Secondary prevention	Severe hypertension	male patients with severe hypertension older than 18 years, resting supine DBP greater or equal than 115 mmHg, receiving no antihypertensive drugs or inadequate controlled hypertension// female, stroke or myocardial infarction in the 6 months preceding the study, hypertensive encephalopathy, severe cardiac failure	4 hours	**Drugs:** nifedipine 10 mg vs. 5 mg	BP (minimun BP after treatment and final BP)	30 (15 vs. 15)	100% male, 30, 0	(19-60) 49.1	SBP 198.1, DBP 129.05	n.r.	South Africa	n.r. (urban)	after 4 hours: SBP: 153.7 (41.1) vs. 157.9 (41.4), DBP: 97.5 (24.8) vs. 105.2 (24.7)
Mangoush M, Singh NK, Kumar S, Basha A, Gupta BS, Bolya YK, et al.		1990		Cross over RCT	Secondary prevention	Mild to severe	hypertension//secondary or malignant hypertension, pregnancy, heart failure, heart block, diabetes, bronchial asthma, peripheral vascular disease, renal or hepatic dysfunction	4 weeks placebo run+ 4 weeks wash-out, 8-10 weeks treatment per drug	**Drugs:** enalapril (starting 10- 20 mg every 2 weeks increasing dosage+20 mg up to 80 mg) vs. atenolol (starting 50 mg, increasing after 4 weeks to 100 mg if required); 4 weeks placebo run in and before cross over	BP (MAP, maximum tolerable dosage of enalapril)	r: 67	49%, 51%, 33, 34	(28-65) 48.3 (2.34)	SBP 175.8 (23.7), DBP 109.5 (10.6), MAP 120.1 (15.6)	n.r.	Libya	Urban	Treatment over 8-10 wks: SBP: 150.8 (22.1) vs. 158.6 (20.5), DBP: 93.4 (11.5) vs. 90.4 (10.6), MAP: 112.5 (13.9) vs. 118.6 (13.1)
Manyemba J.		1997		Cross over RCT	Secondary prevention	Mild to moderate	Both sexes, age between 18-70, BP>140/95 mmHg, after 4 weeks treatment with HCT 25 mg daily, newly diagnosed and previously treated hypertensives// purely systolic hypertension, pregnancy, diabetes mellitus, malignant hypertension, grade 3/4 retinopathy, heart failure, renal impairment (creatinine>115micromol/l), gout, use of steroid or estrogen, stroke or myocardial infarction in the past 6 months, history of adverse effects to reserpine or nifedipine	8 weeks treatment, (4 weeks Run-in, 2x4 weeks treatment with 2 weeks wash-out)	**Drugs:** Reserpine 0,25 mg + HCT 25 mg vs. Nifidipine 20 mg + HCT 25 mg	Primary: SBP, DBP	r: 32, a: 22,	19%, 81%, 4, 18	21-65	SBP: 181,5 (15,5), DBP: 113,1 (8,9)	n.r.	Zimbabwe	Urban (Parirenyatwa)	After 4 wks of treatment: SBP: 163,1 (20,7) vs. 163,6 (19,4), DBP: 101 (12,2) vs. 101,4 (8,9), Change over 4 wks: SBP: 15.9 mmHg (17.95) vs. 18.9 mmHg (16.27) , DBP: 11.1 mmHg (8.5) vs. 9.6 mmHg (5,7)
Maruf FA, Akinpelu AO, Salako BL, Akinyemi JO.		2016	Self-reported quality of life before and after aerobic exercise training in individuals with hypertension: a randomised-controlled trial. 2013, Applied Psychology Health and Well-being. ISRCTN81952488	RCT	Secondary prevention	Mild to moderate	New diagnosed BP, Uncontrolled BP agter 4-6 weeks antihyp. Th. + adipositas (any)//pregnant, diabetic, coronary or valvular heart disease, cerebrovasc, renal or hepatic disease, oyster. Sleep apnea, musculoskeletal. Problems, secondary hypertension, smoking, alc. abuse	12 weeks	**Physical activity:** Exercise (Aerobic dance training ((3d/week, 45 min.))+ antihypertensive drugs) vs. control (antihypertensive drugs)	primary: SBP, DBP, number of antihypertensive drugs, quality of life; Secondatry: physical work capicity, BMI, percent body fat, waist circumference, total cholesterol, LDL, HDL, triglyceride	r+a: 120, 2 (60 vs. 60), (15 vs. 17 lost to follow up -> 88 (45 vs 43))	29%, 71%, 35, 85	52.8 (8.4) 38-65	SBP: 155.7 (11.4), DBP: 93 (10)	70.4 (13.1)// 26.4 (4.8)	Nigeria	Urban (Ibadan)	After 12 wks: SBP: 135.3 (5.6) vs. 142.4 (4.7), DBP: 82.2 (3.4) vs. 83.9 (2.8), Weight: 70.6 (3,9) vs. 69.5 (3,3)
M'Buyamba-Kabangu JR, Anisiuba BC, Ndiaye MB, Lemogoum D, Jacobs L, Ijoma CK, et al.		2013	Osakwe CE, Jacobs L, Anisiuba BC, Ndiaye MB, Lemogoum D, Ijoma CK, et al, Heart rate variability on antihypertensive drugs in black patients living in sub-Saharan Africa. 2014, Blood Pressure, NCT01030458, Odili AN, Richart T, Thijs L, Kingue S, Boombhi HJ, Lemogoum D, Kaptue J, Kamdem MK, Mipinda JB, Omotoso BA, Kolo PM, Aderibigbe A, Ulasi II, Anisiuba BC, Ijoma CK, Ba SA, Ndiaye MB, Staessen JA, M'buyamba-Kabangu JR; NOAAH Investigators. Rationale and design of the Newer Versus Older Antihypertensive Agents in African Hypertensive Patients (NOAAH) trial. Blood Press. 2011 Oct;20(5):256-66. doi: 10.3109/08037051.2011.572614. Epub 2011 Apr 15.	RCT, multicentre	Secondary prevention	Mild to moderate	treatment-naive or previously treated patients of either sex, aged 30–69 years with uncomplicated grade 1 or grade 2 hypertension and a maximum of two additional risk factors//atrial fibrillation, electrocardiographic left ventricular hypertrophy with strain pattern, a serum creatinine concentration higher than 1.4 mg/dl in women or 1.5 mg/dl in men, overt diabetes mellitus and proteinuria or haematuria	6 months	**Drugs:** valsartan 160 mg plus amlodipine 5mg (uptitrated to 160/10 mg) vs. 6.25mg hydrochlorothiazide plus 5 mg bisoprolol (uptitrated to 6.25/10 mg), If blood pressure remained uncontrolled: a-methyldopa up to 2 g per day was added	primary: SBP secondary: time to BP control, AE, BP control	r: 183, 94 vs. 89, a.: 124, 67 vs. 57	48%, 52%, 60, 64	51.3 (9.0)	SBP: 156 (11.7), DBP: 92.7 (10), HR 73.7 (10.3)	//28.1 (4.7)	Sub-Sahara n africa (Cameroon, Cote d'Ivoire, Gabon, Nigeria, Senegal)	Urban (multicentre)	Change over 24 wks.: SBP: -28 (1.7) vs. -22.6 (1.8), DBP: 14.1 (1.3) vs. 13.2 (1.2), HR -1.8 (1.2) vs. -12.5 (1.4)
M'Buyamba-Kabangu JR, Lepira B, Lijnen P, Tshiani K, Fagard R, Amery A.		1988		RCT	Secondary prevention	Mild to moderate	hypertension, creatinine <2mg/dl, serum bilirubin <=1,5 mg/dl//cardiac failure, cerebrovascular accident, major organ damage as a result of hypertension, insulin-requiring diabetes mellitus,COPD, 2nd or 3rs degree atrioventricular block, pregnancy	6 weeks run-in placebo, 6 wks of treatment	**Drugs:** Atenolol 100 mg vs. Nitrendipine 20 mg, 6 week placebo run in	SBP, DBP, HR, Compliance	r: 34 (17 vs. 17),	53%, 47%, 18, 16	44 (10.5)	SBP: 161 (8.3), DBP: 101.5 (4.1), HR: 75 (10.5)	71 (16.5)	Zaire	Urban	Change over 6 wks: SBP: -12.1 (14) vs. -22.2 (8,2), DBP: -7.6 (8,7) vs. -14.1 (5,4), HR: -5.6 (7) vs. +2.0 (7,8)
Mendis S, Johnston SC, Fan W, Oladapo O, Cameron A, Faramawi MF.		2010		Cluster RCT	Secondary prevention	Mild to moderate	primary care facilities, minimum necessary capacity to implement the study algorithm, Males and females 30–70 years, systolic blood pressure between 140 and 179 mmHg, if they were not on treatment for hypertension//previously diagnosed secondary hypertension, other types of circulatory disorders (e.g. heart attack, stroke, transient ischaemic attacks, angina), pregnancy, trauma or other acute condition, history of diabetes or positive urine glucose test, inability to comply with the follow- up requirements or inability to provide informed consent	Recruitment 2005-2006, follow-up over 12 months	**standardized treatment strategies:** WHO CVD risk management package (education+HCT 12.5 - 25 mg) vs. usual practice patterns	primary: SBP (12 months), secondary: rates of smoking cessation, BMI, change in fruit and vegetable consumption, prescription of cost effective antihypertensive drugs (12 months),	China and Nigeria: r.: 40 facilities (20 vs. 20), 2397 participants (1191 vs. 1206), a: 20 vs. 20 facilities, 1114 vs. 1042 participants, Nigeria: 588 vs. 600	42%, 58%, 499, 689	55 (4.7)	SBP: 153.2 (12.4), DBP: 94 (9.7)	//27.4 (4.6)	Nigeria	Urban / rural (mix)	Change over 12 months: SBP: -11.01 (15.37) vs. -6.61 (20.57), DBP: -5.36 (9.99) vs. -2.03 (13.2), Attended visits: 530 (90.1%) vs. 447 (74.5%) quit smokimg: 22 (100%) vs. 32 (74.4%), Increased fruit consumption: 495 (93.4%) vs. 84 (18.8%), increased vegetable consumption: 75 (14.2%) vs. 31 (7.0%) (als Adhärenz?)
Mengesha, H. G., Welegerima, A. H., Hadgu, A., Temesgen, H., Otieno, M. G., Tsegay, K., Fisseha, T., Getachew, S., Merha, Z., Tewodros, H., Dabessa, J., Gebreegzabher, B., Petrucka, P.	Mengesha 2018	2018		RCT	Secondary prevention	Mild to moderate	Essential hypertension, stage I and II, >= 18 years, on-breast feeding, non-pregnant, and with no intention of pregnancy in the next three months//experiencing a hypertensive emergency, known contraindication to any of the study drugs (e.g., ACE-I to patients with angio-edema), secondary hypertension diagnosis, major co-morbidity (i.e., diabetes mellitus, kidney disease, heart failure, stroke, or coronary artery disease), BMI > 40 kg/m2	November 2016 to April 2017, 3 months	**Drugs:** Nifedipine 20 (40) mg po bid vs. Enalapril 5 (15) mg bid vs. HCT 12.5 (25) mg po daily	p.o.: reduction in BP, s.o.: time to cardiovascular events, both mortality and morbidity, and time to achieving goal BP	r: 141, 2 (47 vs. 47 vs. 47), a: 132 (44 vs. 44 vs. 44)	40%; 60%, 56, 85	57 (14.8)	SBP: 166 (17.2), DBP: 96 (10.8), HR: 82.4 (10.7)	//22.5 (3.9)	Ethiopia	Rural (Tigray)	SBP: 126.4 (14.7) vs. 129.4 (15.1) vs. 126 (15.1), HR: 75.9 (9.4) vs. 78 (11.1) vs. 78.5 (8.8); mean reduction: SBP: -37.35 (9.8) vs. -30.3 (10.8) vs. -32.1 (9.6), DBP: -15.66 (6.8) vs. -14.8 (6.9) vs. -15.62 (6.9)
Middlemost SJ, Tager R, Davis J, Sareli P.		1994		RCT	Secondary prevention	Mild to moderate	essential hypertension who completed the double-blind, randomized study, DBP >=95 but <=115//secondary or malignant hypertension, congestive heart failure, any degree of renal or hepatic insufficiency	3 weeks placebo, 9 weeks treatment	**Drugs:** enalapril 20 mg+HCT 12,5 mg vs. enalapril 20 mg	24h BP, exercise SBP, exercise time, LV mass, systolic function, left ventricular mass, various pertinent metabolic parameters	a:38 (19 vs. 19)	47%, 53%, 18, 20	46 (10)	SBP: 172 (18.1), DBP: 104 (6)	n.r.	South Africa	Johannesburg	After 9 wks of treatment: SBP: 148 (20) vs. 170 (25), DBP: 91 (11) vs. 104 (10)
Mngola EN.		1980		Cross over RCT	Secondary prevention	Mild to moderate	Benign essential hypertension, normal renal function, retinopathy not higher than Grade II//history of coronary thrombosis or cerebrovascular accident, presence of cardiac failure	2 weeks run in, 6 week treatment for 3 phases of a treatment schedule	**Drugs:** spironolactone 25 mg + althiazide 15 mg vs. placebo (each 6 weeks: spironolactone 25 mg + althiazide 15 mg vs. placebo, Placebo vs. spironolactone 25 mg + althiazide 15 mg; spironolactone 25 mg + althiazide 15 mg vs. placebo)	BP	r: 22 (9 vs. 13)	n.r., (22)	n.r.	SBP: 154.7 (5), DBP: 101.4 (4.6)	n.r.	Kenia	Nairobi	After 3 phases (each over 6 wks): SBP: 131.6 vs. 153.5, 145.5 vs. 143.7, 133.7 vs. 140.9; DBP: 91.3 vs. 99.5, 95.7 vs. 93.4, 88.3 vs. 90.6
Norton GR, Woodiwiss AJ, Hartford C, Trifunovic B, Middlemost S, Lee A, et al.		1999		RCT	Secondary prevention	Mild to moderate	subjects with an average supine diastolic blood pressure of 95 to 115 mm Hg at the end of the placebo phase//secondary hypertension, severe hypertension (BP 220/115 mm Hg), hypertensive retinopathy, congestive heart failure, clinically important arrhythmia, history of a recent cardiovascular event including a myocardial infarction or a stroke, insulin- dependent diabetes mellitus, previous intolerance to ACE inhibitors, hepatic dysfunction, renal disease, or child-bearing potential	2 weeks wash out, 2 weeks placebo, 8 weeks active treatment	**Drugs:** sampatrilat 50 mg/100 mg vs. lisinopril 10 mg/20 mg, increased dose at the end of 4 wks if DBP<90 mmHg	BP	r: 64, a: 58, (28 vs. 30)	37%, 63%, 21, 37	mean: 50 (range: 36-70)	SBP: 162,5, DBP: 102	n.r.	South Africa	Johannesburg	SBP: 149 vs. 156, DBP: 94 vs. 97; Change over 8 wks in 24-h BP : SBP: -7.84 (8.1) vs. -2.62 (12.7); DBP: -5.22 (5) vs. -1.03 (7.4)

Study	Study name	Year of publication	Other publications	Design	Prevention	Grade	inclusion/exclusion criteria	Duration	Intervention	outcome	amount/groups	male/female %	Age	Baseline values (pooled mean, pooled sd)	Weight /BMI	Country	Region	Results (pooled mean, pooled sd)
Nwachukwu DC, Aneke E, Nwachukwu NZ, Obika LF, Nwagha UI, Eze AA.	Nwachukwu 2015+2017	2015	///Effects of aqueous extract of Hibiscus sabdariffa on the renin-angiotensin-aldosterone system of Nigerians with mild to moderate essential hypertension: A comparative study with lisinopril. 2015, Indian Journal of Pharmacology.; Does consumption of an aqueous extract of Hibscus sabdariffa affect renal function in subjects with mild to moderate hypertension? 2017, Journal of Physiological Sciences: JPS.	RCT	Secondary prevention	Mild to moderate	Newly diagnosed, untreated mild to moderate hypertension using WHO/ISH (2003) classification//Patients with diabetes, nephropathy, cardiopathy, hepatic disease and cancer, Pregnant women, individuals with evidence of secondary hypertension, chronic smokers and alcoholics, those who did not complete the study	5 weeks//4 weeks	**Drugs:** Hibiscus Sabdariffa-Infusion 150 mg/kg) vs. 25 mg HCT vs. placebo///**Drugs:** Hibiscus Sabdariffa-Infusion 150 mg/kg) vs. Lisinopril 10 mg vs. placebo	BP, Serum and urin electrolytes	r: 80, a: 75 (25 vs. 25 vs. 25)///r: 78, a: 75 (26 vs. 23 vs. 26)	n.r.///58%, 42%, 45, 33	50.1 (36)///50.7 (19.9)	SBP: 152.5 (25.6), DBP: 99.9 (23.9), MAP: 117.6 (15.8)///SBP: 152.3 (SEM; 5.8), DBP: 99.9 (SEM 4.8)	27.7 (8.5)	Nigeria	Urban (Enugu)	After 5 wks of treatment: SBP: 137.8 (9.6) vs. 149.7 (11.45) vs. 152.75 (10.9), DBP: 91.1 (6.2) vs. 96.8 (7.3) vs. 99.5 (5.5), MAP: 106.6 (7.1) vs. 114.1 (8.35) vs. 117.3 (6.6)///After 4 wks of treatment: SBP: 134 vs. 141 vs. 152, DBP: 88 vs. 91 vs. 99 ; Change over 4 wks in SBP -17.08 (10.25) vs. -12.6 (5.5) vs. -1.1 (0.3), DBP: -12.12 (5,3) vs. -9.2 (5,3) vs. -0.4 (0.1), MAP: -13.68 (9,3) vs. -10.3 (5,5) vs. -0.95 (1)
Nwachukwu, D. C., Eze, A. A., Nwachukwu, N. Z., Aneke, E. I., Agu, P. U., Azubike, N. C., Obika, L. F., Okoye, O. I.	Nwachukwu 2017	2017		RCT	Secondary prevention	Mild to moderate	newly diagnosed outpatients with mild to moderate hypertension, aged 33 - 60 years//diabetes, chronic kidney disease, chronic heart disease, hepatic disease, cancer, pregnant women, individuals with evidence of secondary hypertension, chronic smokers, alcoholics	5 months, treatment 4 weeks	**Drugs:** Amlodipine 5 mg 1x/d vs. HCT 25 mg 1x/d	BP (antihypertensive efficacy), serum and urine electrolyte	r: 50, 2 (25 vs. 25), a: 49 (	56%, 44%, 28, 22	48.25 (11.3)	From figures: SBP: 157 vs. 154, DBP: 101 vs 99, MAP: 129 vs. 128	//27.16 (3.82)	Nigeria	Urban (Enugu)	After 4 weeks: change in BP: SBP: -17.69 (3.12) vs. -8.55 (1.64), DBP: -12.36 (2.4) vs. -5.22 (1.45), MAP: -15.26 (2.31) vs. -8.12 (2.15)
Obel A, Griffin L, Were J.	Obel 1984	1984		RCT	Secondary prevention	Mild to moderate	blacks, uncomplicated newly diagnosed, moderate essential hypertension, supine DBP 105-115 mmHg on 2 diff. Occasions separated by 2 weeks	42 weeks (2 weeks on no therapy, 4 weeks placebo run in, 36 weeks on active treatment)	**Drugs:** Furosemide 60 mg vs. Bendrofluazide 10 mg	primary: DBP (from sample size calculation), other: BP, Electrolytes	r.: 50, a: pretreatment: 43 (21 vs. 22), post treatment: 30 (16 vs. 14)	53%, 47%, 16, 14	18-65	SBP: 158.3 (16.9), DBP: 104.8 (9.1)	n.r.	Kenia	Urban (Nairobi)	After 28-32 wks of treatment: SBP: 148.4 (24.8) vs. 141.9 (17.1), DBP: 95.4 (15.5) vs. 88.5 (15.9), controlled DBP (≤ 95 mmHg): 42.9% (9/21) vs. 27.3% (6/22)
Obel AO.	Obel 1983	1983		RCT	Secondary prevention	Mild to moderate	Previously untreated mild to moderate hypertension, DBP within 95-120 mmHg after Placebo wash out//secondary hypertension	4 weeks placebo wash out, 16 weeks active treatment	**Drugs:** Fixed combination: timolol 10 mg+ HCT 25 mg + amiloride 2,5 mg 1x/d vs. Methyldopa 500 mg 3x/d up to 3g/d	BP, HR	r: 32, a: 27 (15 vs.12)	34%, 66%, 9, 18	41 (10), 24-61	SBP: 160 (17.6), DBP: 106.9 (8.9), HR: 86 (11.4)	n.r.	Kenia	Urban (Nairobi)	After 16 wks treatment: SBP: 140 (12) vs. 150 (16), DBP: 84 (8) vs. 99 (10), HR: 73 (12) vs. 82 (13)
Obel AO, Gitau W.	Obel 1981	1981		Cross over RCT	Secondary prevention	Mild to moderate	Supine DBP 95-115 mmHg// bronchial asthma, COPD, allergic rhinitis, cardiac failure, ECG evidence of heart block or myocardial ischemia, recent myocardial infarction, renal failure, impaired liver function, d.m., gout, pregnancy, resting HR <54 bpm	16 weeks (2 weeks drug free wash out, 2 weeks placebo run in, 3x4 weeks treatment)	**Drugs:** metipranolol 20 mg vs. butizide 2.5 mg vs. fixed combination metipranolol/butizide 20/2.5 mg	BP	r: 34, a: 30	41%, 59%, 12, 18	42 (22-65)	SBP: 141 (14.2), DBP: 98 (12.04)	n.r.	Kenia	Urban (Nairobi)	SBP: 138 (20.3) vs. 128 (14.8) vs. 121 (13.1), DBP 97 (22.5) vs. 85 (14.2) vs. 84 (10.4)
Obel AO.	Obel 1989	1989		RCT	Secondary prevention	Mild	Age 20-60, DBP >90, <109 mmHg, SBP >160 mmHg, serum potassium <4.5mM, serum creatinine 60-130 microM	16 weeks	**Drugs:** potassium supplements vs. placebo	BP, Sodium and Potassium concentrations in urine and serum	r+a: 48 (24 vs. 24)	44%, 56%, 21, 27	40 (8.5), 23-56	SBP: 174 (9), DBP: 100 (3.5), HR: 75 (7)	65.5 (5.5)	Kenia	Urban (Nairobi)	After 4 months of treatment: SBP: 133 (10) vs. 172 (7), DBP: 83 (4) vs. 100 (4)
Obel AO.	Obel 1990	1990	Effects of chlorthalidone, oxprenolol, and their combination in hypertensive blacks: a randomized double-blind crossover study. 1989, Journal of cardiovascular pharmacology [Internet].	RCT	Secondary prevention	Mild to moderate	untreated supine DBP equal to or above 100mmHg but below 115mmHg,	8 weeks placebo run in, 12 months, entire trial: 3 years	**Drugs:** Oxprenolol (160 mg) 320 mg vs. Chlorthalidone (25 mg) 50 mg vs. Oxprenolol/Chlorthalidone (160/20 mg) 320/40 mg	BP, HR	r+a: 62 (31 vs. 31), entire trial: 3 years	44%, 56%, 27, 35	44 (9), 22-57	SBP: 150.5 (13), DBP: 104.5 (4), HR: 76.5 (8.5)	68.5 (9)	Kenia	Urban (Nairobi)	After 6 months of treatment: SBP: 158 (16) vs. 138 (6) vs. 131.5 (4), DBP: 102 (5) vs. 90 (4) vs. 84 (4), HR: 70 (8) vs. 78 (12)
Obel AO, Koech DK.	Obel 1991	1991		RCT	Secondary prevention	Mild to moderate	Newly diagnosed who had untreated and sustained supine DBP equal to or above 105 mmHg but below 110mmHg,	4 weeks placebo, 28 weeks active medication	**Drugs:** potassium supplements 64 mmol vs. bendrofluazide 10 mg	BP, Sodium and Potassium concentrations in urine and serum	r+a: 84 (42 vs. 42)	52%, 48%, 44, 40	44.5 (3.4) 21-60	SBP: 164 (13), DBP (110 (2.5), HR: 75 (8.5)	69 (7.5)	Kenia	Urban (Nairobi)	After 28 weeks: SBP: 141 (9) vs. ?, DBP: 88 (4) vs. ?, (after 8 weeks: SBP: 148 (8) vs. 144 (4), DBP: 94 (4) vs. 90 (4)))
Ogola EN, Yonga GO.	Ogola 1993	1993	Yonga GO, Ogola EN, Orinda DA., Metabolic effects of propranolol and hydroflumethiazide treatment in Kenyans with mild to moderate essential hypertension. 1993, East African Medical Journal.	RCT	Secondary prevention	Mild to moderate	DBP 100-110 mmHg after 2 weeks drug free run in// pregnancy, contraindication for thiazide or ß-blocker use, bronchial asthma, heart failure, gout, patients with debilitating conditions	12 weeks	**Drugs:** propranolol 80 mg (160 mg) vs. hydroflumethiazide 50 mg	BP, metabolic side effects	r: 60, a: 54 (27 vs. 27)	50%, 50%, 27, 27	42 (9), 22-65	SBP: 156.1 (11.2), DBP: 102.1 (8.6)	n.r.	Kenia	Urban (Nairobi)	After 12 weeks of treatment: SBP: 146.2 (13) vs. 141.6 (7.4), 95.9 (4.4) vs. 90.2 (3.1)
D.B. Ojji, B. Mayosi,* V. Francis, M. Badri, V. Cornelius, W. Smythe, N. Kramer, F. Barasa, A. Damasceno, A. Dzudie, E. Jones, C. Mondo, O. Ogah, E. Ogola, M.U. Sani, G.L. Shedul, G. Shedul, B. Rayner, I.G. Okpechi, K. Sliwa, and N. Poulter	Ojji, 2019	2019	NCT02742467	RCT, multicenter	Secondary prevention	Mild to moderate	Male or female black patients with hypertension, age: 30-79 years, office SBP 150-179 mmHg or 140-159 mmHg while receiving mono- therapy//previous treatment for hypertension, history of cardiovascular disease, secondary hypertension, pregnancy	June 2017 through December 2017, 6 months,	**drugs:** Amlodipine 5 (10) mg+ HCT 12.5 (25) mg (A) vs. Amlodipine 5 (10) mg + Perindopril 4 (8) mg (B) vs. Perindopril 4 (8) mg+ 12.5 (25) mg HCT (C)	p.o.: mean change in the 24-hour ambulatory SBP, s.o.: change at 6 months in the ambulatory DBP; the change in the mean daytime, nighttime ambulatory BP; the change in office BP; the proportion of patients who had a controlled office BP, the proportion of patients who had a response to treatment, changes in blood analytes, pulse rates, and adverse events	r: 728, 3 (244 vs. 243 vs. 241), a: 621, 3 (216 vs. 205 vs. 200)	37%, 63%, 228, 393	51.1 (10.6)	SBP: 158 (11.7), DBP: 97.6 (10.3), HR: 81.8 (13.8)	//28.34 (5.67)	Sub-Saharan africa (Nigeria, South Africa, Kenya, Mozambique, Cameroon, Uganda)		mean change in 24h SBP:-17.2 vs. -18.1 vs. -14.2 mmHg; A vs. C -3.14 (20.7), A vs. B: -0.14 (20.13); B vs C: -3 (20.22), same comparisons: 24h DBP: -1.05 (12.1) vs. -0.41 (11.7) vs. -0.64 (11.7)
Okeahialam B, Ohihoin E, Ajuluchukwu J.		2011	Diuretic drugs benefit patients with hypertension more with night-time dosing, 2012, Therapeutic Advances in Drug Safety	RCT	Secondary prevention	Mild to moderate	grade 1 and 2 hypertensives in outpatient service//current smokers, chronic alcoholic abuse, grade 3 hypertensives, clinical or laboratory evidence of secondary hypertension, renal impairment, pregnant/ lactating females	IV/2007-I/2008, 2 week wash out period, 12 weeks	**standardized treatment strategies:** drug intake in the morning (10:00) vs. drug intake in the evening (22:00), first 2 weeks 1 drug: thiazide (or Ca-channal-blocker, or ß-blocker, or RAS-blocker), after 2 weeks a second drug, when BP not controlled	BP	r: 181, a: 165 (81 vs. 84)	39%, 61%, 64, 101	49.7 (14.2)	SBP: 150.3 (14.8), DBP: 93.7 (9.6), HR 83.6 (12.6), MAP: 112.6 (9.7)	73.6 (14.3)// 28.1 (5.5)	Nigeria	Urban (Jos)	SBP: -14.14 (14.73) vs. -18.08 (17.9), DBP: -8.7 (10.2) vs. -15.6 (12.2), MAP: -10.6 (10.3) vs. 16.5 (12.4)
Onwubere BJ, Obodo JO, Oke DA, Okeahialam BN, Danbauchi SS, Mbakwem AC		2001		RCT, multicentre	Secondary prevention	Mild to moderate	18-70, DBP 95-109//secondary hypertension, orthostatic hypotension, seated SBP >180 mmHg, DBP >110 mmHg, stroke, myocardial infarction in previous 6 months, clinically significant cardiac pathology, pregnancy, lactation, absence of contraception in women of child-bearing potential, use of cimetidine, phenytoin, class 1 anti arrhythmic drugs 3 weeks prior the trial, antifungals, erythromycin, allergy or intolerance of dihydropyridines, significant gastrointestinal disease, drug or alcohol abuse,	1 week drug free, 2 weeks placebo run in, 6 weeks active treatment	**Drugs:** Nifedipine 10 mg2x/d vs. Felodipine 5 mg 1x/d (dose doubled after 3 weeks, if BP uncontrolled	BP, HR	a: 121 (64 vs. 57)	53%, 47%, 64, 57	50.5 (11.8)	SBP: 153.1 (17.9), DBP: 98.5 (9.1), HR: 80.9 (12.2)	n.r.	Nigeria	Urban (Jos, Enugu, Lagos, Zaria)	After 6 wks of treatment: SBP: 135.3 (14.4) vs. 137.1 (13.9), DBP: 86.7 (9.7) vs. 85.8 (9.9), HR: 79 (11.4) vs. 84.5 (14.9), satisfactory control: 79.6 (43/?) vs. 76.3 (45/?)
Opie LH, Haus M, Commerford PJ, Levetan B, Moore K, Brink J		2002		RCT	Tertiary prevention		2-3 months after heart transplantation and abnormality of 24h-ambulatory BP, 24-h ABP mean values of 116/70 mm Hg and below 128/83 mmHg or awake ABP of 133/84 mmHg or below 139/86 mmHg, mean sitting cuff BP exceeded 140/90 mmHg//intolerance to ACE inhibition or adverse reaction to the trial dose of captopril, or a blood urea exceeding 14 mmol/L, or serum creatinine exceeding 200 mol/L, or markedly adverse rejection episodes, or a highly abnormal clinical status	1993, 2 years, + 2 years follow up	**Drugs:** lisinopril 20 mg (40 mg) vs. placebo	primary: BP, secondary: complications of hypertension	r: 40 (20 vs. 20), a: 29 (13 vs. 16)	80%, 20%, 23, 6	50	24h mean: SBP: 136.3 (21.1), DBP: 86.8 (5.3)	n.r.	South Africa	Urban (Cape Town)	After 2 years: from 148/97 to 136/90 mm Hg in the control group, and from 138/92 to 125/85 mm Hg in the lisinopril group. 24h mean after 2 years: SBP: 121.2 (11.6) vs. 132.2 (12.2), DBP: 78.7 (10.9) vs. 86.3 (6), 2-year mortality: 4/20 (20%) vs. 2/20 (10%)
Opie LH, Müller FO, Myburgh DP, Rosendorff C, Sareli P, Seedat YK, et al.	Opie 1997	1997		RCT, multicenter	Secondary prevention	Mild to moderate	between the ages of 18 and 75 years, supine diastolic blood pressure at the end of the placebo run-in phase >= 95 mm Hg, and <= 114 mm Hg//labile hypertension, clinical evidence of major arrhythmias, angina pectoris, conduction disturbance, heart failure, recent or impending myocardial infarction, cerebral vascular accident, women of childbearing age, type I diabe- tes mellitus, impaired renal or hepatic function, a history of allergy to dihydropyridines, concomitant use of other drugs that might affect blood pressure or interact with nisoldipine	4 weeks placebo run in, 6 weeks treatment,	**Drugs:** Nisoldipine 30 mg vs. 20 mg vs. 10 mg vs. Placebo	primary: Supine DBP change from baseline to after 6 weeks o. treatment, secondary : Supine SBP/standing DBP + SBP change from baseline to after 6 weeks of treatment,	r: 206 (49 vs. 51 vs. 48 vs. 58), with placebo, participants without placebo group: 148; 2 were excluded, (table 2)	45%, 55%, 65, 83	52 (range: 20-75)	DBP: 104.3, SBP: 164.1, HR: 73.8	80 (range: 43.5-126)	South Africa (6 centres), US (1 center)	Urban	Change from baseline: DBP: -10.3 vs. -9 vs. -5.5 vs. -2.3; SBP: -15 vs -16.9 vs. 8; HR: 4.3 vs. 1.5 vs. 2.2 vs. -0.7, difference change to placebo*: DBP: -8 (9.56) vs. -6.7 (9.64) vs. -3.2 (9.6); SBP: -15.9 (19.26) vs. -17.8 (19.67) vs. -8.9 (19.4) ; HR: 5 (14.13) vs. 2.2 (14.39) vs. 2.9 (14.12)
Poulter NR, Sanderson JE, Thompson AV, Sever PS, Chang CL.	Poulter 1993	1993		Crossover RCT	Secondary prevention	Mild to moderate	DBP>105mmHg//DPB <90 mmHg after HCT treatment period	2 weeks washout, 4 weeks HCT 25 mg, 6 weeks active treatment	**Drugs:** Nifedipine 2x20 mg + HCT 25 mg vs. Propanolol 2x80 mg +HCT 25 mg	SBP, DBP, HR	r: 37, a: 29 (16 vs. 13)	n.r., (29)	30-69	SBP: 180 (30.2), DBP: 114 (14), HR 70 (11)	n.r.	Kenia	n.r. (urban)	SBP: 141 (16.5) vs. 150 (11), DBP: 91 (11) vs. 95 (11), HR: 77 (13.7) vs. 61 (11)
Radevski I, Skudicky D, Candy G, Sathekge S, Strugo V, Sareli P.	Radevski 1999	1999		RCT	Secondary prevention	Severe	blacks, either gender with essential severe hypertension, which was either newly diagnosed or not adequately controlled previously, sitting DBP at enrollment 115-140 mm Hg, 24-h ambulatory blood pressure monitoring (24-h DBP 110mmHg and140mmHg//systolic BP (SBP) >230 mm Hg, secondary hypertension, myocardial infarction or cerebrovascular insufficiency within the 3 months preceding enrollment, unstable angina, severe aortic stenosis, congestive heart failure, atrioventricular block II/III degree or left bundle branch block, tachycardia or bradycardia, insulin-dependent diabetes mellitus, clinically significant hepatic or renal impairment, history of hypersensitivity to ACE inhibitors, or dihydropyridine calcium channel antagonists	Optional 24h washout, 9 weeks doubleblind, 16 weeks open label (all on Nisoldipine up to 60 mg)	**Drugs:** Nisoldipine 10/20/40 mg vs. Enalapril 10/20/40 mg	BP, HR	r: 143, a: 96 (53 vs. 43)	48%, 52 %, 46, 50	47.5 (9)	SBP: 180 (13.6), DBP: 117.6 (6.2), 24h-BP: SBP: 183.3 (15), DBP: 117.6 (7)	n.r.	South Africa	Urban (Johannesburg)	After 9 weeks (n=96): SBP 144 (16) vs. 171 (17), DBP: 94 (10) vs. 110 (11), HR: 82 (9) vs. 78 (8); 24h-BP (n=143): SBP: 147 (18) vs. 171 (17), DBP: 96 (11) vs. 110 (11)
Radevski IV, Valtchanova ZP, Candy GP, Wald AM, Ngcezula T, Sareli P.	Radevski 2002	2002		RCT	Secondary prevention	Mild to moderate	black patients with mild to moderate hypertension, average sitting DBP >95 and < 115 mmHg, mean daytime ambulatory DBP >90 mmHg and < 115 mmHg//pregnant or lactating women, DBP >115 mmHg, SBP > 200 mmHg, secondary hypertension, myocardial infarction, cerebrovascular insufficiency within the 3 months preceding enrolement, cardiac arrhythmias, insulin-dependent diabetes mellitus, clinically significant alteration in renal or liver function, electrolyte abnormalities, hyperuricaemia, clinically significant depression 6 months before enrolment, history of alcohol or drug abuse, uncooperative or antagonistic personality, previous history of intolerance to any of the study drugs	1 week washout, 2 weeks placebo run-in, 3 months active medication,	**Drugs:** HCT 12.5 mg vs. Indapamide 2.5 mg	BP, HR	r/a): 42 (22 vs. 20)	33%, 67%, 14, 28	57 (11)	SBP: 157 (15), DBP: 96.5 (8.5), HR: 77 (12), 24h BP: SBP: 148 (15), DBP: 94 (7), HR 77 (12)	//31 (8)	South Africa	Urban (Johannesburg)	After 3 months: SBP: 146 (19) vs. 136 (20), DBP: 92 (10) vs. 86 (10), HR 79 (9) vs. 78 (14); 24h-SBP: 139 (19) vs. 130 (19), DBP: 88(12) vs. 82 (9)
Rogers, G. G., Rosendorff, C., Goodman, C., Radford, H. M.,	Rogers 1988	1988		RCT	Secondary prevention	Mild to moderate	Hypertensive volunteers with sitting DBP 90-120 mmHg after 4 wks on placebo	4 weeks placebo run-in, 12 weeks active treatment	**Drugs:** Lisinopril 20-80 mg vs. Atenolol 50-200 mg	BP after exercise	r: 26 (17 vs. 9)	35%, 65%, 9, 17	62 (mean)	*Rest:* SBP: 180.2 (23.5), DBP: 114 (8.8), HR: 79 (13); *after 50 W:* SBP: 208.8 (37.4), DBP: 114 (8.8), HR: 116.4 (16.1)	n.r.	South Africa	Urban (Johannesburg)	*Rest:* SBP: 158 (29.8) vs. 178 (24.4), DBP: 102 (12.3) vs. 100.3 (11.7), HR: 87.8 (19.8) vs. 58.4 (7.3), *after 50 W:* SBP: 188.5 (34) vs. 197.2 (33), DBP: 111.3 (13.4) vs. 108.8 (13.3), HR: 122.4 (17.9) vs. 92.8 (18.2)

Study	Study name	Year of publication	Other publications	Design	Purpose	Grade	Inclusion/exclusion criteria	Duration	Intervention	Outcome	amount/groups	male/female %	Age	Baseline values (pooled mean, pooled sd)	Weight /BMI	Country	Region	Results (pooled mean, pooled sd)
Salako BL, Kadiri S, Walker O, Fehintola FA	Salako 1998	1998		RCT	Secondary prevention	Mild to moderate	Sitting DBP >= 95 but <115 mmHg, SBP =<200 mmHg// history of stroke, heart failure, renal failure, hepatic disease, secondary hypertension	4 weeks placebo run-in, 12 weeks treatment	**Drugs:** Lacidipine 4 (6) mg vs. HCT 25 (50) mg	BP	r: 62 (30 vs. 32), a: 41 (24 vs. 17)	32%, 68%, 13, 28	52.8 (15.8)	SBP: 157.2 (16.8), DBP: 100.6 (5.2)	50.8 (27.9)	Nigeria	Urban (Ibadan)	After 12 weeks: SBP 146 (24) vs. 141 (17); DBP: 87 (15) vs. 89 (7), HR: 83 (10) vs. 80 (10)
Salako LA, Falase AO, Aderounmu AF.	Salako 1979	1979		Crossover RCT	Secondary prevention	Mild to moderate	previously diagnosed, well controlled essential hypertension Staged and II with pre-treatment DBP of 95 to 120 mmHg, regular antihypertensive treatment for periods from 1 to 9 years//chronic renal and liver disease, diabetes mellitus, cardiac failure,	4 weeks washout, 8 weeks alprenolol vs. Placebo, 8 weeks vice versa,	**Drugs:** Alprenolol 200 mg vs. Placebo	BP, HR	r: 20, a: 16	27%, 73%, 4, 12	46.1 (range: 37-60)	SBP: 172.75 (range: 140-220), DBP: 109.1 (97-118)	n.r.	Nigeria	Urban (Ibadan)	After 8 weeks each: SBP: 176.4 (24.8) vs. 180.6 (22.4), DBP: 103.3 (10.8) vs. 104.6 (7.6), HR: 75.5 (10.4) vs. 81 (9.6)
Salako LA, Falase AO, Aderounmu AF.	Salako 1979a	1979		Crossover RCT	Secondary prevention	Mild to moderate	Hypertensive patients, who had been treated for >2 years, DBP 95-120 mmHg//heart failure, hepatic, renal, cerebral complications	4 weeks washout, 6 hours (1 administration), 2 weeks later crossover	**Drugs:** Pindolol 20 mg vs. Propanolol 100 mg vs. Placebo	BP, HR at rest and after exercise	r/a: 9	n.r. (9)	40.9 (6-3) (range: 32-50)	*Rest:* SBP: 143.9 (16.5) vs. 154.4 (27.3) vs. 159.6 (15), DBP: 103.3 (11.1) vs. 106.7 (9.9) vs. 101.8 (9), HR: 76.7 (8.1) vs. 67.3 (4.8) vs. 76.8 (6), *after exercise (6h):* SBP: 157.8 (12.9) vs. 158.3 (23.7) vs. 175.9 (18.9), DBP: 108.4 (6.6) vs, 102.3 (9.9) vs. 106.9 (7.8), HR: 102.4 (8.4) vs. 103.3 (4.2) vs. 117.3 (9)	n.r.	Nigeria	Urban (Ibadan)	*Rest:* SBP: 143.9 (16.5) vs. 154.4 (27.3) vs. 159.6 (15), DBP: 103.3 (11.1) vs. 106.7 (9.9) vs. 101.8 (9), HR: 76.7 (8.1) vs. 67.3 (4.8) vs. 76.8 (6), *after exercise (6h):* SBP: 157.8 (12.9) vs. 158.3 (23.7) vs. 175.9 (18.9), DBP: 108.4 (6.6) vs, 102.3 (9.9) vs. 106.9 (7.8), HR: 102.4 (8.4) vs. 103.3 (4.2) vs. 117.3 (9)
Salako LA, Falase AO, Aderounmu AF, Walker O.	Salako 1990	1990		Crossover RCT	Secondary prevention	Mild to moderate	DBP 90-115 mmHg at the end of placebo	2 weeks washout run in, , 4 weeks placebo, 4 weeks each treatment, no washout between treatments	**Drugs:** Atenolol 100 mg vs. Chlorthalidone 25 mg vs. Atenolol+ Chlorthalidone 100/25 mg separate vs. Atenolol+ Chlorthalidone 100/25 mg combined	BP, HR	r/a: 24	29%, 71%, 7, 17	29-70	SBP: 182.6 (23.8), DBP: 107.8 (9.1), HR: 80 (8.8)	n.r.	Nigeria	Urban (Ibadan)	After 4 weeks: SBP: 157 (12.7) vs. 154.4 (16.2) vs. 148.3 (12.4) vs. 146.6 (11.4); DBP: 91.5 (8.6) vs. 89.1 (9.3) vs. 85.4 (6.5) vs. 85.4 (6.2); HR: 66.3 (6.7) vs. 78.6 (8.9) vs. 65.4 (8.1) vs. 65.2 (7.5)
Sareli P, Radevski IV, Valtchanova ZP, Libhaber E, Candy GP, Den Hond E, et al.	Sareli 2001	2001		RCT	Secondary prevention	Mild to moderate	Black men and women, age 18- 70 years, free of clinically significant cardiovascular or noncardiovascular disorders, Women of reproductive age had to use adequate contraception, mean daytime DBP =>90 mm Hg, mean daytime DBP 90 - 114 mm Hg after placebo run in, count of the returned placebo tablets within 80% to 120% of the expected number	2 weeks placebo run in, 13 months (1.9.1994-30.11.1997)	**Drugs:** Nifedipine 30 (60, 90, HCT 12,5 could be added) mg vs. verapamil 240 (360, 480) mg vs. HCT 12,5 (25, reserpine 0,125 could be added) mg vs. Enalapril 10 (20 (HCT 12,5 could be added) mg	BP, LV mass index	r: 409 (233 vs. 58 vs. 58 vs. 60), a: 257 (154 vs. 35 vs. 39 vs. 29)	23%, 77%, 59, 198	53.3 (10.1)	SBP: 164.7 (18.5), DBP: 99.4 (8), HR: 82.7 (10.5)	//31.1 (6.7)-29 (5.5)	South Africa	Urban (Johannesburg)	After 13 months: SBP: 130 vs. 136 vs. 132 vs. 124, DBP: 86 vs. 87 vs. 85.5 vs. 82,
Sarfo, F. S., Treiber, F., Gebregziabher, M., Adamu, S., Nichols, M., Singh, A., Obese, V., Sarfo-Kantanka, O., Sakyi, A., Ashu-Darko, N., Tagge, R., Agyei-Frimpong, M., Kwarteng, N., Bashe, E., Mensah, N., Ampofo, M., Jenkins, C., Ovbiagele, B., Team, Pings	Sarfo 2019	2019	NCT02568137	Cluster RCT	Tertiary prevention	Uncontrolled	Stroke survivors >=18 years, BÜ >=140/90 mmHg at screening visit at a medical center, recent CT CT scan to confirm stroke of <1 month, uncontrolled HT//severe cognitive impairment (MMSE <=24), severe global disability, renal dialysis, cancer or treatment of cancer per 2 years, planned pregnancy, pregnancy nursing, prisoners, institutionalized individuals	3 months	**Standardized treatment strategies:** IG (blue-toothed BP device and smartphone with a App for monitoring BP measurements + medication intake) vs. CG (usual care)	Primary outcome: proportion of clinic BP<140/90 mmHg at month 9, secondary outcome: medication adherence	r/a: 60, 2 (30 vs. 30)	65%, 35%, 39, 21	55 (13)	SBP 143.8 (26.67), DBP 90.5 (15.66), modified morisky medication adherence score: 10.3 (3.1 vs. 11.5 (2.8)	n.r.	Ghana	Urban	After 9 months: modified morisky medication adherence score: 13 (1.5) vs. 13 (1.7), BP control, clinic SBP<140 mmHg in: 22/30 vs. 13/30, SBP <90 mmHg itt: 14/30 vs. 23/30
Saunders LD, Irwig LM, Gear JS, Ramushiu DL.	Saunders 1991	1991		RCT	Secondary prevention	Mild to moderate	Newly treated hypertensives (one time DBP >=120 mmHg, or two times DBP >= 105 mmHg, no drug treatment in the previous 12 months, <70 years old), patients with history of infrequent attendance (one time DBP >=120 mmHg, or two times DBP >= 105 mmHg or three times DBP >=100 mmHg, antihypertensive drugs initiated in the previous 12 months, attendance too infrequently, to receive 80% of the medication, treatment was not stopped the previous year bei clinic staff, and was not received elsewhere), lived in Soweto,	6 months (Therapie as indicated, thiazide diuretics, methyldopa), 14.2.1983 - 8.8.1983 =newly treated group, 11.11.1983 - 3.5.1983 = infrequent attender group	**Adherence strategies:** health education about compliance for all , routine care vs. sending reminders about appointments/after missed appointments/patient retained BP and medication records	compliance, BP,	r/a: 224, Newly treated group (NTG): 115 (56 vs. 59) vs. infrequent attender group (IAG): 109 (54 vs. 55)	27%, 73%, 60, 164	65% between 40-50 yrs	NTG: DBP: 116.6	n.r.	South Africa	Urban (Johannesburg)	Difference of DBP: newly treated: 93.4 vs. 100.5; MD: 7.1 (95%CI 0.5-13.7), infrequent attenders: 97.5 vs. 94.7; MD: -2.8 (95%CI -6.9: 1.3)
Seedat YK.	Seedat 1980	1980		Crossover RCT	Secondary prevention	Mild to moderate	DBP: 100-115mmHg, patients, that did not require urgent control//cardiac failure, bronchial asthma, gross electrocardiographic evidence of myocardial ischaemia or heart block, myocardial infarction within the past five months, pregnancy, greatly impaired renal or hepatic function, diabetes mellitus requiring treatment, gout	5x 28 days	**Drugs:** Atenolol 100 mg + placebo vs. Chlorthalidone 25 mg + placebo vs. Atenolol/Chlorthalidone 100/25 mg vs. Placebo	BP, HR	r: 24	n.r., (24)	n.r.	(Placebo) SBP: 159 (22.5), DBP: 102.5 (15.2), HR: 76.2 (10.8)	n.r.	South Africa	Urban (Durban)	SBP: 161.5 (21.1) vs. 152.6 (22.5) vs. 145 (27.9), DBP: 98.1 (9.3) vs. 96.3 (16.7) vs. 88.7 (11.8), HR: 67.3 (9.8) vs. 79.5 (11.3) vs. 71.7 (11.8)
Seedat YK, Parag KB.	Seedat 1987	1987		RCT	Secondary prevention	Mild to moderate	DBP 90-115 mmHg after 4 weeks on placebo//secondary hypertension (any cause, such as unilateral or bilateral renal disease, coarctation of the aorta or phaeochromocytoma); malignant hypertension, average sitting DBP at week 0 not between 90 and 115 mmHg; possibility of pregnancy (oral contraceptives were not permitted), under the legal age of consent, congestive heart failure or findings suggestive of congestive heart failure or left ventricular failure and right ventricular failure secondary to pulmonary hypertension; myocardial infarction within the past 6 months or presence of unstable angina pectoris; haemodynamically significant valvular heart disease; an atrioventricular conduction defect (second- or third-degree block); a cerebrovascular accident or one or more episodes of hypertensive encephalopathy within the past year; diabetes mellitus, treatment with one or more of the following drugs: adrenergic psychotropic agents (including monoamine oxidase inhibitors), appetite suppressants, lithium, vasopressor nasal decongestants, or oral contraceptives; other concurrent severe disease, such as collagen disease or neoplasm; confirmed evidence of one or more of the following: significant renal or hepatic involvement, serum urea – 10 mmol/l or serum urea nitrogen – 21.4 mmol/l, serum creatinine> 132,6 micromol/l, aspartate aminotransferase or alanine aminotransferase 100% above normal range, total serum bilirubin values> 18,8 micromol/l, clinically significant abnormal values for any of the following: haematocrit, haemoglobin value, white cell count (– 3 x 10^9/1), platelet count and alkaline phosphatase level; plasma potassium level, measured during base- line, < 3,5 mmol/l or > 5,4 mmol/l; any contraindication to thiazide therapy and/or ß-blocker and/or converting enzyme inhibitor; history of skin rash, recurrent dermatoses or other allergy to drug therapy, or abnormal antinuclear antibody titre	4 weeks placebo run in, 24 weeks active treatment	**Drugs:** Lisinopril 20/40/80 mg (+12,5/25 mg HCT) vs. Atenolol 50/100/200 mg (+12,5/25 mg HCT)	BP, HR	r: 36 (24 vs. 12), a: 35 (23 vs. 12)	25%, 75%, 9, 26	48.8	SBP: 162.7 (22.1), DBP: 104 (6.5), HR: 73.4	68.6	South Africa	Urban (Durban)	SBP: 131 (20.1) vs. 146 (18.1), DBP 86 (10) vs. 93 (8.6), HR 77.5 vs. 64
Seedat YK, Parag KB, Nathoo BC.	Seedat 1990	1990		Crossover RCT	Secondary prevention	Mild to moderate	mild to moderate, stable hypertension (resting SBP 90-114 mmHg), age between 21-65, male and female, compliance during placebo period//major cardiac, hepatic or renal disease, diabetes mellitus	2 weeks washout, 2 week Placebo run in, 12 wks treatment	**Drugs:** Nitrendipin 10/20/40 mg vs. Methyldopa 250 mg	BP, HR	47 (25 vs. 22)	38%/63%, 18, 29	49 (9.7)	SBP: 173.1 (21.7), DBP: 103 (4.9), HR: 70.5 (13.4)	72.5 (14.6)	South Africa	Urban (Durban)	After 12 weeks: SBP: 151 (22.3) vs. 162.6 (22.3), DBP: 87 (9.7) vs. 98.9 (8), HR: 70.5 (12.1) vs. 68.9 (12.1)
Skoularigis J, Fitzmaun L, Davis J, Strugo V, Sareli P.	Skoularigis 1994	1994		RCT	Secondary prevention	Moderate	Blacks, age 21-65 years, an average sitting diastolic BP > 95 mm Hg and < 115 mm Hg, a 24-h mean diastolic ABPM > 90 mm Hg and < 115 mm Hg//secondary hypertension, hypertensive emergency, systolic BP > 215 mm Hg, congestive heart failure, history of recent (< 3 months) myocardial infarction or stroke, previous intolerance to dihydropyridines or Captopril, or hepatic or renal disorders	3 weeks placebo controlled baseline, 12 weeks treatment	**Drugs:** Nifedipine 2x20 (2x40) mg vs. Captopril 2x25 (2x50) mg (after 8 weeks: if target diastolic BP was not reached: HCT/Amilorid 50/5 mg half/1 tablet daily in both groups was added)	BP lowering effects, LV mass, systolic function	r: 45, a: 41 (20 vs. 21)	51%, 49%, 21, 20	47.5 (10)(21-65)	24h-/SBP: 156 (13.6), DBP: 101 (6), HR 74.5 (9.5)	n.r.	South Africa	Urban (Johannesburg)	After 8 weeks: SBP: 128 (11) vs. 158 (17), DBP: 84 (7) vs. 102 (9), HR 81 (12) vs. 76 (13), changes in BP: SBP: -28 (13) vs. -1 (11), DBP: 17 (8) vs. -1 (8)
Skoularigis J, Strugo V, Zumbakides C, Eintracht S, Reddy K, Tshele E, et al.	Skoularigis 1996	1996		RCT	Secondary prevention	Mild to moderate	Blacks, age 18-65 years, essential hypertension, newly diagnosed or inadequately treated, DBP: >95 and <115 mmHg, 24-h mean diastolic ABPM > 90 mm Hg and < 115 mm Hg//childbearing potential, secondary hypertension, hypertensive emergency, systolic BP > 200 mm Hg, congestive heart failure, history of recent (< 3 months) myocardial infarction or stroke, previous intolerance to di- ACE-inhibitors or thiazides, or hepatic or renal disorders	1 week withdrawn previous medication, 3 weeks placebo run in, 12 weeks active treatment	**Drugs:** Captopril + HCT (50/25 mg) vs. Enalapril +HCT (20/12,5 mg)	Reduction of mean DBP ≤90 mmHgby 24h hour ABPM (Efficacy and tolerability	r/a: 47 (24 vs. 23)	45%, 55%, 21, 26	47.5 (10.5)(18-65)	24h-SBP: 154.4 (13.1), DBP: 99.5 (6), HR: 75 (12)	n.r.	South Africa	Urban (Johannesburg)	After 12 weeks: SBP: 133 (13) vs. 141 (18), DBP: 86 (7) vs. 90 (12), HR: 77 (11) vs. 73 (9),
Sobngwi, E., Mfeukeu-Kuate, L., Kouam, M., Tankeu, A. T., Ngamou-Ginnaljo, C. N., Hamadou, B., Etoa, M., Ngnaoum, E., Nkamgna, A., Dehayem, M. Y., Kuate, F. F., Kengne, A. P., Mbanya, J. C.	Sobngwi 2019	2019	NCT 03747978	RCT	Secondary prevention	Mild to moderate	type 2 diabetic patients, newly diagnosed for hypertension (grade I or II), with ambulatory BP monitoring (ABPM), aged 25 - 65 years, naïve to any antihypertensive treatment//grade III hypertension, marked decline in renal function (creatinine clearance <30 mL/min/1.73 m2, acute kidney injury or liver cytolysis (alanine transaminase [ALT] ≥3 normal), patients with a contraindication to molecules used in the study (hypersensitivity), pregnant or breastfeeding women	October 2016 to May 2017, 6 weeks	**Drugs:** perindopril-amlodipine (Coveram 5/5 mg) 1x/d vs. perindopril-indapamide (Bipreterax 5/1.25 mg)	primary: change in circadian blood pressure profile other: relative change in office/clinical blood pressure and slipping profile	r/a: 30 (15 vs. 15)	47%, 53%, 14, 16	median : 57 (IQR 53-60) vs. 60 (IQR 52-64)	SBP-143 (IQR 140-150) vs. 147 (IQR 141-151), DBP: 91 (IQR 85-93) vs. 89 (IQR 84-96), HR: 80 (IQR 75-85) vs. 79 (IQR 73-84), 24h SBP: 144 (IQR 138-152) vs. 145 (IQR137-155), 24h DBP: 85(IQR 75-89) vs.89 (IQR 82-93), 24h HR: 63(IQR 53-67) vs. 58(IQR 48-70)	//29 (IQR 26-31) vs. 28 (IQR 27-33)	Cameroon	Urban	After 6 weeks: 24h BP: SBP: 128 (IQR 125-138) vs. 126 (IQR 116-137), DBP: 78 (IQR 73-83) vs. 79 (IQR 68-86), HR: 54 (IQR 47-55) vs. 49 IQR (46-51)
Stein CM, Neill P, Kusemamuriwo T.	Stein 1992	1992		Crossover RCT	Secondary prevention	Mild to moderate	Black hypertensives, <70 years of age, DBP >95 <115 mmHg//the presence or a history of: heart failure, focal neurological deficit, impaired renal function, gout, diabetes mellitus, pregnancy, oestrogen therapy or an ad- verse reaction to thiazides	4/6 weeks placebo run in, 6 weeks treatment each	**Drugs:** HCT 6,25 vs. 12,5 vs. 25 vs. 50 mg vs. Placebo	Antihypertensive effects of low doses of HCT	r: 25, a: 19	53%, 47%, 10, 9	49.2 (8.8)	SBP 174 (22.2), DBP: 104.3 (7.1)	n.r.	Zimbabwe	Urban (Harare)	After 6 weeks: SBP: 161.1 (22.2) vs. 156.6 (19.1) vs. 154.9 (18.9) vs. 149.1 20.5) vs. 170.2 (20.0), DBP: 98 (11.4) vs. 96 (10.0) vs. 93.6 (11.9) vs. 90.5 (8.7) vs. 101.4 (11.1)
Stewart A, Noakes T, Eales C, Shepard K, Becker P, Veriava Y.	Stewart 2005	2005		RCT	Secondary prevention	All	Patients with hypertension//no exclusion criteria	24 weeks	**Education strategies:** *experimental group* (educational and home-based exercise programme + support of a healthcare practitioner and a family member, by way of a telephonic intervention) vs. *control group* (educational and home-based exercise programme only)	primary: BP change, secondary: adherence to the programme, knowledge about hypertension, exercise capacity, body weight, self-reported ability to control stress, adherence to medication and salt restriction, symptoms	r: 83 (41 vs. 42), a: 74 (38 vs. 36)	n.r. (74)	late middle aged	SBP: 146.4 (18.5), DBP: 93.5 (11.1), knowledge: 47.5% (14.5)	//31	South Africa	Urban (Johannesburg)	After 24 weeks: SBP: 142 (16) vs. 144 (20), DBP: 92 (12) vs. 91 (10), Change: SBP: -2 (18) vs. -5 (22), DBP: 0 (13) vs. -4 (11), knowledge: 72% (20) vs. 62 % (21), weight loss: 1 (4) vs. 0 (4)

Study	Study name	Year of publication	Other publications	Design	Prevention	Circle	Inclusion/exclusion criteria	Duration	Intervention	Outcome	amount/groups	male/female %	Age	Baseline values (pooled mean, pooled sd)	Weight /BMI	Country	Region	Results (pooled mean, pooled sd)
Steyn K, Lombard C, Gwebushe N, Fourie JM, Everett-Murphy K, Zwarenstein M, et al.	Steyn 2013	2013	PACTR2013 03000493351.	Cluster -RCT	Secondary prevention	All	public sector community health centers (CHC) in working-class residential areas with ≥25 patients with diabetes and ≥35 patients with hypertension, ≥15 years, a documented attendee at the particular CHC with at least four visits during the previous year for hypertension or diabetes, and having received treatment for these conditions at each visit.//participants unable to provide answers to a questionnaire	1 year (1999-2000)	**standardized treatment strategies:** multifaced intervention (structured record of national guidelines + visits for train the clinicians) vs. usual care (included the guidelines passively disseminated)	primary: Mean SBP and DBP, secondary: the proportion of patients in the hypertension group with controlled BP BP:<140/90 mmHg	r: 18 centres (9 vs. 9)/ Patients: 920 (461 vs. 459), a: 837 (429 vs. 408),	21%, 79%, 176, 661	60.3 (11.1)	SBP: 151.2 (26.7), DBP: 87.1 (12.4)	//31.5 (6.7)	South Africa	Urban (Cape Town)	After 1 year: SBP: 161 (28.9) vs. 158.2 (29.5), DBP: 88.1 (13) vs. 87.1 (12.6), uncontrolled BP: 76.9 vs. 74
Turky K, Elsahas N, Onuch R.	Turky 2013	2013		RCT	Secondary prevention	Postmenopausal Hypertension	sedentary, overweight or obese women, >= 1 year history of postmenopausal hypertension//any postmenopausal hormone therapy, previous history of hypertension, antihypertensive drugs, history of diabetes, any other pathology within the spectrum of metabolic syndrome, orthopedic nor neuromuscular disorders that could have interfered with the training program	2011, 8 weeks	**Physical activity:** treatment group (5-10 min warm up, moderate aerobic exercise training, 20 min. Treadmill 4km/h, 5-10 min cool down; 3x/week) vs. control group	Nitric oxide levels, BP	r: 30 (15 vs. 15), a: 25 (12 vs. 13)	0%, 100%, 0, 25	52.8 (2.4), 40-50	SBP: 151 (6.2), DBP: 94.5 (4.2), NO: 24 micromol/l (0.7)	85.9 (11)//3 4.4 (3.8)	Egypt	Urban (Cairo)	After 8 weeks: SBP: 124 (5.6) vs. 145 (6.7), DBP: 85 (5.4) vs. 95 (3.7), NO: 31.7 (0.7) vs. 26.4 (0.3), BMI: 32.8 (1.5) vs. 34.7 (1.8)
Vedanthan, R., Kamano, J. H., DeLong, A. K., Naanyu, V., Binanay, C. A., Bloomfield, G. S., Chrysanthopoulou, S. A., Finkelstein, E. A., Hogan, J. W., Horowitz, C. R., Inui, T. S., Menya, D., Orango, V., Velazquez, E. J., Were, M. C., Kimaiyo, S., Foster, V.	Vedunthan 2019	2019	NCT01844596	Cluster RCT	Secondary prevention	All	adults with elevated BP (SBP≥140 mmHg or DBP≥ 90 mmHg) during community-based BP-screening performed by trained research assistants,//acutely ill who required immediate medical attention at the time of testing, no informed consent, persons actively engaged in hypertension care	04/2014-08/2017. 1 year	**Adherence strategies:** smartphone intervention (tailored behavioral communication, using smartphone technology) vs. paper based intervention (tailored behavioral communication, using paper-based tools) vs. usual care (standard training)	primary: linkage to care, change in SBP	r: 24 cluster, 8 per arm, 1460 (469 vs. 500 vs. 491), a: 1106 (356 vs. 395 vs. 355)	42%, 58%, 611, 849	54.2 (16.4)	SBP: 159.4 (19.5), DBP: 89.7 (12)	n.r.	Kenia	Rural	after 1 year: SBP: 149.4 (20.8) vs. 150.2 (21.6) vs. 150.0 (22.9), change: -13.1 (20.5) vs. -8.4 (24.0) vs. -9.7 (25.1) DBP: 91.3 (12.7) vs. 91.0 (14.1) vs. 90.1 (13.7), change: 1.5 (12.7) vs. 0.4 (15.2) vs. 0.1 (14.7)
Venter CP, Joubert PH, Booyens J.	Venter 1988	1988		Cross over RCT	Secondary prevention	Mild to moderate	Black patients, DBP remained above 95 mmHg after placebo run in//obese, target organ damage, DBP >120 mmHg	4 weeks placebo run in, 12 weeks treatment, 4 weeks placebo washout, 12 weeks treatment	**Drugs:** Efamolmarine vs. sunflower seed and linseed oil capsules	SBP,	r: 25, a: 18 (11 vs. 7)	n.r., (18)	40-65	SBP: 157, DBP: 102	n.r.	South Africa	Urban (Medunsa)	After 12 weeks: SBP: 140 vs. 151, DBP: 90 vs. 91
Venter CP, Venter HL, Muntingh GL.	Venter 1991	1991		Cross over RCT	Secondary prevention	Mild to moderate	black, resting DBP between 95 and 115 mm Hg//cardiac failure, grade 2 or 3 heart block, obstructive airways disease, diabetes mellitus, peripheral vascular disease, severe obesity or pregnancy, and hypersensitivity to beta blockers	4 weeks placebo run in, 12 weeks treatment, 4 week placebo wash out, crossover	**Drugs:** Penbutolol 40 mg (80 mg) vs. Placebo	BP, HR	r: 50, a: 35	n.r., (35)	25-65	SBP: 164 (17), DBP: 103 (7), HR: 67 (10)	n.r.	South Africa	Urban (Medunsa)	After 12 weeks: SBP: 152 (16) vs. 155 (14), DBP: 96.5 (11) vs. 99 (7.5), HR: 62 (10) vs. 66 (9.5)
Wadhawan DN.	Wadhawan 1981	1981		RCT	Secondary prevention	Mild	DBP >95 to <110//cardiac, renal, endocrine, cerebral, fundal changes >grade 2, under antihypertensive treatment	2 weeks placebo run in, 24 weeks	**Drugs:** Furosemide 40 mg vs. HCT 50 mg	BP, HR	r: 40 (20 vs. 20), a: 21 (10 vs. 11)	70%, 30%, 15, 6	41.5	SBP: 162.5, DBP: 105.2, HR: 76.1, MAP: 124.4 (5.05)	n.r.	Zambia	Urban (Lusaka)	After 24 weeks: MAP: 112.5 (9.26) vs. 113.4 (11.06)
Wahab KW, Owolabi M, Akinyemi R, Jenkins C, Arulogun O, Akpa O, et al.	Wahab 2017	2017		RCT	Tertiary prevention		>=18 years with a diagnosis of stroke, confirmed by either computed tomography (CT) or magnetic resonance imaging (MRI) scans and with a modified Rankin Score<=2//cognitive impairment/dementia (Mini Mental State Examination (MMSE) score ≤ 24), severe global disability (modified Rankin Score ≥ 3) and any condition that would limit participation in follow up assessment	2 weeks	**standardized treatment strategies:** IG (education and skill-building, BP monitor given+taught how to handle, review later, phone calls) vs. CG (standard care)	successful execution of the protocol, subject retention, short-term BP effects.	r/a: 35 (17 vs. 18)	66%, 34%, 23, 12	58.11 (10.54)	SBP: 138.27 (24.23), DBP: 85.01 (12.43), MMA Score: 6.91 (1.42)	//26.72 (6.2)	Nigeria	Urban (Ibadan, Ilorin)	after 2 weeks: SBP: 137.5 (23.05) vs. 133.14 (18.24), DBP: 84.06 (9.67) vs. 84.17 (13.12), MMA Score: 7.32 (0.93) vs. 7.03 (1.36)

9.8 Curriculum vitae

1. WORK EXPERIENCE	
07/2017 - present	**Establishment in own practice** for general medicine as a group practice in Halle
07/2012 - 06/2017	**Employment as a general practitioner** in a group practice of general medicine in Halle
2. MEDICAL SPECIALIST TRAINING	
06/06/2012	**Medical specialist exam** for general medicine in front of the Saxony-Anhalt Medical Association
04/2010 – 04/2012	**Intern for general medicine** at general practices and surgical practice in Halle
12/2005 – 03/2010	**Intern for internal medicine** at Berufsgenossenschaftliche Kliniken Bergmannstrost, medical clinic
07/2005 – 09/2005	**Intern for internal medicine** at internistic group practice in Mölln
3. EDUCATION	
07/2017 – 11/2020	**Postgraduate studies** at the Institut of General Medicine, Faculty of Medicine at the Martin Luther University of Halle-Wittenberg, Director: Prof. Dr. med. Thomas Frese
2004	**Third medical state exam** at the Martin Luther University of Halle-Wittenberg, Germany and license to practice medicine
1997 - 2004	**Study of human medicine** at the Martin Luther University of Halle-Wittenberg, Germany
1997	**Abitur (A-Level)**
5. VOLUNTARY WORK	
2016 - 2019	**Worked with PAGEL,** Partnership for Chronic diseases health service teaching and research in Ethiopia, coordinations and supervisors: Dr. Adamu Addissie coordinator at SPH, Dr. Eva Kantelhardt, Dr. Susanne Unverzagt coordinator at MLU

9.9 Declaration on oath

I declare that the present work reports about original research and I confirm that the dissertation was written in accordance with the terms and conditions of good academic practice.
I declare under oath that I wrote this thesis entirely on my own, without using any other than the declared sources and references. All passages included from other works, whether verbatim or in content, have been identified as such. I declare that all information given is accurate and complete.

The thesis has not been used previously at this or any other university in order to achieve an academic degree. The content of the presented dissertation has not been used as a whole for another scientific work or publication so far.

I exclude every financial or other significant conflict of interest, which can be interpreted as influencing the results or interpretations of the results.

16/03/2020

9.10 Declaration of previous attempts at doctoral application

I declare that I have not completed or initiated a doctorate procedure at this or any other university.

16/03/2020

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