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Research Article

Clinical Trial Participation and Health Behavior Modification: Secondary Prevention of Small Subcortical Strokes (SPS3)

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Abstract

Background: Smoking, alcohol use, and physical inactivity represent health behaviors that, if modified, may significantly reduce the burden of stroke.

Purpose: To evaluate the impact of trial participation on health behavior modification.

Methods: Secondary Stroke Prevention Study (SPS3) enrolled 3020 subjects followed for an average of 3.7 years. This analysis included 2983 subjects. Univariate and hypothesis tests compared the SPS3 group at baseline with the general population (CDC 2009, n=227,371). In the SPS3 group, Kaplan-Meier plots were used to determine baseline to behavior changes. Log-rank tests were used to determine the influences of age, gender, education, ethnicity, interviewer type, and intervention method.

Results: SPS3 subjects were more likely to stop smoking than to start (38% vs 4 %; $p<0.001$) over the course of the study. Blacks and those older than 65 were the least likely to stop smoking ($p<0.0001$; $p=0.05$ respectively). Subjects who used alcohol regularly were more likely to stop than to start (47% vs 7%; $p<0.001$) over the course of the study. Hispanics and subjects counseled by physicians were more likely to stop drinking ($p<0.0001$; $p=0.01$ respectively). There was no significant net benefit for exercise.

Conclusion: Sustained health behavior modifications are attainable and best facilitated by a systematic approach with regular patient contact.

INTRODUCTION

Stroke is the fourth leading cause of death, and it is also a major cause of long-term disability. About 80% of patients return home after a stroke, but about half of these need permanent or temporary care in the home or nursing facility setting. Recurrent strokes account for almost 25% of the 795,000 cases in the United States each year [1]. Of the 610,000 patients with a new stroke, 14% are expected to have a second stroke within one year. The direct cost for stroke is estimated to increase from $71.55 billion in 2012 to $183.13 billion in 2030 [2]. Given the clinical and public health burden of stroke, it is important to focus our attention and resources on modifiable risk factor management strategies for secondary stroke prevention. The 2010 AHA Special Report categorized cardiovascular risk factors into health behaviors (i.e. smoking) and health factors (i.e. LDL). Among the modifiable health behaviors, smoking, alcohol use, and physical inactivity represent treatment targets that may significantly reduce the burden of stroke if these behavioral changes are sustained over time [3].

Smokers are twice as likely to have a stroke compared with non-smokers [4,5]. This risk is recognized among passive smokers as well. As observed in the Framingham Study and the Nurses' Health Study, smoking cessation reduces stroke risk to almost that of a nonsmoker within 2 to 5 years [6,7,8].

Moderate consumption of alcohol may reduce cardiovascular disease, including stroke. A meta-analysis of stroke studies showed a J-shaped association curve for alcohol consumption and ischemic stroke [9].The relative risk of ischemic stroke associated with moderate alcohol use (1-2 drinks per day) when compared with non-drinkers is between 0.3 and 0.5 and increases to 2 for individuals consuming three or more drinks per day [10].

Physical inactivity increases the risk for stroke because of its effect on obesity, metabolic syndrome, and hypertension [2]. Regular physical activity reduces stroke risk through the moderation of atherosclerotic disease. It reduces blood pressure, weight, and pulse rate; raises HDL cholesterol and lowers LDL cholesterol; and it promotes tendency to healthy diet and smoking cessation [11,12].

Successful risk factor management is estimated to reduce stroke recurrence by up to 80% [13]. Unfortunately, preventive measures and promotion of healthy lifestyle are difficult to implement and even more difficult to sustain. Recommendations are oftentimes not consistently followed in practice by patients or physicians. Medication noncompliance among patients is relatively high, between 50% and 75% [14]. Stroke risk factors like hypertension are optimally managed in only 60% of patients [15]. Literature points to non-systematic approaches to clinical care as one barrier to effective risk factor management [16]. Although literature suggests that clinical trials with its systematic approaches may have a positive effect on participant outcome, these indirect "trial effects" are not well studied [17-20].

AIMS

Secondary Prevention of Small Subcortical Strokes (SPS3) is a large randomized clinical trial (RCT) that assessed the effects of anti platelet therapy and blood pressure control on stroke recurrence and cognitive decline [21,22]. Within the context of the SPS3 study, we evaluated the impact of participation in a trial designed with systematic clinical care guidelines on health behavior modifications by assessing changes in smoking, alcohol use and exercise habits.

METHODS

SPS3 is a randomized, multicenter clinical trial, sponsored by the U.S. NINDS/NIH. Details of the study design have been published [21,22]. In summary, patients were eligible if they had a clinical lacunar stroke syndrome with brain MRI confirmation in the six months prior to enrollment. Patients were randomized following a 2-by-2 factorial design to two interventions: (i) anti platelet therapy: aspirin (325 mg/day) vs. aspirin (325 mg/day) plus clopidogrel (75 mg/day) (double blind, placebo control); and (ii) two target levels of systolic blood pressure control: "higher" (130-149 mmHg) vs. "lower" (<130 mmHg).

Patients were seen monthly for the first 3 months post randomization and then quarterly thereafter. These study visits were conducted by the study coordinator (nurse) and/or the study physician (neurologist or internist). Quarterly visits lasted about 45 minutes and followed a template for neurological/physical evaluations, health status updates, medication reviews, and discussion of health behaviors such as smoking, alcohol use, and exercise. The depth of these discussions and the extent of subsequent interventions were left up to individual study centers. Annual study visits lasted about 2 hours. These included additional safety labs, cognitive examinations, and quality of life questionnaires. At the conclusion of the study, a survey was sent to all study centers to ascertain information concerning the clinician conducting these study visits (nurse vs. physician) and the method of health behavior management (discussion only vs. discussion with action – i.e. referral to specialists, nutritional counseling).

Study sample: A total of 3020 patients were randomized into the SPS3 study between 2002 and 2012 and followed for an average of 3.7 years. Of these, 2,983 (98.7%) patients had at least one quarterly follow-up visit and were therefore included in the present analysis. The baseline comparison group is derived from the 2009 CDC census (n= 227,371). This comparison group was used to determine that the SPS3 subjects did not deviate significantly from the general population in terms of the health behaviors being studied.

COVARIATES

1) Smoking status- Subjects self-reported status at quarterly visits as "current", "former", or "never". If "current", subjects were asked to report the average number of cigarettes per day, followed by a discussion of smoking risk. Depending on the individual centers, suggestion for smoking cessation groups and/or nicotine patch may be offered.

2) Alcohol use- Subjects were asked if they regularly used alcohol. Regular use was defined as at least one or more alcoholic drinks during a 7-day period. If 'yes', then they were asked the number of days per week and the quantity per week. This was followed by a discussion of recurrent stroke risk associated with alcohol use and contraindications with medications. Depending on the center, suggestions for support groups and intervention with the primary care physician may be offered.

3) Exercise- Regular exercise is self-report of at least three days per week of physical exertion sustained for at least 10 minutes exclusive of work and home activities. Patient's weight at each clinic visit was included in the health behavior discussion. Depending on the center and insurance coverage, suggestions for gym and/or other activity programs may be offered.

4) Interviewer- An end of study survey collected information regarding study visit interviewer from each site. The two final categories were: nurse vs. physician.

5) Intervention method- An end of study survey collected information regarding intervention methodologies from each site. The two final categories were: discussion only vs. discussion with action. Common actions included

notification to the patient's primary care physician and referral to specialists (i.e. smoking cessation, nutritional counseling).

Data analyses: Univariate and hypothesis tests were performed to determine differences between the SPS3 group at baseline and the general population (CDC). Kaplan-Meier plots were used to determine time from baseline to behavior changes. Log-rank tests and Cox proportional modeling were performed to determine influence of age, gender, education, ethnicity, interviewer type and intervention method on risk factor outcomes.

RESULTS

The 2009 CDC census (n=227,371) was used as a comparison group for the SPS3 sample in regards to the three health behaviors. Baseline smoking status was comparable between the SPS3 and CDC groups (20.4% vs 20.6%). Significant age differences were not noted. Smoking was more prevalent in SPS3 Blacks (31.1%) than in CDC Blacks (20.4%). Baseline regular alcohol use was significantly lower in the SPS3 group (28.1%) compared with the CDC group (52%).

Cigarette smoking

Of the 2983 subjects, 610 (20%) smoked at baseline. Over the course of the study, 367 (60%) smokers quit but only231 (38%) remained non-smokers at the last study visit. The data suggests a positive net trial participation benefit in that smokers were much more likely to quit (38%) than non-smokers were to start over the course of the trial (4%; p<0.001) (Table 1).

There was a highly significant effect observed between race and the rate of smoking cessation with Blacks the least likely to stop smoking over the course of the study (p<0.001) (Figure 1). Fitting a Cox proportional hazards model with race as a predictor suggests a marginally significantly higher smoking cessation rate in Whites vs. Blacks (HR=1.39; 95% CI: 0.99, 1.98) and a significantly higher smoking cessation rate in Hispanics vs. Blacks (HR=2.13; 95% CI: 1.5, 3.1). There was also a marginally significant association observed between age at baseline and the rate of smoking cessation that suggests younger patients (≤64 years old at baseline) were more likely to stop smoking over the course of the study (p=0.05) (Figure 2). Fitting a Cox proportional hazards model with age group as a predictor shows that younger patients were almost 1.4 times more likely to stop smoking over the course of the study compared with older patients (HR=1.39; 95% CI: 1.00, 1.95). No significant differences in the rate of smoking cessation were found with respect to gender (p=0.89), education (p=0.17), interviewer type (p=0.37), or intervention method (p=0.28).

Table 1: P Smoking Status of SPS3 Subjects at Baseline and Last Study Visit.

	Non-Smoker (at last study visit)	Smoker (at last study visit)	
Non-Smoker (at baseline)	2289 (96%)	85 (4%)	P<0.001
Smoker (at baseline)	231 (38%)	379 (62%)	

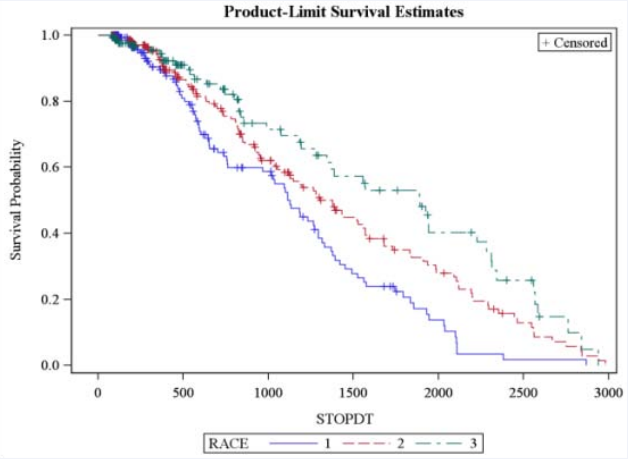

Figure 1 Time to Smoking Cessation by Race/Ethnicity for SPS3.

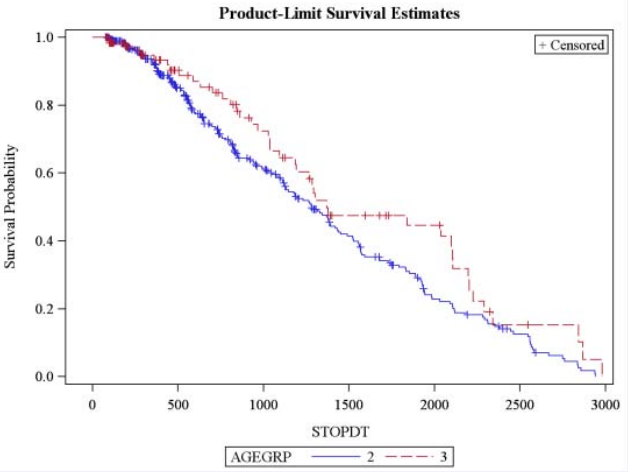

Figure 2 Time to Smoking Cessation by Age Group for SPS3 Smokers.

Alcohol use

Of the 2983 subjects, 838 (28%) drank regularly at baseline. Over the course of the study, 536 (65%) subjects quit but only393 (47%) remained non-drinkers at the last study visit. The data suggests a positive net trial participation benefit in that those who drank at baseline were much more likely to quit (47%) than non-drinkers were to start over the course of the study (7%; p<0.001) (Table 2).

There was a highly significant effect observed between race and cessation of alcohol use with Hispanics the most likely to stop alcohol use during the study (p<0.001) (Figure 3). Fitting a Cox proportional hazards model with race as a predictor suggests no significant difference between Whites and Blacks for cessation of alcohol use, but a highly significant increase in cessation of alcohol use for Hispanics versus the combined group of Whites and Blacks (HR=2.14; 95% CI: 1.62, 2.82). There was also a highly significant effect observed between the type of interviewer and the cessation of regular alcohol use that suggests subjects seen only by the nurse were less likely to stop regular alcohol use during the study (p=0.01) (Figure 4). Fitting a Cox proportional

Table 2: Alcohol Use Status of SPS3 Subjects at Baseline and Last Study Visit.

	Non-Alcohol User (at last study visit)	Alcohol User (at last study visit)	
Non-Alcohol User (at baseline)	1992 (93%)	154 (7%)	P<0.001
Alcohol User (at baseline)	393 (47%)	445 (53%)	

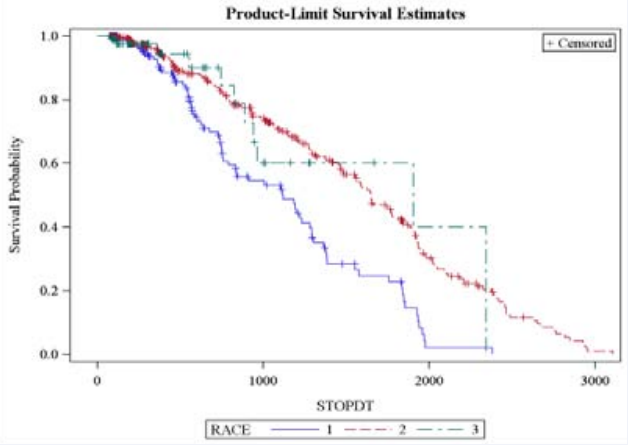

Figure 3 Time to Cessation of Alcohol Use by Race/Ethnicity for SPS3 Alcohol Users.

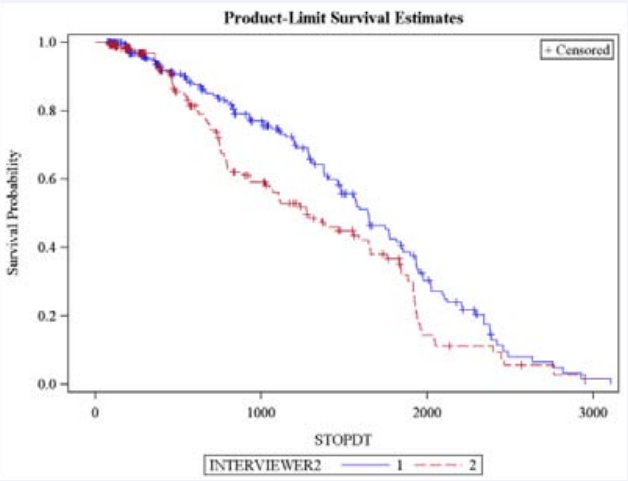

Figure 4 Time to Stopping Alcohol Use by Interviewer Type for SPS3 Alcohol Users.

hazards model with interviewer type as a predictor suggests a hazard ratio of 0.70 (95% CI: 0.54, 0.93). No significant differences were found with respect to gender (p=0.07), education (p=0.10), age at baseline (p=0.19), or intervention method (p=0.61).

Physical exercise

The data suggest no net benefit of trial participation with respect to exercise. The proportion of subjects who did not exercise at baseline and started exercising at the latest study visit (36%) was similar to the proportion of subjects who did regularly exercise at baseline and stopped exercising at the latest study visit (38%; p = 0.12) (Table 3).

Of the 2983 SPS3 subjects, 1467 (49%) subjects did not exercise regularly at baseline. Of these, 1157 (79%) started exercising at some point during the study but only 575 (38%) continued to exercise by the end of the study. No significant differences were found with respect to age at baseline (p=0.47), gender (p=0.33), education (p=0.53), race (p=0.34), or interviewer type (p=0.84). Nevertheless, there was a highly significant effect observed between intervention method and the initiation of exercise (p = 0.006). The Kaplan-Meier plot of time from baseline to starting regular exercise by intervention method suggests that "discussion only" was more effective than "discussion with action". Fitting a Cox proportional hazards model with intervention method as a predictor suggests a hazard ratio of 1.49 (95% CI: 1.12, 1.99).

At the end of the study, a survey was distributed to each site to obtain information about the study visit interviewer and counseling method. Of the 49 (60%) SPS3 participating sites that returned the survey, 61% of the sites reported the nurse as the primary interviewer. "Discussion only" was reported as the main intervention method for tobacco use (61%), alcohol use (75%), and exercise (61%).

DISCUSSION

In summary, the data suggests net trial participation benefit in modifying smoking and alcohol use behaviors. SPS3 subjects were much more likely to stop smoking than to start smoking over the course of the study. Blacks and those older than 65 were the least likely to stop smoking. Study subjects who were regular alcohol users were more likely to stop than to start over the course of the study. Hispanics and subjects counseled by physicians were more likely to stop alcohol use. There was no significant net benefit for exercise.

Of the three modifiable health behaviors evaluated in this study, only exercise failed to see sustained improvements. One can argue that subjects with minor to moderate functional residuals could have reduced abilities to exercise or to sustain exercise over the course of the study. Furthermore, the average age subjects at study entry was 62, a group that is less likely to participate in regular exercise and more likely to suspend the routine due to other health issues. Subjects were more likely to start exercising based on "discussion only" rather than "discussion with action". We speculate that patients short on time and resources may have chosen noncompliance with prescribed interventions such as gyms, support groups, nutritionists, etc. whereas "discussion only" was more likely to prompt self-directed lifestyle modifications which did not require additional resource or expense (i.e. walking).

Table 3: Exercise Use Status of SPS3 Subjects at Baseline and Last Study Visit.

Baseline Status	No Exercise (at last study visit)	Exercise (at last study visit)	
No Exercise (at baseline)	942 (64%)	524 (36%)	P=0.12
Exercise (at baseline)	575 (38%)	942 (62%)	

Although health behavior or lifestyle factor modification is an important aspect of primary and secondary stroke prevention, ensuring long-term adherence to recommendations is challenging. Jin et al. estimate that compliance with long-term medication therapy is between 40% and 50% and that compliance with short-term medication therapy is between 70% and 80%. Nevertheless, compliance with health behavior changes is only 20% to 30% [23]. This suggests that changing health behaviors remains the most challenging arena in risk factor modification. Studies in behavior modification highlight the complexities of helping patients to accept the need to change, to find the motivation to change, to act on the prescribed plan, and finally to persist with the modified behavior [24-27]. Our findings indicate that participation in the SPS3 study resulted in behavior modification regarding alcohol use and smoking, net gains for the patients. Whether these modifications persisted after completion of the study remains unknown.

As with other clinical trials, we recognize the possibility of a healthy volunteer effect, though difficult to quantify, in our study. Patients who are selected or volunteer are more likely to make lifestyle changes [28,29]. Less certain and not well studied is the causative effect of the disease event (stroke) as a trigger for the patient's subsequent behavior changes [30].

Although many primary care physicians recognize and advocate for systematic clinical guidelines, they are often constrained by time and resources. Moreover, because clinical trialists usually focus on primary outcomes, indirect effects like health behavior changes are overlooked. In contrast to the heterogeneity of normal clinical practice, subjects in clinical trials follow systematic medical treatment protocols. These guide clinicians through explicit processes of care that can result in improved outcomes for trial participants in both intervention and control groups (the "trial effect"). Accordingly, we propose that general clinicians incorporate a systematic element to their clinical care analogous to the standardized protocols used in clinical trials such as SPS3. Furthermore, we propose that future stroke clinical trials incorporate and experiment with health behavior management methodologies in their designs in order to more fully answer some of the questions we have introduced in this paper.

We recognize the limitations inherent in this post-hoc analysis from a randomized clinical trial. Since lifestyle modification interventions were left up to individual study centers, leading to variations among individual clinics, results garnered in this analysis are suggestive rather than conclusive. Although we captured data at baseline, first behavior change, and latest study visit, we were not able to evaluate compliance over time. In future studies, additional scrutiny in this area may help better define time windows for beneficial health behavior changes. Nevertheless, these promising results should encourage and generate discussions on lifestyle modification methodologies in stroke prevention.

CONCLUSION

Given the clinical and public health burden of stroke, it is important to focus our attention and resources on modifiable risk factor management strategies in secondary stroke prevention. Experience gained from the SPS3 trial is that sustained health behavior modifications are best facilitated by structured patient contact, wherein health behaviors can be systematically reviewed with patients.

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Clinical Trial Registration Information: www.clinicaltrials.gov NCT00059306

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