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A cardiovascular polypill for secondary stroke prevention in a tertiary centre in Ghana (SMAART): a phase 2 randomised clinical trial

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Summary

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Contributors

FSS and BO designed the study; FSS wrote the first draft of the manuscript, and BO supervised. JV and SBN performed data analysis; FSS and JV have directly accessed and verified the data reported in the manuscript. All authors reviewed and approved the final draft of the manuscript. All authors had full access to the data and had final responsibility for the decision to submit for publication.

For the Akan (Twi) translation of the abstract see **Online** for appendix 1

Declaration of interests

We declare no competing interests.

Background—A cardiovascular polypill containing generic drugs might facilitate sustained implementation of and adherence to evidence-based treatments, especially in resource-limited settings. However, the impact of a cardiovascular polypill in mitigating atherosclerotic risk among stroke survivors has not been assessed. We aimed to compare a polypill regimen with usual care on carotid intima-media thickness (CIMT) regression after ischaemic stroke.

Methods—In SMAART, a phase 2 parallel, open-label, assessor-masked, randomised clinical trial, we randomly allocated individuals (aged ≥18 years) who had an ischaemic stroke within the previous 2 months, using a computer-generated randomisation sequence (1:1), to either a polypill or usual care group at a tertiary centre in Ghana. The polypill regimen was a fixed-dose pill containing 5 mg ramipril, 50 mg atenolol, 12·5 mg hydrochlorothiazide, 20 mg simvastatin, and 100 mg aspirin administered as two capsules once per day for 12 months. Usual care was tailored guideline-recommended secondary prevention medications. The primary outcome was the change in CIMT over 12 months with adjustment for baseline values, compared using ANCOVA in all participants with complete data at month 12. Safety was analysed in all randomly assigned participants. This trial is registered at ClinicalTrials.gov, NCT03329599, and is completed.

Findings—Between Feb 12, 2019, and Dec 4, 2020, we randomly assigned 148 participants (74 to the usual care group and 74 to the polypill group), 74 (50%) of whom were male and 74 (50%) female. CIMT was assessed in 62 (84%) of 74 participants in the usual care group and 59 (80%) of 74 participants in the polypill group; the main reason for loss to follow-up was participants not completing the study. The mean CIMT change at month 12 was −0·092 mm (95% CI −0·130 to −0·051) in the usual care group versus −0·017 mm (−0·067 to 0·034) in the polypill group, with an adjusted mean difference of 0·049 (−0·008 to 0·109; p=0·11). Serious adverse events occurred among two (3%) participants in the usual care group, and eight (11%) participants in the polypill group (p=0·049).

Interpretation—The polypill regimen resulted in similar regression in subclinical atherosclerosis and many secondary and tertiary outcome measures as the tailored drug regimen, but with more serious adverse events. Larger, longer-term, event-based studies, including patients with stroke in primary care settings, are warranted.

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Introduction

Secondary prevention guidelines recommend that antihypertensive, statin, and anti-platelet therapy should be initiated promptly after a stroke, and adhered to in a persistent method to achieve optimal vascular risk reduction.[1–4] People who have survived a stroke are confronted with polypharmacy and complex treatment regimens, which engender low adherence to therapy aimed at reducing adverse cardiovascular events.[5] Furthermore, the affordability of lifelong secondary prevention therapies is a daunting proposition in low-resource settings.[6] Therefore, identifying cost-effective interventions for vascular risk reduction is an urgent global health priority.

Fixed-dose combination pills, also known as polypills, containing aspirin, a statin, and either one or multiple blood pressure lowering medications could improve medication adherence and consequently reduce vascular risk as a cost-effective intervention among patients at

high vascular risk.[7] Among individuals at intermediate to high vascular risk, efficacy of the polypill was shown for primary prevention of major adverse vascular events in three major clinical trials: Heart Outcomes Prevention Evaluation-3 (HOPE-3),[8] PolyIRAN,[9] and The International Polypill Study (TIPS-3).[10] However, published data on the effect of polypills for secondary prevention after stroke are scarce. Although the PolyIRAN study included 11% of participants with previous vascular disease, it could not provide evidence of effect of the polypill for secondary stroke prevention, due to its exclusion of participants with a history of stroke.[9] The only other published polypill trial for secondary prevention, the Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) trial, focused on people who had recently survived myocardial infarction.[11]

To our knowledge, no previous secondary prevention polypill trial has being conducted in sub-Saharan Africa, a region with an unprecedented rise in stroke burden. The stroke profile across sub-Saharan Africa is characterised by a younger age of onset, higher case fatality rates, and more severe disability among people who have had a stroke compared with those in high-income countries.[12–14] The polypill has been posited to potentially be of most benefit in low-income settings and under-resourced communities in high-income countries due to its cost-effectiveness.[15] In this phase 2, randomised, controlled, single tertiary centre trial we assessed whether a polypill containing fixed doses of three antihypertensives, a statin, and antiplatelet therapy taken once per day orally would result in carotid intimal thickness regression compared with standard of care, consisting of separate individual secondary preventive medications, among people in Ghana after first-time ischaemic stroke.

Methods

Study design and participants

The Stroke Minimization through Additive Anti-atherosclerotic Agents in Routine Treatment (SMAART) study is a phase 2 parallel, open-label, assessor-masked, randomised clinical trial. The protocol for the study has been published previously,[16] and a summary has been provided in appendix 2 (pp 2–9). Institutional approvals for the study were obtained from the Committee of Human Research Publication and Ethics in Kumasi, Ghana, and the Northern California Institute of Research and Education in San Francisco, CA, USA. SMAART was conducted at the Department of Medicine of the Komfo Anokye Teaching Hospital (KATH), a tertiary medical centre situated in the middle belt of Ghana. Kumasi is a metropolitan city with a population of 4 million people and the neurology unit of KATH admits approximately 600 people with stroke annually.

Eligible participants were 18 years or older, with a recent CT-scan-confirmed ischaemic stroke that occurred less than 2 months before study enrolment, and at least one of the following additional conditions: documented diabetes or previous treatment with an oral hypoglycaemic or insulin; documented hypertension (>140/90 mm Hg) or previous treatment with antihypertensive medications; or mild to moderate renal dysfunction (estimated glomerular filtration rate [eGFR] 30–60 mL/min per 1·73 m^2). Ischaemic stroke types eligible for inclusion were small vessel occlusive disease, atherosclerotic large vessel disease, and ischaemic stroke with undetermined cause.

Exclusion criteria were the inability to sign informed consent; contraindications to any of the components of the polypill; intracerebral haemorrhagic stroke; cardioembolic ischaemic stroke; severe cognitive impairment, dementia, or severe physical or mental global disability limiting the capacity of self-care; severe congestive cardiac failure (New York Heart Association classifications III–IV); severe renal disease (eGFR <30 mL/min per 1·73 m^2), renal dialysis, awaiting a renal transplant, or having received a renal transplant; cancer diagnosis or treatment in previous 2 years; need for oral anticoagulation at the time of random allocation or planned in future months; clinically significant arrhythmias (including unresolved ventricular arrhythmias or atrial fibrillation); people who were breastfeeding or pregnant; and not agreeing to the filing, forwarding, and use of their pseudonymised data. Patients self-reported their sex as male or female.

Randomisation and masking

The potential study participants provided written informed consent before screening, and those meeting eligibility criteria were invited to the research office for enrolment. Eligible participants were randomly allocated to either the polypill group or active control comparator group in a 1:1 ratio using a computer-generated randomisation sequence. Each sequence generated was kept concealed in an opaque envelope and opened by the Research Coordinator in the presence of the consenting eligible participant at enrolment. Neither participants nor investigators were masked to group assignment in this open-label trial. Measurements of the primary outcome measure were performed by two trained medical sonographers who were masked to participant study group allocation. A masked nurse and doctor pair who were not part of the study investigator team assessed secondary and tertiary outcome measures.

Procedures

Patients allocated to the experimental group were provided with two Polycap pills (Cadila Pharmaceuticals, Ahmedabad, India), taken orally once a day for 12 months. Each capsule of Polycap contained 100 mg of aspirin, 20 mg of simvastatin, 12·5 mg hydrochlorothiazide, 5 mg of ramipril, and 50 mg of atenolol. Patients assigned to the polypill had their antihypertensive agents, lipid modifiers, and antithrombotic agents withdrawn and replaced with the polypill if they were already receiving such treatments before enrolment.

Patients allocated to the control group received standard-of-care therapies for secondary stroke prevention, with drugs and doses left to the discretion of the treating doctor. Routine secondary prevention medications available in Ghana include antithrombotics (aspirin or clopidogrel), statins (atorvastatin or rosuvastatin), and antihypertensive classes (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, and centrally acting agents). Of four study doctors, who were either senior registrars or junior doctors in neurology or general medicine, two took care of participants in the polypill group and two took care of participants in the usual care group to avoid contamination.

When available, stroke subtype information was collected to classify ischaemic stroke using the TOAST classification[17] into large-artery, lacunar, and unclassified ischaemic strokes.

Stroke severity and functional status at enrolment were assessed using the modified National Institutes of Health Stroke Scale[18] and Modified Rankin score,[19] followed by an assessment of vascular risk factors from history and physical examination: hypertension, diabetes, dyslipidaemia, cigarette smoking, and alcohol use. Blood samples for baseline assessments of renal and liver function, lipid profile, and glycated haemoglobin were collected and contraindications for study medications assessed. Study participants were followed up for 12 months with scheduled visits in KATH at months 1, 3, 6, 9, and 12 for clinical assessments and primary, secondary, and tertiary study outcome evaluations. Adverse events were assessed via both self-reports or reports by relatives, for any clinical event on a continuous basis during follow-up, or assessed as abnormalities in monitored laboratory parameters, such as liver and kidney function tests. Study doctors assessed participants for adverse events and graded these as mild, moderate, severe, or serious based on the common terminology criteria for adverse events, and recorded these into the case record forms. Serious adverse events were reported to the Ghana Foods and Drugs Authority and institutional review board within 48 h of the study team becoming aware.

Outcomes

The primary outcome measure was change in the common carotid intima-media thickness (CIMT) over 12 months from baseline compared between the two groups. CIMT was measured using a Samsung SonoAce R7 Ultrasound machine (Gangwon-do, South Korea) at 1 cm portions of the distal left and right common carotid artery far walls with a linear transducer (transducer frequency of 7·5 MHz) with axial resolution of 0·10 mm, and calculated automatically over three cardiac cycles following the Mannheim consensus.[20] Average thickness of the left and right carotid arteries was used as the outcome measure. Each of the two sonographers obtained measurements independently of one another, and the readings were averaged. A post-hoc intracluster correlation coefficient for common CIMT measurements by the two sonographers of 0·51 for the left carotid artery and 0·53 for the right carotid artery, were deemed fair agreement (excellent agreement was deemed as 0·81–1·00).

Secondary outcome measures included medication adherence, assessed via the self-reported Morisky-Green Adherence Scale score and the Hill Bone medication adherence scale. Medication possession ratio by pill counts, although proposed, could not be performed consistently in the usual care group, so was not reported. Safety and tolerability measures, such as changes in eGFR over 12 months, transaminitis on liver function tests, side-effects, and discontinuation of study medications and regimen adjustments, including the need to add on other secondary prevention interventions during follow-up, were also monitored. Other secondary outcomes were health-related quality-of-life changes measured by the EQ-5D questionnaire,[21] patient satisfaction measured by the Treatment Satisfaction Questionnaire for Medication,[22] global cognitive scores over 12 months measured by the Montreal Cognitive Assessment score,[23] and depression risk measured by the Hamilton Rating Scale for Depression.[24] Prespecified tertiary or exploratory outcomes included assessment of changes in systolic blood pressure, diastolic blood pressure, and LDL-cholesterol at 12 months from baseline. In addition, all-cause mortality, major adverse cardiovascular events, and rehospitalisation for any cardiovascular-related events were also

assessed as prespecified outcomes. A full list of outcome measures is provided in appendix 2 (pp 5–6) and in the published protocol;[16] a limited summary of outcomes is listed on ClinicalTrials.gov.

Statistical analysis

To generate the sample size, we estimated the rate of change in common CIMT among people on statin therapy to be approximately 0·085 mm per year with a standard deviation of 0·035.[25] On the assumption that the polypill would slow CIMT progression, at an annualised rate of 0·064 mm per year, with a two-sided α of 0·05 and 90% power, we would require 118 patients (148 patients with a 20% drop-out rate) for our primary outcome measure. We sought, and were granted, ethical approval to amend our initial published sample size of 120 to 148.

Primary, secondary, and tertiary efficacy outcome measures were performed according to a modified intention-to-treat (ITT) principle, whereby participants with missing data at month 12 for datapoints collected at both baseline and the end of the study were excluded. All participants who were randomly assigned were assessed for safety outcomes. A p value of less than 0·05 was considered to indicate statistical significance. Mean differences (with 95% CI) in CIMT changes, systolic and diastolic blood pressures, adherence scores, treatment satisfaction scores, quality of life, cognitive measures, and functional status at 12 months from baseline by study group were compared using an ANCOVA with adjustment for baseline values. The numbers of safety outcomes were summarised according to the treatment group, and compared with the use of χ^2 tests or Fisher exact tests. Sensitivity analyses, with imputation for missing data, were conducted using multiple imputations by chain equations in all randomly assigned participants. All analyses were performed with the use of Stata software (version 16.0) and the R statistical software (version 4.3.0). A Data Safety and Monitoring Board made up of three members met twice a year to review the safety, ethics, and outcomes of the study. The trial was registered at ClinicalTrials.gov, NCT03329599.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 12, 2019, and Dec 4, 2020, we assessed 247 potential participants for eligibility. 99 people were ineligible due to not meeting the eligibility criteria (n=55) or because they declined to participate (n=44). Of the 148 who were eligible, 74 were randomly allocated to either the usual care group or polypill group. In the usual care group 64 (86%) of 74 patients completed the study and were in the modified ITT population and analysed for the primary outcome and the secondary and tertiary outcomes, versus 59 (80%) of 74 patients in the polypill group. Reasons for loss to follow up are shown in the figure. The study was conducted between Feb 12, 2019, and Dec 7, 2021.

Baseline characteristics are shown in table 1. The mean age was 58·5 years (SD 10·7) for the polypill group and 58·1 years (13·3) in the usual care group.

Before random allocation, the proportion of participants on antiplatelet therapy was 62 (84%) of 74 in the polypill group and 66 (89%) of 74 in the usual care group, and the number of participants on high intensity atorvastatin was 55 (74%) and 63 (85%), respectively. The most frequently prescribed antihypertensive drug class was calcium channel blockers, followed by angiotensin receptor blockers (table 1). After random allocation, all prescribed secondary prevention medications were stopped and replaced with the polypill for participants assigned to the polypill group, but continued for those assigned to the usual care group.

The mean change in CIMT at month 12 from baseline was −0·017 mm (95% CI −0·067 to 0·034) in the polypill group versus −0·092 mm (−0·130 to −0·051) in the usual care group, with an adjusted mean difference between the two groups of 0·049 mm (−0·008 to 0·109; p=0·11; table 2).

No between-group differences were observed in secondary outcome measures, namely quality of life, medication adherence, treatment satisfaction, global cognitive performance, functional status, and depression scores at month 12 (table 2). Compared with baseline values, at month 12 systolic blood pressure reduced by 15·7 mm Hg (95% CI −23·1 to −8·3) in the polypill group and 17·6 mm Hg (−24·8 to −10·5) in the usual care group, and diastolic blood pressure reduced by 7·9 mm Hg (−12·2 to −3·5) and 3·3 mm Hg (−7·7 to 1·0) in each group, respectively. At month 12, 29 (49%) of 59 in the polypill group versus 27 (42%) of 64 in the usual care group had blood pressure less than 140/90 mm Hg (p=0·44). Change in LDL-cholesterol was −7·87 mg/dL (−19·98 to 4·24) in the polypill group versus 3·43 mg/dL (−8·77 to 15·63) in the usual care group (p=0·088), with 41 (72%) of 57 on an LDL-cholesterol target of less than 100 mg/dL at month 12 in the polypill group versus 37 (59%) of 63 in the usual care group (p=0·82). Appendix 2 (p 12) shows comparisons between baseline and month 12 outcome measurements by study group.

In table 3, the primary and secondary outcome measures were similar compared with the analysis without imputation for missing data. However, the mean reduction in diastolic blood pressure by month 12 was significantly greater in the polypill group (−12·04 mm Hg [95% CI −16·22 to −7·86]) versus the usual care group (−5·65 mm Hg [−9·91 to −1·39]; p=0·020). The adjusted mean difference in LDL-cholesterol between groups was −12·99 mg/dL (−27·30 to 1·32; p=0·075).

Serious adverse events occurred in eight (11%) of 74 participants on the polypill versus two (3%) of 74 in the usual care group (p=0·049). All-cause deaths occurred in five (7%) participants in the polypill group versus two (3%) in the usual care group, post-stroke seizures occurred in two (3%) versus none, and hospitalisation in one (1%) versus none, respectively (table 4). Four of the five deaths in the polypill group and both deaths in the usual care group occurred among participants who also had type 2 diabetes. Specific causes of death by study group include two cardiovascular deaths in the polypill group versus one

cardiovascular death in the usual care group; three sepsis deaths occurred in the polypill group but none in the usual care group (appendix 2 p 13).

Treatment discontinuations were all due to side-effects, notably ACE-inhibitor-associated cough in three (4%) of 74 participants in the polypill group. No participants in the usual care group discontinued treatment due to adverse events. Cardiovascular medication regimens were modified infrequently during follow-up of the trial, occurring in five (7%) of 74 participants in the polypill group versus seven (10%) of 74 in the usual care group (p=0·55). In the polypill group, treatment regimen adjustments involved the addition of antihypertensive drug classes among participants whose blood pressure was not controlled during follow-up. Rates of bradycardia, severely elevated blood pressure (>180/110 mmHg), and hypotension (<90/60 mm Hg) by study group are shown in appendix 2 (p 14). Appendix 2 (p 15) shows changes in liver enzymes and eGFRs. Clinical assessment data by scheduled follow-up month are shown in appendix 2 (p 14).

Discussion

In this phase 2 clinical trial, secondary prevention after stroke using standard-of-care therapy of individual antihypertensive, statin, and antithrombotic medications selected at the discretion of doctors resulted in no difference in regression of CIMT over 12 months than a fixed-dose polypill. Although the absolute mean difference in CIMT regression over 12 months of −0·080 mm significantly favoured the usual care group compared with the polypill group, this difference was not significant when baseline CIMT values were accounted for using ANCOVA, and an even smaller difference was found between groups after imputation for missing data in our sensitivity analysis. For randomised controlled trials assessing quantitative treatment effects assessed before and after treatment, the use of ANCOVA is deemed a more rigorous approach than Student's *t* tests in terms of bias, precision, and statistical power.

There were similar reductions in blood pressure and LDL-cholesterol concentrations in both groups at 12 months, both of which are key pathophysiological determinants of CIMT regression. It is plausible that differences in statins and antihypertensive drug classes used in the polypill group relative to the usual care group could have accounted for the adjusted mean difference of −0·049 mm per year of regression in CIMT, which, although not significant, favoured the usual care group. Although the usual care group was prescribed high intensity atorvastatin at doses ranging between 40 mg and 80 mg at stroke onset, which continued during the trial, the polypill group were dosed with simvastatin at 40 mg (equivalent to 20 mg of atorvastatin). A previous study among individuals with familial hypercholesterolaemia treated with 80 mg of atorvastatin compared with 40 mg of simvastatin reported a −0·067 mm per year regression in CIMT in favour of atorvastatin.[26] Again, although the polypill group homogeneously received a combination of three antihypertensive drug classes (ACE inhibitor, β blocker, and a diuretic), drug regimens for the usual care group were quite heterogeneous, and contained predominantly angiotensin receptor blockers, calcium channel blockers, and a diuretic as the most common combination. Meta-analytical data suggest that, among antihypertensive drug classes, calcium channel blockers reduce CIMT more potently than other drug classes,

independently of blood pressure lowering.[27] Despite the compositional differences in the drug regimens between the two groups, regression of CIMT—a validated surrogate marker of cardiovascular events—was similar among people who recently had a stroke in the present study.

Treatment with the polypill was tolerated well, with an overall withdrawal rate of 4% on account of persistent cough. It is important to emphasise that, in our study design, participants assigned to the polypill were switched from their existing secondary prevention medication directly to the polypill. We did not incorporate a run-in period to assess tolerability and probable adherence of the polypill before randomisation, unlike previous primary prevention polypill trials. The TIPS-3 study[10] had an active run-in period of 1 month, in which 715 (9·5%) of 7534 participants were not randomly allocated due to side-effects, and 560 (7·4%) of 7534 were excluded as they did not reach 80% adherence. It is noteworthy that although asymptomatic bradycardia was more frequently documented in the polypill group, no treatment withdrawals were indicated on these accounts. Treatment satisfaction ratings were similar between the two groups. Serious adverse events were more frequent in the polypill group than the usual care group. However, individual frequencies of serious adverse events (deaths, hospitalisations, and seizures) were not significantly different between the two groups (table 4). Although adherence to the polypill has been hypothesised to be its main advantage, we did not observe superior self-reported adherence in the polypill group compared with usual care. Furthermore, no between-group differences were discovered in other exploratory secondary outcomes, including quality of life, functional status, depression scores, and cognitive performance scores over 12 months. Nonetheless, within-group comparisons from baseline to month 12 showed salutary effects in these secondary outcome measures in each study group (appendix 2 p 12).

Regarding blood pressure control, participants in the polypill group had a mean systolic blood pressure reduction of 16 mm Hg compared with 18 mm Hg in the usual care group, and a diastolic blood pressure reduction of 8 mm Hg versus 3 mm Hg in the usual care group. In our sensitivity analysis with imputation for missing data in the ITT dataset, diastolic blood pressure reduced significantly in the polypill group by −12 mm Hg versus −6 mm Hg in the usual care group (p=0·020). Despite these reductions, only 49% of participants in the polypill group versus 42% of participants in the usual care group achieved blood pressure targets of less than 140/90 mm Hg at month 12. For a clinical trial on secondary stroke prevention, this lower-than-expected control of blood pressure is concerning. The most plausible proximate cause for the poor blood pressure control is clinical inertia, whereby trial clinicians did not intensify therapy appropriately when blood pressure goals were not reached. Among participants in the polypill group, only 7% had additional classes of antihypertensive medications added during follow-up, compared with 10% in the usual care group. For participants on the polypill, doctors might have been reluctant to consider additional drug classes during follow-up due a perception that the polypill should be taken as a single pill for secondary prevention of cardiovascular diseases. However, for those in the usual care group, clinical inertia might have been due to concerns with increasing the number of pills patients would take at a single time, from treatment intensification, blood pressure measurements that were close to the target, and a focus on other more urgent needs of patients who have had a stroke, such as rehabilitation and a host

of other post-stroke complications. Another possible explanation could be the high burden of treatment-resistant or refractory hypertension among people who have had a stroke, resulting in difficulties in controlling blood pressure in this population.

An LDL-cholesterol target of less than 100 mg/dL was achieved by 72% of participants in the polypill group versus 59% in the usual care group. In the sensitivity analysis, the polypill group had an 18·39 mg/dL reduction in LDL-cholesterol compared with a 4·65 mg/dL reduction in the usual care group, a difference of nearly −12·99 mg/dL; p=0·075. It is notable that the numerically better (although non-significant) reduction in LDL-cholesterol was achieved with a polypill containing simvastatin, a moderate intensity statin, compared with the usual care group, in which most participants were on atorvastatin or rosuvastatin. It is likely that differences in adherence and quality of statins prescribed in the usual care group could account partly for this observation. The polypill was taken once daily in the morning, whereas the usual care participants had multiple individual medications that they took throughout the day plus a nightly dose of atorvastatin or rosuvastatin (more likely to be missed than medications taken during the daytime). A pill-count analysis for medication adherence instead of self-reported adherence might help to elucidate the underlying determinants of LDL-cholesterol outcomes in future planned studies. Our analyses of key vascular risk factor targets, although exploratory in nature, do seem to suggest that the polypill has a similar effect to usual care on blood pressure and LDL-cholesterol control for secondary stroke prevention. In the SECURE trial,[11] the only published secondary polypill trial among people who had a myocardial infarction, blood pressure and LDL-cholesterol control were similar between the polypill and usual care groups at 24 months, akin to the findings in our present study. Deaths reported in the present study were predominantly among participants with diabetes, a vascular risk group at heightened risk of mortality.[28] Cardiovascular deaths occurred infrequently, with two (3%) events in the polypill group versus one (1%) event in the usual care group in the ITT analysis.

This study was conducted in a single tertiary medical centre, limiting its generalisability. Usual care was provided by physician specialists who were familiar with stroke guidelines for secondary prevention. Future study designs should consider inclusion of primary and secondary levels of health-care delivery in resource-limited settings to compare the clinical utility and performance of polypills in these settings. For context, a previous study found that up to 75% of people who had a stroke received post-discharge stroke care in primary and secondary cadres of health-care delivery in Ghana.[29] Up to 50% of the study population had ischaemic stroke of an undetermined cause, due to lack of diagnostic investigation such as CT or magnetic resonance angiography, and Holter monitoring to detect intracranial atherosclerotic disease and paroxysmal arrhythmias. Although having a cardioembolic stroke was an explicit exclusion criterion because of the need for therapy with anticoagulant, the challenge with diagnostic evaluation means that there is a possibility that a proportion of participants with undetermined ischaemic stroke might have had a cardioembolic stroke. We also acknowledge that the inter-rater agreement between the two independent CIMT readings per participant by the sonographers using a post-hoc intracluster correlation coefficient was fair.

A study completion rate of 80% (59 of 74) in the polypill group versus 86% (64 of 74) in the usual care group over 12 months for a stroke trial conducted during the COVID-19 pandemic is encouraging, and supports the feasibility of conducting similar clinical trials in a resource-limited setting. To our knowledge, this is the first published trial assessing the effect of the polypill for secondary stroke prevention in a population of people who had already had a stroke. Another registered ongoing trial, the PROPS study on the preventive role of a fixed-dose combination pill in patients with stroke in the UK (ISRCTN58452386), is yet to publish their full results from a high-income country context.

Future studies should consider a longer follow-up to assess whether clinically relevant outcomes, such as major adverse cardiovascular events, occur differentially in polypill groups compared with usual care groups. It might be worthwhile considering polypill preparations with high intensity statins, and different formulations of the polypill with flexibility to allow for adjustments. For example, the CNIC (Spanish Centre for Cardiovascular Research) polypill used in the SECURE trial[11] had two dose formats for atorvastatin (20 mg and 40 mg) and three doses of ramipril (2·5 mg, 5 mg, or 10 mg) plus 100 mg of aspirin, giving a total of six versions of the polypill for enhanced flexibility and ease of dose adjustment. For antihypertensive combinations in future polypill formulations, replacing ACE inhibitors, of which cough is a side-effect, with angiotensin receptor blockers and atenolol with longer-acting calcium channel blockers might further improve the tolerability and efficacy of the polypill for a much larger population of patients for secondary prevention purposes. Understandably, such modifications of the composition of the polypill would require further bioequivalence studies and regulatory approvals before clinical testing for use. Given the heterogeneity of pathophysiological mechanisms for ischaemic stroke, future trials should be powered to assess treatment effects by stroke subtypes. Finally, robust implementation of outcome measures must be performed in future polypill trials to understand the barriers and facilitators associated with the uptake of this intervention in resource-limited settings across the globe, as well as underserved populations in high-income countries. It is conceivable that the polypill could be positioned as a viable and cost-effective treatment strategy for people who have had a stroke, a population who are often burdened by complex treatment regimens and polypharmacy.

In conclusion, there was similar regression of CIMT over 12 months among people who had recently had a stroke assigned to either the polypill or usual care group. Furthermore, no significant differences in key cardiovascular risk factor outcomes, such as blood pressure control, LDL-cholesterol targets, adherence, or individual safety endpoints were observed. A phase 3 clinical trial with a non-inferiority design and longer follow-up is warranted to assess the effect of a polypill among patients with ischaemic stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data sharing

The de-identified participant data, including a data dictionary that underlies the results reported in this Article (texts, tables, figures, and appendix 2) and the study protocol, statistical analysis plan, informed consent, and case record form will be shared for meta-analysis and observational study analysis with anyone who wishes to access the data for further research in this field after signing an agreement. To access the data, proposals should list the purpose of the study and analysis and be directed to: stephensarfo78@gmail.com.

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Research in context

Evidence before this study

We performed a literature search of articles published between Jan 1, 1990, and Jan 1, 2023, on clinical trials assessing effect of cardiovascular polypills for secondary prevention among patients with established cardiovascular diseases including stroke. We searched PubMed for articles in English using the terms “secondary prevention”, “cardiovascular polypill”, “stroke survivors”, and “atherosclerotic risk reduction”. We did not identify any published polypill-based clinical trial dedicated to people who had survived a stroke.

Added value of this study

In this phase 2 randomised controlled clinical trial, conducted in a tertiary medical centre in Ghana, we assigned 148 patients with ischaemic stroke within the previous 2 months to either a polypill-based strategy or to usual care. To our knowledge, this study shows for the first time that the polypill is similar to standard care for achieving regression in carotid intimal media thickness, a validated marker of atherosclerotic event risk among people who have recently had a stroke.

Implications of all the available evidence

Given the heterogeneity of mechanisms leading to stroke occurrence and the requirement for a tailored approach to secondary prevention, future polypill trials in this patient population should consider a range of formulations of the polypill that allows for greater flexibility in dosing to accommodate a variety of dosing requirements for this patient group. Implementation outcomes are urgently needed to understand the barriers and facilitators to the diffusion and uptake of the polypill across diverse health-care settings, especially in resource-limited settings in Africa.

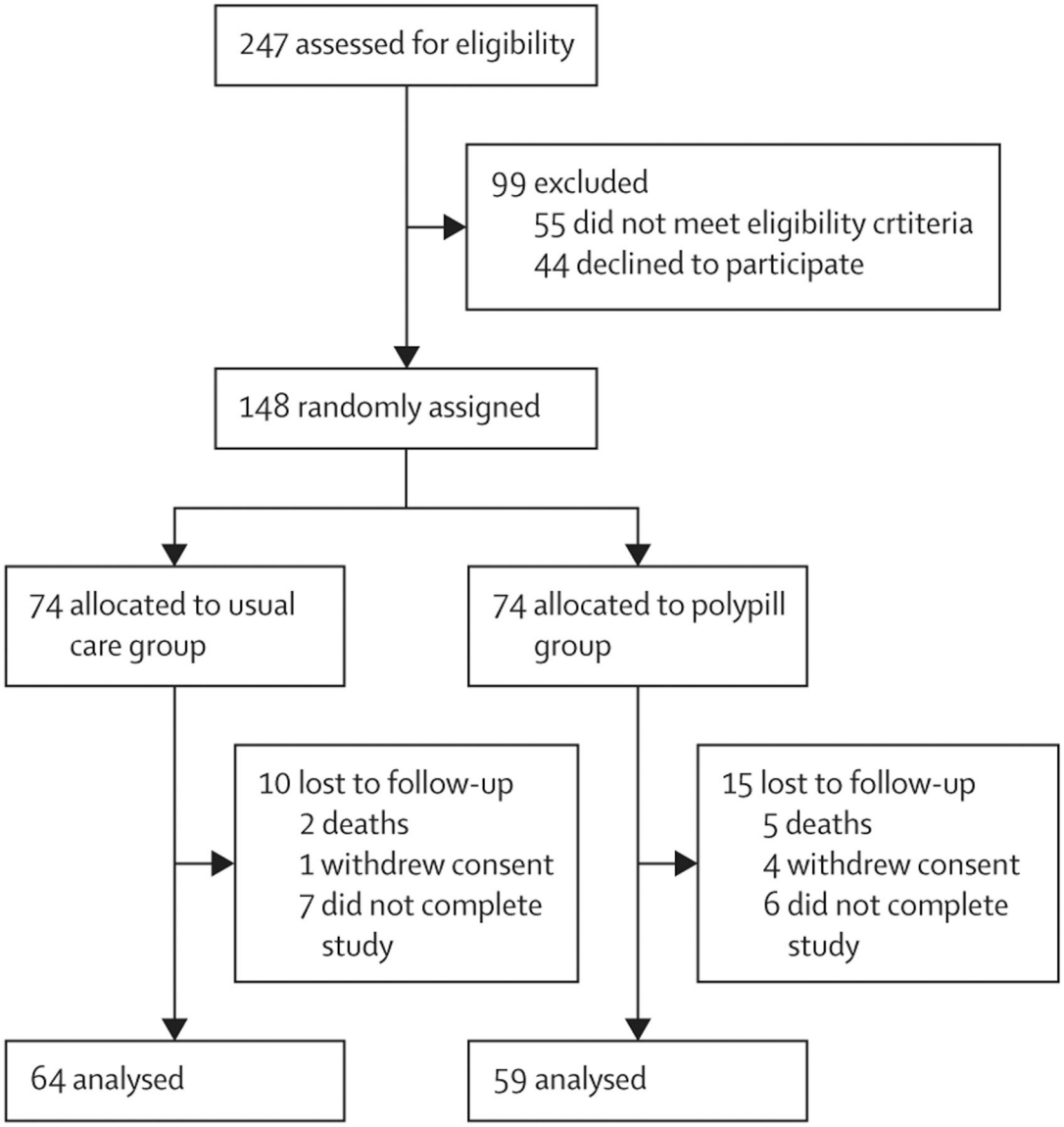

Figure:
Trial profile

Table 1:

Baseline characteristics

	Polypill group (n=74)	Usual care group (n=74)
Sex		
Male	36 (49%)	38 (51%)
Female	38 (51%)	36 (49%)
Age, years	58·5 (10·7)	58·1 (13·3)
Educational status		
None	11 (15%)	15 (20%)
Primary	42 (57%)	28 (38%)
Secondary	12 (16%)	18 (24%)
Tertiary	9 (12%)	12 (16%)
Postgraduate	0	1 (1%)
Urban residence	42 (54%)	37 (50%)
Marital status		
Never married	6 (8%)	5 (7%)
Married	43 (58%)	47 (64%)
Separated	12 (16%)	5 (7%)
Widow or widower	11 (15%)	14 (19%)
Cohabiting	0 (0%)	1 (1%)
Divorced	2 (3%)	2 (2%)
Employment status *		
Employed	54 (73%)	44/73 (60%)
Retired	11 (15%)	10/73 (14%)
Unemployed	9 (12%)	19/73 (26%)
Monthly income, US$		
0–100	7 (9%)	11 (15%)
101–250	37 (50%)	37 (50%)
250–500	27 (36%)	24 (32%)
>500	3 (4%)	2 (3%)
Vascular risk factors		
Hypertension	74 (100%)	74 (100%)
Diabetes	15 (20%)	21 (28%)
Cigarette smoking	0	1 (1%)
Alcohol use, current	8 (11%)	11 (15%)
Haemoglobin A_{1c}, %	6·5% (1·7)	7·0% (2·5)
BMI, kg/m^2	25·4 (4·3)	25·7 (5·1)
Obesity, BMI ≥30 kg/m^2	11 (15%)	16 (22%)
Waist-to-hip ratio, cm	92·2 (10·3)	90·6 (12·1)
LDL-cholesterol, mg/dL	94·0 (43·8)	98·1 (43·5)
Stroke subtype		
Small vessel disease	11 (15%)	23 (31%)

	Polypill group (n=74)	Usual care group (n=74)
Large vessel disease	20 (27%)	16 (22%)
Undetermined	43 (58%)	35 (47%)
Stroke severity and functional status		
NIHSS score	2·9 (3·4)	2·4 (2·8)
Modified Rankin score	2·60 (0·97)	2·74 (0·85)
Common CIMT, mm	1·00 (0·17)	1·03 (0·16)
Adherence to medication		
Morisky Adherence Scale score	6·7 (0·51)	6·7 (0·37)
Hill-Bone score	50·4 (1·81)	50·1 (1·76)
EQ-5D quality-of-life score	83·7 (11·6)	80·6 (11·7)
Treatment Satisfaction Questionnaire for Medication score	53·5 (2·8)	52·7 (2·8)
Montreal Cognitive Assessment score	16·0 (6·70)	16·2 (5·78)
Hamilton Rating Scale for Depression score	5·6 (4·36)	6·8 (4·13)
Systolic blood pressure, mm Hg	161·3 (17·2)	160·4 (18·0)
Diastolic blood pressure, mm Hg	92·0 (13·9)	92·6 (14·6)
Cardiovascular medications before enrolment		
Antiplatelet therapy (aspirin or clopidogrel)	62 (84%)	66 (89%)
Atorvastatin at 40 mg or 80 mg daily	55 (74%)	63 (85%)
Angiotensin converting enzyme inhibitor	15 (20%)	16 (22%)
Angiotensin receptor blocker	43 (58%)	43 (58%)
β blocker	12 (16%)	10 (14%)
Calcium channel blocker	62 (84%)	58 (78%)
Diuretics	25 (34%)	29 (39%)
Methyldopa	1 (1%)	2 (3%)
Hydralazine	10 (14%)	8 (11%)
Mineralocorticoid receptor blocker	7 (9%)	7 (9%)

Data are n (%) or mean (SD). CIMT=carotid intima-media thickness. NIHSS=National Institutes of Health Stroke Scale.

*One participant in the usual care group did not have data on employment status.

Table 2:

Outcome measures at month 12 in the modified intention-to-treat group

	Polypill group (n=59)	Usual care group (n=64)	Adjusted between-group difference	p value
Primary outcome				
Common CIMT, mm	−0·017 (−0·067 to 0·034)	−0·092 (−0·130 to −0·051)	0·049 (−0·008 to 0·109)	0·11
Secondary outcomes				
Morisky Adherence Scale score	−0·19 (−0·48 to 0·10)	−0·14 (−0·53 to 0·24)	−0·07 (−0·55 to 0·41)	0·77
Hill-Bone score	−0·51 (−1·37 to 0·36)	−1·11 (−2·31 to 0·09)	0·79 (−0·54 to 2·13)	0·24
EQ-5D quality-of-life score	7·63 (5·08 to 10·18)	10·23 (8·00 to 12·47)	−1·23 (−4·42 to 1·96)	0·45
Treatment Satisfaction Questionnaire for Medication score	−10·92 (−15·88 to −5·96)	−6·72 (−10·80 to −2·63)	−4·39 (−10·91 to 2·13)	0·19
Montreal Cognitive Assessment score	5·17 (4·17 to 6·17)	5·39 (4·13 to 6·64)	−0·27 (−1·83 to 1·28)	0·73
Modified Rankin score	−0·92 (−1·14 to −0·69)	−0·89 (−1·09 to −0·69)	−0·04 (−0·34 to 0·26)	0·79
Hamilton Rating Scale for Depression score	−3·51 (−4·44 to −2·57)	−4·06 (−4·91 to −3·22)	−0·34 (−1·31 to 0·62)	0·48
Tertiary outcomes				
Vascular risk factor control				
Systolic blood pressure, mm Hg	−15·68 (−23·06 to −8·29)	−17·62 (−24·80 to −10·45)	2·53 (−7·39 to 12·46)	0·61
Diastolic blood pressure, mm Hg	−7·88 (−12·24 to −3·53)	−3·31 (−7·67 to 1·05)	−5·30 (−11·25 to 0·64)	0·080
LDL-cholesterol, mg/dL	−7·87 (−19·98 to 4·24)	3·43 (−8·77 to 15·63)	−13·81 (−29·75 to 2·11)	0·088
Incidence of adverse events *				
Major adverse cardiovascular events	2/74 (3%)	1/74 (1%)	··	0·56
Rehospitalisation for any cardiovascular cause	0	0	··	NA

Data are mean (95% CI) unless otherwise stated. CIMT=carotid intima-media thickness. NA=not applicable.

*Assessed in the intention-to-treat population.

Table 3:

Sensitivity analysis with imputation of missing data with comparison between two groups using analysis of covariance

	Polypill group (n=74)	Usual care group (n=74)	Adjusted between-group difference	p value
Primary outcome				
Common CIMT, mm	−0·058 (−0·106 to −0·011)	−0·090 (−0·125 to −0·054)	0·028 (−0·02 to 0·078)	0·27
Secondary outcomes				
Morisky Adherence Scale score	0·97 (0·38, 1·60)	0·31 (−0·17 to 0·80)	0·58 (−0·19 to 1·35)	0·14
Hill-Bone score	−4·58 (−6·58 to −2·58)	−3·53 (−5·34 to −1·72)	−0·57 (−3·13 to 1·99)	0·66
EQ-5D quality-of-life score	4·53 (1·64 to 7·42)	6·96 (3·82 to 10·10)	−1·82 (−5·95 to 2·31)	0·39
Treatment Satisfaction Questionnaire for Medication score	−10·92 (−15·88 to −5·96)	−6·72 (−10·80 to −2·63)	−4·39 (−10·91 to 2·13)	0·19
Montreal Cognitive Assessment score	6·97 (5·75 to 8·19)	6·43 (5·15 to 7·72)	0·20 (−1·46 to 1·85)	0·82
Modified Rankin score	−1·11 (−1·32 to −0·90)	−1·07 (−1·28 to −0·86)	−0·06 (−0·36 to 0·23)	0·66
Hamilton Rating Scale for Depression score	−2·08 (−3·11 to −1·05)	−2·08 (−3·11 to −1·05)	0·005 (−1·23 to 1·24)	0·99
Tertiary outcomes				
Vascular risk factor control				
Systolic blood pressure, mm Hg	−17·91 (−24·32 to −11·49)	−20·69 (−27·27 to −14·11)	3·32 (−5·50 to 12·15)	0·46
Diastolic blood pressure, mm Hg	−12·04 (−16·22 to −7·86)	−5·65 (−9·91 to −1·39)	−6·74 (−12·40 to −1·08)	0·020
LDL-cholesterol, mg/dL	−18·39 (−29·46 to −7·33)	−4·65 (−16·38 to 7·08)	−12·99 (−27·30 to 1·32)	0·075

Data are mean (95% CI). CIMT=carotid intima-media thickness.

Table 4:

Safety and tolerability measures

	Polypill group (n=74)	Usual care group (n=74)	p value
Serious adverse events (overall)	8 (11%)	2 (3%)	0·049
All-cause mortality	5 (7%)	2 (3%)	0·43
Post-stroke seizures	2 (3%)	0	0·50
Hospitalisation	1 (1%)	0	1·00
Treatment discontinuation	3 (4%)	0	0·24
Reasons for discontinuation			
Side-effects	3 (4%)	0	0·24
Regimen adjustments	5 (7%)	7 (9%)	0·55
Treatment-related side-effects	4 (5%)	0	0·12
Cough	3 (4%)	0	0·24
Gastrointestinal bleeding	1 (1%)	0	1·00

Data are n (%) unless otherwise stated.