Preventing recurrence of thromboembolic events through coordinated treatment in the District of Columbia

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Rationale **PROTECT DC examines whether stroke navigators can improve cardiovascular risk factors in urban underserved individuals newly hospitalized for stroke or ischemic attack. Within one-year of hospital discharge, up to one-third of patients no longer adhere to secondary prevention behaviors. Adherence rates are lower in minority-underserved groups, contributing to health disparities. In-hospital programs increase use of stroke prevention therapies but may not be as successful in underserved individuals. In these groups, low literacy, limited healthcare access, and sparse community resources may reduce adherence. Lay community health workers (navigators) improve adherence in other illnesses through education and assisting in overcoming barriers to achieving desired health behaviors and obtaining needed healthcare services.**

Aims and design **PROTECT DC is a Phase II, single-blind, randomized, controlled trial comparing in-hospital education plus stroke navigators to usual care. Atherogenic ischemic stroke and transient ischemic attack survivors are recruited from Washington, DC hospitals. Navigators meet with participants during the index hospitalization, perform home visits, and meet by phone. They focus on stroke education, medication compliance, and overcoming practical barriers to adherence. The interventions are driven by the theories of reasoned action and planned behavior.**

Study outcomes **The primary dependent measure is a summary score of four objective measures of stroke risk factor control: systolic blood pressure, low-density lipoprotein, hemoglobin Hb A1C, and antiplatelet agent pill counts. Secondary outcomes include stroke knowledge, exercise, dietary modification, and smoking cessation.**

Conclusion **PROTECT DC will determine whether a Phase III trial of stroke navigation for urban underserved individuals to improve adherence to secondary stroke prevention behaviors is warranted.**

Key words: clinical trials, community health education, health behavior, healthcare disparities, patient adherence, patient compliance, secondary prevention, stroke

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Introduction

Stroke remains the third leading cause of death and a leading cause of adult disability in the United States. Healthcare costs related to stroke total over US$50 billion per year in the United States alone (1). Decades of research in cardiovascular risk reduction have led to guidelines which, if optimally implemented, could prevent secondary stroke in 50–80% of patients (2).

Stroke is particularly prominent in urban underserved populations. Sacco and colleagues found a 2·4-fold greater stroke incidence in African Americans and a twofold increase in Hispanics compared with Caucasians, with higher mortality and lower three-year survival (3). At older ages, when stroke mortality is the highest, the stroke mortality rate in

non-Hispanic Caucasians approached the stroke mortality rate of African Americans (4). Compared with Caucasians, minority groups suffered greater neurological impairment and had poorer outcomes (5, 6).

Adherence to evidence-based therapies for the prevention of ischemic stroke in patients remains inadequate. Even in the general population, there is marked room for improvement in the implementation of antithrombotics, lipid-lowering therapies, antihypertensives, and smoking cessation counseling in individuals who have experienced a cerebrovascular event (7), particularly in African Americans. Superimposed are racial differences in the use of aspirin and smoking cessation for secondary prevention in veterans with coronary artery disease (8). African Americans are less likely to receive a comprehensive diagnostic evaluation compared with white patients and are less likely to have a neurologist as their attending physician (9).

Several barriers to stroke prevention have been identified in minority populations. A telephone study in African Americans found that stroke knowledge was related to stroke risk factors and that stress and inadequate finances were the most frequently reported barriers (10). Schneider and colleagues found that individuals with the highest risk and incidence of stroke, including African Americans, were the least knowledgeable about stroke warning signs and risk factors (11). Reasons for these disparities likely include cultural, biological, and environmental factors (e.g. access to healthcare, education and socioeconomic status (SES), variations in lifestyle, religious and cultural beliefs, language barriers, and genetic factors). Resolution of these disparities is urgently needed to improve the health status of underserved communities.

Education of patients is one approach to overcoming these issues, and in-hospital education has been emphasized by many organizations. For example, the American Heart Association (AHA) 'Get with the Guidelines' effort (12) uses in-hospital presentation of education materials about stroke and management of cardiovascular risk factors (13). Other efforts have increased the intensity of the patient's in-hospital education experience by incorporating a nurse educator into this process. For example, the original PROTECT LA study (14) used a nurse to educate a predominantly white high SES stroke population who later self-reported increased adherence to medications and other risk factor modification efforts (14, 15).

Other programs have demonstrated success in targeting underserved populations. Rimmer *et al.* (16) evaluated a 12-week health promotion intervention for a predominantly black population with stroke. Improvements in total serum cholesterol, cardiovascular fitness, and strength were achieved compared with the control group. A related example of coordinated care for stroke patients is STEPS CARE: A Post Discharge Intervention to Improve Stroke Outcomes. STEPS CARE was a randomized clinical trial (RCT) of a geriatrics-based model of post acute care provided by a geriatrician and advanced practice geriatrics nurse. Results of a preliminary study showed improvements at three-months in a health and function global end-point composed of five domains (17).

The overall aim of this project is to perform a Phase II RCT designed to prepare for a Phase III assessment of whether PROTECT DC (hospital-based initiation of secondary prevention strategies coupled with stroke navigation) can significantly reduce secondary vascular events (stroke, MI, and vascular death) rates in an underserved population at high risk for subsequent stroke or serious cardiovascular events. Health navigators are lay health workers recruited from the community to be served; they are trained and supervised by physicians, nurses, social workers, or health educators (18). The goal of navigation is to improve self-management of chronic diseases and to reduce the barriers to healthcare. Since only 20% of disease self-management skills are disease specific (19), we expect that techniques developed in other conditions will be relevant to stroke patients. Navigation is effective in increasing compliance in primary care (20), diabetes (21, 22), cancer (23), cardiovascular disease, HTN (24, 25), and asthma (26). Our goals are to refine the intervention and gather data necessary to design that Phase III trial.

Methods

Design

In this Phase II trial, a total of 250 participants admitted to four acute care urban hospitals and one rehabilitation hospital for atherogenic stroke are being randomized. In the experimental arm, community-based 'stroke navigators' facilitate compliance and health care access. The usual and customary care control arm consists of the American Heart Association (AHA) materials tailored for African Americans ('Power to End Stroke' http://www.powertoendstroke.org) distributed during hospitalization.

The primary dependent measure will be the percentage of four objective markers of stroke risk that are normal one-year after stroke onset. Effects on secondary behavioral goals will also be evaluated; the eight PROTECT DC goals are listed in Table 1. Vascular event rates will be measured to optimize study methodology and inform sample size calculation for a subsequent Phase III trial.

The National Rehabilitation Hospital is the coordinating site and the Institutional Review Board (IRB) of record is Georgetown University. PROTECT DC is designated a

Table 1 Primary PROTECT DC goals

Primary goals	1. Compliance with prescribed antithrombotic therapy confirmed by pill count
	2. Normal systolic blood pressure
	3. Normal LDL
	4. Normal HbA1c
Secondary goals	5. Compliance with smoking cessation
	6. Compliance with American Heart Association diet
	7. Compliance with exercise regimen
	8. Stroke awareness

minimal risk study. The study is funded by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health and a supplemental grant from National Center on Minority Health and Health Disparities.

Patient population

The study sample is intended to be representative of stroke patients in the District of Columbia (DC), a region over-represented in African Americans and low SES individuals. No racial, ethnic, or gender groups are excluded. Participants are recruited from the inpatient stroke services from five hospitals that serve a majority of the stroke patients within DC: Washington Hospital Center, Howard University Hospital, Georgetown University Hospital, Providence Hospital and National Rehabilitation Hospital (NRH). Potential participants are identified from emergency department and hospital admission records; coordinators screen and consent participants (Fig. 1).

The sample consists of adults (age >18) hospitalized within 30 days of an ischemic stroke or TIA due to atherogenic cerebrovascular or cardiac disease. Ischemic stroke is defined as rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 h. In the case of TIA or clinical stroke with no lesion visualized on neuroimaging, a stroke neurologist confirms the diagnosis. Atherogenic stroke is defined as large vessel, small vessel, or cryptogenic etiology with at least one stroke risk factor (27). Persons with embolic stroke due to atherogenic cardiac disease are also included. Participants reside within DC or within five miles of the DC border. A caregiver or interested party must be available if the participant is moderately or severely disabled. To minimize loss to follow-up, a sufficient number of collateral contacts (more than three preferred) are required. Subjects must be judged likely to return to community setting at completion of postacute care.

Individuals are excluded if they have one or more of the following:

- nonatherogenic cause of stroke or embolic stroke due to nonatherogenic heart disease
- NIHSS >20
- any medical condition that would limit participation in follow-up assessments
- baseline dementia per informant report (AD 8 (28)) or screening assessment (Short Blessed Memory Orientation Concentration Test (29)).

Randomization

Study participants are randomized to navigation or control in a 1 : 1 ratio using a baseline adaptive randomization algorithm, stratified by recruitment site. The algorithm uses Pearson's χ^2 statistic to measure treatment imbalance in baseline NIHSS (≤ 6 vs. >6), age (≤ 65 vs. >65) or gender (30, 31). A new subject is randomly assigned with probability 0·75 to the group that would achieve the best treatment balance among these three characteristics. The first 12 participants in each site were randomized with a fair coin, and their baseline characteristics used to start the adaptive randomization. The randomization algorithm is embedded in a web-based data management application, and treatment assignments are available immediately upon baseline data entry. The inclusion/exclusion criteria were incorporated into the application to ensure all randomized patients are eligible. We chose to stratify randomization based on the admitting hospital because of concerns that differences in hospital practices and procedures could be a source of systematic bias. These biases could stem from differences in patient populations, acute management, post-discharge planning and support, or other unanticipated

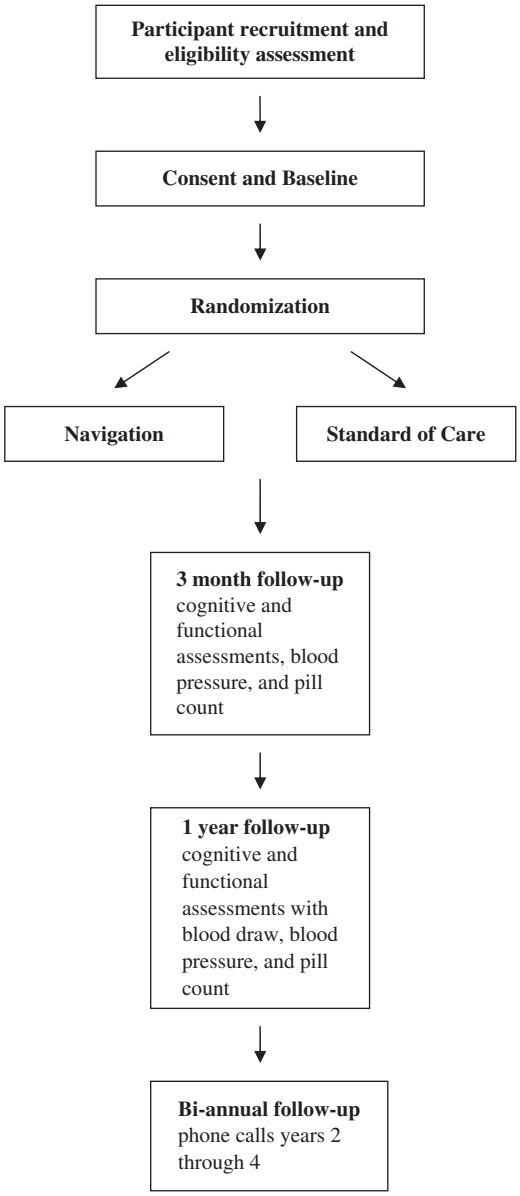

Fig. 1 Study design.

factors. Stratified randomization by hospital will minimize these effects.

Experimental intervention

Participants randomized to the experimental arm initially meet the stroke navigator as an inpatient; that same navigator becomes the primary navigator for that participant during the one-year intervention. At hospital discharge, the navigator ensures that the patient has a participant handbook specific to the assigned treatment group, tailored AHA educational materials, and prescriptions. After discharge, the stroke navigator assesses adherence and actively screens for barriers to medication adherence and access to healthcare services. The navigators also provide tailored health education regarding each of the primary and secondary study goals namely medication compliance, smoking cessation, AHA diet, physical activity/exercise and stroke awareness. Interactions occur with a minimum of two home visits and monthly phone calls. Many individuals need more frequent contact to help resolve family and social barriers to adherence that are identified. Techniques used include motivational interviewing, application of the principles of health behavior, and practical problem solving regarding issues such as transportation, insurance, and fear of medication side effects. Navigators interact with primary care doctors when necessary and assist the participant in obtaining medications. Aside from navigation, no additional resources are provided to participants by the study. Navigators are supervised by a team of physicians, health educators and social workers on a daily basis.

The PROTECT DC intervention is based on the Theories of Reasoned Action and Planned Behavior (TRA, TPB) (32, 33). Thus, navigators focus efforts on increasing the participant's behavioral intention toward taking medications, not simply toward avoiding stroke. They also focus on increasing the participant's actual and perceived control over barriers to adherence. The TRA/TPB model provides several targets for improving medication compliance for secondary stroke prevention. For example, education of the individual/family caregivers/healthcare providers about medications' beneficial effects can tilt behavioral and normative beliefs more firmly toward compliance. Motivation is likely to be highest immediately after stroke, during the acute hospitalization. Education about solutions to difficulties in taking medication and assistance in elimination of barriers, increases the individual's perception of control over their situation, again increasing the likelihood of adherence.

Control intervention: usual and customary care

The control intervention retains subjects while minimizing any study-related impact on stroke prevention behaviors. The control intervention is a standardized version of the usual and customary care delivered at each hospital, and participants receive the same tailored AHA materials as the experimental arm without navigator input. Control subjects are provided with a participant handbook specific to their study assignment. Control subjects are contacted by phone monthly to confirm contact information and to inquire about hospitalizations. If the participant requests information, study staff mail relevant materials.

Blinding

Blinded raters obtain all follow-up data. Raters are supervised by research staff outside the study; participants are instructed not to reveal their treatment assignment. Vascular events, rehospitalizations, and other clinical events are adjudicated by a physician blinded to treatment assignment.

Baseline data

Trained study coordinators collect data regarding demographics, cognitive status (1), stroke type, and severity.

Table 2 Selected study assessments

	Domain assessed	Baseline	3-months	12 months
History and physical	Medical status	X		
Vital signs	Medical status, risk factor management	X	X	X
Demographics	Social and economic status	X	X	X
NIH Stroke Scale	Stroke severity	X	X	X
Cognitive assessments		X	X	X
Geriatric Depression Scale				
Vascular Dementia Battery				
Functional assessments	Disability, participation	X	X	X
Barthel Index				
Modified Rankin Scale				
Lawton Instrumental ADL				
Activity Card Sort				
WISSE diet				
Physical activity log				
Short Form-12				
Laboratory data (LDL, Hb A_{1C})	Risk factor management	X		X

Prestroke functional status, health behaviors, and health beliefs are also assessed. Selected baseline measurements can be found in Table 2.

Primary outcome measures

The primary dependent measure is defined as the proportion of four objective measures of stroke risk (SBP, LDL, Hb A_{1C}, and antiplatelet compliance documented by pill count) which are within normal range (34) (Table 3) at the primary time point of one-year. Compliance with antiplatelet agents is defined as pill counts documenting use of 80% of prescribed medication (35). Risk factors that are within normal limits at study enrollment (e.g., normal prerandomization Hb A_{1C}, LDL, SBP) will be included in this analysis. These are physiological indicators of stroke risk that are the targets of secondary stroke reduction efforts and are intermediate steps to vascular event rate reduction. Each is associated with medication compliance. A secondary analysis of these measures will examine whether PROTECT DC improved laboratory values by a clinically significant amount. For those participants prescribed more than one antiplatelet agent, compliance with each will be averaged into a single value.

Secondary outcome measures

Four stroke prevention behaviors were defined as secondary goals of navigation (Table 3). The rate of primary vascular events is another secondary measure; these are defined as the documented occurrence of a subsequent stroke, MI, or vascular death. Subjects and families will be contacted annually, and medical records will be obtained where available for review for blinded adjudication.

A secondary aim of the study is to assess the contribution of health status, depression, cognition, SES, race and other factors to the incidence of barriers and the rate of response to the study interventions. Covariates collected to achieve this aim include measures of disability (Barthel Index, Functional Independence Measure and Lawton Instrumental ADL scale), social participation (Activity Card Sort), and HR-QOL (SF-12 and Stroke Impact Scale). These measures are collected at baseline and at the one-year assessment by a blinded rater.

Ethics approval

All hospitals participating in this study have received IRB approval; Georgetown University is the primary study IRB. This trial is registered in clinicaltrials.gov (NCT00703274).

Data quality

Data quality control includes data checks that are built into a data system to ensure the integrity of all data entered for each study participant. These checks include range validator for continuous variables, date and time pickers, and comparison validators for consistency checks. In addition, the database contains an audit trail of all data entries and edits with the username and timestamp to monitor data entry and updates.

The web-based system also contains reports of form status (completed, pending, or missing) and a report of key variables to regularly check for data completeness and accuracy of these data elements.

The second component of quality control process is a 100% check of the baseline data in addition to annual 10% CRF verification audits at each hospital to compare data in the study database to data on CRF documents. The audit includes verification of signed informed consents, checks for lab procedures and records, verification of measurement tool specifications, and checks that the clinical staff has up to date study documentation available. Data errors are reported to the study team for correction and a data entry error rate is established after each audit.

Adverse event monitoring

Adverse events from this protocol are reported to the IRB. Because navigation is a minimal risk intervention, adverse events are monitored by the study investigators. A formal Data Safety and Monitoring Board was not appointed.

Sample size

Sample size was determined based on a two-sided Wilcoxon rank-sum test to compare the proportion of normal secondary prevention stroke risk measures – a nonnormally distributed outcome – in navigation and control groups. To achieve this, a

Table 3 Medication compliance goals

Medication goal	Primary analysis: normalization	Secondary analysis: clinically significant improvement
LDL	LDL < 100 mg/dl (< 70 for very high risk)*	1 mmol/dl
SBP	SBP < 120 mmHg	SBP 10 mmHg reduction
Hb A_{1C}	< 7%	1% reduction
Antiplatelet therapy	Pill count documentation of 80% of prescribed medications taken	Pill count documentation of 50% of prescribed medications taken

*Very high risk defined as patients who have established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides (200 mg/dl) with low HDL cholesterol (40 mg/dl)), and (4) patients with acute coronary syndromes (34).

sample size using Student's *t*-statistic assuming a 0·05 significance level and 80% power was first calculated, and then adjusted based on the lower bound of the asymptotic relative efficiency of the Wilcoxon rank-sum test relative to the *t*-test (i.e. inflating the sample size by 15·7%) (36). Pilot data were obtained from the PROTECT LA study (15) in which the mean and standard deviation of the proportion of risk factor compliance were 0·690 and 0·21 in the intervention group, and 0·585 and 0·27 in the control group. The sample size required is 198. However, a 20% dropout rate was assumed; hence the target for enrollment is 230 participants.

Statistical analyses

Descriptive statistics will be computed for all study variables including average follow-up time, retention rate, protocol deviations, and violations, and will be compared by treatment group. The primary analysis will be performed according to the principle of intention to treat. Given that adaptive randomization was used to assign patients to treatment or control, all outcome analyses will be conducted by regression analyses adjusted by the factors used in the adaptive randomization (37, 38). A nominal *P* value of 0·05 or less will be considered as statistically significant in the primary analysis. Linear, logistic or ordered logistic regression will be used as appropriate depending on the distributions of the outcome measure. Assessment of the fit of the models will be made using residual plots for continuous variables and other measures of goodness of fit such as the Hosmer Lemeshow test for categorical response models.

A sequence of *post hoc* analysis will be conducted depending on the results of the analyses of the primary outcome. If no statistically significant difference is found between the intervention groups, we will perform *post hoc* analyses to elucidate whether the negative finding was likely due to true absence of a treatment effect, or to design factors that resulted in an underpowered study. Careful examination of these issues is critical for considering the feasibility and utility of a future Phase III trial of the PROTECT DC intervention. Analyses will also be performed by subgroups, such as by race and age, in order to determine whether there is any differential efficacy found among any key subgroups of patients. If statistically significant differences are found between treatment and control arms, we will conduct regression analyses. They will be further adjusted by variables selected based on a combination of clinical judgment and descriptive statistical findings comparing baseline characteristics between the control and PROTECT DC intervention groups. These adjustments will help describe the likely pathways by which the treatment influenced outcome. Additional analyses will assess the patient's adherence to the intervention. Similar methods will be used to assess the impact of the PROTECT DC intervention on secondary behavioral goals.

Finally, we will conduct analyses to refine the inclusion/exclusion criteria to identify those who cannot respond to the intervention. This will help in planning a subsequent Phase III trial of the PROTECT DC intervention. Specifically, we will seek to identify baseline barriers such as poorer health status, depression, SES, and other potential barriers that are associated with less favorable response to the PROTECT DC intervention at the one-year follow-up. Any barriers found to be associated with a significantly reduced response to intervention will be further examined at the patient level to ensure that all the possible barriers/factors are considered. Participant-specific barriers will be assessed by the stroke navigators using various sources of information including participants, caregivers, and the navigators themselves. These analyses will be restricted to the intervention group because some barrier interview questions are specifically related to this group.

Summary

Improved secondary stroke prevention may reduce the frequency of subsequent stroke or other vascular events. This reduction is of great importance to society for reducing disability and healthcare expenditures. Improving access to healthcare for underserved populations will also reduce rates of illness, disability, and poor quality of life. PROTECT DC will determine whether navigation in combination with TRA can improve health behavior and adherence to prevent future strokes.

To date, PROTECT DC has recruited 162 participants across five sites in Washington, DC. Findings will be reported in 2012.

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