THE PREDICTABILITY OF C-REACTIVE PROTEIN, LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2, AND DEPRESSION ON LATER HEALTH OUTCOMES IN PATIENTS EXPERIENCING A FIRST-TIME STROKE

by

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THE PREDICTABILITY OF C-REACTIVE PROTEIN, LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2, AND DEPRESSION ON LATER HEALTH OUTCOMES IN PATIENTS EXPERIENCING A FIRST-TIME STROKE

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ABSTRACT

Stroke is the third leading cause of death and the most common cause of neurologic disability for adults in developed nations. Strokes trigger an acute inflammatory response prompted by brain tissue injury at the infarct site and the surrounding ischemic penumbra raising plasma levels of inflammatory markers. C-reactive protein (CRP), an acute-phase inflammatory marker, has been significantly correlated with infarct size and post-stroke complications. Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) may also predict long-term cardiovascular risk in the stroke population. In addition to physiologic changes, up to 60% of all stroke survivors are known to experience depression, which may contribute to decreased physical and cognitive functioning, decreased health-related quality of life, and deterioration of mobility after stroke.

The specific aims of this study are to: (1) determine the effect of baseline CRP and Lp-PLA₂ levels shortly after first-time stroke on subsequent health outcomes (functionality, neurological impairment, and quality of life) at 3 months post stroke, (2) determine the effect of baseline depression shortly after first-time stroke on subsequent health outcomes at 3 months post stroke, and (3) determine the interactive effect of CRP and Lp-PLA₂ and depression on subsequent health outcomes at 3 months post-stroke.
A prospective, descriptive cohort design was used. Participants with a first time stroke, over the age of 45, were recruited from the emergency department at a large, hospital in Northern Alabama with 881 licensed beds.

The biological markers of CRP and Lp-PLA$_2$ were collected at baseline and at 3 months post-stroke. Depression and health outcomes were assessed on hospital admission, on day 4 of hospital admission or on the day of discharge whichever occurred first, and at 3 months post-stroke. Recurrence of stroke was monitored for 3 months post-stroke.

For the specific aims 1-3, data were analyzed using hierarchical multiple regression. Controlling for the effects of the covariates (age, baseline National Institute of Stroke Scale (NIHSS), and t-PA usage), the main effects of CRP, Lp-PLA$_2$, and depression as well as their interactive effects (CRP x depression, Lp-PLA$_2$ x depression, and CRP x Lp-PLA$_2$ x depression) on health outcomes were determined. In this small study, only depression was predictive of functionality and quality of life at 3 months post-stroke.

Keywords: Stroke, CRP, Lp-PLA$_2$, Depression, Health Outcomes
DEDICATION

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Statement of the Problem</td>
<td>1</td>
</tr>
<tr>
<td>Purpose of the Study</td>
<td>3</td>
</tr>
<tr>
<td>Specific Aims &amp; Hypotheses of the Study</td>
<td>3</td>
</tr>
<tr>
<td>2. CONCEPTUAL FRAMEWORK</td>
<td>5</td>
</tr>
<tr>
<td>Neuman’s Systems Model</td>
<td>5</td>
</tr>
<tr>
<td>Integrative Model of Biobehavioral Interaction</td>
<td>7</td>
</tr>
<tr>
<td>Conceptual Model of the Study</td>
<td>8</td>
</tr>
<tr>
<td>3. REVIEW OF THE LITERATURE</td>
<td>10</td>
</tr>
<tr>
<td>Introduction</td>
<td>10</td>
</tr>
<tr>
<td>Inflammatory Markers and Stroke</td>
<td>12</td>
</tr>
<tr>
<td>Stroke and CRP</td>
<td>12</td>
</tr>
<tr>
<td>Stroke and Lp-PLA₂</td>
<td>13</td>
</tr>
<tr>
<td>CRP and Lp-PLA₂</td>
<td>15</td>
</tr>
<tr>
<td>Stroke and Depression</td>
<td>17</td>
</tr>
<tr>
<td>Health Outcomes</td>
<td>18</td>
</tr>
<tr>
<td>CRP and Health Outcomes</td>
<td>18</td>
</tr>
<tr>
<td>Depression and Health Outcomes</td>
<td>18</td>
</tr>
<tr>
<td>Recurrent Stroke</td>
<td>21</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS (Continued)

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4</strong> METHODOLOGY</td>
<td>22</td>
</tr>
<tr>
<td>Study Design</td>
<td>22</td>
</tr>
<tr>
<td>Setting</td>
<td>23</td>
</tr>
<tr>
<td>Participants</td>
<td>23</td>
</tr>
<tr>
<td>Recruitment</td>
<td>24</td>
</tr>
<tr>
<td>Variables</td>
<td>25</td>
</tr>
<tr>
<td>Measurements/Instruments</td>
<td>25</td>
</tr>
<tr>
<td>Biological Markers</td>
<td>25</td>
</tr>
<tr>
<td>Psychological Factor</td>
<td>26</td>
</tr>
<tr>
<td>Health Outcomes</td>
<td>27</td>
</tr>
<tr>
<td>Recurrent Stroke</td>
<td>29</td>
</tr>
<tr>
<td>Threats to Validity—Potential Bias</td>
<td>29</td>
</tr>
<tr>
<td>Study Size and Power Analysis</td>
<td>29</td>
</tr>
<tr>
<td>Statistical Methods</td>
<td>30</td>
</tr>
<tr>
<td>Missing Data</td>
<td>31</td>
</tr>
<tr>
<td><strong>5</strong> RESULTS</td>
<td>32</td>
</tr>
<tr>
<td>Sample Characteristics</td>
<td>32</td>
</tr>
<tr>
<td>Predictor Variables</td>
<td>33</td>
</tr>
<tr>
<td>Inflammatory Markers</td>
<td>33</td>
</tr>
<tr>
<td>Depression</td>
<td>33</td>
</tr>
<tr>
<td>Independent Variables</td>
<td>35</td>
</tr>
<tr>
<td>Health Outcomes</td>
<td>35</td>
</tr>
<tr>
<td>Instrument Reliability</td>
<td>35</td>
</tr>
<tr>
<td>Regression Models</td>
<td>36</td>
</tr>
<tr>
<td>Specific Aims and Hypothesis Testing</td>
<td>38</td>
</tr>
<tr>
<td>Baseline Biological Markers</td>
<td>38</td>
</tr>
<tr>
<td>Baseline Psychological Markers</td>
<td>38</td>
</tr>
<tr>
<td>Baseline Interaction of Biological and Psychological Markers</td>
<td>39</td>
</tr>
<tr>
<td>Summary</td>
<td>43</td>
</tr>
<tr>
<td><strong>6</strong> DISCUSSION</td>
<td>45</td>
</tr>
<tr>
<td>CRP and Stroke</td>
<td>48</td>
</tr>
<tr>
<td>Lp-PLA₂ and Stroke</td>
<td>48</td>
</tr>
<tr>
<td>Interaction of CRP and Lp-PLA₂ and Stroke</td>
<td>50</td>
</tr>
<tr>
<td>Depression and Stroke</td>
<td>51</td>
</tr>
<tr>
<td>Recurrent Stroke Risk</td>
<td>52</td>
</tr>
<tr>
<td>CHAPTER</td>
<td>Page</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Limitations of the Study</td>
<td>53</td>
</tr>
<tr>
<td>Future Research</td>
<td>55</td>
</tr>
<tr>
<td>Implication for Practice</td>
<td>55</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>56</td>
</tr>
<tr>
<td>APPENDIX</td>
<td></td>
</tr>
<tr>
<td>A Institutional Review Board Approvals</td>
<td>65</td>
</tr>
<tr>
<td>B Informed Consent</td>
<td>70</td>
</tr>
<tr>
<td>C Instruments</td>
<td>81</td>
</tr>
</tbody>
</table>
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Demographic Characteristics of Sample</td>
</tr>
<tr>
<td>2</td>
<td>Reliability of Instruments – published</td>
</tr>
<tr>
<td>3</td>
<td>Reliability of Instruments – this study</td>
</tr>
<tr>
<td>4</td>
<td>Regression Model Examining CRP on 3-month Health Outcomes</td>
</tr>
<tr>
<td>5</td>
<td>Regression Model Examining CRP (category) on 3-month Health Outcomes</td>
</tr>
<tr>
<td>6</td>
<td>Regression Model Examining Lp-PLA$_2$ on 3-month Health Outcomes</td>
</tr>
<tr>
<td>7</td>
<td>Regression Model Examining Lp-PLA$_2$ (category) on 3-month Health Outcomes</td>
</tr>
<tr>
<td>8</td>
<td>Regression Model Examining BDI-II on 3-month Health Outcomes</td>
</tr>
<tr>
<td>9</td>
<td>Regression Model Examining CRP on 3-month Quality of Life Subscales</td>
</tr>
<tr>
<td>10</td>
<td>Regression Model Examining Lp-PLA$_2$ on 3-month Quality of Life Subscales</td>
</tr>
<tr>
<td>11</td>
<td>Regression Model Examining BDI-II on 3-month Quality of Life Subscales</td>
</tr>
<tr>
<td>12</td>
<td>Regression Model Examining Interaction Terms on 3-month Health Outcomes</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Conceptual Diagram</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Revised Conceptual Diagram</td>
<td>47</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

Statement of the Problem

Stroke is the third leading cause of death and the most common cause of neurologic disability for adults in developed nations (American Heart Association, 2003). Strokes may be linked with acute inflammation, or an inflammatory state, in response to tissue injury encompassing either the area of infarct in the brain or the ischemic penumbra—the vulnerable area of the brain (Kushner, Rzewnicki, & Samols, 2006). Local and systemic inflammatory processes are activated by the stroke process, and persist for months afterward. CRP is an acute-phase inflammatory marker, the level of which has been correlated with atherothrombotic cardiovascular disease, future vascular events, and infarct size in patients experiencing an acute stroke (DiNapoli & Papa, 2002; Ridker, Glynn, & Hennekens, 1998; Rost et al., 2001). Higher CRP levels have been associated with decreased mobility, increased depression, and a decreased subjective health-related quality of life after discharge in stroke patients (Di Napoli, Papa, & Bocola, 2001; Nannetti, Paci, Pasquini, Lombardi, & Taiti, 2004; Van de Port, Kwakkel, Wijk, & Lindeman, 2006). Lp-PLA2 is an emerging biomarker, which may also have utility in predicting both first-time and recurrent coronary disease and stroke (Ballantyne et al., 2005; Caslake & Packard, 2005; Hok-Hay et al., 2005; Gorelick, 2008; Lerman & McConnell, 2008; Wassertheil-Smoller et al., 2008).
It is known that 20-60% of all stroke survivors experience post-stroke depression (Haacke et al., 2006). Depression may contribute to decreased physical and cognitive functioning, decreased health-related quality of life, and deterioration of post-stroke mobility. Decline in mobility affects patients’ ability to perform activities of daily living and may negatively impact independence and socialization. In their analysis of the Cardiovascular Health Study (CHS) Data, Arbelaez et al. (2007) attempted to establish inflammation as a mediator in the relationship between depressive symptoms and ischemic stroke. Their analysis suggested that there was a positive association between depressive symptoms and stroke risk, as well as CRP and stroke risk; however, their research design, which utilized only baseline measurements of CRP and depression, was not able to establish CRP as an important mediator.

Although stroke mortality remains high, as treatment options improve, the number of stroke survivors is increasing. However, the rate of recurrent stroke is significant; approximately 200,000 of the 700,000 strokes each year in the United States are recurrent strokes (Sacco et al., 2006). With improved treatment options for acute stroke, and the high rate of recurrent strokes, it becomes increasingly important to identify factors that might help to predict health outcomes, as well as the risk of recurrent stroke. Current stroke management is centered on acute treatment and risk factor reduction. This study will attempt to establish a link between inflammation and depression on health outcomes and recurrent stroke for first-time stroke patients.
Purpose of the Study

The purpose of this study was to determine the effect of baseline CRP and Lp-PLA₂ levels and depression and their interactive effect on health outcomes in first-time stroke patients over a 3-month period.

Specific Aims & Hypotheses of the Study

The specific aims and hypotheses of this study were to:

1. Determine the effect of baseline CRP and Lp-PLA₂ levels shortly after first-time stroke on subsequent health outcomes at 3 months post-stroke in patients with first-time stroke. Health outcomes include functionality, neurological impairment, quality of life, and recurrence of stroke.

Hypothesis 1a

Stroke patients with higher CRP levels shortly after first-time stroke will have lower functionality, higher neurological impairment, poorer quality of life, and higher recurrence of stroke at month 3 post-stroke.

Hypothesis 1b

Stroke patients with higher Lp-PLA₂ levels shortly after first-time stroke will have lower functionality, higher neurological impairment, poorer quality of life, and higher recurrence of stroke at month 3 post-stroke.

Hypothesis 1c

Stroke patients with both higher CRP and Lp-PLA₂ levels shortly after first-time stroke will have the lowest functionality, highest neurological impairment, poorest quality of life, and highest recurrence of stroke at month 3 post-stroke.
2. Determine the effect of baseline depression shortly after first-time stroke on subsequent health outcomes at 3 months post-stroke in patients with first-time stroke.

*Hypothesis 2a*

Stroke patients with higher levels of baseline depression will have lower functionality, higher neurological impairment, poorer quality of life, and higher recurrence of stroke at month 3 post-stroke.

3. Determine the interactive effects of CRP and Lp-PLA₂ and depression on subsequent health outcomes at 3 months post-stroke in patients with first-time stroke.

*Hypothesis 3a*

Stroke patients with both higher CRP levels and higher depression shortly after first-time stroke will have worse health outcomes than those with either higher CRP or higher depression alone (lower functionality, higher neurological impairment, and poorer quality of life) at month 3 post-stroke.

*Hypothesis 3b*

Stroke patients with both higher Lp-PLA₂ levels and higher depression shortly after first-time stroke will have worse health outcomes than those with either higher Lp-PLA₂ or higher depression alone (lower functionality, higher neurological impairment, and poorer quality of life) at month 3 post-stroke.

*Hypothesis 3c*

Stroke patients with a combination of higher CRP and higher Lp-PLA₂ levels and higher depression shortly after first-time stroke will have worse health outcomes than described in Hypotheses 3a and 3b (lower functionality, higher neurological impairment, and poorer quality of life) at month 3 post-stroke.
CHAPTER 2
CONCEPTUAL MODEL

The conceptual model for this study is based on Neuman’s Systems Model and an Integrative Model of Biobehavioral Interactions developed by Kang, Rice, and Weaver (personal communication, Dr. Kang). A biobehavioral orientation for the conceptual model enables integration between the psychosocial, behavioral, and biological processes an individual might experience after a first-time stroke.

Neuman’s Systems Model

Dr. Neuman’s model was developed in the early 1970’s to emphasize a holistic view of patients (Reed, 1993). The Neuman Systems Model is especially applicable to the individuals experiencing a first time stroke. Her model depicts an individual holistically within a systems perspective. Although predominantly emphasizing on wellness, the model also incorporates the actual stress response by building in primary, secondary and tertiary prevention, along with recovery and or rehabilitation. The system itself is a boundary for the individual and provides explanation for the achievement of system stability in response to stressors. The goal of primary prevention is protection of the normal lines of defense. The goal of secondary prevention, however, is to strengthen the lines of resistance thereby protecting the basic structure. The stroke patient enters the health care system at Neuman’s secondary prevention level. A stressor, conceptualized
as a first-time stroke, penetrates both the flexible and normal lines of defense, as well as, the lines of resistance. The client system, as presented by Neuman, is composed of concentric rings around the core of the system. The outermost boundary, or the flexible line of defense, comprises the boundary of the client. This boundary protects the normal line of defense or the client’s usual state of health. It can act as a “buffer” for the client, and is the first line of defense in response to stressors. Closer in to the core are multiple lines of resistance which are flexible, and can expand or contract, in response to the needs of the client in dealing with stressors. Tertiary prevention is the return to a wellness state. An important component in prevention of a recurrent vascular event is the identification of modifiable risk factors and early intervention. The intervention serves to restore “optimal client system stability or wellness” (Neuman, 1995, pg. 35).

Stressors, according to Neuman (1995), differ in their potential for disturbing the normal defense lines. Each individual has developed a set of responses to the environment, which comprises the normal defense lines with internal resources known as the “lines of resistance”. These systems are dynamic. When the flexible lines of defense are incapable of protection, the defense lines are broken (Reed, 1993). A person experiencing a first-time stroke, a significant stressor, has had their normal defense lines penetrated. How well the stressor is handled by the individual will depend on the lines of resistance established by the individual (Reed, 1993).

Although Neuman takes a wellness/prevention orientation, which may be seen as a weakness in her approach, her framework can be well adapted to a stress response model and is applicable to first-time stroke patients. The client’s basic structure, or energy resources, acts to buffer the stress reaction. Implied here are the patient’s
strengths and patterns of response to stressors, including the immune response, as well as social and psychological support. This is an important strength of the model. The model is useful, not only in explaining the disease process, but also can be utilized in evaluation of interventions. The lines of resistance are the client’s coping mechanisms, which may help the patient choose to make lifestyle changes to prevent a subsequent stroke. In order to achieve recovery, secondary and tertiary interventions are vital. The risk factors for recurrent stroke must be quickly assessed, and tertiary interventions must be initiated to prevent further disease.

Integrative Model of Biobehavioral Interaction

The Integrative Model of Biobehavioral Interaction is based on the assumption that mind-body interactions can influence health states (personal communication Dr. Kang). This model is a comprehensive biobehavioral model based on Hans Selye’s Model of Stress and Physiologic Responses, Lazarus and Folkman’s Theory of Cognitive Appraisal, and McEwen’s Model of Allostasis and Allostatic Load.

The Integrative Model of Biobehavioral Interaction includes six domains: individual, environmental, psychosocial, behavioral, biological, and health outcomes. Briefly, the individual domain includes the factors that are unique to an individual such as age and gender. The environmental domain includes the factors arising from the individual’s social, cultural, and physical environment. The psychosocial domain includes psychological and social factors such as stress, support, coping, and quality of life. The behavioral domain includes the lifestyle choices of individuals such as tobacco and alcohol use, physical activity, and adherence with health screening. The biological
domain includes the individual’s immune, neuroendocrine, and other biological functioning. Health outcomes include health-related and functional outcomes. The main propositions of this model are that several factors within and across the domains may present simultaneously; over a long period, these factors interact to have cumulative effects on health outcomes. Most typically, factors in the individual, environmental, psychosocial, and behavioral domains influence biological processes, which, in turn, influence health outcomes. The biobehavioral orientation allows examination of interrelationships between the factors in other domains.

Conceptual Model of the Study

The conceptual model for this study is based on these two models. In this study, a first-time stroke is considered a significant “stressor” and is conceptualized to affect the inflammatory markers of CRP and Lp-PLA₂ (biological factors) and depression (a psychological factor). The biological factors of inflammation and the psychological factor of depression are conceptualized to have an independent, as well as an interactive effects on the health outcomes of first-time stroke patients over time. The construct of health outcomes encompasses the concepts of functionality, neurological impairment, quality of life, and recurrence of stroke that are specific and significant to this population of patients with first-time stroke. The concept of health outcome will be assessed over time to indicate the cumulative effects of biological and psychological factors.
Figure 1. Conceptual Diagram.
CHAPTER 3
REVIEW OF THE LITERATURE

Introduction

The term “stroke” has been in existence since the 16th century. The effects of neurovascular diseases, or cerebrovascular accidents, were attributed to a “stroke” of the hand of God. A stroke is defined as a rapidly evolving syndrome involving a sudden onset deficit, which is non-epileptic in nature (Alexandrov, 2008). This sudden deficit results in a reduction in blood flow causing cerebral ischemia. A reduction in cerebral blood flow for as short as 10 seconds can produce neurologic symptoms, due to a lack of glycogen supply to the neurons which results in rapid energy failure (Braunwald et al., 2001).

One method for classifying strokes, developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST), utilizes probable stroke mechanisms to assign stroke subtypes. This stroke classification has been extensively validated and is utilized in both clinical research and general practice (Goldstein et al., 2001; Hakan et al., 2005). In this classification scheme, strokes are distinguished as resulting from: (1) large artery atherosclerosis, (2) cardioembolic, (3) small artery occlusion, (4) other causes, such as a disease process, or (5) undetermined or cryptogenic cause.

CRP, an acute phase inflammatory marker, has been implicated in the disruption of the lining of the endothelium of cerebral blood vessels and as such contributes to both
local and systemic inflammatory changes. This disruption has been considered as a
mediator for intraluminal thrombosis, which can cause stroke (Ross, 1999).

With their use of an azetidinone inhibitor of Lp-PLA₂, Macphee et al. (1999)
proposed the mechanism for the pro-inflammatory role of Lp-PLA₂ in atherogenesis. As
early as 1987, Quinn, Parthasarathy, Fong, and Steinberg established that oxidized LDL
was a chemoattractant for circulating monocytes. A critical step in the atherosclerotic
process involves a continued monocyte infiltration into the cell intima; thereby, directly
influencing the regulation of monocyte functioning (Davies & Woolf, 1993). Lp-PLA₂ is
a calcium-independent member of the phospholipase A₂ (PLA₂) superfamily, and is
involved in the oxidative modification of LDL. It is produced by macrophages mainly,
and is predominantly bound to low-density lipoproteins; however, a small percentage is
bound to high-density lipoproteins. A consequence of the oxidation of LDL is an
increase in the concentration of lysphophatidylcholine (lyso-PtdCho), which is a
proatherogenic mediator (Macphee et al., 1999); Lp-PLA₂ can account for the increased
lyso-PtdCho concentration in oxidized LDL particles. Macphee et al. (1999) were able to
establish that Lp-PLA₂ was uniquely responsible for the increased concentration of Lyso-
PtdCho within oxidized LDL particles. When dense LDL particles are enriched with Lp-
PLA₂, their susceptibility to oxidation is increased. Luoma et al. (1996) demonstrated
that both Lp-PLA₂ and mRNA are upregulated in artherosclerotic lesions.
Inflammatory Markers and Stroke

Stroke and CRP

Numerous studies have demonstrated a strong correlation between elevated levels of CRP and cardiovascular and/or cerebrovascular events. Elevated CRP levels were detected within 24 hours of ischemic stroke onset in approximately 75% of stroke patients (DiNapoli & Papa, 2002; DiNapoli, Papa, & Bocola, 2001). The authors utilized a prospective hospital-based, stroke data bank to study a cohort of 473 first-time stroke patients who presented to the hospital within 24 hours of stroke onset. Higher median CRP levels within 24 hours of stroke onset were significant predictors of recurrent stroke risk \( (p = 0.006) \). Rost et al. (2001) examined the effects of CRP levels at study entry on the risk of stroke in cardiovascular disease-free participants (591 men and 871 women) in the Framingham study. Within the 12 to 14 year follow-up period, there were 196 ischemic strokes and TIAs within the study population. Subjects whose CRP levels at study entry were in the highest quartile had twice the risk of first-time stroke during the 12 to 14 year follow-up period than subjects in the first, second, and third quartiles \( (RR = 2.0, p = 0.027) \).

Beamer and colleagues (1998) studied CRP levels in 136 adults with acute ischemic stroke who were aged matched with 76 subjects with comparable risk factors for stroke and 48 healthy control subjects. They followed these subjects for at least a year after the sentinel event or until a subsequent vascular event occurred, measuring CRP levels at stroke onset, 6 weeks, 6 months, and 1 year post-enrollment. The CRP levels were highest in the “at risk” subjects at stroke onset or at study enrollment. However, they found that CRP levels did not correlate with recurrent cerebrovascular
events. In contrast, Rost et al. (2001), following subjects enrolled in the Framingham study, reported that CRP levels in the highest quartile at study entry were highly predictive of subsequent stroke risk over the 12 to 14 year follow-up period. Baseline CRP levels were collected on 591 men and 871 women. During the 12 to 14 year follow-up, 196 ischemic strokes and TIAs were reported.

Di Napoli, Papa, and Bocola (2001) measured CRP levels within the first 24 hours following first-ever ischemic stroke and correlated these levels to 1-year outcomes in 128 patients included in the Villa Pini Stroke Bank database. Their results suggested that CRP levels could be used effectively in the stratification of risk for subsequent stroke. CRP levels at hospital admission for ischemic stroke were highly predictive of combined 1 year end points ($p < 0.002$) including new vascular events and death. A CRP level of $\geq 1.5 \text{ mg/dL}$ at discharge was associated with significantly worse outcomes measured by combined vascular end points and death ($p < .001$). This study was subsequently extended for a mean follow-up of 2 years with the inclusion of 473 subjects diagnosed with first-ever ischemic stroke (Di Napoli & Papa, 2002). These results also indicated a strong correlation between elevated levels of CRP at discharge and future cardiovascular and cerebrovascular events.

*Stroke and Lp-PLA₂*

The contribution of Lp-PLA₂ to an estimation of stroke risk was examined by Ballantyne et al. (2005). In their interpretation of the Atherosclerosis Risk in Communities (ARIC) Study, they found that Lp-PLA₂ levels in the highest tertiles contributed to approximately double the risk of stroke in this healthy United States adult population. When adults with both the highest levels of CRP and Lp-PLA₂ were
considered, their risk of stroke was 11 times higher than adults with lower levels of both these inflammatory markers. These findings, however, were challenged by Greenland and O’Malley (2005). They argued that Ballantyne et al. (2005) should have evaluated the predictive value of CRP and Lp-PLA₂ by calculating the receiver operating characteristics (ROC) curves or the plot of true-positive rates versus false-positive rates. Merely reporting hazard ratios and p values, in their opinion, was not sufficient to establish the validity of the use of CRP and/or Lp-PLA₂ as predictors of first-time stroke risk, as well as, recurrent stroke risk.

Oei et al. (2005) also considered the Lp-PLA₂ levels of subjects in the Rotterdam Study which examined 7,983 subjects ≥ 55 years of age including 308 subjects with coronary heart disease, and 110 with ischemic strokes. The multivariate-adjusted hazard ratios for ischemic stroke were 1.08, 1.58, and 1.97 for the second, third, and fourth quartiles of Lp-PLA₂ in this subject population. These authors also established that Lp-PLA₂ was an independent predictor of ischemic stroke risk in the general population.

Persson, Hedblad, Nelson, and Berglund (2007) evaluated the prognostic risk value of elevated Lp-PLA₂ to cardiovascular disease in subjects with metabolic syndrome utilizing a prospective cohort of the Malamo Diet and Cancer Study. The study population included 5,540 men and women aged 45 to 69 years, without a history of heart attack, stroke, diabetes, or elevated fasting blood glucose. Although they found that Lp-PLA₂ was associated with the metabolic syndrome, higher plasma levels of Lp-PLA₂ appeared to be independently associated with cardiovascular risk. They proposed that individuals with both metabolic syndrome and elevated Lp-PLA₂ levels are at especially high risk of cardiovascular disease.
Persson, Berglund, Nelson, and Hedblad (2008), examined the association of increased mass and activity levels of Lp-PLA$_2$ and ischemic stroke in 152 subjects enrolled in the Malmo Diet and Cancer Study (MDCS). This was a prospective, population-based cohort study. In this study, participants were followed from baseline through the first event. Pre-event measurements were analyzed, with elevated Lp-PLA$_2$ levels associated with an increased incidence of ischemic stroke with an increase in relative risk of 1.48. This is a significant increase in the risk of stroke compared with the general population.

**CRP and Lp-PLA$_2$**

Several studies have explored the interaction or combined predictive and prognostic value of measuring both CRP and Lp-PLA$_2$ after ischemic stroke. Elkind, Wanling, Coates, Paik, and Sacco (2006) measured both CRP and Lp-PLA$_2$ in 467 first-time stroke patients. Measurements were obtained within 72 hours for 83.7% of the patients, and within 6 days for an additional 7%. The risk of recurrent stroke was 17.9% for patients with CRP levels in the highest quartile and 20.4% for those in the lowest quartile. When risk was stratified for Lp-PLA$_2$, the patients with levels in the highest quartile had a risk of 27.1% compared with a risk of 13.2% for the patients in the lowest quartile. However, the authors determined that the effect was greater in patients with LDL values < 130mg/dL. In their analysis; CRP was strongly associated with stroke severity; however, levels of Lp-PLA$_2$ were more predictive of recurrent stroke risk as well as heart attack and vascular mortality.

In addition to examining the predictive value of CRP and Lp-PLA$_2$ levels, Elkind, Tai, Coates, Paik, and Sacco (2009), also utilizing the North of Manhattan Stroke Study
population, concluded that Lp-PLA$_2$ activity levels in the top quartile predicted recurrent stroke, but not overall ischemic events. For the 467 subjects, they were able to obtain Lp-PLA$_2$ measurements within 72 hours of incident stroke for 84% of the subjects and within 6 days for 90% of their subjects. They reported that Lp-PLA$_2$ levels were not influenced by stroke severity. Patients with levels in the highest quartile had a 2.5 time greater risk of stroke recurrence.

Elkind, Leon, Moon, Paik, and Sacco (2009) also reported the stability of CRP and Lp-PLA$_2$ before and after stroke. They collected CRP and Lp-PLA$_2$ levels for 37 first-time stroke patients participating in the North of Manhattan Study before and within 5 days of the incident stroke. Both activity levels were stable over time; however, Lp-PLA$_2$ mass levels decreased approximately 5% annually following a stroke. The risk categories were essentially unchanged over time. CRP levels increased after stroke ($p = 0.0067$); the mass and activity levels of Lp-PLA$_2$ decreased significantly ($p = 0.03$) after stroke. Based on their findings, they concluded measurements of these inflammatory markers in the acute setting may not be reliable for long-term risk evaluation, as levels measured shortly after stroke onset may not reflect a true baseline.

Cucchiara et al. (2009) measured both CRP and Lp-PLA$_2$ mass and activity levels in 167 patients experiencing a suspected TIA who presented to the ED within 48 hours of symptom onset. Patients were followed for 90 days with end-points of stroke, death, or the identification of “high-risk stroke mechanics” which they defined as > 50% stenosis of a responsible vessel or the identification of a cardioembolic source necessitating anticoagulation. Approximately 25% of patients experienced a composite end-point during the study period. CRP levels were not significantly correlated with outcomes
(\(p = 0.82\)); however, Lp-PLA\(_2\) mass (\(p = 0.04\)) achieved significance, with Lp-PLA\(_2\) activity not achieving significance at (\(p = 0.06\)). The authors concluded that Lp-PLA\(_2\) levels may add valuable prognostic information to the traditional TIA risk assessment tool the ABCD\(^2\). This tool is used in the assessment of the risk of stroke after TIA or suspected TIA, and guides decision-making in the ED regarding the need for hospital admission versus out-patient follow-up (Tsivgoulis et al., 2010).

**Stroke and Depression**

Post-stroke depression has been reported to be as high as 30-60\% (Carota & Bogousslavsky, 2003; Kotila et al., 1998) measured at 3, 6, and 12 months post-stroke. Carota et al. (2005) studied the behavior of 273 patients admitted to a stroke unit within 48 hours of a first-time ischemic stroke. Subjects who were younger than 68, and had suffered a more severe disability, were also more likely to have post-stroke depression. Age may be an important factor in the development of post-stroke depression, and was used as a covariate in this research project. A potential flaw in the Carota study was the inclusion of 24 patients (9\%) on the stroke unit who were treated with psychotropic medications prior to admission. The use of psychotropic medications prior to stroke admission may have affected overt behavior post stroke. One of the strengths of that study was the long period of observation by the nursing staff. Nurse observers were on the unit for 12-hour shifts during the day. In the present study, the researcher attempted to exclude any subject with a history of depression or psychiatric illness.
Health Outcomes

**CRP and Health Outcomes**

The time course of CRP elevation in acute stroke was studied by Di Napoli, Papa, and Bocola (2001). CRP levels were obtained at admission and repeated within 24 hours after stroke onset, between 48 and 72 hours after stroke onset, and at hospital discharge which varied between 7 and 17 days. In their cohort of 193 patients presenting to a stroke center, 128 patients were included in the derivation set, with 65 in the validation subset. All patients were followed for one year post-stroke. The authors found that patients with CRP levels > 1.5mg/dL at discharge had significantly worse outcomes. Additionally, the CRP level at discharge was the strongest predictor of one year outcome. They reported two patterns of CRP change after admission: a “benign pattern” with normal or decreasing values, and an “adverse pattern” with persistently elevated and/or increasing levels. The later pattern was associated with larger infarct size and more disability. Approximately 75% of the patients did exhibit CRP elevation post-stroke. The early and sustained increase in CRP levels in acute ischemic stroke patients was also found by Emsley et al. (2003) in their study which involved 36 patients.

**Depression and Health Outcomes**

Health-related quality of life is an essential component of a holistic approach to patient care in the post-stroke period. Depression may negatively impact health outcomes through its effect on functionality and quality of life. Furthermore, it is possible that CRP can interact with post-stroke depression to influence quality of life. As a reaction to the stressor of a first-time stroke, post stroke depression (PSD) has been identified in a significant number, between 30 and 60%, of stroke survivors (Carota et al.,
2005; Gandolfo, Provinciali, Torta, Sommacal, & Toso, 2005; Nannetti, Paci, Pasquini, Lombardi, & Taiti, 2004; Suenkeler et al., 2002) with the consequences of the pathophysiological changes of PSD negatively impacting clients’ quality of life post-stroke (Suenkeler et al., 2002).

Haacke et al. (2006) utilized the German version of the European Quality of Life Index and the Health Utility Index 2 and 3 to evaluate 77 stroke patients, whose diagnoses included ischemic strokes, TIAs, and hemorrhagic strokes, four years after their sentinel event. The authors concluded that depression was a major contributor to a decreased health-related quality of life in addition to physical and cognitive functioning. Health-related quality of life was inversely related to subject’s age.

Not only does post-stroke depression negatively impact health-related quality of life, its effect on the deterioration of mobility after stroke is also important. Decline in mobility status affects subjects’ abilities to perform activities of daily living and may negatively impact independence and social integration. Van de Port, Kwakkel, Wijik, and Lindeman (2006) followed a cohort of 205 first-time stroke patients admitted for in-patient rehabilitation for 3 years after their sentinel event. Approximately 20% of these patients had significant deterioration in their mobility status at 3-years post-stroke. The presence of depression at 1-year post stroke was associated with significant decline in mobility status. A weakness of this study was the absence of data on antidepressant use among this subject population.

Nannetti, Paci, Pasquini, Lombardi, and Taiti (2004) also studied the incidence and impact of post-stroke depression on motor and functional recovery. Their study included only first-ever stroke patients with no prior history of depression or use of
antidepressant medications, and no pre-stroke co-morbid orthopedic or neurological deficits. Depression was measured with the Geriatric Depression Scale and functional outcomes were assessed with the Barthel scale. Subjects identified with post-stroke depression had significantly lower performance measures on all the indices measured; however, in this study, motor recovery was not significantly different for the depressed group compared with the group which did not show post stroke depression. These results were inconsistent with Haacke et al. (2006) and Van de Port, Kwakkel, Wijik, and Lindeman (2006). Nanetti, Paci, Pasquini, Lombardi, and Taiti (2004) suggested their results were different since their subjects were admitted to an intensive inpatient rehabilitation unit and received continued outpatient physical therapy for 6 months following discharge.

The actual time course of health-related quality of life after stroke was studied by Suenkeler et al. (2002). This prospective study included 144 survivors of stroke/TIA who were evaluated at 3, 6, and 12 months post-event. Post-stroke depression was observed in 47-55% of the subjects, but was not validated with a psychiatric evaluation. Depression was measured with the Montgomery-Ashberg Depression Rating Scale. Quality of life remained below pre-stroke levels as long as 1 year after event. Quality of life was assessed by the SF-36, a generic measure of “perceived health status” which includes evaluation of “behavioral functioning, subjective well-being and perceptions of health” (Ahmed et al., 2004).

Several weaknesses were identified in the depression and quality of life studies reviewed. There was a definite inconsistency with instruments utilized in the studies. Although the Rankin and Barthel (Mahoney & Barthel, 1965) instruments have been used
extensively, several other measurement tools were utilized which did not have the same level of reliability and validity.

Recurrent Stroke

Subjects who have experienced a stressor in the form of a first-time stroke have as high as a 10.5% chance of recurrent stroke or another vascular event within the first 90 days, with the highest risk occurring within the first week (Sacco et al., 2006).

In summary, this study will attempt to introduce a biobehavioral orientation to stroke research. The majority of stroke research has concentrated on isolated factors, and has not presented an integrated model. The traditional stroke outcome measures of neurological impairment were measured by the National Institute of Health Stroke Scale (NIHSS); functionality measured by the modified Rankin Scale (mRS); and quality of life evaluated by the Short Form 36 (SF-36). These outcome measures were studied along with a psychological component, post stroke depression, assessed with the Beck Depression Inventory II (BDI-II), and their interaction with the inflammatory markers of CRP and Lp-PLA₂. Recurrent stroke rates were also reported for these study participants.
CHAPTER 4

METHODOLOGY

The purpose of this study was to determine the effect of baseline CRP and Lp-PLA₂ levels and depression and their interactive effect on health outcomes in first-time stroke patients to provide evidence to support a causal relationship between inflammation and depression, and to examine the changes in CRP, Lp-PLA₂, depression, and health outcomes over time.

Study Design

A prospective, descriptive cohort design was used to investigate the specific aims of the study. Laboratory data were collected prospectively on admission to the emergency department or the stroke unit, with a diagnosis of first time ischemic stroke (baseline) and at 3 months post-stroke for biological markers. Additionally, depression and health outcomes data (functionality, neurological impairment, and quality of life) were collected at day 4 of hospitalization or on hospital discharge whichever occurred first. The 3-month time period was selected because a majority of the recovery post-stroke is accomplished within the first 3 months (Beamer et al., 1998).
Setting

All participants were recruited from the emergency department (ED) or the Stroke Unit of Huntsville Hospital (HH). The first participant was enrolled on September 3, 2010, and the final participant was recruited on February 27, 2011. A total of 24 participants were enrolled in the study, with 20 participants completing evaluation at month 3. The follow-up period was completed on May 18, 2011, for the last participant. Data were analyzed after the final patient completed follow-up at month 3.

Participants

Participants for the study were recruited from the emergency department (ED) or the Stroke Unit of Huntsville Hospital (HH). Potential participants were identified by the stroke team, which responds to all acute stroke patients who present to the ED with symptom onset \( \leq 8 \) hours. Cooperation and support were elicited from the hospital neurologists and the ED physicians. Follow-up was arranged by the PI’s collaborating physician’s office, and patients were seen at the Huntsville Hospital Neurological Associates’ office. Subjects were contacted by telephone to arrange follow-up clinic visits. Letters were mailed to addresses of record when subjects were not able to be reached by telephone.

Inclusion criteria were (1) diagnosis of ischemic stroke, (2) presentation to the ED within 24 hours of known symptom-onset of acute stroke symptoms, and (3) age greater than 45 years. Exclusion criteria were (1) presence of hemorrhage on computed tomography scan, (2) poor functionality prior to first-time stroke (Rankin Scale \( \geq 2 \)), (3) pre-existing neurological conditions which affected mobility, such as multiple sclerosis.

23
and Parkinson’s disease, (4) significant co-morbidities (such as end-stage cancer or cardiac disease) and/or predicted life expectancy of less than 6 months, (5) inability to speak or write English, and (6) global aphasia.

Recruitment

Stroke diagnosis was established by the attending or consulting neurologist in conjunction with World Health Organization imaging criteria (Culebras et al., 1997). Potential participants and their families were approached in the ED or on admission to the Stroke Unit regarding the study. The purpose and procedure of the study was fully explained to the patient and family members. Informed consent was obtained, and a copy of the informed consent document was provided to each patient. Based on the 2005 statistics at Huntsville Hospital, there were approximately 400 ischemic stroke patients: 54% were females and 46% were males; 77% were Whites; 33% Black and less than 1% non-White.

The study protocol was approved by the Institutional Review Committee/Board at Huntsville Hospital and the University of Alabama at Birmingham, prior to collecting any data. Ethical considerations included participant confidentiality and anonymity, as well as freedom from coercion. Data collection for participant tracking used an encrypted medical record number which was password protected. All files were maintained in a locked file cabinet in a locked office.
Variables

Health outcomes, including functionality (as measured by modified Rankin Scale Score), neurological impairment (as measured by NIHSS score), and quality of life (as measured by the SF-36) were investigated for this study. Measurements of CRP and Lp-PLA₂ were taken within 24 hours of stroke onset and at month 3. Depression and health outcomes were measured at hospital admission, at hospital day 4 or day of discharge whichever was first, and again at 3 months. All hospital records were reviewed, and data were analyzed by PASW-18. The predictor variables for the study were inflammatory markers (CRP and Lp-PLA₂) and depression. Potential confounders were identified as age, admission NIHSS and use of intravenous t-PA (Ovbiagele et al., 2011). The diagnosis of ischemic stroke was established by the attending or consulting neurologist according to the World Health Organization definition (Culebras et al., 1997). CRP results were further divided into low risk at < 0.1; moderate risk 0.1-0.5, and high risk > 0.5 mg/L according to normalized published laboratory values at Huntsville Hospital. Lp-PLA₂ results were also further divided into risk categories. The referenced norms for Lp-PLA₂ were obtained from LabCorp and were defined as low risk < 200; moderate risk 200-235, and high risk > 235 mg/L.

Measurements/Instruments

*Biological Markers*

**CRP and Lp-PLA₂.** CRP and Lp-PLA₂ levels were measured from serum samples with high-sensitivity immunoradiometric assays. Blood samples were drawn by venipuncture performed by either the nurse researcher or hospital phlebotomists, on
admission to the ED or the Stroke Unit, and at month 3 during the patient’s routine clinic visit with the neurologist or nurse practitioner. CRP samples were processed by Huntsville Hospital’s laboratory and Lp-PLA₂ samples were sent to The Mayo Clinic, Rochester, Minnesota, for processing by LabCorp in Huntsville. CRP results were further divided into low risk at < 0.1; moderate risk 0.1-0.5, and high risk > 0.5 mg/L according to normalized published laboratory values at Huntsville Hospital. The referenced norms for Lp-PLA₂ were obtained from LabCorp and are defined as low risk < 200; moderate risk 200-235, and high risk > 235 mg/L.

**Psychological Factor**

**Depression.** Depression was assessed using the Beck Depression Inventory II (BDI-II). The BDI-II was completed after patients were transferred from the ED and admitted to either the stroke unit, or another hospital unit, to insure privacy, and minimize distractions. The validity of the BDI-II in stroke patients has been well established. Cronbach’s α was 0.83 for this tool in stroke patients (Aben, Verhey, Lousberg, Lodder, & Honig, 2002; & Goldstein, Samsa, 1997). The BDI-II was developed in 1996, and contains 21 questions. Each question is scored from 0 to 3. Subjects were determined to be depressed if they scored > 10 on the BDI-II, and scores with scores from 0–13 indicated minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicated more severe depressive symptoms. The BDI-II is positively correlated with the Hamilton Depression Rating Scale with a Pearson r = 0.71, showing good agreement. The test was also shown to have a high one-week test–retest reliability (Pearson r = 0.93), suggesting that it was not overly sensitive to daily variations in mood (Beck, Steer, & Brown, 1996).
The test also has high internal consistency with an $\alpha$ level approaching .91 (Beck, Steer, Ball, & Ranieri, 1996). The BDI-II was administered by the nurse researcher. Question 21, regarding loss of sexual interest was not queried and therefore not scored for this study.

**Health Outcomes**

*Functionality.* Functionality is conceptualized as the ability to perform activities of daily living. The modified Rankin Scale has been extensively used with stroke patients and addresses both physical and cognitive functioning, driving, preparing meals, dressing, and ambulation. The scale has 7 categories from 0 or no symptoms to 6 or death, with higher scores indicating more severe impairment. The scale aids in differentiation between mild, moderate, and severe disability in stroke patients. The modified Rankin Scale (mRS) value has also been shown to correlate with stroke infarct size (Banks & Marotta, 2007; Paithankar & Dabhi, 2003). According to Kasner (2005), the scale showed high reliability when the assessment was done in person, but its reliability declined when assessment was done with phone interviews. In this study, all assessments were done in person. Additionally, the inter-rater reliability increased from 57% to 78% with use of a structured interview, with a Cronbach’s $\alpha = .74$ (Wilson et al., 2005). Determination of the Rankin scale rating was performed by the nurse researcher using the structured interview format.

*Neurological Impairment.* Neurological impairment was conceptualized as cognitive ability, orientation, and speech, as well as evaluation of motor and sensory capacity. Neurological impairment was measured using the National Institute of Health
Stroke Scale (NIHSS). The NIHSS has been accepted as a standardized outcome measure for stroke patients. The scale was initially developed for use in clinical trials by the National Institute of Health. The scale has 11 items, with a grading of 0-5. A normal response is scored as 0, with items not scored when untestable, such as speech in an intubated patient. The scale addresses level or consciousness, language, neglect, vision and extraocular eye movements, motor strength and ataxia, and sensorium. The reliability and validity of the scale has been extensively established (Kasner, 2005) with an interclass correlation coefficient of 0.93 and an interobserver reliability of 0.95. An increase of 2 or more points on the NIHSS has been used in clinical trials to represent clinically relevant neurological impairment (Kasner, 2005). The assessment of neurological impairment was performed by the nurse researcher who is certified in the administration of this scale by the American Heart/American Stroke Association.

Quality of Life. The Short-Form General Health Survey (SF-36) has been used in numerous stroke studies (Naess, Waje-Anderson, Thomassen, Nyland, & Myhr, 2006). The tool consists of 8 subscales which include physical functioning, role limitations resulting from physical impairment, pain, perception of general health, vitality, social functioning, role limitations resulting from emotional problems, and emotional well-being. Subscale scores range from 0 to 100; higher values represent better functioning. Each subscale has been separately validated with Cronbach’s α internal consistency reliability ≥ 0.80 (Scott, Tobias, Sarfati, & Haslett, 1999). For the purpose of this study, the scales of Physical Functioning, Role-Physical, and Role-Emotional only were utilized. These categories were felt to be most appropriate by the researcher for acute stroke patients in the hospital setting.
Recurrent Stroke

Recurrent stroke rates were assessed for 3 months following first-time stroke through self-report and hospital admission logs. Whenever possible, imaging studies and confirmation of new stroke by a staff neurologist or radiologist was obtained.

 Threats to Validity – Potential Bias

Every effort was undertaken to minimize potential sources of bias in this study. All eligible participants were approached for inclusion in the study. Bias may result from conducting the study at a single source, Huntsville Hospital (HH), as this hospital has significant differences from other institutions in the same geographic area. The hospital is large (> 800 bed), private, not-for-profit, in a region of the United States known as “the Stroke Belt”. Patients presenting to HH may not be reflective of stroke patients elsewhere in the country. Participants were only eligible for inclusion in the study if they presented to the ED within 24 hours of stroke symptom onset which excluded many potential participants.

Study Size and Power Analysis

This study was initially designed to enroll 67 participants in order to achieve a power of 0.80 with an alpha level of 0.05 based on a medium to high effect size calculation (Polit & Beck, 2004). Although the association between depression and quality of life for stroke patients is fairly well established (Haacke et al., 2006; Nannetti, Paci, Pasquini, Lombardi, & Taiti, 2004; Van de Port, Kwakkel, Wijik, & Lindeman,
the exact effect sizes have not been reported. Similarly, although the association between CRP and health outcomes for stroke patients has also been established, the exact effect sizes have not been established. Lp-PLA2 is a fairly new biomarker in stroke literature, and therefore, its effect size has not been clearly established in the area of stroke. Therefore, prior to collecting data, the effect size was estimated to be moderate to high in the calculation of sample size for this study. An interim analysis was planned for 24 participants to determine the actual effect size and calculate the same size required to adequately power the study. A decision was made a priori that unless an effect size of > .50 was achieved, this study would be terminated for futility.

Statistical Methods

All analyses were performed using PASW 18.0 for Windows. Based on the literature reviewed, variables previously shown to impact ischemic stroke outcomes were considered. Hierarchical multiple regression analyses were conducted to assess the longitudinal associations between baseline predictor variables (i.e., CRP, Lp-PLA2, Beck depression score) and 3-month modified Rankin scale score, (b) 3-month NIH Stroke Scale score, and (c) 3-month Quality of Life SF-36.

To reduce the number of predictor variables in the regression models, Spearman correlations were conducted to examine associations among age, baseline NIH Stroke scale (NIHSS) score, treatment with intravenous tissue plasminogen activator (IV t-PA) and each of the outcome measures (3 month mRS score, 3-month NIHSS score, and 3-month SF-36 score). Only significant (p < 0.10) relationships were included in the regression models.
Three hierarchical multiple regression models were conducted, each examining an outcome measure, and including only potential confounding variables significantly associated with the outcome of interest in each model. Potential multicollinearity of measures was examined using tolerance. In Step 1, relationships were examined between the baseline predictor variables (i.e., CRP, Lp-PLA₂, and Beck depression score) and the dependent variables (i.e., 3-month mRS score, 3-month NIHSS score, and 3-month SF-36 score). In Step 2, each model was adjusted for potential confounders, as indicated by the Spearman correlations.

Missing Data

Only available data were analyzed. No data were imputed or estimated due to small sample size.
CHAPTER 5

RESULTS

The findings of the study are presented in this chapter. The characteristics of the participants were described including demographics, smoking prevalence, baseline low-density lipoprotein values, admission blood pressure and heart rate, and the predominant heart rhythm. The study variables were described with descriptive statistics (mean, standard deviation, median and range) and multivariate correlations. Instrument reliability for this study was presented. Finally, the findings for each specific aim and hypothesis were summarized.

Sample Characteristics

A convenience sample of 24 participants, who were eligible for this study, was sequentially recruited from Huntsville Hospital between September 2, 2010, and February 27, 2011. Demographic data including age, gender, race/ethnicity, stroke subtypes, treatment, smoking prevalence, baseline statin use and low-density lipoprotein values are presented in Table 1. Participants’ ages ranged from 45 to 85 years with a median age of 62. A majority of the participants were male (62%). Race was 25% African American and 75% Caucasian. Stroke subtypes were 62% lacunar, 4% large vessel; and 33% cardioembolic. Of the participants enrolled, 17% were treated with intravenous tissue plasminogen activator (IV t-PA); and 45% were taking a statin class
medication; with the baseline LDL noted as 108.6 ± 33.8 (range 66-189). At 3 months post-stroke, 92% of the participants were taking a statin and LDL values ranged from 41-191 with a mean of 89.71 ± 42.6, and 71% were at goal with an LDL goal of <100mg/dL.

Predictor Variables

*Inflammatory Markers*

Baseline CRP values ranged from <0.1 to 34.9 with a median of 0.3. Approximately 8% were at low risk (<0.1); 9% at moderate risk (0.1 to 0.5) and 7% at high risk (>0.5). CRP values at 3 months post-stroke ranged from <0.1 to 5.2 with a mean of 0.53 ± 1.24. Baseline Lp-PLA₂ values ranged from 85 to 617 with a median of 194. Approximately 15% were classified as low risk (<200); 3% moderate risk (200-235) and high risk (>235). Lp-PLA₂ values at 3 months post-stroke ranged from 114 to 212 with a mean of 158.47 ± 28.344.

*Depression*

The mean Beck Depression Inventory score on admission was 5.9 ± 4.6 with a range (0-15); 5.13 ± 4.6 with a range (0-17) at hospital discharge or at Day 4; and 4.72 ± 4.73 with a range (0-17) at 3 months post-stroke.
Table 1

**Demographic Characteristics of Sample (N = 24)**

<table>
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<th>Mean (SD)</th>
<th>n (%)</th>
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<td>Baseline NIHSS</td>
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<td>Baseline mRS</td>
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<tr>
<td>Baseline SF-36 (adapted instrument)</td>
<td>32.3 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>Baseline BDI-II</td>
<td>5.9 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>Treatment with IV t-PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (83)</td>
<td></td>
</tr>
<tr>
<td>Smoking Preference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (37.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>155 ± 32.4</td>
<td></td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>87 ± 17.4</td>
<td></td>
</tr>
<tr>
<td>Baseline Heart Rate</td>
<td>74 (59 – 122)</td>
<td></td>
</tr>
<tr>
<td>Dominant Heart Rhythm</td>
<td>Sinus Rhythm</td>
<td></td>
</tr>
<tr>
<td>Baseline CRP</td>
<td>0.3 (0 – 34.9)</td>
<td></td>
</tr>
<tr>
<td>Low risk &lt; 0.10</td>
<td>8 (33)</td>
<td></td>
</tr>
<tr>
<td>Moderate risk 0.1 – 0.5</td>
<td>9 (38)</td>
<td></td>
</tr>
<tr>
<td>High risk &gt; 0.5</td>
<td>7 (29)</td>
<td></td>
</tr>
<tr>
<td>Baseline Lp</td>
<td>194 (85 – 617)</td>
<td></td>
</tr>
<tr>
<td>Low risk &lt; 200</td>
<td>15 (65)</td>
<td></td>
</tr>
<tr>
<td>Moderate risk 200 – 235</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>High risk &gt; 235</td>
<td>5 (22)</td>
<td></td>
</tr>
<tr>
<td>Baseline LDL</td>
<td>109 ± 33.8</td>
<td></td>
</tr>
<tr>
<td>Pre-Hospital Statin Therapy</td>
<td>11 (46)</td>
<td></td>
</tr>
</tbody>
</table>

*Notes: NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey; IV t-PA = Intravenous tissue plasminogen activator; LDL = low-density lipoprotein.*
Independent Variables

Health Outcomes

The median NIHSS score on admission was 3.1 with a range (0-15). NIHSS values at discharge or on Day 4 ranged from 0 to 12 with a mean of 2.86 ± 3.1. The mean NIHSS score at 3 months post-stroke was 1.67 ± 2.4 with a range (0-8). The mean Modified Rankin Score on admission was 1.5 ± 0.98 with a range (0-3); 1.3 ± 1.15 with a range (0-3) at hospital discharge or at Day 4; and 1.00 ± 1.03 with a range (0-3) at 3 months post-stroke. The mean SF36 score on admission was 32.33 ± 7.3 with a range (20-43); 33.91 ± 7.3 with a range (20-44) at hospital discharge or at Day 4; and 36.33 ± 8.6 with a range (17-44) at 3 months post-stroke. Because only a subset of the complete instrument was utilized, results were expressed as a percentage of possible points. For the purpose of this study, only 3 of the subscales were utilized: physical functioning, role-physical, and role emotional.

Instrument Reliability

Well-established physiological and psychological instruments were used to assess subjective and objective measures of neurological impairment, functionality, quality of life, and depression. These instruments included the National Institute of Health Stroke Scale (NIHSS), the Modified Rankin Scale, The Beck Depression Inventory, and the Short-form Quality of Life. Cronbach’s α coefficients were used to assess the internal consistency of the instruments. Cronbach’s α coefficients ranged from > 0.5 for the NIHSS to 0.83 for the BDI-II and are presented in Table 2. Cronbach’s α coefficients for
this study for the NIHSS and the BDE-II are presented in Table 3 and are similar to the published data.

Table 2

*Reliability of Instruments – published*

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Number of Items</th>
<th>Possible Score</th>
<th>Cronbach’s α coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS</td>
<td>11</td>
<td>0 - 42</td>
<td>&gt; 0.5</td>
</tr>
<tr>
<td>mRS</td>
<td>7</td>
<td>0 - 6</td>
<td>0.74</td>
</tr>
<tr>
<td>BDI-II</td>
<td>20</td>
<td>0 - 63</td>
<td>0.83</td>
</tr>
<tr>
<td>SF-36</td>
<td>36</td>
<td>0 – 100</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Notes:* NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.

Table 3

*Reliability of Instruments – this study*

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Number of Items</th>
<th>Possible Score</th>
<th>Cronbach’s α coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS</td>
<td>11</td>
<td>0 - 42</td>
<td>.650</td>
</tr>
<tr>
<td>NIHSS-3 month</td>
<td>11</td>
<td>0 - 42</td>
<td>.631</td>
</tr>
<tr>
<td>BDI-II</td>
<td>20</td>
<td>0 - 60</td>
<td>0.842</td>
</tr>
<tr>
<td>BDI-II – 3 month</td>
<td>20</td>
<td>0 – 60</td>
<td>0.872</td>
</tr>
</tbody>
</table>

*Notes:* NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.

Regression Models

To reduce the number of predictor variables in the regression models, Spearman correlations were conducted to examine associations among age, baseline NIH Stroke scale (NIHSS) score, treatment with intravenous tissue plasminogen activator (IV t-PA) and each of the outcome measures (3-month mRS; 3-month NIHSS score; and 3-month SF-36 score). Only significant (p<0.10) relationships were included in the regression
models. Age, baseline NIHSS score, and treatment with IV t-PA were associated with 3-month mRS score. None of the potential confounders (i.e., age, baseline NIHSS score, IV t-PA) were associated with 3-month NIHSS score. Baseline NIHSS score and IV t-PA treatment were associated with 3-month SF-36 score. Variables not correlated with outcome measures were not explored further.

Three hierarchical multiple regression models were conducted, each examining an outcome measure, and including only potential confounding variables significantly associated with the outcome of interest in each model. Confounders were entered in the following order when appropriate: age, NIHSS on admission, and use of IV t-PA. Potential multicollinearity of measures was examined using Tolerance. No tolerance values were less 0.2. In Step 1, relationships were examined between the baseline predictor variables (i.e., CRP, Lp-PLA₂, Beck depression score) and the dependent variables (i.e., 3-month modified Rankin score, 3-month NIHSS score, 3-month SF-36).

In Step 2, each model was adjusted for potential confounders, as indicated by the Spearman correlations. Results of the adjusted models are presented in Tables 4-8. As noted, only Beck at baseline was correlated with 3-month health outcomes of functionality (mRS) and quality of life (SF-36). Additionally, each of the 3 regression models was employed to examine the effects of the predictor variables (i.e., CRP, Beck) on the Quality of Life subscales (i.e., physical functioning, role physical, role emotional).

In the subgroup analysis of Quality of Life, only Beck was found to be an independent significant predictor of the subscales physical functioning and role physical. These results are presented in Tables 9-11.
Specific Aims and Hypothesis Testing

Baseline Biological Markers

Specific aim 1. Determine the predictability of baseline CRP and Lp-PLA₂ levels shortly after first-time ischemic stroke on subsequent health outcomes at 3 months. Health outcomes include functionality (as measured by modified Rankin Scale Score), neurological impairment (as measured by NIHSS score), and quality of life (as measured by SF-36).

The first specific aim of this study was to examine the effects of baseline biological markers (CRP and Lp-PLA₂) on health outcomes at 3-months post stroke. Hierarchical multiple regression analyses were used to test Hypothesis 1a that higher levels of CRP and Lp-PLA₂ would predict poorer health outcomes and Hypothesis 1b that higher levels of Lp-PLA₂ would also predict poorer health outcomes at 3-months post stroke. The interactive effect of both higher CRP and Lp-PLA₂ levels was examined in Hypothesis 1c. Accepted covariates of stroke recovery age, baseline NIHSS score, and IV t-PA usage were also examined. Neither of the baseline biological markers, or their interaction, was a significant independent predictor of health outcomes at 3-months post stroke. Therefore, hypotheses 1a, 1b, and 1c were not supported in this study.

Baseline Psychological Markers

Specific aim 2. Determine the predictability of baseline depression level (as measured by the Beck Depression Inventory) shortly after first-time ischemic stroke on subsequent health outcomes at 3 months. Health outcomes include functionality (as measured by modified Rankin Scale Score), neurological impairment (as measured by NIHSS score), and quality of life (as measured by SF-36).
The second specific aim of this study was to examine the effect of baseline depression level (as measured by the Beck Depression Inventory) on health outcomes at 3-months post stroke. Hierarchical multiple regression analyses were used to test Hypothesis 2a that higher levels baseline depression would predict poorer health outcomes at 3-months post stroke. Accepted covariates of stroke recovery age, baseline NIHSS score, and IV t-PA usage were also examined. Functionality as measured by the mRS score \( (p = .009) \) and Quality of Life as measured by the SF36 \( (p = .002) \) were significant independent predictors of 3-month health outcomes. Baseline depression was not an independent predictor of neurological impairment at 3 months post-stroke measured by the NIHSS score. Therefore hypothesis 2a was only partially supported in this study.

*Baseline Interaction of Biological and Psychological Markers*

**Specific aim 3.** Determine the interactive predictability of CRP and Lp-PLA\(_2\) and depression on subsequent health outcomes at 3 months post-stroke.

The third specific aim of this study was to examine whether there was an interaction between the baseline biological markers and health outcomes at 3-months post-stroke, and whether there was an interaction between baseline biological markers and baseline depression and health outcomes at 3 months post-stroke. Hierarchical multiple regression analyses were used to test Hypothesis 3a that higher levels of baseline CRP and depression would predict poorer health outcomes at 3 months post stroke, hypothesis 3b that higher levels of baseline Lp-PLA\(_2\) and depression would predict poorer health outcomes at 3 months post stroke. Accepted covariates of stroke recovery age, baseline NIHSS score, and IV t-PA usage were also examined. None of the
interaction terms were independent significant predictors of health outcomes at 3 months post-stroke. Therefore hypotheses 3a and 3b were not supported in this study.

Table 4

Regression Model Examining CRP on 3-month Health Outcomes

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>*mRS score</td>
<td>.022</td>
<td>.034</td>
<td>.161</td>
<td>.532</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>-.013</td>
<td>.072</td>
<td>-.042</td>
<td>.861</td>
</tr>
<tr>
<td>**SF-36</td>
<td>-.031</td>
<td>.295</td>
<td>-.027</td>
<td>.918</td>
</tr>
</tbody>
</table>

Notes: NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.  
*Adjusted for age, admission NIHSS, and use of IV t-PA  
**Adjusted for admission NIHSS and use of IV t-PA

Table 5

Regression Model Examining CRP (category) on 3-month Health Outcomes

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>*mRS score</td>
<td>.016</td>
<td>.315</td>
<td>.013</td>
<td>.960</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>.126</td>
<td>.659</td>
<td>-.045</td>
<td>.850</td>
</tr>
<tr>
<td>**SF-36</td>
<td>.171</td>
<td>2.794</td>
<td>.017</td>
<td>.952</td>
</tr>
</tbody>
</table>

Notes: NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.  
*Adjusted for age, admission NIHSS, and use of IV t-PA  
**Adjusted for admission NIHSS and use of IV t-PA
Table 6

*Regression Model Examining Lp-PLA$_2$ on 3-month Health Outcomes*

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>$B$</th>
<th>$SE$</th>
<th>$\beta$</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>*mRS score</td>
<td>-.002</td>
<td>.002</td>
<td>-.240</td>
<td>.278</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>-.004</td>
<td>.004</td>
<td>-.230</td>
<td>.344</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td>.027</td>
<td>.015</td>
<td>.394</td>
<td>.083</td>
</tr>
</tbody>
</table>

*Notes:* NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.

*Adjusted for age, admission NIHSS, and use of IV t-PA
**Adjusted for admission NIHSS and use of IV t-PA

Table 7

*Regression Model Examining Lp-PLA$_2$ (category) on 3-month Health Outcomes*

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>$B$</th>
<th>$SE$</th>
<th>$\beta$</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>*mRS score</td>
<td>-.281</td>
<td>.254</td>
<td>-.237</td>
<td>.287</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>-.182</td>
<td>.648</td>
<td>-.068</td>
<td>.782</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td>3.604</td>
<td>2.142</td>
<td>.365</td>
<td>.113</td>
</tr>
</tbody>
</table>

*Notes:* NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.

*Adjusted for age, admission NIHSS, and use of IV t-PA
**Adjusted for admission NIHSS and use of IV t-PA

Table 8

*Regression Model Examining BDI-II on 3-month Health Outcomes*

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>$B$</th>
<th>$SE$</th>
<th>$\beta$</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>*mRS score</td>
<td>.119</td>
<td>.039</td>
<td>.546</td>
<td>.009</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>.140</td>
<td>.111</td>
<td>.284</td>
<td>.224</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td>-1.163</td>
<td>.306</td>
<td>-.642</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Notes:* BDI-II = Beck Depression Inventory II; NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.

*Adjusted for age, admission NIHSS, and use of IV t-PA
**Adjusted for admission NIHSS and use of IV t-PA
Table 9

*Regression Model Examining CRP on 3-month Quality of Life Subscales*

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Physical Functioning</td>
<td>.133</td>
<td>.160</td>
<td>-.193</td>
<td>.419</td>
</tr>
<tr>
<td>Role Physical</td>
<td>.024</td>
<td>.049</td>
<td>.117</td>
<td>.625</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>-.002</td>
<td>.036</td>
<td>-.012</td>
<td>.959</td>
</tr>
</tbody>
</table>

_Notes:_ *Adjusted for admission NIHSS and use of IV t-PA*

Table 10

*Regression Model Examining Lp-PLA₂ on 3-month Quality of Life Subscales*

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Physical Functioning</td>
<td>.033</td>
<td>.021</td>
<td>.317</td>
<td>.134</td>
</tr>
<tr>
<td>Role Physical</td>
<td>.014</td>
<td>.007</td>
<td>.436</td>
<td>.062</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>.005</td>
<td>.005</td>
<td>.198</td>
<td>.417</td>
</tr>
</tbody>
</table>

_Notes:_ *Adjusted for admission NIHSS and use of IV t-PA*

Table 11

*Regression Model Examining BDI-II on 3-month Quality of Life Subscales*

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Physical Functioning</td>
<td>-.483</td>
<td>.212</td>
<td>-.426</td>
<td>.037</td>
</tr>
<tr>
<td>Role Physical</td>
<td>-.224</td>
<td>.062</td>
<td>-.649</td>
<td>.002</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>-.104</td>
<td>.054</td>
<td>-.417</td>
<td>.067</td>
</tr>
</tbody>
</table>

_Notes:_ BDI-II = Beck Depression Inventory II  
*Adjusted for admission NIHSS and use of IV t-PA*
In addition to the above regression models, the interaction terms (CRP x Depression) and (Lp-PLA2 x Depression) were also investigated. As noted below, in Table 12, there were no significant relationships between the interaction variables. Because there was no statistical significance between any of the interaction variables, the interaction variable (CRP x Lp-PLA2 x depression) was not analyzed.

Table 12

Regression Model Examining Interaction Terms on 3-month Health Outcomes

<table>
<thead>
<tr>
<th>Interaction Terms</th>
<th>Health Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mRS score</td>
<td>NIHSS score</td>
</tr>
<tr>
<td>CRP</td>
<td>p = .100</td>
<td>p = .949</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>p = .090</td>
<td>p = .495</td>
</tr>
<tr>
<td>CRP x Lp-PLA2</td>
<td>p = .079</td>
<td>p = .943</td>
</tr>
<tr>
<td>CRP x Depression</td>
<td>p = .183</td>
<td>p = .877</td>
</tr>
<tr>
<td>Lp-PLA2 x Depression</td>
<td>p = .764</td>
<td>p = .973</td>
</tr>
</tbody>
</table>

Notes: NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; SF-36 = 36-Item Short Form Health Survey.

Summary

In conclusion, 24 subjects met inclusion criteria and were enrolled in the study. Of those, 20 completed evaluation at 3 months post-stroke. All data were analyzed and reported in this section. For Specific Aim 1, using hierarchical multiple regression analyses, the biological markers of CRP and Lp-PLA2 were not independent predictors of health outcomes at 3 months post-stroke. For Specific Aim 2, using hierarchical multiple regression analyses, depression was a significant independent predictor of functionality and quality of life at 3 months post-stroke. For Specific Aim 3, using hierarchical
multiple regression analyses, the interaction between biological and psychological markers was not an independent predictor of health outcomes at 3 months post-stroke.
CHAPTER 6
DISCUSSION

The purpose of this study was to determine the effect of baseline CRP and Lp-PLA₂ levels and depression and their interactive effect on health outcomes in first-time stroke patients over a 3-month period. Findings of this prospective, descriptive cohort design indicated that only baseline depression was a significant independent predictor of the health outcomes of functionality (measured by the mRS) and quality of life (measured by the SF-36) at 3 months post-stroke. The baseline levels of inflammatory markers CRP and Lp-PLA₂ were not significant independent predictors of 3 month health outcomes post-stroke. There was no additional predictive value when the interaction terms of (CRP x Depression) and (Lp-PLA₂ x Depression) were considered. Because there was no predictive statistical significance with any of the interaction variables, the interaction variable (CRP x Lp-PLA₂ x depression) was not analyzed. The original study was also designed to track recurrent strokes. Of the 24 participants enrolled, only 3 (12.50%) had a subsequent stroke or TIA within the study period. Only 2 of those 3 participants completed the study at 3 months post-stroke.

The conceptual framework for this study was based on Neuman’s Systems Model and an Integrative Model of Biobehavioral Interactions developed by Kang, Rice, and Weaver (personal communication, Dr. Kang). A first-time stroke was conceptualized as a stressor, which in turn, activates the stress response resulting in inflammation and,
impacting the psychological domain of an individual which may result in depression. If
the model is valid, these changes would have an independent, as well as, an interactive
effect on health outcomes; ultimately affecting an individual’s functionality, neurological
impairment, and quality of life. This study did show statistical significance in the
predictive value of depression on the health outcomes of functionality \( (p = .009) \) and
quality of life \( (p = .002) \). This study was unable, however, to establish the predictive
ability of the biological markers of inflammation of CRP and Lp-PLA\(_2\) on 3-month health
outcomes after a first-time stroke. Therefore, either the model is flawed, or the study
sample size was inadequate to establish significance. This study was initially designed to
enroll 67 participants in order to achieve a power of 0.80 with an alpha level of 0.05
based on a medium to high effect size calculation (Polit & Beck, 2004). Although the
association between depression and quality of life for stroke patients has been fairly well
established (Haacke et al., 2006; Nannetti, Paci, Pasquini, Lombardi, & Taiti, 2004; Van
de Port, Kwakkel, Wijik, & Lindeman, 2006), the exact effect sizes have not been
reported. Similarly, although the association between CRP and health outcomes for
stroke patients has also been established, the exact effect sizes have also not been
established. Lp-PLA2 is a fairly new biomarker in stroke literature, and therefore, its
effect size has not been clearly established. An interim analysis was accomplished with
24 participants recruited over a 5 month period. Due to the finding of a very low effect
size with \( r^2 = .002 \) for CRP; a sample size of 3,800 would have been required to achieve
statistical significance. The highest \( r^2 = .076 \) was noted for the BDI-II which would have
required 95 participants to achieve statistical significance. The study was therefore
terminated for futility.
If, in fact, the conceptual model was flawed, an alternative model could be proposed, addressing only the significant predictive value of depression on the 3 month outcomes of functionality and quality of life. This revised model is presented below.

Figure 2. Revised Conceptual Diagram.

This model would only address the behavioral component of a stressor, and would negate the biobehavioral interaction implied in the original diagram.
CRP and Stroke

Elevated CRP levels were detected within 24 hours of ischemic stroke onset in approximately 75% of stroke patients in several published studies (DiNapoli & Papa, 2002; DiNapoli, Papa, & Bocola, 2001). Their results also suggested that CRP levels could be used effectively in the stratification of risk for subsequent stroke. CRP levels at hospital admission for ischemic stroke were also highly predictive of combined 1 year end points \((p < .002)\) including new vascular events and death. A CRP level of \( \geq 1.5 \) mg/dL at discharge was associated with significantly worse outcomes measured by combined vascular end points and death \((p < .001)\).

This study partially supported other published findings. Of the 24 participants enrolled in this study, 67\% had CRP levels in the moderate to high risk tertiles measured within 24 hours of symptom onset. There was no significance difference, however, between baseline and 3-month values \((p = 0.271)\). In addition, in this study 3 participants had a recurrent stroke/TIA within the 3 month study duration. All 3 participants had elevated CRP levels at baseline: 2 with moderate risk and 1 with high risk levels. If the study could have been extended for a longer follow-up period, more cerebrovascular events may have occurred.

Lp-PLA\(_2\) and Stroke

The contribution of Lp-PLA\(_2\) to an estimation of stroke risk was examined by Greenland and O’Malley (2005). In their interpretation of the Atherosclerosis Risk in Communities (ARIC) Study, they found that Lp-PLA\(_2\) levels in the highest tertiles contributed to approximately double the risk of stroke in this healthy United States adult
population. Of the 24 participants enrolled in this study, 35% had baseline levels of Lp-PLA₂ in the moderate and high risk ranges. There was no significant difference ($p = .064$) in Lp-PLA₂ values at 3 months post-stroke. Oei et al. (2005) also considered the Lp-PLA₂ levels of subjects in the Rotterdam Study which examined 7,983 subjects ≥ 55 years of age including 308 subjects with coronary heart disease, and 110 with ischemic strokes. The multivariate-adjusted hazard ratios for ischemic stroke were 1.08, 1.58, and 1.97 for the second, third and fourth quartiles of Lp-PLA₂ in this subject population.

Persson, Berglund, Nelson, and Hedblad (2008), examined the association of increased mass and activity levels of Lp-PLA₂ and ischemic stroke in 152 subjects enrolled in the Malmo Diet and Cancer Study (MDCS), a prospective, population-based cohort study, where participants were followed from baseline through the first event. Pre-event measurements were analyzed; elevated Lp-PLA₂ levels were associated with an increased relative risk of ischemic stroke of 1.48. Further evaluation of Lp-PLA₂ and the risk of recurrent stroke were studied by Elkind, Tai, Coates, Paik, and Sacco (2009). In the North of Manhattan Stroke Study, 467 first-time stroke patients were followed for 4 years. The recurrent stroke rate was 18% overall, with the patients with Lp-PLA₂ levels in the highest quartile having an increased risk of recurrent stroke (adjusted HR 2.54).

The recurrent stroke rate in the present study was lower at 12.5%; however, these participants were only followed for 3 months. If participants had been followed longer, the rate may have been higher.

The majority of participants in this study 65%, had baseline Lp-PLA₂ levels in the low risk category. These levels were drawn within 24 hours of symptom onset after a first-time stroke; however, no pre-stroke Lp-PLA₂ levels were available for comparison.
In their research Elkind, Leon, Moon, Paik, and Sacco (2009) also evaluating subjects in the North of Manhattan Stroke Study, reported that Lp-PLA₂ levels decreased acutely after stroke; however, the median time from stroke onset to laboratory measurement was 5 days. Therefore, levels drawn at less than 24 hours from symptom onset may truly represent baseline assessment. It should be noted that there was no significant difference between baseline and 3 month Lp-PLA₂ levels in this study.

Interaction of CRP and Lp-PLA₂ and Stroke

If inflammation is truly a consequence of the tissue injury resulting from an acute ischemic stroke, then evaluating acute phase inflammatory markers should yield important information regarding stroke size, future vascular events, and possibly even stroke recovery. Additionally, the measurement of 2 such acute phase inflammatory markers should increase the prognostic value. When adults in the ARIC study with both the highest levels of CRP and Lp-PLA₂ were considered by Greenland and O’Malley (2005), they found that their risk of stroke was 11 times higher than adults with lower levels of both these inflammatory markers. Although this study failed to support this theory, of the 24 participants in this study, 7 or 29% had both CRP, and Lp-PLA₂ levels, in the moderate or high risk categories. Of those 7 participants, 2 had recurrent stroke or TIA within the 3 month study duration. The ARIC study data were true baseline data, which were not available for the present study.

Elkind, Leon, Moon, Paik, and Sacco (2009) reported the stability of CRP and Lp-PLA₂ before and after stroke. They collected CRP and Lp-PLA₂ levels for 37 first-
time stroke patients participating in the North of Manhattan Study before, and within 5 days, of an incident stroke. Both activity levels were stable over time; however, Lp-PLA₂ mass levels decreased approximately 5% annually following a stroke. The risk categories were essentially unchanged over time. CRP levels increased after stroke ($p = 0.0067$); the mass and activity levels of Lp-PLA₂ decreased significantly ($p = 0.03$) after stroke. Based on their findings, they concluded measurements of these inflammatory markers in the acute setting may not be reliable for long-term risk evaluation, as levels measured shortly after stroke onset may not reflect a true baseline. However, they did not report the length of time from “true” baseline to incident stroke.

**Depression and Stroke**

Post-stroke depression has been extensively studied. The incidence of post-stroke depression has been reported to be as high as 30-60% (Carota, & Bogousslavsky, 2003; Kotila et al, 1998) measured at 3, 6, and 12 months post-stroke. The mean Beck Depression Inventory score on admission was $5.9 \pm 4.6$ with a range (0-15); $5.13 \pm 4.6$ with a range (0-17) at hospital discharge or at Day 4; and $4.72 \pm 4.73$ with a range (0-17) at 3 months post-stroke. For the purpose of this study, participants were considered depressed if they scored $> 10$ on the BDI-II, with scores from 0-13 indicating minimal depression; 14-19 mild depression; 20-28 moderate depression; and 29-63 severe depression. In this study 5 participants had BDI-II scores $> 10$ on any of the measurements, with 2 scoring at least minimal depression at all 3 time periods assessed. No participants scored $> 17$ (mild depression). The depression rates in this study were very low, with only 13% of participants scoring $> 10$ on the BDI-II at any assessment
period. Baseline depression scores may have been low due to the high number of mild strokes with the median NIHSS score of 3.10.

As reported previously, baseline depression was a significant independent predictor of 3-month functionality and quality of life. The conceptual diagram links depression, as well as its interactive effect with the inflammatory markers of CRP and Lp-PLA₂, and the results of this study partially support this diagram.

Recurrent Stroke Risk

Recurrent stroke risk as pertinent to our study was investigated by Beamer and colleagues (1998) as well as Rost et al. (2001). Rost et al. (2001) reported that CRP levels in the highest quartile in healthy subjects enrolled in the Framingham Study were highly predictive of subsequent stroke risk. Although, Beamer and colleagues (1998) reported that CRP levels were highest in subjects experiencing a stroke; high levels of CRP in their study group were not correlated with recurrent cerebrovascular events. DiNapoli, Papa, and Bocola (2001) measured CRP levels within the first 24 hours following first-ever stroke, and reported that CRP levels were highly predictive ($p < .002$) of 1 year end-points including combined vascular end points and death ($p < .001$).

The 3 participants with recurrent stroke/TIA in this study had CRP levels in the moderate to high tertiles at baseline. In addition, 2 or the 3 participants with recurrent stroke, cardioembolic in mechanism, had the highest Lp-PLA₂ levels measured at baseline. The other participant’s Lp-PLA₂ was in the low risk category at baseline and at 3 months post-stroke when she had a second stroke, lacunar in mechanism. At 3 months post-stroke, 1 of the participant’s CRP had normalized but his Lp-PLA₂ remained in the
high risk category; 1 remained in the moderate risk category, and the third participant did not complete the study. The participant who did not complete the study was hospitalized with recurrent stroke, cardioembolic in mechanism, (MRI confirmed); however, the PI was not notified of his admission, and CRP and Lp-PLA2 levels were not ordered by his admitting physician. The other 2 stroke mechanisms for the participants with recurrent stroke/TIA were cardioembolic and lacunar—identical to their incident stroke mechanism. This study does support Rost et al. (2001) that higher CRP levels were predictive of subsequent stroke risk and DiNapoli, Papa, and Bocola (2001) that higher levels of CRP drawn within 24 hours of first-time stroke were predictive of 1 year endpoints; however, this study was not designed to track outcomes through 1 year.

Limitations of the Study

There were several serious limitations to this study. First and foremost, the sample size was inadequate to achieve statistical significance except with regards to depression and functionality and quality of life at 3 months post-stroke. When the study was initially designed, a moderate to high effect size was theorized. A sample size of 67 was proposed for this study in order to achieve a power of .80, with an α level of .05, based on a medium to high effect size calculation (Polit & Beck, 2004). Although the association between depression and quality of life for stroke patients was fairly well established (Haacke et al., 2006; Nannetti, Paci, Pasquini, Lombardi, & Taiti, 2004; Van de Port, Kwakkel, Wijik, & Lindeman, 2006), the exact effect sizes have not been reported. Our assumption of a moderate to high effect size was not supported by this study. Our least robust correlation between CRP and neurological impairment ($r^2 = .002$)
for the 24 participants enrolled, would have required a minimum sample size of 3,800 participants, in order to achieve a power of .80, with an $\alpha$ level of .05.

Secondly, this study may not have been designed appropriately. As noted above, the conceptual diagram may be flawed. There may not be an adequate, or any, biobehavioral interaction between depression, inflammation, and subsequent health outcomes in order to establish predictability between these variables.

A third consideration is: were these stroke patients unique? Their strokes were MRI confirmed first-time ischemic strokes; however, neurological impairment at baseline was low with the median NIHSS score on admission of 3, with a range (0 - 15); the median NIHSS score at discharge or on Day 4 of 2, with a range (0 - 12); and the median NIHSS score at 3 months post-stroke of 1, with a range (0 - 8). Would the results have differed if participants with larger stroke burdens had been enrolled? The type of ischemic stroke should also be considered. The majority of the participants (62%) enrolled had lacunar strokes. Other stroke subtypes included cardioembolic (33%) and large vessel (4%). Because stroke patients with significant aphasia were excluded from this study due to the importance of assessing cognitive functioning, this study may not be generalizable to patients with large artery strokes. Also, as noted above, 17% of the participants were treated with IV t-PA. Unfortunately, 2 of these participants did not complete the study. Because of this, it would be inappropriate to comment on whether reperfusion cases with good outcomes may have confounded 3-month outcomes or the potential for future strokes. Another consideration should be the number of participants (45%) taking a statin class medication at baseline, and the high rate of post-stroke statin use (92%). The use of statin medications post-stroke was not routinely prescribed when
some of the initial studies examining CRP were completed, and given the actions of these agents, this may have confounded study results. Lastly, all the participants were recruited from a single source: Huntsville, Alabama, and this first-time stroke cohort may not be representative of stroke patients elsewhere in the state or the county. This factor may have introduced sample bias as well and limits generalizability.

Future Research

The sample size estimate (3,800 stroke patients) places a properly designed prospective study within the range of feasible multi-center observational studies being conducted to evaluate associations and interactions between risk factors that could affect stroke outcomes. Such a prospective study would require funding, and our present study results could provide pilot data to support this application. However, the utility of such work must be considered alongside widespread use of statin agents which may challenge the need for future research. A study designed to evaluate early identification and intervention with regard to post-stroke depression may also be proposed again within a multi-center observational study.

Implication for Practice

If in fact, depression is a significant independent predictor of 3-month functionality and quality of life post-stroke, this risk factor for impaired recovery should be evaluated and treated aggressively.
REFERENCES


Culebras, A., Kase, C. S., Masdeu, J. C., Fox, A. J., Bryan, R. N., Grossman, C. B., ...


APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVALS
UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00003960 and it expires on October 26, 2010. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines.

Principal Investigator: BRETHOUR, MARY KING
Co-Investigator(s): ALEXANDROV, ANNE WOJNER
Protocol Number: F091217001
Protocol Title: The Predictability of C-reactive Protein, Lipoprotein-associated Phospholipase A2, and Depression on Later Health Outcomes in Patients Experiencing a First-Time Stroke

The IRB reviewed and approved the above named project on 1/13/2010. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 1/13/2010
Date IRB Approval Issued: 1/2/10
Identification Number: IRB00000726

Albert Oberman, M.D., MPH
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

- The IRB approved consent form used in the study must contain the IRB approval date and expiration date.
- IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.
- Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.
- Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on September 29, 2013. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: BRETHOUR, MARY KING
Co-Investigator(s): ALEXANDROV, ANNE WOJNER
Protocol Number: F091217001
Protocol Title: The Predictability of C-reactive Protein, Lipoprotein-associated Phospholipase A2, and Depression on Later Health Outcomes in Patients Experiencing a First-Time Stroke

The IRB reviewed and approved the above named project on 1/5/2011. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 1/5/2011
Date IRB Approval Issued: 1/7/11
Identification Number: IRB00000726

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
Huntsville Hospital’s Institutional Review Committee (IRC) has an approved Federal Wide Assurance with the Office for Human Research Protections (OHRP) (FWA # 00003286; IRB # 00002730). The IRC is also in compliance with The Common Rule and Subparts B, C, and D of the HHS Regulations at 45 CFR Part 46. This is to certify that the IRC has reviewed/approved the named project. Review was conducted in accordance with applicable guidelines/assurance and will be subject to continuing review.

**Principal Investigator:** Mary Brethour, CRNP

**Protocol Name/Title/Number:** The Predictability of C-Reactive Protein, Lipoprotein-Associated Phospholipase A2, and Depression in Patients Experiencing a First-Time Stroke on Later Health Outcomes

**Action:** Approval of New Protocol, Informed Consent.

**Expedited Review Date:**

<table>
<thead>
<tr>
<th>IRC Approval Date</th>
<th>Continuing Review Expires</th>
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<tr>
<td>December 8, 2009</td>
<td>October 31, 2011</td>
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</table>

**Investigators please note:**

- The IRC approved the consent form (if applicable) that contains the stamped IRC approval date. Only the stamped consent form may be used for study participants.
- The IRC approval is given for twelve months unless otherwise noted above. For projects subject to continuing review, activities may not continue past this twelve-month anniversary.
- Any modifications in the study methodology, protocol, consent form, and/or investigator’s drug brochure must be submitted for review and approval by the IRC prior to implementation.
- Global and local Serious Adverse Events (SAEs) and/or unanticipated risks to subjects or others at Huntsville Hospital or other participating institutions must be reported promptly to the IRC in accordance with the guidelines outlined in the Huntsville Hospital Institutional Review Committee Policies and Procedures, a copy of which is supplied to all Principal Investigators.
- Current IRC Policies and Procedures can be viewed on Huntsville Hospital’s website under Policies and Procedures or can be obtained from the IRC Coordinator.
- Questions regarding IRC activities may be directed to:

  Allison Greene, IRC Coordinator, Huntsville Hospital, 101 Sivley Road, Huntsville, AL 35801
  (256) 266-6990 (Telephone); (256) 265-8020 (Fax); allison.e.greene@hhhs.org (Email)
The Huntsville Hospital Institutional Review Committee
Continuing Review Form for Investigational Studies

1) Title & Phase of Study: [Handwritten text]
2) Principal Investigator: [Handwritten text]
3) Original Date of HH IRC Approval: Dec 8, 2009
4) Date of Current Protocol: Dec 8, 2009
5) Date of Current Consent Form: Dec 8, 2009
6) Have all modifications to Protocol & Consent Form been to HH IRC for approval? Yes: [ ] No: [ ] NA: [ ]
(Right) The Principal Investigator or his designee must review all Local/Global Serious Adverse Events to assure that no revisions are necessary to the Informed Consent. The Informed Consent must also be reviewed to assure that it is up to date with the required contact information, updated hospital phone number, and the complete list of blinda.
7) Number of Patients Enrolled in Study:
8) Number of Patients Withdrawn From Study & Reason(s) for Withdrawals From Study:
   Total # Withdrawn From Study: [ ]
   Reason(s) for Withdrawals From Study:
   [ ] Death
   [ ] Toxicity
   [ ] Disease Progression
   [ ] Other (Specify):
9) Serious Adverse Events: [ ] Total # of Local SAEs:
   [ ] Reported to IRC
   [ ] Total # of National/Global SAEs:
   [ ] Reported to IRC
10) Attach copies of any FDA or Non-FDA inspection findings.
11) Study is:
    [X] Open
    [ ] Closed to Accrual
    [ ] Closed (Patients on Follow Up)
    [ ] Permanently Closed
    [ ] (Continuing Review Not Required)

Signature: [Handwritten text]
Date: 9-26-10

Institutional Review Committee Action:
[ ] Full Board Review
[ ] Expedited Review
Date: 10/12/10

1) Study Approved for Continuing Review: [ ]
   (Continuing Review Due: [ ])
2) Continuing Review Not Required Due to Permanent Closure: [ ]
3) Study Denied Continuing Review: [ ]
   Reason: [ ]
4) Signature of IRC Chair/Designee:
   [Handwritten text]
   (Revised: 08/10/05)
APPENDIX B

INFORMED CONSENT
Informed Consent Document

TITLE OF RESEARCH: The Predictability of C-reactive Protein, Lipoprotein-associated Phospholipase A2, and Depression on Later Health Outcomes in Patients Experiencing a First-Time Stroke.

IRB PROTOCOL: F091217001

INVESTIGATOR: Mary Brethour, CRNP

SPONSOR: UAB School of Nursing

Purpose of the Study

Explanation of Procedures

If you choose to participate in the study, you will be asked questions about your symptoms and have a physical and neurological examination. The neurological examination will include an NIHSS (National Institute of Health Stroke Scale) test that assesses how you are neurological functioning, a Rankin Scale to measure your ability to complete your activities of daily living, the SF-36 to measure your quality of life, and the BDI (Beck Depression Inventory) to assess your level of depression. Blood samples of about 2 teaspoons will also be drawn. A small tube called an IV will be inserted into your vein for direct administration of fluids.

You may undergo perfusion scanning of your brain using CT (computerized x-rays) or MR (imaging with magnets). These scans use imaging with and without dye to understand how your blood is flowing in your brain during your stroke. Your doctor can explain to you how these scans work.

If you give consent and are selected to participate in the study, your medical care will not be affected. You will receive medical care recommended by the American Stroke Association.

Your care will include making sure you have enough fluids and oxygen, and that your blood pressure, blood sugar, and temperature remain normal. You will be observed in a stroke unit or intensive care unit (ICU). You will receive neurological examinations, blood work, and diagnostic procedures during the study as shown in the table below.
Schedule of Tests and Evaluations

<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline at Admission</th>
<th>Day 4 or Day of Discharge</th>
<th>3 Months Post-stroke</th>
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<tbody>
<tr>
<td>Sign Informed Consent</td>
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<tr>
<td>Med History And Physical</td>
<td>xx</td>
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<td>Heart 12 Lead EKG</td>
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<td>Vital Signs</td>
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<td>Blood Work</td>
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<td>CT or MR of Scans</td>
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<tr>
<td>NIHSS Neuro Test</td>
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<tr>
<td>Modified Rankin Scale</td>
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<tr>
<td>SF-36 Qual of Life</td>
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<tr>
<td>Depression BDI</td>
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</table>

Your condition will be monitored for this study on your admission to the hospital, Day 4 or Day of Discharge whichever comes first, and at 3 months post-stroke. Blood tests will be done on admission and at 3 months post-stroke for this study. These tests will require less than 2 teaspoons of blood. You will have neurological evaluations on admission, Day 4 or Day of discharge whichever comes first, and at 3 months post-stroke.

Risks and Discomforts

Every medical procedure involves risks; however, the risks involved in participation in this study are minimal. You may feel some pain or discomfort, or develop a bruise when your blood is taken. Rarely, people develop infection at the needle site. The amount of blood taken will not cause anemia or other significant health consequences.

Benefits

We do not know if you will benefit from participating in this study; however, the information gained may help in the treatment of future patients with conditions like yours.

Alternative Treatments
You do not have to participate in this study to receive treatment for your condition.

Confidentiality

Confidentiality of your records will be strictly maintained. The Institutional Review Board may need to review your medical records to verify information. No pictures, names, initials, or other information that could disclose your individual identify will be made available to the public, or in any publication of these study results, without specific consent from you to do so. Results of this study may be used for teaching, research, publications, or presentations at scientific meetings. If your medical records are included, your identity will be protected by using a study code number rather than your name or other identifying information.

Refusal or Withdrawal without Penalty

Your taking part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study at any time if the study investigator decides it is not in the best interest of your health, or if you are not following the study rules.

Cost of Participation

There will be no cost to you from taking part in this study. The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

Payment for Research-Related Injuries

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by your doctor or his staff if new information becomes available and might affect your choice to stay in the study.
Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Mary Brethour, CRNP. She will be glad to answer any of your questions. Ms. Brethour’s number is 205-975-7574. Ms. Brethour may also be reached after hours by paging her at 205-934-3411 (beeper 7164).

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact Ms. Sheila Moore. Ms. Moore is the Director of the Office of the Institutional Review Board for Human Use (OIRB). Ms. Moore may be reached at (205) 934-3789 or 1-800-822-8816. If calling the toll-free number, press the option for “all other calls” or for an operator/attendant and ask for extension 4-3789. Regular hours for the Office of the IRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.
## Signatures

Your signature below indicates that you agree to participate in this study. You will receive a copy of this signed document.

<table>
<thead>
<tr>
<th>Signature of Participant</th>
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<th>Signature of Investigator reviewing consent document</th>
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University of Alabama at Birmingham

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION
FOR RESEARCH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant Name: ____________________________

UAB IRB Protocol Number: F091217001

Research Protocol: The Predictability of C-reactive Protein, Lipoprotein-associated Phospholipase A2, and Depression on Later Health Outcomes in Patients Experiencing a First-Time Stroke

Principal Investigator: Mary Brethour, CRNP

Sponsor: UAB School of Nursing

What health information do the researchers want to use? All medical information and personal identifiers including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: ____________________________ Date: __________

or participant's legally authorized representative: ____________________________ Date: __________

Printed Name of participant's representative: ____________________________

Relationship to the participant: ____________________________

Page 6 of 6
2/17/2019
Participants Initials: ________
INFORMED CONSENT FORM

The Predictability of C-reactive Protein, Lipoprotein-associated Phospholipase Aandle Depression on Later Health Outcomes in Patients Experiencing a First-Time Stroke

STATEMENT OF RESEARCH
You are being asked to participate in a research study for a doctoral dissertation. Before you agree to be a part of this study, it is important that you read and understand the risks and potential benefits so that you can make an informed decision. This is known as informed consent.

PURPOSE OF THE RESEARCH
Your physician has determined that you have symptoms of an acute ischemic stroke (a stroke caused by blockage of a blood vessel that supplies blood to the brain). The blockage of blood flow to your brain may cause injury or death of the brain tissue.

You have been asked to participate in a research study that will attempt to establish a relationship between laboratory tests which indicate inflammation with depression. You will be asked to complete several surveys, and your blood will be drawn for testing. You will also be seen at 3 months post-stroke for repeated surveys and blood tests. The purpose of the research is to determine the effect of baseline blood tests for inflammation depression on how well you recover from your stroke.

This study is being conducted here at Huntsville Hospital, as well as at the University of Alabama at Birmingham. Your participation in the study will last for approximately 90 days and will involve 1 hospital follow-up visit.

ENROLLMENT ELIGIBILITY
This study will involve patients who have a first-time stroke. Your eligibility for participation in the research study will be determined by the results of physical exams, neurological evaluations, and diagnostic procedures.

PROCEDURE
If you choose to participate in the study, you will be asked questions about your symptoms and have a physical and neurological examination. The neurological examination will include an NIHSS (National Institute of Health Stroke Scale) test that assesses how you are neurological functioning, a Rankin Scale to measure your ability to complete your activities of daily living, the SF-36 to measure your quality of life, and the BDI (Beck Depression Inventory) to assess your level of depression. Blood samples of about 2 teaspoons will also be drawn. A small tube called an IV will be inserted into your vein for direct administration of fluids.

You may undergo perfusion scanning of your brain using CT (computed x-rays) or MR (imaging with magnets). These scans use imaging with and without dye to
RISKS/BENEFITS
Every medical procedure involves risks; however, the risks involved in participation in this study are minimal. You may feel some pain or discomfort, or develop a bruise when your blood is taken. Rarely, people develop infection at the needle site. The amount of blood taken will not cause anemia or other significant health consequences.

POTENTIAL BENEFITS
We do not know if you will benefit from participating in this study; however, the information gained may help in the treatment of future patients with conditions like yours.

ALTERNATIVE TREATMENTS
You do not have to participate in this study to receive treatment for your condition.

CONFIDENTIALITY
Confidentiality of your records will be strictly maintained. The Institutional Review Board may need to review your medical records to verify information. No pictures, names, initials, or other information that could disclose your individual identity will be made available to the public, or in any publication of these study results, without specific consent from you to do so. Results of this study may be used for teaching, research, publications, or presentations at scientific meetings. If your medical records are included, your identity will be protected by using a study code number rather than your name or other identifying information.

QUESTIONS ABOUT RESEARCH
If you have any questions about the study, or think you have developed a study-related problem, you should contact your doctor, or his designate, at the phone numbers that he provided to you.

If you think that you have been injured as a result of participation in this study, contact the investigator to discuss your treatment options.

Mary Brethour, CRNP 256-265-9123
Principal Investigator Name Contact Phone

If you have any questions about your rights as a research-related subject, you should contact the IRC/MEC at this hospital.

Dr. John B. Cox 256-265-8858
IRC/MEC Chairperson Contact Phone

SUBJECTS' RIGHTS
Your participation in this study is voluntary. Your refusal to participate will not prejudice your future treatment or benefits at this hospital. You are free to discontinue
understand how your blood is flowing in your brain during your stroke. Your doctor can explain to you how these scans work.

If you give consent and are selected to participate in the study, your medical care will not be affected. You will receive medical care directed by your physician with recommendations by the American Stroke Association.

Your care will include making sure you have enough fluids and oxygen, and that your blood pressure, blood sugar, and temperature remain normal. You will be observed in a stroke unit or intensive care unit (ICU). You will receive neurological examinations, blood work, and diagnostic procedures during the study as shown in the table below.

**Schedule of Tests and Evaluations**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline at Admission</th>
<th>Day 4 or Day of Discharge</th>
<th>3 Months Post-stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sign Informed Consent</td>
<td>xx</td>
<td></td>
<td>xx</td>
</tr>
<tr>
<td>Med History And Physical</td>
<td>xx</td>
<td></td>
<td>xx</td>
</tr>
<tr>
<td>Heart 12 Lead EKG</td>
<td>xx</td>
<td></td>
<td>xx</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Blood Work</td>
<td>xx</td>
<td></td>
<td>xx</td>
</tr>
<tr>
<td>CT or MR of Scans</td>
<td>xx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS Neuro Test</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Modified Rankin Scale</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>SF-36 Qual of Life</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Depression BDI</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
</tbody>
</table>

**FOLLOW-UP EXAMINATIONS**

Your condition will be monitored for this study on your admission to the hospital, Day 4 or Day of Discharge whichever comes first, and at 3 months post-stroke. Blood tests will be done on admission and at 3 months post-stroke for this study. These tests will require less than 2 teaspoons of blood. You will have neurological evaluations on admission, Day 4 or Day of discharge whichever comes first, and at 3 months post-stroke.
your participation in this study at any time, and you will not lose any benefits or be treated differently as a result of withdrawing.

**PATIENT'S CONSENT**
I have read this form and the research study has been explained to me. I have been given the opportunity to discuss it, ask questions, and have my questions answered. I agree to participate in the research study described above. I will receive a copy of this consent form after I have signed it.

I understand that Huntsville Hospital has made no provision for monetary compensation to me in the event of physical injury resulting from the research procedures. Should physical injury occur, medical treatment is available, but treatment is not provided free of charge.

I certify that I am at least 19 years of age.

<table>
<thead>
<tr>
<th>Patient’s Name (Print)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Signature Date Time</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Patient’s Legally Authorized Representative (Print)</td>
</tr>
<tr>
<td>Patient’s Legally Authorized Representative’s Signature Date Time</td>
</tr>
<tr>
<td>Relationship to Patient</td>
</tr>
<tr>
<td>Investigator’s Signature Date</td>
</tr>
<tr>
<td>Witness’ Signature Date</td>
</tr>
</tbody>
</table>
APPENDIX C

INSTRUMENTS
### National Institute of Health Stroke Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Level of Consciousness</td>
<td>0=alert; 1=drowsy; 2=stuporous; 3=coma</td>
</tr>
<tr>
<td>1b</td>
<td>LOC questions</td>
<td>0=both correct; 1=1 correct; 2=neither correct</td>
</tr>
<tr>
<td>1c</td>
<td>LOC commands</td>
<td>0=both correct; 1=1 correct; 2=neither correct</td>
</tr>
<tr>
<td>2</td>
<td>Best gaze</td>
<td>0=normal; 1=partial gaze palsy; 2=forced deviation</td>
</tr>
<tr>
<td>3</td>
<td>Visual</td>
<td>0=no loss; 1=partial hemianopsia; 2=complete Hemianopsia; 3=bilateral hemianopsia</td>
</tr>
<tr>
<td>4</td>
<td>Facial palsy</td>
<td>0=normal facial movement; 1=minor paralysis; 2=partial paralysis; 3=complete paralysis</td>
</tr>
<tr>
<td>5a</td>
<td>Left Arm</td>
<td>Motor Function Scores (for 5a-6b)</td>
</tr>
<tr>
<td>5b</td>
<td>Right Arm</td>
<td>0=no drift</td>
</tr>
<tr>
<td>6a</td>
<td>Left Leg</td>
<td>1=drift</td>
</tr>
<tr>
<td>6b</td>
<td>Right Leg</td>
<td>2=some effort against gravity; 3=no effort against gravity; 4=no movement</td>
</tr>
<tr>
<td>7</td>
<td>Limb Ataxia</td>
<td>0=absent; 1=present in 1 limb; 2=present in 2 limbs</td>
</tr>
<tr>
<td>8</td>
<td>Sensory</td>
<td>0=normal; 1=mild--mod loss; 2=severe--total loss</td>
</tr>
<tr>
<td>9</td>
<td>Best Language</td>
<td>0=normal; 1=mild--mod; 2=severe; 3=mute, global</td>
</tr>
<tr>
<td>10</td>
<td>Dysarthria</td>
<td>0=normal; 1=mild--mod; 2=severe</td>
</tr>
<tr>
<td>11</td>
<td>Extinction and Inattention</td>
<td>0=no abnormality; 1=1 modality; 2=severe or Profound hemi-inattention or 2 modalities</td>
</tr>
</tbody>
</table>

---

82
Modified Rankin Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities.</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance.</td>
</tr>
<tr>
<td>4</td>
<td>Moderate to severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.</td>
</tr>
<tr>
<td>6</td>
<td>Death.</td>
</tr>
</tbody>
</table>
Beck Depression Inventory

1. Sadness
   0  I do not feel sad
   1  I feel sad much of the time.
   2  I am sad all the time.
   3  I am so sad or unhappy that I can’t stand it.

2. Pessimism
   0  I am not discouraged about my future.
   1  I feel more discouraged about my future than I used to be.
   2  I do not expect things to work out for me.
   3  I feel my future is hopeless and will only get worse.

3. Past Failure
   0  I do not feel like a failure.
   1  I have failed more than I should have.
   2  As I look back, I see a lot of failures.
   3  I feel I am a total failure as a person.

4. Loss of Pleasure
   0  I get as much pleasure as I ever did from the things I enjoy.
   1  I don’t enjoy things as much as I used to.
   2  I get very little pleasure from the things I used to enjoy.
   3  I can’t get any pleasure from the things I used to enjoy.

5. Guilty Feelings
   0  I don’t feel particularly guilty.
   1  I feel guilty over many things I have done or should have done.
   2  I feel quite guilty most of the time.
   3  I feel guilty all of the time.

6. Punishment Feelings
   0  I don’t feel I am being punished.
   1  I feel I may be punished.
   2  I expect to be punished.
   3  I feel I am being punished.

7. Self-Dislike
   0  I feel the same about myself as ever.
   1  I have lost confidence in myself.
   2  I am disappointed in myself.
   3  I dislike myself.
8. **Self-Criticalness**  
   0  I don’t criticize or blame myself more than usual.  
   1  I am more critical of myself than I used to be.  
   2  I criticize myself for all of my faults.  
   3  I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes**  
   0  I don’t have any thoughts of killing myself.  
   1  I have thoughts of killing myself, but I would not carry them out.  
   2  I would like to kill myself.  
   3  I would kill myself if I had the chance.

10. **Crying**  
   0  I don’t cry anymore than I used to.  
   1  I cry more than I used to.  
   2  I cry over every little thing.  
   3  I feel like crying, but I can’t.

11. **Agitation**  
   0  I am no more agitated or wound up than usual.  
   1  I feel more restless or wound up than usual.  
   2  I am so restless or agitated that it’s hard to stay still.  
   3  I am so restless or agitated that I have to keep moving or doing something.

12. **Loss of Interest**  
   0  I have not lost interest in other people or activities.  
   1  I am less interested in other people or things than before.  
   2  I have lost most of my interest in other people or things.  
   3  It’s hard to get interested in anything.

13. **Indecisiveness**  
   0  I make decisions about as well as ever.  
   1  I find it more difficult to make decisions than usual.  
   2  I have much greater difficulty in making decisions than I used to.  
   3  I have trouble making any decisions.

14. **Worthlessness**  
   0  I do not feel I am worthless.  
   1  I don’t consider myself as worthwhile and useful as I used to.  
   2  I feel more worthless as compared to other people.  
   3  I feel utterly worthless.
15. Loss of Energy
   0  I have as much energy as ever.
   1  I have less energy than I used to have.
   2  I don’t have enough energy to do very much.
   3  I don’t have enough energy to do anything.

16. Changes in Sleeping Pattern
   0  I have not experienced any change in my sleeping pattern.
   1a I sleep somewhat more than usual.
   1b I sleep somewhat less than usual.
   2a I sleep a lot more than usual.
   2b I sleep a lot less than usual.
   3a I sleep most of the day.
   3b I wake up 1-2 hours early and can’t get back to sleep.

17. Irritability
   0  I am no more irritable than usual.
   1  I am more irritable than usual.
   2  I am much more irritable than usual.
   3  I am irritable all the time.

18. Changes in Appetite
   0  I have not experienced any change in my appetite.
   1a My appetite is somewhat less than usual.
   1b My appetite is somewhat greater than usual.
   2a My appetite is much less than before.
   2b My appetite is much greater than before.
   3a I have no appetite at all.
   3b I crave food all the time.

19. Concentration Difficulty
   0  I can concentrate as well as ever.
   1  I can’t concentrate as well as usual.
   2  It’s hard to keep my mind on anything for very long.
   3  I find I can’t concentrate on anything.

20. Tiredness or Fatigue
   0  I am no more tired or fatigued than usual.
   1  I get more tired or fatigued more easily than usual.
   2  I am too tired or fatigued to do a lot of the things I used to do.
   3  I am too tired or fatigued to do most of the things I used to do.
21. Loss of Interest in Sex
0    I have not noticed any recent change in my interest in sex.
1    I am less interested in sex than I used to be.
2    I am much less interested in sex now.
3    I have lost interest in sex completely.
Short Form 36  
Quality of Life

Short Form 36  
Quality of Life

1) In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) Compared to one year ago, how would you rate your health now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3) The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Vigorous Activities, such as running, lifting heavy objects, participating in strenuous sports  
   |                           |                        |

b. Moderate Activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf  
   |                           |                        |

c. Lifting or carrying groceries  
   |                           |                        |

d. Climbing several flights of stairs  
   |                           |                        |

e. Climbing one flight of stairs  
   |                           |                        |

f. Bending, kneeling, or stooping  
   |                           |                        |

g. Walking more than a mile  
   |                           |                        |

h. Walking several hundred yards  
   |                           |                        |

i. Walking one hundred yards  
   |                           |                        |

j. Bathing or dressing yourself  
   |                           |                        |
4) During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Were limited in the kind of work or other activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5) During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Did work or activities less carefully than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6) During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7) How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very Mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
</table>
8) During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

9) These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

- a. Did you feel full of life? 
- b. Have you been very nervous? 
- c. Have you felt so down in the dumps that nothing could cheer you up? 
- d. Have you felt calm and peaceful? 
- e. Did you have a lot of energy? 
- f. Have you felt downhearted and depressed? 
- g. Did you feel worn out? 
- h. Have you been happy? 
- i. Did you feel tired? 

10) During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
11) How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. I seem to get sick a little easier than other people</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>b. I am as healthy as anybody I know</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>c. I expect my health to get worse</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>