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Polypill and RiskOMeter to Prevent StrOke and CogniTive ImpairmEnt in Primary Health Care (PROMOTE) Randomized Clinical Trial: Rationale and Design

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Short Title: PROMOTE Trial: Rationale and Design

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ABSTRACT

Introduction: Stroke and dementia have common modifiable risk factors. Current prevention strategies primarily focus on high-risk populations, leaving a gap in addressing the broader population. We report the protocol for a randomized controlled trial (RCT) that aims to evaluate the feasibility, tolerability, and effectiveness of a polypill (valsartan 80mg, amlodipine 5mg, and rosuvastatin 10mg), with and without use of the Stroke Riskometer app, on systolic blood pressure (SBP) and other cardiovascular disease (CVD) risk factors at 9 months after randomization in a population of low to borderline CVD risk.

Methods: Prospective, pragmatic, multicentre, factorial, phase III, placebo-controlled, cluster RCT in low to moderate CVD risk (10-year risk <20%) individuals aged 50-75 years with no prior history of hypertension, diabetes mellitus, stroke, or other CVD, with a SBP of 121-139 mmHg and at least one lifestyle-related CVD risk factor. Primary Care Units in Porto Alegre, Brazil, were centrally randomized to either use of the Stroke Riskometer app or standard care for lifestyle modification. All eligible individuals underwent a 28-day open run-in phase using the active medication. Participants who tolerated and had high adherence were randomized to either polypill or placebo, using a minimization process according to age, sex, SBP, cholesterol, and education level. The dual primary outcomes were change in SBP and Life Simple 7 (LS7) score at 9 months post-randomization. A sample of 354 participants was estimated to provide 80% statistical power (two sided α=0.05, β =0.20) for 6 clusters with intra-cluster correlation of 0.01 to detect a clinically significant 2.5 mmHg (SD±8) difference in SBP change and 0.65 points (SD±1.61) difference in the LS7 score at 9 months post-randomization between the polypill/Stroke Riskometer group and placebo/usual care group, assuming 10% lost to follow-up. All analyses were conducted according to the intention-to-treat principle. Regression analysis models (ANCOVA) assessed the differences among the four groups concerning changes in SBP, cholesterol levels, cognitive function, and behavioral risk factors over time.

Conclusion: The findings will provide critical information to allow the development of primary stroke and CVD prevention strategies in low to borderline CVD risk adults.

Clinicaltrials.gov NCT05155137.

INTRODUCTION

Stroke and dementia rank as the second most common global causes of death and disability(1-3). About 90% of strokes(3-5) and 45% of dementia cases(3, 6, 7) are attributed to modifiable risk factors, with a substantial risk factors overlap(1, 3, 6, 7). Elevated blood pressure (BP), hypercholesterolemia, and unhealthy lifestyle are important risks for both diseases(1, 8), making them key targets for primary prevention. Elevated systolic blood pressure (SBP) is the most significant risk factor for stroke, accounting for nearly three-quarters of the impact of stroke and cardiovascular disease (CVD)(4, 8). Current strategies primarily focus on high-risk CVD populations, leaving a gap in addressing the broader population at risk,(9, 10) contributing to the increasing burden of stroke and dementia(1, 4, 5, 8, 11). However, the increased risk of CVD (including stroke) is continuous, down to at least 115/75 mmHg of BP and a total cholesterol level of 135 mg/dL(12, 13). As up to 80% of all strokes and other CVDs occur in people with low to borderline CVD risk(14-16), there is an urgent need for new, well-tolerated, and affordable preventive strategies for this majority of individuals(5). A 2.5 mmHg reduction in SBP is associated with a 10% reduction in stroke incidence on a population level(17, 18). There is strong evidence supporting the use of statin and antihypertensive medications across different levels of BP(19) and multifactorial lifestyle interventions in individuals with high CVD risk(20-22) and the use in people at intermediate CVD risk who do not yet have symptomatic CVD(23, 24). However, uncertainty remains about the benefits of such polypills for primary prevention in those without or with borderline hypertension or dyslipidaemia and low to moderate CVD risk (10-year risk of <20%)(25).

There is also strong evidence that polypills containing low doses of antihypertensives and statins are effective for primary stroke prevention in intermediate to high CVD risk individuals(24, 26, 27). Additionally, emerging research suggests that mass individual digital technologies(28) - such as the Stroke Riskometer app)(29, 30) - and health community workers (31, 32) are both cost-effective and medically effective in managing CVD and lifestyle risk factors and reducing the risk of stroke(33, 34). Primary health care provides a critical platform for implementing large-scale prevention strategies, especially in low- and middle-income countries. However, there is no evidence for the efficacy of polypill and the Stroke Riskometer app in individuals with low to borderline risk of CVD (including stroke).

In the PROMOTE trial, we hypothesized that a polypill (containing valsartan 80 mg, amlodipine 5 mg, and rosuvastatin 10 mg) and the Stroke Riskometer app could lower SBP by at least 2.5 mmHg (effect primarily of polypill) and increase the Life's Simple 7 (LS7)(35) score by 0.65 points (effect of primarily the Stroke Riskometer app) at 9-months in individuals aged 50 to 75 years with low to borderline CVD risk, SBP between 121-139 mmHg and at least one lifestyle risk factor.

METHODS

The PROMOTE trial Study Protocol followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for Clinical Trial Protocol.(36, 37)

Study design

The study was a prospective, phase III, factorial, pragmatic, multicentre, cluster randomized clinical trial (RCT) that includes a double-blinded, placebo-controlled RCT of polypill vs. a matching placebo and a single-blinded lifestyle modification RCT (implemented through the Stroke Riskometer app) vs. usual care in subjects at low to moderate risk of CVD (10-year risk <20%)(25).

The primary objective of this study was to determine whether a fixed dose of antihypertensive and statin medications (polypill), administered once daily, either alone or combined with lifestyle modification (implemented through the Stroke Riskometer app), could reduce SBP by 2.5 mmHg and increase the LS7 score by 0.65 points at 9-months in individuals aged 50 to 75 years with low to borderline CVD risk.

Study Population

The inclusion and exclusion criteria for the trial are detailed in Table 1. Participants with a Montreal Cognitive Assessment (MOCA)(38) score below 21 may be enrolled but will be excluded from the cognitive outcome assessment. The PROMOTE RCT began recruiting participants in December 2021 and finished the last follow-up assessment of 354 study participants at the end of 2024.

Randomization

Centralized randomization took place at two levels. Primary Health Care Units, which serve the population of Porto Alegre, South of Brazil, were randomized by a computer as clusters for lifestyle counselling into two arms: the Stroke Riskometer app arm (Riskometer), provided by community health workers or other trained health professionals, compared to the non-Stroke Riskometer arm (Usual Care). Eligible individuals who have provided

informed consent to participate in the trial were then randomized into either the Polypill arm (comprising valsartan 80mg, amlodipine 5mg, and rosuvastatin 10mg) or the matching Placebo arm, resulting in four intervention groups: (1) polypill and Stroke Riskometer app; (2) placebo polypill and Stroke Riskometer app; (3) polypill and usual care; and (4) placebo polypill and usual care. Randomization at the individual level followed a computerised minimisation process based on age (50-64 vs. 65-74), sex at birth, SBP (121-130 vs. 131-139), total cholesterol (<194 mg/dL vs. ≥194 mg/dL), and education level (≤5 years vs. >5 years). Figure 1 illustrates the study design.

Study Interventions

Stroke Riskometer App

The app calculates absolute and relative risk of stroke and promotes behaviour change by offering customized self-management strategies, including goal setting, and information on risk factors and stroke warnings signs (29). Push notifications were used to motivate users to achieve their goals, thus supporting the lifestyle changes and medication adherence. To generate personalized risk assessments, the app collects input on various factors, including age, sex, ethnicity, SBP, smoking status, dietary habits, physical activity, presence of heart disease, family history of stroke or heart disease, use of medications for hypertension or diabetes mellitus, Body Mass Index (BMI), psychosocial stress, history of traumatic brain injury, memory issues, and dementia. Using a validated algorithm(39, 40), the app calculates individual 5- and 10-year stroke risk.

Participants assigned to the Riskometer group received guidance on downloading and using the app, as well as information about their stroke risk and preventive strategies, which were reiterated during in-person assessments and follow-up phone calls. Participants in the usual care group (UCG) received a standardized summary of their risk factors based on the LS7 items. They were not actively informed about the Stroke Riskometer app. Any lifestyle modifications or prescribed medications given to study participants were recorded, along with their access to the app.

Polypill

The polypill under investigation consisted of a unique combination of valsartan 80mg, amlodipine 5mg, and rosuvastatin 10mg. It was specifically formulated and manufactured for this trial along with the matching placebo. All eligible participants, after signing the trial consent form, underwent an initial assessment and received a 4-week run-in open-label polypill trial. In cases of symptomatic hypotension or other adverse events (e.g., swelling of the hands or lower legs, headache etc.), the dose of amlodipine was adjusted from 5mg to 2.5mg, allowing the patient to continue active treatment for an additional two weeks. If study participants tolerated this adjusted dose well, they were included in the randomization, with the amlodipine dose maintained at 2.5 mg post-randomization. Those who demonstrated sufficient adherence to the regimen (≥80%) and were unlikely to experience unacceptable adverse events, such as symptomatic hypotension, hand or lower leg oedema, or muscle pain, were randomized into four groups: The polypill (polypill group – PPG) or a matching placebo (placebo group – PG) taken once daily for 9 months, with or without the Stroke Riskometer app. Baseline characteristics of participants who did not proceed to randomization were compared with those randomized to assess potential selection bias.

Study participants who required additional active treatments during the trial (antiplatelet, antihypertensive, or statin), were managed as below:

- If antiplatelet therapy was warranted, open-label 75-100mg aspirin or 75mg clopidogrel was introduced alongside the existing combination polypill.
- If active BP reduction was necessary, physicians considered, in order of preference, open-label diuretic (indapamide), calcium channel blocker (amlodipine), angiotensin receptor blocker (valsartan), then beta-blocker (e.g., bisoprolol), in either group without the need for unblinding. If other antihypertensive medications were indicated, they were provided as open-label treatment, and the combination pill was discontinued.
- If cholesterol-lowering was deemed necessary, open-label fibrate and/or open-label rosuvastatin calcium up to 10mg daily could be initiated and added to the existing combination pill without the need to distinguish between active and placebo. For higher doses or other statins, open-label treatment provided, and the combination pill was discontinued. Study participants who developed stroke or other CVD during the trial remained in the trial.

Baseline Measures

All participants underwent thorough evaluations, including assessment of demographic information, current medications, behavioural risk factors, systolic and diastolic blood pressure (measured using automated

oscillometric devices), atrial fibrillation screening, anthropometric measurements, cholesterol levels, glycated haemoglobin, creatinine, potassium, quality of life (measured through the Euro Quality of Life 5D-EQ5D)(41), cognitive status (assessed using MOCA)(38), and functional status (according to the modified Rankin scale, mRS)(42). Baseline cardiovascular risk stratification was completed using the LS7 score(35). The pattern of physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), and dietary patterns were evaluated using the Diet Quality Questionnaire (DQQ) adapted to align with the LS7 criteria. The cardiovascular and stroke risks were assessed using the ASCVD (Atherosclerotic Cardiovascular Disease)(43) calculator, the Stroke Riskometer,(44) and the HEARTS risk calculator(45).

Follow-up Measures

Blinded to randomization group assessments of the study participants who were assigned to either polypill or matching placebo was conducted in person at baseline, 6 and 9 months (primary outcomes), while telephone assessments occurred at 3 months and 12 months. Due to the nature of the Stroke Riskometer app intervention, study participants were not blinded to group randomization, but statisticians who analysed the data were blinded to the group assignment.

Outcome Measures

The dual primary outcomes included a 2.5 mmHg changes from the baseline in SBP and a 0.65-point in the LS7 score at 9 months. If either of the dual primary outcomes were achieved, the trial would be considered positive. The secondary outcomes are outlined in Table 2.

Statistical Analysis Plan and Sample Size Calculation

The sample size calculation was based on the evaluation of SBP after the run-in period involving the first 50 study participants. With an average SBP of 130 mmHg (standard deviation of 8 mmHg) following the run-in and anticipating a reduction of 2.5 mmHg due to polypill treatment, it was estimated that the study requires 162 individuals in each group to achieve 80% power with a significance level (alpha) of 0.05. Given that the trial is nested within the primary care clusters, even if the study participant do not continue to take the study intervention, it was considered possible to collect primary outcome data for the majority of the study participants and, therefore, we considered a 10% allowance for potential losses to follow-up(46) and the total sample size was adjusted to 354 study participants (177 in each group) for this study. Considering six clusters with an intra-cluster correlation of 0.01,(47-49) this sample size provided 80% power to detect a treatment difference at a two-sided 0.05 significance level, assuming a true difference of 0.65 points (SD = 1.61) in the LS7 score between the Stroke Riskometer and Usual Care treatments, with an expected 10% drop-out rate.

All analyses will be conducted according to the intention-to-treat principle. Regression analysis models (ANCOVA) will evaluate the differences among the four groups regarding changes in SBP, total blood cholesterol level, cognitive functioning and the behavioural components of the LS7 score at 3, 6, 9- and 12 months post-randomization. Mixed-effects linear models planned to use to assess the change in lifestyle and quality of life measures between each intervention and control group from baseline to 9 months post-randomization. The maintenance of intervention effects on the lifestyle factors at 12 months post-randomization planned to be evaluated using ANCOVA. Missing data will be addressed using multiple imputation techniques, and sensitivity analyses will assess the robustness of primary outcome findings.

Discussion

Effective primary prevention is crucial to mitigate the growing burden of stroke and CVD. Without significant improvements in primary prevention, projections estimate a 50% rise in stroke and CVD burden by 2050(50). This upward trend will place substantial pressure on healthcare systems, increasing the demand for acute care and rehabilitation services and straining societal resources.

Addressing known behavioural risks could result in up to 70% reduction in stroke burden.(1, 51-53) Emerging approaches, including polypills(54, 55), community health workers,(32, 56) and mobile technologies(57) have shown efficacy in reducing risk factors and enhancing prevention efforts(54). For testing management of lifestyle risk factors, we used the Stroke Riskometer app (Brazilian-Portuguese version) that can be downloaded and used for free on smartphones and tablets. The app is endorsed by the World Stroke Organization, World Heart Federation, World Federation of Neurology, European Stroke Organization and several national stroke organizations, including the Chinese Stroke Association, Australian Stroke Foundation, among others. Translated into 25 languages it uses the validated algorithm to calculate absolute and relative 5- to 10-year risk of stroke and evidence-based recommendations for tailored management of stroke and CVD risk factors(28, 29, 40, 57, 58).

Our study tested a polypill that contains amlodipine and valsartan, selected for their proven antihypertensive benefits and the fact that this combination has already been studied in a polypill placebo-controlled RCT for intermediate and high CVD risk individuals for primary CVD prevention with proven efficacy(59, 60). There is strong evidence supporting the safety and effectiveness of blood pressure-lowering medications and statins in reducing both stroke and cognitive decline, particularly in high-risk individuals(27, 59). By combining these agents in a single pill, our approach aims to simplify treatment regimens and enhance patient adherence in low to borderline CVD risk individuals, potentially improving outcomes in primary stroke/CVD prevention and cognitive health.

Community health workers, integral to Brazil's primary healthcare system, can effectively implement technology-based interventions, particularly in BP reduction, as demonstrated in China and India(32). Consequently, they are ideally positioned to implement or support primary stroke prevention programs in Brazil. Smartphone technologies, exemplified by the free Stroke Riskometer app, offer a promising paradigm for primary stroke prevention. Endorsed by international organizations, the app aligns with stroke prevention guidelines(61), utilizing tailored strategies and reminders for behavioural change(1, 29).

By addressing both the metabolic (elevated blood pressure and cholesterol level) and unhealthy lifestyle factors, the combined intervention, integrating the polypill with the Stroke Riskometer app, shows promise in preventing stroke/CVD and cognitive decline, with potential benefits extending to other major non-communicable disease risks, such as diabetes mellitus, cancer and impaired brain health, as each component works independently and additively. Previous studies demonstrated the feasibility and effectiveness of implementing polypills and lifestyle modifications in primary care services in low- and middle-income countries, reducing blood pressure and cholesterol(24) and decreasing cardiovascular events in high and moderate risk populations, without cardiovascular disease(27,64). The strategies can be managed by nurses and community health workers under the supervision of doctors, which can facilitate large-scale implementation(64). Integrating our new polypill and Stroke Riskometer, along with training for health professionals and community health workers within public primary health care services, enhances their scalability and real-world applicability for population-level prevention. The findings from this study could significantly impact public health policies and clinical practices, potentially resulting in more comprehensive and accessible primary preventive measures regardless of the level of CVD risk.

Summary and Conclusions

The findings of this phase III RCT represent a significant step forward in advancing stroke and CVD primary prevention. For the first time, this trial not only addresses critical research questions about preventative strategies for low to borderline CVD risk population but also plays a vital role in improving the structure of primary care services in Brazil and internationally.

Statements

Statement of Ethics

This study has been conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent before enrolling in the study. The study was approved by the Ethics Committee of Hospital Moinhos de Vento and the Primary Care Units (approval number 4.491.874). The trial is registered at clinicaltrials.gov under the identifier NCT05155137.

Conflict of Interest

VLF declares that the free Stroke Riskometer app is copyrighted and owned by Auckland University of Technology. He is the Editor in Chief of Neuroepidemiology. RDL reports research grants or contracts from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi-Aventis; funding for educational activities or lectures from Pfizer, Daiichi Sankyo, and Novo Nordisk; and funding for consulting from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Novo Nordisk. CSA reports grants from the National Health and Medical Research Council (NMHRC) of Australia, the Medical Research Foundation of the UK, and AstraZeneca; and advisory board fees from AstraZeneca. He is President-elect of the World Stroke Organization and Editor-in-Chief of Cerebrovascular Diseases. PMB is Stroke Association Professor of Stroke Medicine and an emeritus NIHR Senior Investigator. He reports personal honoraria outside the submitted work from CoMind and DiaMedica. GJH reports personal honoraria outside the submitted work from the American Heart Association (Associate Editor, Circulation) and Janssen Research and Development (Co-chair, Executive Committee, Librexia Stroke trial of milvexian for secondary stroke prevention). LAS reports speaker and consulting honoraria from Boehringer Ingelheim, Pfizer, AstraZeneca, Medtronic, and Simcere, as well as grants from Medtronic, Philips, and Gore. MF is managing partner of Inova Medical, which has provided services unrelated to the submitted work in the fields of clinical research and Health Technology Assessment (HTA) to the following companies within the past 24 months: Abbott, Adium, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, CSL Vifor, Daiichi Sankyo, Gilead Sciences, JCR Pharmaceuticals, Knight Therapeutics, Medison Pharma, Merck, MSD, Novartis, Pfizer, PTC Therapeutics, Recordati, Roche, Sanofi, and Ultragenyx. ERZ has served in the scientific advisory board, as a consultant or as a speaker of Nintx, Novo Nordisk, masima, Biogen and Magdalena Biosciences. He is also a co-founder and a minority shareholder at masima. MB is a Review Board Member of Neuroepidemiology. The others have no disclosures to declare related to this paper.

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Author Contributions

MB and VLF conceptualized the theme and created the initial project. VLF wrote the first draft of the Study Protocol. SM made the final version of the Study Protocol, secured funding and implemented the trial in Brazil, wrote the first draft of the paper, revised it and made the final edits of the manuscript. TLS and APP wrote the first draft of the article and participated in the execution of the project. BJT, FPS, JR, JE, MOM, DAP, FWQ, LVS, MRG, GPM, MC, JEB, AP, GBA, and CSP participated in the execution of the project. GJH reviewed serious adverse events. AZ, DS, and EZ designed the strategies to produce the polypill. AZ was responsible for the production and quality of the polypill. All others provided important insights into the study protocol. All authors reviewed and approved the article.

Data Availability Statement

The data that from this study will be available from the corresponding author upon reasonable request.

Figure Legend

Fig. 1 Study Design

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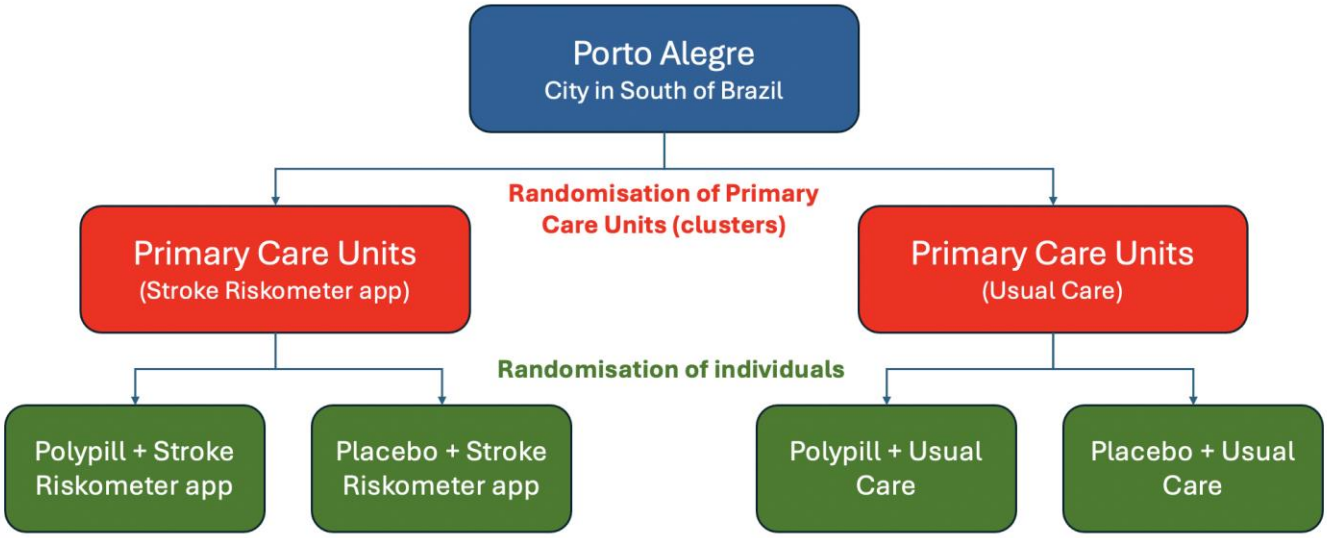

Table 1 - Inclusion and exclusion criteria

Inclusion	**Exclusion**
50-75 years old	Diagnosis of hypertension, hypercholesterolemia or diabetes or take other open label antihypertensives or statins
Systolic blood pressure (SBP) 121-139mmHg	Established vascular disease (e.g. previous myocardial infarction, angina, stroke, transient ischemic attack, peripheral vascular disease)
Own a smartphone or tablet device	Life-threatening conditions with a life-expectancy <5years
One or more of the lifestyle risk factors listed below: ● Smoking ● Overweight* ● Physical inactivity[&] ● Unhealthy diet[#]	Medically unstable, as judged by the treating physician
Informed consent signed to participate in the trial	Participation in another randomized clinical trial

*Body Mass Index >25kg/m^2

[&]World Health Organization (WHO) criteria for aerobic physical activity is < 150 minutes/week or < 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous-intensity activity. The short version of the International Physical Activity Questionnaire (IPAQ)(62) will assess physical activity levels.

#Low intake of fruits, vegetables, fish, and whole grains, and high intake of sodium and sugar-sweetened beverages(63). The Diet Quality Questionnaire (DQQ), adapted to align with the LS7 criteria, was used to assess the dietary patterns.

Table 2. Secondary outcomes

Cognitive functioning
2. Fatal and non-fatal cardiovascular (CVD) events (stroke, TIA and myocardial infarction)
3. Change in SBP/DBP
4. Change in HbA1c, LDL cholesterol, HDL cholesterol, triglycerides
5. Modification in individual LS7 score components
6. Change in quality of life Euro Quality of Life 5D-EQ5D)(41)
7. Proportion of participants with improved cardiovascular health according to the LS7 score (defined by an increase of 0.65 points)
8. Treatment adherence
9. Tolerability of the polypill (proportion of withdrawals from trial treatment caused by adverse event)
10. Any adverse events
11. User engagement in the App (measured through a self-reported questionnaire)