Secondary prevention with a structured semi-interactive stroke prevention package in INDIA (SPRINT INDIA): a multicentre, randomised controlled trial

*SPRINT INDIA trial collaborators**

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*Collaborators listed in the appendix pp 16–18

Correspondence to:
Dr Jeyaraj Durai Pandian, Christian Medical College and Hospital, Ludhiana, Punjab 141008, India
jeyaraj.pandian@cmcludhiana.in

See **Online** for appendix

Summary

Background There is a high burden of stroke, including recurrent stroke, in India. We aimed to assess the effect of a structured semi-interactive stroke prevention package in patients with subacute stroke to reduce recurrent strokes, myocardial infarction, and death.

Methods This was a multicentre, randomised, clinical trial conducted in 31 centres of the Indian Stroke Clinical Trial Network (INSTRuCT). Adult patients with first stroke and access to a mobile cellular device were randomly allocated (1:1) to intervention and control groups by the research coordinators at each centre using a central, in-house, web-based randomisation system. The participants and research coordinators at each centre were not masked to group assignment. The intervention group received regular short SMS messages and videos that promoted risk factor control and medication adherence and an educational workbook, in one of 12 languages, and the control group received standard care. The primary outcome was a composite of recurrent stroke, high-risk transient ischaemic attack, acute coronary syndrome, and death at 1 year. The outcome and safety analyses were done in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, NCT03228979 and Clinical Trials Registry-India (CTRI/2017/09/009600) and was stopped for futility after interim analysis.

Findings Between April 28, 2018, and Nov 30, 2021, 5640 patients were assessed for eligibility. 4298 patients were randomised to the intervention group (n=2148) or control group (n=2150). 620 patients were not followed up at 6 months and a further 595 patients were not followed up at 1 year because the trial was stopped for futility after interim analysis. 45 patients were lost to follow-up before 1 year. Acknowledgment of receipt of the SMS messages and videos by the intervention group patients was low (17%). The primary outcome occurred in 119 (5·5%) of 2148 patients in the intervention group and 106 (4·9%) of 2150 patients in the control group (adjusted odds ratio 1·12; 95% CI 0·85–1·47; p=0·370). Among the secondary outcome measures, alcohol cessation and smoking cessation were higher in the intervention group than in the control group (alcohol cessation 231 [85%] of 272 in the intervention group *vs* 255 [78%] of 326 in the control group; p=0·036; smoking cessation 202 [83%] *vs* 206 [75%]; p=0·035). Medication compliance was better in the intervention group than in the control group (1406 [93·6%] of 1502 *vs* 1379 [89·8%] of 1536; p<0·001). There was no significant difference between the two groups in other secondary outcome measures at 1 year: blood pressure, fasting blood sugar (mg/dL), low-density lipoprotein cholesterol (mg/dL), and triglycerides (mg/dL), BMI, modified Rankin Scale, and physical activity.

Interpretation A structured semi-interactive stroke prevention package did not reduce vascular events when compared with standard care. However, there was an improvement in some lifestyle behavioural factors, including adherence to medication, which might have long-term benefits. There was a possibility of type 2 error owing to reduced power since there were fewer events and a high number of patients could not be followed up.

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Introduction

Stroke remains a global health concern with high morbidity and mortality. The past three decades have seen a 70% increase in stroke cases and a 43% increase in stroke deaths globally.[1] India has a high burden of stroke, attributable to its large population and epidemiological shift and also to a high prevalence of risk factors.[2–4] High recurrent stroke rates, which range from 15% to 21% in population and hospital-based registries, are a substantial factor in the stroke burden in India.[5–7] Together, recurrent stroke and coronary artery disease are the major predictors of mortality in India, and with 60% mortality at 1 month post stroke.[8]

Hypertension, diabetes mellitus, smoking, inadequate physical activity, cardiac causes, dyslipidaemia, obesity, and alcohol consumption are some of the major risk factors for stroke globally.[9] Use of secondary prevention medicines for stroke and other cardiovascular diseases is low across the world, especially in low-income countries.[10] There are several barriers and challenges in

Research in context

Evidence before this study

Recurrent stroke is a major cause of death and disability, which can be minimised by lifestyle modification and improved medication adherence. Various intervention techniques have been used to improve the efficacy of secondary prevention. We searched PubMed on April 2, 2022 using the terms "secondary prevention", "risk factor management", "patient care management", "health education" and "patient compliance". We found 12 studies, including five randomised controlled trials, that used text messaging exclusively as an intervention to improve medication adherence in patients. Most of the studies had a small sample size. The evidence suggested that text messages were effective in reducing risk factors by altering lifestyle choices. We did not find any randomised controlled trials that had used regionally and linguistically tailored, structured education packages for vascular risk reduction.

Added value of this study

This is the first large randomised trial to use a structured education package inclusive of SMS, videos, and workbook in different regional languages aimed to reduce stroke recurrence and mortality in stroke survivors. Compared with routine care, this approach did not improve primary outcomes, although there was an improvement in some lifestyle behavioural factors and medication compliance.

Implications of all the available evidence

This trial showed that a well designed intervention can contribute to improving some of the secondary prevention factors including behavioural outcomes (alcohol cessation and smoking cessation) and medication adherence, which might provide long-term benefits.

the secondary prevention of stroke in low-income and middle-income countries.[11] Inadequate control of blood pressure, blood sugar and lipid concentrations, and lifestyle factors are all salient causes for recurrent strokes. Non-availability of medicines, poor drug compliance, poor awareness about stroke prevention, and out-of-pocket expenses for treatment are important barriers in delivering stroke preventive measures.[11]

Mobile health (mHealth) is a popular strategy that has been used in the control of cardiovascular risk factors. One study[12] in patients with stroke suggested that the use of short, tailored text messages (eg, medication reminders and periodic health and lifestyle messages) had a possible benefit in medication adherence for cardiovascular risk factor control. Lifestyle-focused text messaging on risk factor modification has been reported to result in reduced systolic blood pressure, low-density lipoprotein, cholesterol, BMI, increased physical activity, and improved smoking habits in individuals with coronary artery disease.[13] Simple tools such as workbooks on the modification, assessment, and management of risk factors were used as an intervention in a previous study[14] in patients with coronary artery disease, with favourable results in long-term care.

Regardless of establishing an objective improvement in blood sugars, cholesterol concentrations, and drug compliance, the effect of mHealth interventions on the reduction of vascular events is still uncertain. A previous study[15] on educational and behavioural interventions for the improved management of modifiable risk factors did not show meaningful improvement in the prevention of recurrent cardiovascular events. However, further research is needed to evaluate innovative strategies for improving secondary prevention in stroke. Furthermore, new strategic interventions need to be designed and evaluated across a variety of languages and cultures, to establish efficacy and reproducibility of benefit.

Therefore, considering the primary hypothesis that a tailored and structured intervention can result in improved secondary prevention in stroke, our study aimed to develop a structured semi-interactive stroke prevention package that included text and video messages and workbooks in the local language, and assess its effect on the reduction of recurrent stroke, myocardial infarction, and death in patients with subacute stroke.

Methods

Study design and participants

The Secondary Prevention by Structured Semi-Interactive Stroke Prevention Package in India (SPRINT INDIA) was a multicentre, randomised controlled clinical trial of subacute stroke patients. The study was done in the Indian Stroke Clinical Trial Network (INSTRuCT), which comprises 31 stroke centres across India[16] and included 17 private hospitals, 13 government hospitals, and one secondary level hospital. All the hospitals had a functioning stroke unit run by either a physician or a neurologist. The study received institutional ethics committee approval from all the sites before initiation. The initial duration of the study was planned for 5 years, with 4 years for recruitment and 1 year for follow-up.

Eligible patients were older than 18 years with a first ischaemic stroke or first intracerebral haemorrhage with CT or MRI confirmation of a recent stroke (ie, infarct, or haemorrhage, or both, between 2 days and 3 months after stroke symptom onset), a modified Rankin Scale of 2–5, and had to possess a working personal mobile cellular device for receiving SMS messages and videos and be able to read and complete simple tasks suggested in the workbook, either themselves or with help from their caregiver. Investigators or research coordinators confirmed patient inclusion and exclusion criteria status before enrolling eligible patients who had given written informed consent.

Randomisation and masking

Patients were allocated (1:1) to the intervention or control groups by the research coordinator using EasyResearch (version 2.4), a central, in-house, web-based computer randomisation. The enrolled patients spoke 12 different languages between them, which covered languages spoken by around 80% of the Indian population. The US National Institutes of Health Stroke Scale score and the modified Rankin Scale for each patient were assessed before randomisation. The treating physician, principal investigator, and those assessing outcomes were masked to group allocation. Participants and the research coordinators who randomly assigned participants to groups and documented outcome measures were not masked.

Procedures

The development of the intervention group education materials was done in three phases. In the formative stage, the preliminary package was developed in English; in the acceptability stage, the package was translated into 11 Indian languages with the help of stakeholders; and in the implementation stage, a feasibility study that involved 20 patients in total, from two of the 31 centres, explored issues with the delivery of the intervention package. There were no feasibility issues noted during the pilot testing.[17] We developed 68 text messages and six short video messages (each 2–4 min long) that focused on important stroke risk factors and translated these into 11 Indian languages for the study. The SMS texts and video messages were designed to illustrate a problem and to convey a positive sentiment focused on the reduction of risk factors (appendix p 10). The videos were made with age-appropriate commercial actors who had an engaging narrative presentation designed to have a national appeal. The intervention package had a good Simple Measure of Gobbledygook (SMOG) Index readability score and was acceptable to patients, caregivers, doctors, nurses, physiotherapists, and research coordinators in all the translated languages.[17] The entire package development process was completed between April 1, 2017, and March 9, 2018.

Patients assigned to the intervention group received a daily SMS message for the first 6 weeks, then an SMS message twice a week until 6 months and, thereafter, one message a week until 1 year. Each message was sent at a prespecified time of the day, according to patients' preferences, to maximise the likelihood of the patient reading the message immediately. Message sending was coordinated by the Christian Medical College Ludhiana, the main national coordinating centre. The patients or caregivers were asked to read the messages and to acknowledge them by calling a predesignated number, which was logged as a missed call.

Patients in the intervention group also received short video messages once a week for the first 6 weeks, then once a month until 1 year (appendix p 11). As with SMS messages, once patients or caregivers had watched each video, they were asked to acknowledge this by logging a missed call. If a patient did not send an acknowledgment for two consecutive SMS messages or two consecutive videos, the research coordinator placed a follow-up call with the patient to identify and troubleshoot any issues with receiving the messages, viewing the videos, or providing an acknowledgment.

For more on **EasyResearch** see https://easyresearch.instructnetwork.in/EasyResearch/AribaWeb

Patients in the intervention group also received a printed stroke prevention workbook at the baseline visit. The workbook contained interactive activities focusing on stroke prevention, such as board games, pair matching, true-or-false questions with answers, simple physical exercises, and an exercise calendar. The patients or caregivers were asked to perform the workbook activities and games with family and friends and were expected to complete the workbook within 6 weeks and to revise the contents monthly thereafter. To increase the inclusivity of the trial, patients with aphasia or hemianopia, and illiterate patients were also included, whereby the primary caregiver was accountable for viewing and acknowledging the messages and videos. The caregiver was instructed to bring about the necessary changes in diet, physical activity, and medication intake. Throughout the study period, all patients received a telephone call once a month to enquire about outcome events. Follow-up visits with the patient or caregiver occurred at 6 months and at 1 year.

Various measures were taken to restrict the contamination of patient educational material. The centre research coordinator obtained patient consent, enrolled and randomly assigned participants and, for patients in the intervention group, delivered the educational material to individuals without anyone else being present. All participants received an explanation about the need for confidentiality. The SMS and videos were delivered to only one assigned number, which could be either that of the patient or the caregiver. The SMS, videos, and workbooks were not to be shared with anyone (other than with the care recipient, if sent to a caregiver).Intervention fidelity (assessment of the degree to which the intervention was carried out as intended and planned, to appraise its efficiency in achieving the desired results) was assessed through the process evaluation, which involved qualitative and quantitative data. Using mixed methods, qualitative interviews were done among patients, caregivers, centre investigators, research coordinators, and non-SPRINT hospital staff from 11 sampled sites that were representative of the regional languages in which the intervention was delivered. Quantitative data included case report forms, patients' workbooks, and patient questionnaires to measure intervention fidelity and contamination. For the intervention group, we also used the SMS and video acknowledgments.[18]

Patients in the control group received standard care, plus a phone call once a month throughout the study period to enquire about outcome events.

Baseline assessment comprised demographic characteristics, stroke subtype, risk factor profile, blood pressure, fasting blood sugar, lipids, total physical activity metabolic equivalent,[19] and medication non-compliance.[20] Imaging data included vascular evaluation of intracranial and extracranial arteries and the location of infarct or haemorrhage. TOAST classification[21] was used to categorise the ischaemic stroke mechanism and the Oxfordshire Community Stroke Project (OCSP)[22] classification system was used for stroke subtypes. Current smoker was defined having smoked tobacco in the 12 months before the trial and current alcohol intake was defined as consumption within the same period.[23] Medication non-compliance was assessed by use of a self-report questionnaire that probed the reasons for any missed medication doses. All patients enrolled in the study were followed up at 6 months and 1 year. Outcome measures were documented at 6 months and at 1 year by the research coordinator at each centre. The Christian Medical College, Ludhiana, was the main national coordinating centre. Monitoring of the south Indian sites was done by Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, and the Christian Medical College, Ludhiana monitored the North Indian sites.

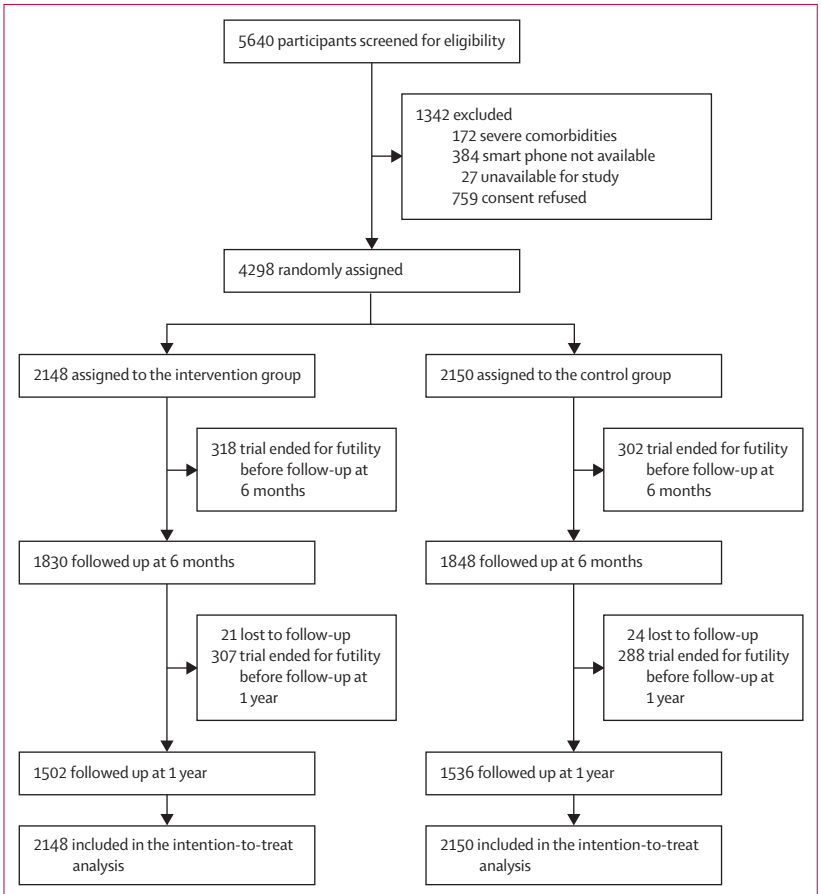

Figure: **Trial profile**
318 patients in the intervention group and 302 patients in the control group could not complete follow-up at 6 months, and 307 in the intervention group and 208 in the control group could not complete follow-up at 1 year, because the trial was stopped for futility after interim analysis.

Outcomes

The primary outcome was a composite endpoint of recurrent stroke, high-risk transient ischaemic attack acute coronary syndrome, and all-cause mortality at 1 year after randomisation. Patients were followed up for vascular events at two time points, 6 months and 1 year, although during the COVID-19 pandemic the follow-up periods were extended (follow-up at 6 months was extended by 2 months and follow-up at 1 year by 6 months) to document vascular events reported to the study coordinator even after this period. A high-risk transient ischaemic attack was defined as one with MRI evidence of infarct.

The secondary outcomes assessed at 1 year after randomisation were change in BMI, physical activity total metabolic equivalent (min per week),[19] current smoking, current alcohol intake, modified Rankin Scale, and medication non-compliance.[20]

The laboratory-measured secondary outcomes were systolic and diastolic blood pressure (mm Hg), fasting blood sugar (mg/dL), low-density lipoprotein cholesterol (mg/dL), and triglycerides (mg/dL) at 1 year after randomisation.

All events were adjudicated by an independent event adjudication committee of three specialists (one neurologist and two cardiologists), to whom all event details were sent. If there was a discrepancy between two committee members, the third committee member adjudicated the event.

There was a decrease in the number of patients recruited during two waves of the COVID-19 pandemic (March–October, 2020, and March–June, 2021), owing to lockdowns (appendix p 12). To mitigate the effect of the pandemic, the follow-up period was extended by 2 months for the 6-month follow-up and by 6 months for the 1-year follow-up. The reporting of outcomes by telephone or WhatsApp, and telemedicine follow-up were approved by the steering committee. For some secondary outcome measures (eg, blood pressure, fasting blood sugar, and lipids), patients were asked to send via WhatsApp reports from local laboratories and physicians. Weekly meetings were held between the Christian Medical College Ludhiana and the local team and investigators, to troubleshoot practical problems faced in doing the trial during the pandemic. Virtual monitoring of the trial was done by the central coordinating team.

Statistical analysis

Based on population and hospital-based data, the estimated recurrent stroke rate in India is around 15–21%.[5–7] We calculated the sample size on the basis of this rate. We estimated a priori a reduction of 3% in the intervention

arm, thereby assuming the composite endpoint rate to be 20% in the standard care group and 17% in the intervention group. A minimum of 2915 patients in each of the two groups was required to achieve 80% power with 5% α error and an expected 10% dropout.[24]

All analyses were done in the intention-to-treat population. The primary outcome was analysed using the χ^2 test. Logistic regression was used to adjust odds ratios (ORs) for study site, age, region, highest level of education, US National Institute of Health Stroke Scale, stroke characteristics, revascularisation, and medical history. The secondary outcome measures were analysed using linear mixed models at three time intervals: baseline, 6 months, and 1 year. We used a logistic regression model to analyse categorical variables and a linear regression model for continuous variables. Changes in smoking and alcohol intake were assessed using the McNemar test. Unadjusted and adjusted ORs for primary and secondary outcomes were calculated using logistic regression after adjusting for study site, age, region, education, National Institutes of Health Stroke Scale, stroke characteristics, revascularisation, and medication history. The prespecified subgroup analyses (by age, National Institutes of Health Stroke Scale score, sex, stroke type, medical history, region, arterial involvement, TOAST, and OCSP classification) were done as fixed effects using the same logistic regression model as for the primary analysis. Within each subgroup, summary measures included raw counts and percentages within each treatment group, and the OR (95% CI) for treatment effect. The results were displayed in a forest plot (appendix p 14) that included the p value for heterogeneity corresponding to the interaction between the study group intervention and the subgroup variables. The statistical analysis plan[25] was completed before the unblinding of the results. One analyst was masked to group allocation and the other was not. $p<0·05$ was considered significant. All analysis were done with SPSS (version 26.0) and R (version 4.1.3).

An independent data and safety monitoring board monitored the unblinded results and the adverse events as per the board's charter. An interim futility analysis was planned after 50% enrolment or occurrence of 50% of events, whichever came first. However, owing to the pandemic, the interim analysis was done at 67% of recruitment. The difference between groups in the proportion of patients with events at 1 year was taken as the endpoint to calculate the conditional power (appendix p 6). The trial was stopped for futility by the data and safety monitoring board because of fewer vascular events than expected and low conditional power. The unavailability of funds for an extended follow-up of the trial cohort led to the closure of the trial. We assumed that patients who could not be assessed for the primary outcome at 1 year owing to the trial ending early did not have one of the composite events. For the secondary outcomes intention-to-treat analysis, we assumed that

	Intervention group (n=2148)	Control group (n=2150)
Sex		
Male	1543/2148 (71·8%)	1579/2150 (73·4%)
Female	605/2148 (28·2%)	571/2150 (26·6%)
Median age, years	56 (18–88)	56 (18–89)
Highest level of education completed		
No schooling	156/2148 (7·3%)	121/2150 (5·6%)
<High school	1178/2148 (54·8%)	1172/2150 (54·5%)
≥High school	794/2148 (37·0%)	830/2150 (38·6%)
Region		
Urban	1092/2148 (50·8%)	1124/2150 (52·3%)
Rural	1056/2148 (49·2%)	1026/2150 (47·7%)
Medical history		
Hypertension	1457/2148 (67·8%)	1388/2150 (64·6%)
Diabetes	879/2148 (40·9%)	888/2150 (41·3%)
Coronary artery disease	222/2148 (10·3%)	229/2150 (10·7%)
Dyslipidaemia	378/2148 (17·6%)	391/2150 (18·2%)
Non-valvular atrial fibrillation	50/2148 (2·3%)	43/2150 (2·0%)
Valvular heart disease	61/2148 (2·8%)	56/2150 (2·6%)
Symptomatic intracranial atherosclerosis	55/2148 (2·6%)	56/2150 (2·6%)
Symptomatic extracranial atherosclerosis	29/2148 (1·4%)	32/2150 (1·5%)
Obesity	147/2148 (6·8%)	144/2150 (6·7%)
Other	112/2148 (5·2%)	105/2150 (4·9%)
Stroke type		
Ischaemic	1781/2148 (82·9%)	1787/2150 (83·1%)
Haemorrhagic	367/2148 (17·1%)	363/2150 (16·9%)
NIHSS score		
Mean (SD)	5 (4·5)	5 (4·5)
Median (IQR)	4 (1–7)	4 (1–7)
<5	1244 (57·9%)	1244 (57·9%)
5–10	648 (30·2%)	675 (31·4%)
11–14	188 (8·8%)	168 (7·8%)
≥15	68 (3·2%)	63 (2·9%)
TOAST classification[21]		
Large artery atherosclerosis	607/1781 (34·1%)	567/1787 (31·7%)
Cardioembolism	208/1781 (11·7%)	232/1787 (13·0%)
Small artery occlusion	462/1781 (25·9%)	466/1787 (26·1%)
Other	51/1781 (2·9%)	63/1787 (3·5%)
Undetermined	453/1781 (25·4%)	459/1787 (25·7%)
OCSP classification		
Total anterior circulation syndrome	264/1781 (14·8%)	245/1787 (13·7%)
Partial anterior circulation syndrome	896/1781 (50·3%)	893/1787 (50·0%)
Posterior circulation syndrome	380/1781 (21·3%)	413/1787 (23·1%)
Lacunar syndrome	241/1781 (13·5%)	236/1787 (13·2%)
Revascularisation therapy		
Revascularisation therapy given	185/1781 (10·4%)	163/1787 (9·1%)
Intravenous thrombolysis tissue plasminogen activator initiated	151/1781 (8·5%)	139/1787 (7·8%)
Endovascular thrombectomy done	47/1781 (2·6%)	40/1787 (2·2%)

Data are n/N (%), mean (SD), or median (IQR). NIHSS=US National Institute of Health Stroke Scale. OCSP=Oxfordshire Community Stroke Project.

Table 1: **Baseline characteristics**

	Intervention group (n=2148)	Control group (n=2150)
Alcohol intake		
Past history	186 (8·7%)	190 (8·8%)
Current	419 (19·5%)	459 (21·3%)
Never	1543 (71·8%)	1501 (69·8%)
Tobacco—smoked		
Past history	206 (9·6%)	207 (9·6%)
Current	346 (16·1%)	386 (18·0%)
Never	1596 (74·3%)	1557 (72·4%)
Tobacco—chewed		
Past history	54 (2·5%)	58 (2·7%)
Current	171 (8·0%)	187 (8·7%)
Never	1923 (89·5%)	1905 (88·6%)
Drug addiction		
Past history	3 (0·1%)	4 (0·2%)
Current	8 (0·4%)	14 (0·7%)
Never	2137 (99·5%)	2132 (99·2%)
Self-reported medication non-compliance		
Yes	323 (15·0%)	304 (14·1%)
No	1825 (85·0%)	1846 (85·9%)
Reasons for medication non-compliance		
Stopped	217/323 (67·2%)	204/304 (67·1%)
Forgot	78/323 (24·1%)	75/304 (24·7%)
Other	28/323 (8·7%)	25/304 (8·2%)
Median physical activity total metabolic equivalent, min	4900 (1680–12324)	5040 (1779–8520)

Data are n (%) or median (IQR).

Table 2: **Baseline behavioural history and medication compliance**

patient data were the same at 1 year as they were at baseline.

This study was registered with ClinicalTrials.gov (NCT03228979) and the Clinical Trials Registry-India (CTRI/2017/09/009600). The study protocol has been published previously.[26]

Role of the funding source

The task force of the funder was involved in the trial design. Two members of the Indian Council of Medical Research (MS and RDh) were in the task force but were not involved in the data collection, analysis, and data interpretation. The funder had no role in the data collection, data analysis, data interpretation, or the writing of the report.

Results

Between April 28, 2018, and Nov 30, 2021, 5640 patients were assessed for eligibility. The reasons for exclusion were severe comorbidities, smartphone unavailability, and refusal of consent. 4298 eligible patients (median age 56 years [IQR 18–88]; 72·6% male, 27·4% female) were enrolled and randomly assigned to the semi-structured package intervention group (n=2148) or standard care (n=2150; figure). 318 patients in the intervention group and 302 patients in the control group could not complete follow-up at 6 months, and 307 in the intervention group and 208 in the control group were unable to complete follow-up at 1 year, as the trial was stopped for futility after interim analysis (at 67% recruitment). 3038 patients (1502 in the intervention group and 1536 in the control group) completed 1 year of follow-up (figure). Baseline demographic characteristics and stroke characteristics, subtypes, classification, severity, risk factors, and lifestyle behaviours were similar between the two groups (tables 1, 2). In the cohort that completed 1-year follow-up, baseline characteristics were also similar between groups (appendix pp 1–3), and there were no significant differences in baseline characteristics between groups for patients who did complete 1-year follow-up and those who did not (appendix pp 2–3, 8–9).

A total of 128 SMS messages were received by the patients over 1 year. There was no significant difference between groups in the primary composite outcome (119 [5·5%] in the intervention group *vs* 106 [4·9%] in the control group; adjusted OR 1·12 [95% CI 0·85–1·47]; p=0·370; table 3). However, fewer vascular events and deaths than we had planned for in our sample size calculation (17% and 20%, respectively) were noted in both the control and intervention groups. There was no significant difference between groups in median time to event (14·7 months [95% CI 12·1–17·3] in the intervention group *vs* 14·6 months [13·3–15·9] in the control group; p=0·363; appendix pp 4, 13).

For secondary outcomes at 1 year, smoking and alcohol use were lower in the intervention group than in the control group (current smoker 48 [3·2%] *vs* 76 [4·9%]; adjusted OR 0·65 [95% CI 0·44–0·94]; alcohol intake 53 [3·5%] *vs* 85 [5·5%]; adjusted OR 0·64 [0·44–0·91]; table 4). Also, self-reported medication compliance was higher in the intervention group than in the control group (1406 [93·6%] *vs* 1379 [89·8%]; OR 0·60 [95% CI 0·46–0·79]; table 4). The other secondary outcome measures, such as blood pressure, fasting blood sugar, BMI, lipid profile, and modified Rankin Scale, did not significantly differ between the two groups (table 4).

Improvements between baseline and follow-up at 1 year in secondary outcome measures were noted for alcohol cessation (231 [84·9%] of 272 in the intervention group *vs* 255 [78·2%] of 244 in the control group; p=0·036), smoking cessation (202 [82·8%] *vs* 206 [75·2%]; p=0·035) and medication compliance (133 [58·8%] *vs* 83 [36·1%]; p<0·001; table 5). The relative reduction for the intervention versus standard care was 41·3% for alcohol use and 36·3% for smoking. There was no difference in serious adverse events between groups (appendix p 5). Unexpectedly, the total number of deaths reported in the intervention group was 61 (2·8%) of 2148 compared with 50 (2·3%) of 2150 in the control group; (p=0·694; table 3). Prespecified subgroup analysis did

	Intervention (n=2148)	Control (n=2150)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	p value
Composite primary outcome	119 (5·5%)	106 (4·9%)	1·13 (0·86–1·48)	1·12 (0·85–1·47)	0·370
High-risk transient ischaemic attack	5 (0·2%)	7 (0·3%)	0·72 (0·23–2·27)	0·73 (0·23–2·31)	0·694
Ischaemic stroke	39 (1·8%)	40 (1·9%)	0·98 (0·63–1·53)	0·97 (0·62–1·52)	0·694
Intracerebral haemorrhage	5 (0·2%)	2 (0·1%)	2·52 (0·49–4·04)	2·52 (0·49–4·05)	0·694
Acute coronary syndrome	9 (0·4%)	7 (0·3%)	1·30 (0·48–3·48)	1·27 (0·47–3·43)	0·694
Death	61 (2·8%)	50 (2·3%)	1·23 (0·84–1·80)	1·22 (0·83–1·78)	0·694

Data are n/N (%) or odds ratio (95% CI). *Adjusted using logistic regression for study site, age, region, highest level of education, US National Institute of Health Stroke Scale, stroke characteristics, revascularisation, and medical history.

Table 3: **Primary outcomes at 1 year**

	Intervention (n=1502)*	Control (n=1536)*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)†	β coefficient (95% CI)‡	p value
All secondary outcomes	119/2148 (5·5%)	106/2150 (4·9%)	1·13 (0·86–1·48)	1·12 (0·85–1·47)	..	0·370
Modified Rankin scale						
0–2 (good outcome)	1394/1502 (92·8%)	1412/1536 (91·9%)	1	1	..	0·360
3–5 (bad outcome)	108/1502 (7·2%)	124/1536 (8·1%)	0·88 (0·68–1·15)	0·93 (0·34–2·51)	..	0·360
Alcohol use	53/1502 (3·5%)	85/1536 (5·5%)	0·62 (0·44–0·89)§	0·64 (0·44–0·91)§	..	<0·0081
Alcohol cessation	57/1502 (3·8%)	85/1536 (5·5%)	0·67(0·48–0·95)	0·70 (0·49–0·98)	..	0·023
Smoker	48/1502 (3·2%)	76/1536 (4·9%)	0·63 (0·44–0·92)§	0·65 (0·44–0·94)§	..	0·015
Smoking cessation	53/1502 (3·5%)	76/1536 (4·9%)	0·70 (0·49–1·01)	0·73 (0·51–1·04)	..	0·052
Medication non-compliance reported by patient						
Yes	96/1502 (6·4%)	157/1536 (10·2%)	0·60 (0·46–0·78)§	0·60 (0·46–0·79)§	..	<0·0001
No	1406/1502 (93·6%)	1379/1536 (89·8%)	0·60 (0·46–0·78)§	1	..	<0·0001
Reason for medication non-compliance						
Forgot	22/96 (22·9%)	24/157 (15·3%)	1·46 (0·67–3·03)	1·41 (0·65–3·09)	..	0·242
Stopped	27/96 (28·1%)	42/157 (26·8%)	0·80 (0·44–1·46)	0·81 (0·44–1·48)	..	0·242
Other¶	47/96 (49·0%)	91/157 (57·9%)	1	1	..	0·242
Systolic blood pressure, mm Hg	131 (14·3)	131 (13·9)	..	..	–0·359 (–1·366 to 0·648)	0·484
Diastolic blood pressure, mm Hg	83 (8·6)	83 (8·4)	..	..	0·026 (–0·583 to 0·636)	0·932
BMI, kg/m²	24·9 (3·9)	25·1 (4·6)	..	..	–0·19 (–0·495 to 0·115)	0·221
Fasting blood sugar, mg/dL	117·2 (38·9)	117·8 (38·9)	..	..	–0·517 (–3·489 to 1·246)	0·733
Lipid profile, mg/dL						
Cholesterol	152·8 (37·8)	153·9 (40·9)	..	..	–1·108 (–4·264 to 2·049)	0·491
Triglyceride	133·9 (62·8)	136·1 (72·2)	..	..	–2·166 (–7·564 to 3·233)	0·432
Low-density lipoproteins	84·6 (32·3)	84·9 (32·9)	..	..	–0·355 (–2·948 to 2·239)	0·789
High-density lipoproteins	47·1 (19·4)	46·6 (17·8)	..	..	0·486 (–1·003 to 1·975)	0·522
Physical activity total metabolic equivalent, min	3780 (1622–6720)	3590 (1680–6780)	..	..	103·363 (–173·193 to 379·921)	0·748

Data are n/N (%), mean (SD), or β coefficient (95% CI). *The trial was stopped for futility after interim analysis, hence the difference in patient numbers at baseline and at follow-up at 1 year (2148 *vs* 1502 in the intervention group and 2150 *vs* 1536 in the control group). †Adjusted using logistic regression for study site, age, region, education, US National Institute of Health Stroke Scale, stroke characteristics, revascularisation, and medical history. ‡Linear regression using ordinary least square was used. §p value <0·05. ¶Included: no help to buy medicines, shortage of money, patient felt that they were fine, and medicine not available in the pharmacy.

Table 4: **Secondary outcomes at 1 year**

not show any interaction between variables and outcomes in either group (appendix p 14).

The intervention fidelity questionnaire was completed by 1418 (66·0%) of 2148 patients in the intervention group. Of these 1418 patients, the number of SMS messages viewed was reported as 996 (70·2%) at 6 weeks, 571 (40·3%) at 6 months, and 506 (36·0%) at 1 year, and the number of videos viewed was 769 (54·2%) at 6 weeks,

	Intervention group (n=1502)*			Control group (n=1536)*			Relative change or mean difference from baseline to 1 year		Difference in relative change or mean difference between groups	p value
	Baseline	1 year	p value	Baseline	1 year	p value	Intervention group	Control group		
Modified Rankin Scale bad outcome (3–5)	576 (38·3%)	108 (7·2%)	<0·001	631 (41·1%)	124 (8·1%)	<0·001	468/576 (81·3%)	507/631 (80·3%)	1·0%	0·744
Systolic blood pressure, mm Hg	134 (17·8)	130·6 (14·3)	<0·001	133 (18·0)	130·9 (13·9)	<0·001	−3·61 (−4·66 to −2·57)	−2·54 (−3·52 to −1·57)	−1·1 (−2·5 to 0·3)	0·138
Diastolic blood pressure, mm Hg	83 (10·8)	82·6 (8·6)	0·138	82·7 (10·1)	82·5 (8·4)	0·532	−0·47 (−1·10 to 0·15)	−0·19 (−0·80 to 0·21)	−0·28 (−1·1 to 0·57)	0·515
BMI, kg/m^2	25·0 (3·9)	24·9 (3·9)	0·194	25·0 (4·0)	25·1 (4·6)	0·387	−0·07 (−0·18 to 0·04)	0·06 (−0·21 to 0·08)	−0·13 (−0·3 to 0·05)	0·142
Alcohol intake	272 (18·1%)	41 (2·7%)	<0·001	326 (21·2%)	71 (4·6%)	<0·001	231/272 (84·9%)	255/326 (78·2%)	6·7%	0·036
Current smoker	244 (16·2%)	42 (2·7%)	<0·001	274 (17·8%)	68 (4·4%)	<0·001	202/244 (82·8%)	206/274 (75·2%)	7·6%	0·035
Fasting blood sugar, mg/dL	133·8 (57·4)	117·2 (38·9)	<0·001	135·2 (58·9)	117·8 (38·9)	<0·001	16·53 (13·48 to 19·58)	16·76 (13·89 to 19·63)	0·23 (−3·9 to 4·4)	0·913
Lipid profile, mg/dL										
Cholesterol	170·5 (46·6)	152·8 (37·8)	<0·001	172·2 (46·4)	153·9 (40·9)	<0·001	14·95 (12·13 to 17·76)	16·79 (13·85 to 19·73)	1·84 (−2·2 to 5·9)	0·374
Triglyceride	142·8 (78·4)	133·9 (62·8)	0·004	147·9 (94·4)	136·1 (72·2)	<0·001	6·30 (2·0 to 10·6)	9·04 (4·28 to 13·79)	2·74 (−3·7 to 9·2)	0·403
Low-density lipoproteins	99·6 (41·0)	84·6 (32·3)	<0·001	100·4 (41·6)	84·9 (32·9)	<0·001	13·42 (11·01 to 15·82)	14·51 (12·01 to 17·02)	1·09 (−2·4 to 4·6)	0·537
High-density lipoproteins	46·6 (21·0)	47·1 (19·4)	0·636	4·5 (20·8)	46·6 (17·8)	0·222	−0·30 (−0·93 to 1·52)	0·61 (−0·37 to 1·58)	0·31 (−1·2 to 1·9)	0·695
Medication non-compliance	226 (15%)	93 (6·2%)	<0·001	230 (15%)	147 (9·6%)	<0·001	133/226 (58·8%)	83/230 (36·1%)	22·7%	<0·001

Data are n (%), mean (SD), n/N (%), mean difference (95% CI), or %. *The trial was stopped for futility after interim analysis, hence the difference in patient numbers at baseline and at follow-up at 1 year (2148 *vs* 1502 in the intervention group and 2150 *vs* 1536 in the control group).

Table 5: **Changes in secondary outcomes from baseline to follow-up at 1 year**

534 (38·0%) at 6 months, and 460 (32·4%) at 1 year. In the intervention group, a total of 231781 SMS messages or videos were delivered, and 38 545 (17·0%) acknowledgments of receipt were logged as missed calls. The intervention contamination questionnaire was completed by 1864 (86·7%) of 2150 in the control group, none of whom reported any knowledge of the study intervention material. The median number of workbook exercises completed by patients in the intervention group was nine exercises (IQR 4–14) of 15. Acknowledgment of receipt of the SMS messages and videos by the intervention group patients was low (17%).

Discussion

A structured semi-interactive stroke prevention package using SMS messages, videos, and a workbook did not lead to a reduction in recurrent stroke, myocardial infarction, or death in patients with subacute stroke. However, there were few composite cardiovascular events in both groups. In addition, there is a possibility of a type 2 error owing to reduced power because a high number of the patients could not be followed up. Improvement was noted in specific lifestyle behavioural factors at 1 year, such as smoking cessation, alcohol cessation, and medication compliance. The number of deaths in our study was slightly higher in the intervention group than in the control group, although this difference was non-significant. The increased proportion of deaths in the intervention group could be spurious and be because of a lower number of total events than expected.

The components of the intervention package were developed using formative research. The entire process of developing the intervention package took 1 year to complete and included rigorous formative research methods. The SMS messages, videos, and workbook had a good SMOG readability score, and after translation into 11 Indian regional languages, the interventional educational material was acceptable to the patients, relatives, and all health-care professionals involved in the study.[17] The trial showed a moderate to high fidelity of the intervention, with no contamination in the control group regarding knowledge about the interventional education package.

Despite all these measures, the intervention was not effective. Globally, and in India during two waves of COVID-19 pandemic lockdown, there was a reduction in the number of stroke patients presenting to hospital.[27] Increased awareness about healthy diets and a reduction

in exposure to air pollution and infections because of social distancing and face masks being worn could be plausible reasons for a reduction in stroke and coronary syndromes during lockdown. The recruitment of patients with only a mild stroke in the initial phase of the trial could be a reason for fewer vascular events than expected. Inadequate documentation of cardiovascular events by the research staff or non-reporting of events by the patients and relatives could also be reasons for a low event rate. However, we adopted several mitigation measures, such as frequent telephone calls by research staff to remind patients to inform staff of any new symptoms. It is also likely that there would have been a change in behaviour in the control group by virtue of participating in a trial and being monitored. Inclusion of a higher number of well established stroke centres in the trial could have contributed to a selection bias, and could have led to fewer vascular events compared with rates reported in community-based data.[5] Furthermore, the study cohort was younger than the average reported age group of patients with stroke or recurrent stroke,[28] with a median age of 56 years (IQR 18–88), and a longer follow-up period might have resulted in a higher number of cumulative events. We noted a surprisingly high representation of males in our trial cohort (72·6%). This could indicate a higher prevalence of stroke in men than in women in India but could also reflect gender disparities in access to stroke care.

The behavioural changes noted in smoking, alcohol intake, and medication adherence in the intervention group are promising. One small previous trial[12] noted increased adherence to medications in patients receiving SMS messages for a period of 2 months. A randomised controlled trial (RCT)[13] in patients with coronary artery disease observed reductions in systolic blood pressure and low-density lipoprotein and changes in lifestyle factors (eg, improved physical activity and smoking cessation) in patients receiving customised text messages. In a health-systems trial in Australia,[29] an integrated approach that involved coordination with primary health-care physicians, education of patients, and telephone tracking of progress showed a reduction in systolic blood pressure, cholesterol, and triglycerides, and a reduction from baseline in alcohol intake at 1 year. However, the study did not use customised text messages and vascular outcome was not an endpoint.

A relative reduction of 10% in alcohol use and of 30% in tobacco use in adults has been outlined as a target for 2025 by the Indian National Non-Communicable Disease Monitoring Framework.[30] In our study, between baseline and 1 year we achieved a relative reduction of 41% for alcohol use and 36% for smoking in the intervention group. The above findings are very important, not only for India, but also globally. Changes in lifestyle and behavioural factors can have substantial long-term effects on cardiovascular events and mortality. A small pilot trial[31] in Ghana, in which nurses used a smartphone-based intervention to monitor blood pressure, suggested that this intervention improved medication adherence and control of blood pressure after stroke compared with usual standard of care without a smartphone-based intervention. However, an RCT in Nigeria that compared use of text messages, educational videos, and financial incentives versus control found no significant difference in blood pressure at 1 year between groups.[32]

Our study has several strengths. It was a large, high-quality RCT and loss to follow-up was less than 1·5% despite the effect of the COVID-19 pandemic, although 69·9% in the intervention group and 71·4% in the control group were followed up at 1 year, as the trial was ended early. The intervention package was developed in 12 languages, representing increased generalisability within India. To our knowledge, this study was the first trial done within the INSTRuCT network and has led to capacity building among collaborators to do future large stroke trials in India, funded by the Indian Council of Medical Research.[16]

The follow-up duration initially planned for the study was 12 months; however, it was noted that about 15% of events occurred after 1 year. Acknowledgment of receipt of the SMS messages and videos by the intervention group patients was low (17%). Apart from the missed-call acknowledgment and the fidelity questionnaire, we did not have a definite means of confirming that the patients had watched the videos or read the SMS messages. Furthermore, in patients who were largely dependent on their caregivers, there was no way to confirm whether the SMS messages or videos were shared with, or viewed by, the stroke patient themselves. However, based on the process-evaluation fidelity questionnaire, the number of patients who viewed the SMS messages in the first few weeks and months revealed a moderate to high fidelity. It is possible that patients and relatives would have felt fatigued in replying by making a missed call. Furthermore, the pandemic added several challenges in the follow-up of patients. However, by use of several measures we were able to keep the loss to follow-up low. The secondary outcome measures were self-reported, with no assured way to confirm data, except via the patient's relatives, thereby introducing the possibility of a social-desirability bias. Also, the medication non-compliance data were not collected separately for antiplatelets, statins, antihypertensives, and antidiabetic medications. This trial was conducted in high-functioning centres with well functioning stroke units and an evidence-based standard of stroke care, which might have affected the absence of a significant outcome between the intervention and control groups. If implemented in lower-level care centres in the community, this intervention package might yield better outcomes when compared with standard care. Additionally, the centres involved in the study were all located in urban areas of the country. Whether the results obtained from this trial can be generalised to the entire Indian population requires further investigation.

There are several lessons that we can learn from this trial. Future large trials should identify the best intervention (ie, text messages or videos) to promote changes in health behaviour aimed at the control of risk factors. The beneficial effect of behavioural interventions might wear off over time. Studies need to be done to find out how frequently the mHealth interventions should be delivered for optimum effect. The ongoing process-evaluation findings will help us to answer some of these questions.[18] By contrast to traditional (and expensive) prospective population-based methodological approaches, smartphone technology offers a cost-effective way to gather information from potential study participants on a global scale. This intervention package would be cheaper economically than most of the existing secondary stroke interventions in India. Also, almost every person in India has a smartphone; therefore, this intervention can be easily scalable in highly populated countries such as India. mHealth interventions can be used as a post-stroke intervention for resource-constrained settings with a shortage of health-care personnel.

In conclusion, compared with standard care, a structured semi-interactive stroke prevention package did not reduce recurrent strokes, myocardial infarction, and death in patients with subacute stroke. There was an improvement in specific lifestyle behavioural factors, including adherence to medication, which might translate into long-term benefits. The role of mHealth interventions in the reduction of recurrent stroke and cardiovascular events has yet to be proven in large trials.

SPRINT India trial collaborators
See appendix pp 16–18.

Contributors
JDP conceived the trial, obtained the study funding, had full access to the data, and produced the draft of the manuscript. JDP and MPK were involved in study design. JDP, DA, SJV, AD, VR, and RH were the central coordinating team involved in data management. DA, SJV, AD, and VR were involved in data monitoring and central coordinating. RH was the technical head for EasyResearch and SMS and video delivery. HK and JDP led the statistical analysis with input from all the authors. JDP and MS led the administrative, technical, and material support. All the authors reviewed and approved the final draft of the manuscript. All authors had full access to the data from their centre and had final responsibility for the decision to submit for publication. DA and SJV accessed and verified the data.

Declaration of interests
We declare no competing interests.

Data sharing
The deidentified participant data that underlie the results reported in this Article (texts, tables, figures, and appendix) and the study protocol, statistical analysis plan, informed consent form, 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 assess the data, proposals should list the purpose of the study and analysis and be directed to: jeyarajpandian@hotmail.com.

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