DISABILITY IN STROKE:
EFFECTIVENESS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITOR
ON POST-STROKE RESIDUAL DISABILITY

By

SOOYEON KWON

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2004
Copyright 2004

by

Sooyeon Kwon
To my parents
ACKNOWLEDGMENTS

During this journey of my doctoral dissertation, I made many friends, in the department of Pharmacy Health Care Administration; and in the Rehabilitation Outcomes Research Center. I would like to thank all of them. I thank Phyllis (Dr. Phyllis Howren), my friend in Chapel Hill, who was originally my English professor in the very first semester in the US; and the Sauer family. I especially thank my advisor and committee: Dr. Hartzema, Dr. Duncan, Dr. Ried. Dr. Kimberlin, and Dr. Yarandi. Most of all, I thank my Parents, my brother, Hyuk-Jin, and my daughter Jooyoung who gave me strength and hope to complete this journey.
TABLE OF CONTENTS

ACKNOWLEDGMENTS ........................................................................................................ iv

LIST OF TABLES ................................................................................................................ viii

LIST OF FIGURES ............................................................................................................... x

ABSTRACT ........................................................................................................................ xii

CHAPTERS

1 INTRODUCTION ........................................................................................................ 1
   Problem Statement ..................................................................................................... 1
   Significance ................................................................................................................. 2
   Purpose, Objectives, Aims and Research Questions .................................................. 3
   Assumptions & Limitations ........................................................................................ 8

2 REVIEW OF LITERATURE ..................................................................................... 11
   Stroke Epidemiology – Mortality and Morbidity of Stroke ........................................ 11
   Measuring Post Stroke Illness: Physical Functioning Instruments ................................ 17
      Barthel Index ........................................................................................................... 17
      Functional Independence Measure, the Motor Component ................................... 18
      The Modified Rankin Scale .................................................................................... 18
   Decision Analysis and Modeling ............................................................................ 19
      The Need for Modeling .......................................................................................... 19
      Structuring the Problem ......................................................................................... 21
      Probability and Conditional Probability ................................................................ 23
   Valuing Outcomes: Utilities ...................................................................................... 23
      Standard Gamble .................................................................................................... 24
      Time Trade-Off ........................................................................................................ 25
      Rating Scale ............................................................................................................ 26
      Willingness to Pay (Contingent Valuation) ............................................................. 26
      Equivalence Measure (Person Trade-Off) .............................................................. 26
   Sensitivity analysis .................................................................................................... 28
   Long-term Disability Evaluation in Stroke Outcomes Research ................................ 30
   Extracting Articles: Inclusion and Exclusion Criteria ................................................. 31
   Findings of the Literature Search .............................................................................. 40
Economic Analysis ................................................................. 42
Time Frame ............................................................................. 42
Intervention ............................................................................. 42
Age ........................................................................................... 43
Residual Disability ................................................................. 43

3 CONCEPTUALIZATION OF DISABILITY EVALUATION MODEL ............. 47

4 METHODS .............................................................................. 55

Study Design ............................................................................. 56
Setting ....................................................................................... 56
Sampling, Inclusion and Exclusion Criteria .................................. 57
Randomization .......................................................................... 58
Data Collection ......................................................................... 59
Post-Stroke Disability Evaluation Model ...................................... 59
Data Analysis Overview ........................................................... 60
Aim 1. Stage Development ......................................................... 62
Research Question 1 .................................................................. 62
Aim 2. Utility Development ......................................................... 63
Research Question 2 .................................................................. 63
Research Question 3 .................................................................. 65
Aim 3. Transition Probabilities ..................................................... 66
Research Question 4 .................................................................. 66
Research Question 5 .................................................................. 67
Research Question 6 .................................................................. 68
Research Question 7 .................................................................. 69
Aim 4. Effectiveness of the Intervention ........................................ 71
Research Question 8 .................................................................. 71

5 RESULTS AND DISCUSSIONS ...................................................... 78

Aim 1. Disability Stage Development ........................................... 78
Aim 2. Utility Development ......................................................... 86
Aim 3. Disability Evaluation & Transition Probability ...................... 97
Aim 4. Disability Evaluation & Transition Probability in Recurrent Stroke .... 110
Aim 5. Disability Evaluation for Stroke Preventive Intervention ............ 117

6 DISCUSSION ........................................................................... 124

APPENDICES

A INSTRUMENTS ........................................................................ 131

Modified Rankin Scale ............................................................ 131
Barthel Index ............................................................................. 132
Functional Independence Measure (FIM) ................................. 135
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Objectives, Aims and Research questions</td>
</tr>
<tr>
<td>2.1</td>
<td>Leading causes of death and number of deaths in the U.S. 1980, 1998</td>
</tr>
<tr>
<td>2.2</td>
<td>Decrease in stroke mortality</td>
</tr>
<tr>
<td>2.3</td>
<td>Literature review: economic stroke outcomes evaluation using a modeling approach</td>
</tr>
<tr>
<td>2.4</td>
<td>Summary of findings</td>
</tr>
<tr>
<td>4.1</td>
<td>Objectives, Aims and Research questions</td>
</tr>
<tr>
<td>4.2</td>
<td>Disability transition probability table</td>
</tr>
<tr>
<td>4.3</td>
<td>Summary of research questions, hypotheses, and statistical test for each aim</td>
</tr>
<tr>
<td>5.1</td>
<td>Missing data for each month</td>
</tr>
<tr>
<td>5.2</td>
<td>Result of Kruskal-Wallis tests and Pairwise Comparisons (Dwass, Steel, Critchlow-Fligner)</td>
</tr>
<tr>
<td>5.3</td>
<td>Result Summary of Research Question 1</td>
</tr>
<tr>
<td>5.4</td>
<td>Correlations between employed measures: the Barthel Index, the Categorized Barthel Index, the Modified Rankin Scale, the reduced Modified Rankin Scale, and the Time-Trade Off</td>
</tr>
<tr>
<td>5.5</td>
<td>Descriptive information, TTO distribution</td>
</tr>
<tr>
<td>5.6</td>
<td>Comparison of same disability level for different time points</td>
</tr>
<tr>
<td>5.7</td>
<td>Kruskal-Wallis test of TTO for four different time points: baseline, month 1, month 3, and month 6 (df = 3)</td>
</tr>
<tr>
<td>5.8</td>
<td>Statistical difference in TTO among four different disability levels</td>
</tr>
<tr>
<td>5.9</td>
<td>Pair wise comparisons</td>
</tr>
</tbody>
</table>
5.11 Result Summary of Research Question 2 and 3 .................................................................98
5.12 Missing data over four year time period ........................................................................99
5.13 Kruskal-Wallis test: Categorized Barthel Index outcome in active and placebo treatment groups .........................................................................................................................100
5.14a Transition probabilities for active treatment group .........................................................107
5.14b Transition probabilities for placebo treatment group .......................................................108
5.15 Result summary of research question 4 and 5 .................................................................109
5.16 Recurrent stroke time in the sample population ...............................................................110
5.17 Recurrent stroke and death in the sample population .........................................................111
5.18 Frequency of disability category after recurrent stroke ..................................................112
5.19 Comparison of disability outcome after recurrent stroke event in active and placebo treatment groups with Categorized Barthel Index .................................................................113
5.20a Transitions in active treatment group for recurrent stroke ..............................................114
5.20b Transitions in placebo treatment group for recurrent stroke .........................................115
5.21 Result summary of research question 6 and 7 .................................................................116
5.22 Summary of model parameters, stages, utility and transition probabilities .......................117
5.23 Ten year outcome projection in terms of utility in active and placebo treatment groups .................................................................................................................................123
5.24 Result summary of research question 8 ..............................................................................123
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Study Outline</td>
<td>7</td>
</tr>
<tr>
<td>2.1</td>
<td>Age-adjusted death rates for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke by year, United States, 1900–1996</td>
<td>12</td>
</tr>
<tr>
<td>2.2</td>
<td>Rating scale, horizontal and vertical visual aid to elicit a utility score for the current state of health</td>
<td>27</td>
</tr>
<tr>
<td>3.1</td>
<td>Disability outcomes of drug and placebo intervention</td>
<td>47</td>
</tr>
<tr>
<td>3.2</td>
<td>Disability outcome evaluation at specific point</td>
<td>49</td>
</tr>
<tr>
<td>3.3</td>
<td>Prognoses of disability (Individual)</td>
<td>51</td>
</tr>
<tr>
<td>3.4</td>
<td>Prognoses of disability in the population</td>
<td>52</td>
</tr>
<tr>
<td>3.5</td>
<td>Exhaustive and exclusive pathways of disability transition in post-stroke population</td>
<td>54</td>
</tr>
<tr>
<td>4.1</td>
<td>Concept of disability transition</td>
<td>60</td>
</tr>
<tr>
<td>4.2</td>
<td>Recurrent stroke and measurement points</td>
<td>70</td>
</tr>
<tr>
<td>4.3</td>
<td>Illustration of how the information explored in this dissertation supports the suggested disability evaluation model</td>
<td>72</td>
</tr>
<tr>
<td>5.1</td>
<td>Distribution of Barthel Index score for each Modified Rankin Scale level</td>
<td>80</td>
</tr>
<tr>
<td>5.2</td>
<td>Probability Distribution of Modified Rankin Scale (MRS) given the Barthel Index Score</td>
<td>83</td>
</tr>
<tr>
<td>5.3</td>
<td>Probability Distribution of Modified Rankin Scale (MRS) given Barthel Index scores for each wave</td>
<td>84</td>
</tr>
<tr>
<td>5.4</td>
<td>Relationship between Modified Rankin Scale and Barthel Index, and categorized measures</td>
<td>86</td>
</tr>
<tr>
<td>5.5</td>
<td>TTO value distribution at baseline, 1, 3, and 6 month post-stroke</td>
<td>88</td>
</tr>
</tbody>
</table>
5.6 TTO distribution, mean, median, and quartiles by Categorized Barthel ...............94
5.7 TTO distribution, mean, median, and quartiles by reduced Modified Rankin Scale........................................................................................................................................95
5.8 Complete disability evaluation model, active treatment group. ..........................118
5.9a Predicted and actual disability outcomes in active treatment group for the study period........................................................................................................................................119
5.9b Predicted and actual disability outcomes in placebo treatment group for the study period........................................................................................................................................120
5.10 Predicted and actual disability levels for a ten years of observation period.......121
5.11 Predicted disability comparison between active and placebo groups for the extended time period........................................................................................................................................122
Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

DISABILITY IN STROKE:
effectiveness of Angiotensin Converting Enzyme Inhibitor on
post-stroke residual disability

By
Sooyeon Kwon

May 2004

Chair: Abraham G. Hartzema
Major Department: Pharmacy Health Care Administration, College of Pharmacy

Background: Stroke is the third leading cause of death and one of the major causes
of disability in the population. Due to the high mortality rate, stroke outcomes research
usually focuses on death rate, and often looks over the impact of stroke in survivors,
which is mostly the residual disability. This dissertation provides a method to evaluate
the impact of stroke not only in terms of mortality, but also morbidity in survivors.

Objectives: Five aims of this dissertation are (1) to develop a categorization
scheme of the Barthel Index defining the discrete disability states, (2) to investigate
representative utility (time trade-off) estimate in stroke survivors in relation to Barthel
Index, (3) to examine the disability prognoses of stroke survivors in active drug and
placebo groups, (4) to examine the disability prognoses among the people who
experienced the recurrent stroke, and (5) to examine the effectiveness of drug
intervention considering residual disability after stroke. Each aim has one or two research questions to fulfill its objective.

Methods: Four objectives were organized to address the purpose of this study. For the first two aims, Kansas City Stroke Study (KCSS), and for the next two aims, Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) data were used. Appropriate statistical methods, such as logistic regression, Kruskal Wallis one way ANOVA tests, t-test, chi-square methods were chosen based on the data characteristics, and the nature of research questions. By applying the result from aim 1 to 4, in the fifth aim, two stroke preventive interventions were compared in terms of disability outcomes.

Results: Four disability stages were identified: C-BI1 (0<=BI<15), C-BI3 (15<=BI<70), C-BI4 (70<=BI<95), and C-BI5 (95<=BI<=100) <Aim1>. Using this categorization scheme, the Barthel Index scores in the PROGRESS sample population were categorized. ACE inhibitor treatment group showed significantly better functioning compared to the placebo treatment group <Aim3>, but did not show significant difference in the disability who had recurrent stroke <Aim 4>.

Ten year disability among study population was predicted using their disability transition probabilities in the four year time window. Utility estimates were identified from KCSS data: The utility estimates for each disability level were determined: 9 (10, 7.5) for C-BI1, 8 (10, 5) for C-BI3, 7 (9, 2.5) for C-BI4, and 1 (5, 0.083) for C-BI5 <Aim 2>, and applied to disability compare patient outcomes in terms of utility. Active treatment group showed better physical functioning. The difference in two groups for ten year outcome, utility was 0.12 <Aim 5>.
Conclusion: Active ACE inhibitor treatment to the people who had previous stroke to prevent recurrent stroke showed significantly better physical functioning outcome compared to placebo ACE inhibitor treatment.
CHAPTER 1
INTRODUCTION

Problem Statement

Stroke is a devastating life event for the patient. The Centers for Disease Control and Prevention (CDC) have reported that stroke is ranked the third leading cause of death in the United States – it has been reported to cause 166,028 deaths in the year 2000.\(^1\) Considering that 700,000 strokes occur each year in the U.S., more than 500,000 stroke victims survive with various degrees of disability.\(^2\)

Stroke also carries a large financial burden to society. The estimated economic burden of stroke is $51.2 billion per year, and the ratio of indirect to direct cost is approximately 1.3. This ratio indicates that indirect costs, which are a result of compromised physical functioning and care giver involvement, are larger than the direct medical costs.\(^3\) The high indirect costs of stroke make the reduction of disability in post-stroke patients a major interest of individual patients and society.

Because of the large stroke burden in the population, health care providers, researchers and policy makers are interested in post-stroke management and recurrent stroke prevention. Stroke outcomes research, however, often does not evaluate long-term residual disability even though more than 70% of people who experienced stroke survive with various levels of disability. Researchers tend to emphasize clinically clear end points such as mortality or recurrent event to demonstrate the effectiveness of interventions, and often overlook residual disability. Even though residual disability is
the major problem survivors face everyday for the rest of their lives, there is a paucity of information on post-stroke residual disability at the population level.

This paucity of information may be due to limited resources. However, the lack of residual disability information significantly undermines the quality of stroke outcomes research. Population level evaluation on disability and the prognosis of disability over time after a stroke event from an epidemiologic perspective is important to evaluate stroke outcomes per se. It is also important to achieve precision in the measurement of outcomes in stroke prevention and rehabilitation programs.

**Significance**

Health maintenance of the aging population is a major societal challenge. Development in science and medicine has drastically increased our life expectancy especially for the several past decades. Moreover, the baby boomers, who will turn 65 in the 2010’s, will require a greater amount of health care resources. In the 2030’s, a quarter of Americans will be over 65. An aging population will trigger significant changes in the structure of health care services, health care resource utilization, and health services toward the elderly population and chronic diseases.

The aging of the population is important in stroke outcomes research because age is the most significant risk factor for stroke. For those 65 years of age and above, the prevalence of stroke is approximately 6 to 12.5 percent, compared with less than 4 percent for those under 64. It is expected that stroke prevalence for the U.S. population will increases in the future based on the aging of the population and an extended life expectancy. With the improvement in medical technology and critical care management, stroke case mortality has decreased, and this trend is expected to continue. The aging population, lengthy life expectancy, and the advances in medical technologies forecast
increasing prevalence of residual stroke disability in society. It is important for stroke outcomes researchers to understand the significance of the appropriate evaluation of stroke outcomes. This dissertation is about stroke outcomes evaluation and it will focus on post-stroke residual disability in patients.

**Purpose, Objectives, Aims and Research Questions**

The purpose of this study is to understand disability prognosis over time among stroke survivors, and to develop a stroke long-term disability outcome model that will be used to evaluate stroke prevention intervention with ACE Inhibitor in terms of long-term post-stroke disability. To fulfill this purpose, this dissertation project poses four objectives five aims and eight research questions. The structure of this dissertation is explained in Table 1.1.

Table 1.1. Objectives, Aims and Research questions

<table>
<thead>
<tr>
<th>objective</th>
<th>Aims</th>
<th>Data source</th>
<th>Research Questions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability Stage development</td>
<td>(1) to develop a categorization scheme of the Barthel Index defining discrete disability states</td>
<td>KCSS</td>
<td>RQ1</td>
</tr>
<tr>
<td>Utility development</td>
<td>(2) to investigate representative utility (time trade-off) estimates in stroke survivors in relation to the Barthel Index</td>
<td>KCSS</td>
<td>RQ2s, 3s</td>
</tr>
<tr>
<td>Transition Probability development</td>
<td>(3) to examine the disability prognoses of stroke survivors in active drug and placebo groups</td>
<td>PROGRESS</td>
<td>RQ4s, 5s</td>
</tr>
<tr>
<td></td>
<td>(4) to examine the disability prognoses among the people who experienced recurrent stroke</td>
<td>PROGRESS</td>
<td>RQ6s, 7s</td>
</tr>
<tr>
<td>Drug Effectiveness Evaluation</td>
<td>(5) to examine the effectiveness of drug interventions considering residual disability after stroke</td>
<td>KCSS, PROGRESS</td>
<td>RQ8s</td>
</tr>
</tbody>
</table>

Multiple research questions exist under RQ 2 – RQ 8
The first objective is to develop the disability stages. The specific aim is to develop a categorization scheme for the Barthel Index defining discrete disability states. The second objective is to develop utilities corresponding to the disability stages. The specific aim is to investigate representative time trade-off estimates in stroke survivors in relation to the Barthel Index. The third objective is to determine transition probabilities. For this objective, two aims are posed: to examine the disability prognoses of stroke survivors, and to examine the disability prognoses especially among the subject who had recurrent stroke. The fourth objective is to evaluate drug effectiveness in terms of residual disability.

Each objective, aim, and research question facilitates and directs this dissertation to achieve the purpose: to understand disability prognosis over time among stroke survivors, and to develop a stroke long-term disability outcome model. The research questions are listed below.

Objective 1. Disability Stage development

Aim 1. To develop a categorization scheme the Barthel Index defining discrete disability states

RQ1. What are the cut-off points in the Barthel index that match with the Modified Rankin Scale?

Objective 2. Utility development

Aim 2. To investigate representative utility (time trade-off) estimates in stroke survivors with relation to the Barthel Index
RQ2-1. Is there a correlation between the Barthel Index and time-trade off?

RQ2-2. Is there a correlation between the C-BI and time-trade off?

RQ2-3. Is there a difference in time-trade off among the disability levels defined by the Categorized Barthel?

RQ3-1. Is there a correlation between the Modified Rankin Scale (MRS) and time-trade off?

RQ3-2. Is there a correlation between the reduced Modified Rankin Scale (rMRS) and time-trade off?

RQ3-3. Is there a difference in time-trade off among the disability levels defined by the reduced Modified Rankin Scale (rMRS)?

Objective 3. Determine Transition Probabilities

Aim 3. To examine the disability prognoses of stroke survivors in active drug and placebo intervention groups

RQ4-1. Based on the categorization scheme developed in RQ1, produce Categorized Barthel (CB). Is there a significant difference in patient’s disability between ACE inhibitor and placebo groups in respect to the Barthel Index at 1 year?

RQ4-2. Same procedures will be applied for year 2

RQ4-3. Same procedures will be applied for year 3

RQ4-4. Same procedures will be applied for year 4

RQ5-1. Based on the Categorized Barthel, is there a difference in the prognosis of disability in ACE inhibitor and placebo group from baseline to year 1?

RQ5-2. Same procedure; year 1 \(\rightarrow\) year 2
RQ5-3. Same procedure; year 2 $\rightarrow$ year 3

RQ5-4. Same procedure; year 3 $\rightarrow$ year 4

Aim 4. To examine the disability prognoses among the people who experienced recurrent stroke

RQ6-1. Is there a significant difference in Categorized Barthel at the first year of recurrent stroke between active and placebo ACE inhibitor intervention groups when patient experienced recurrent stroke?

RQ6-2. Same procedure will be applied for the second year after the recurrent stroke.

RQ6-3. Same procedure will be applied for the third year.

RQ6-4. Same procedure will be applied for the fourth year.

RQ7-1. For the subpopulation that had recurrent stroke - Based on the Categorized Barthel, is there a difference in the prognosis of disability between ACE inhibitor and placebo group between two time point: before and after the recurrent stroke?

RQ7-2. Same procedure will be applied for: from ‘first year after stroke’ to ‘second year after stroke’.

RQ7-3. Same procedure will be applied for: from ‘second year after stroke’ to ‘third year after stroke’.

RQ7-4. Same procedure will be applied for: From ‘third year after stroke’ to ‘fourth year after stroke’.

Objective 4. Evaluation of Drug Effectiveness
using KCSS

- Develop a categorization scheme
- Interpret disability level in terms of patient reported utility

RQ1. Categorization of Barthel scores
RQ 2 and 3. Interpretation of disability levels in terms of utility

using PROGRESS

- Disability prognoses for each treatment group
- Transition probability for each treatment group, recurrent stroke subject only

RQ4 and 5. Transition probability (overall)
RQ6 and 7. Transition probability (recurrent stroke subject only)

RQ8, Benefit of drug intervention in terms of disability and utility

Prognosis of post-stroke disability with/without ACE inhibitor
Prognosis of post-stroke disability after recurrent stroke

Stroke Long-term Disability Outcome Evaluation

Figure 1.1. Study Outline
Aim5. To examine the effectiveness of drug intervention considering residual
disability post stroke

RQ8-1. What is the integrated benefit of ACEI (placebo) treatment compared to
placebo (ACEI) treatment in terms of utility considering four year disability and
transitions of disability?

RQ8-2. For the recurrent stroke victims, what is the integrated benefit of ACEI
(placebo) treatment compared to placebo (ACEI) treatment in terms of utility considering
four year disability and transitions of disability?

Assumptions and Limitations

This study utilizes two different datasets: the Kansas City Stroke Study (KCSS)
and the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS). These
data have their own respective features to contribute to the current dissertation’s research
purpose. The information presented by each dataset complement each other.

KCSS is a prospective cohort study with a medium size in terms of the number of
enrolled subjects and follow-up period. Four hundred and fifty nine patients were
enrolled and observed from the stroke onset to the six month point. In performing the
current dissertation project, the major advantage of KCSS dataset is that this dataset
provides comprehensive information on two aspects of patient’s post-stroke disability
outcomes: (1) physical functioning prognosis in critical period of stroke, and (2) various
outcome measures including disability, quality of life, and utility measures with
employing different instruments.

PROGRESS is a large multi-national and multi-centered randomized clinical trial
that examines the effectiveness of an ACE inhibitor (perindopril) in preventing recurrent
stroke. More than seven thousand subjects were enrolled from ten different countries and
followed up for four years. The sample size and extended follow-up period make these
data valuable even though it does not provide detailed information, which is virtually
impossible for such a large study. The enrollees of the PROGRESS clinical trial had a
previous stroke on average eight months prior to enrollment, so the patients enrolled in
this study were already recovered from the previous stroke impact.

As described above, Both KCSS and PROGRESS datasets will provide important
information to perform the current dissertation project. A categorization scheme
developed from KCSS data will be applied to the PROGRESS data to interpret four-year
outcomes, and predict long-term disability prognosis after stroke. The patient reported
outcomes information from the KCSS data will be linked to disability level allowing for a
better understanding and interpretation of the long-term disability outcomes.

As described above, since this dissertation project utilizes two datasets to fill a gap
of information in each dataset, the limitation of the current dissertation is the
generalizability related to the sample population, time, and location is compromised as
compared to the ideal situation, i.e., a ‘perfect’ data are utilized.

Another limitation of this study is the lack of information on diverse races.
PROGRESS data does not include any African or African American subjects. The study
subjects were only Caucasian and Asian living in Europe and Asia. Considering that the
African American population in the United States has a higher incidence and risk of
stroke, this may be a significant weakness of the current study from the U.S. perspective.
By assuming that the physical functioning prognosis after stroke is not significantly
different by race, the information of this dissertation project may be generalized to the
African Americans. Further studies are needed to generate detailed data on racial differences in post-stroke residual disability.

This study lacks the information on natural deterioration of physical functioning with aging. Stroke causes a drastic decline in physical functioning, but there are many attributing factors, such as age, and other chronic diseases such as arthritis. Since this study focuses on the effectiveness of an ACE inhibitor on long-term disability between the randomized groups, the lack of information on natural deterioration of physical functioning does not undermine the integrity of this project.
CHAPTER 2
REVIEW OF LITERATURE

The purpose of this study is to understand stroke survivors’ disability prognosis over time, and to develop a stroke outcome model including mortality and disability. This would evaluate stroke prevention intervention with an ACE Inhibitor from a long-term perspective including post-stroke disability.

The literature review chapter is organized in four subsections. The first two sections discuss the epidemiology of stroke, and outcome measurement instruments commonly used in post-stroke disability. The last two chapters discuss the current stroke outcomes studies and literature. In the third chapter, general concepts on medical outcomes analysis will be introduced, and discussion on stroke outcomes research will be addressed in the fourth section.

**Stroke Epidemiology – Mortality and Morbidity of Stroke**

Stroke is a medical term for cerebral vascular disease caused by one of following conditions. First, blood clots in an atherosclerotic artery can cause cerebral thrombosis. Second, a rupture of the wall of a cerebral artery can lead to a cerebral hemorrhage. Third, cerebral embolism, which indicates a clot (or a piece of clot) or other material from the systemic arterial tree or the heart, flows to the brain and obstructs a cerebral vessel. The last is not a very common; a brain tumor causes stroke by placing pressure on the cerebral blood vessels. Regardless of pathology, stroke causes high mortality and morbidity in the U.S. and worldwide.
Due to the high fatality of the disease, the mortality rate of stroke is well documented. The World Health Organization estimated that stroke deaths accounted for 10% of all worldwide deaths in 1999, and between 3 and 11% of the total disease burden (deaths and disability) is attributed to stroke. In the United States, stroke is the third cause of death, behind diseases of heart and cancer. Stroke killed 158,448 people in 1998 in the United States and accounts for approximately one out of fifteen deaths.  

The Centers for Disease Control and Prevention (CDC) have observed the decreasing trend of stroke mortality since 1900. In 1900, the age-adjusted mortality rate of stroke was approximately 140 per 100,000. In 1996, however, stroke mortality dropped to 26 per 100,000. <Figure 2.1> In addition, the contribution of stroke to all causes of death also decreases. In 1998, the contribution of stroke to all death was 6.78% compared to 8.55% in 1980.

![Figure 2.1. Age-adjusted death rates for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke by year, United States, 1900–1996](image-url)
Table 2.1. Leading causes of death and number of deaths in the U.S. 1980, 1998

<table>
<thead>
<tr>
<th></th>
<th>1980</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>1,989,841</td>
<td>2,337,256</td>
</tr>
<tr>
<td>Heart disease</td>
<td>761,085</td>
<td>724,859</td>
</tr>
<tr>
<td>Cancer</td>
<td>416,509</td>
<td>541,532</td>
</tr>
<tr>
<td>Stroke</td>
<td>170,225</td>
<td>158,448</td>
</tr>
</tbody>
</table>

The decreasing trend in stroke mortality is encouraging; however, the degree of decreasing trend in mortality has slowed down since the 1990’s. Table 2.2 shows the drastic decrease in stroke mortality in the 1980’s but this downward trend has weakened during the 1990’s.

Table 2.2. Decrease in stroke mortality

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>WM</th>
<th>BM</th>
<th>WF</th>
<th>BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>88.8</td>
<td>87</td>
<td>146.2</td>
<td>79.7</td>
<td>155.6</td>
</tr>
<tr>
<td>1960</td>
<td>79.7</td>
<td>10.25%</td>
<td>7.70%</td>
<td>114.2</td>
<td>3.42%</td>
</tr>
<tr>
<td>1970</td>
<td>66.3</td>
<td>16.81%</td>
<td>68.8</td>
<td>14.32%</td>
<td>122.5</td>
</tr>
<tr>
<td>1980</td>
<td>40.8</td>
<td>38.46%</td>
<td>41.9</td>
<td>39.10%</td>
<td>77.5</td>
</tr>
<tr>
<td>1985</td>
<td>32.5</td>
<td>20.34%</td>
<td>33</td>
<td>21.24%</td>
<td>62.5</td>
</tr>
<tr>
<td>1990</td>
<td>27.7</td>
<td>14.77%</td>
<td>27.7</td>
<td>16.06%</td>
<td>56.2</td>
</tr>
<tr>
<td>1995</td>
<td>26.7</td>
<td>3.61%</td>
<td>26.5</td>
<td>4.33%</td>
<td>52.2</td>
</tr>
<tr>
<td>1997</td>
<td>25.9</td>
<td>3.00%</td>
<td>25.7</td>
<td>3.02%</td>
<td>48.6</td>
</tr>
<tr>
<td>1998</td>
<td>25.1</td>
<td>3.09%</td>
<td>24.5</td>
<td>4.67%</td>
<td>46.8</td>
</tr>
</tbody>
</table>

The decrease of stroke mortality is accepted as an important indicator of improvement of public health in stroke, stroke incidence is also important because if stroke incidence remains the same and only mortality decreases, the burden of overall stroke, which includes residual disability in post-stroke patients, may increase. Unlike stroke mortality, the trend of stroke incidence did not seem to decrease. Wolf and colleagues (1992) examined the trend of stroke incidence and fatality by exploring data from the Framingham study. They concluded that stroke incidence did not follow a
clear pattern of decline; incidence of infarction fell only in women and total case fatality rates decline occurred only in men. In addition, their article reported that the decrease in stroke mortality largely resulted from an increased incidence of isolated transient ischemic attacks (TIA). The improvement of diagnostic tools in medicine may contribute to an increasing trend of stroke incidence. However, at the same time, it is possible to be attributed by increase of stroke incidence in the population.

Compared with mortality attributable to stroke, stroke incidence has not been comprehensively examined for the entire population. Data collection and data validity are difficult to control as compared with mortality census. For this reason, stroke incidence is often studied in small studies at the regional/local level, while mortality research includes larger populations. Pessah-Rasmussen et al. examined stroke incidence and mortality in Malmo, Sweden. These authors monitored stroke incidence and mortality continuously from 1989 to 1998 for the 250,000 citizens in Malmo, and found that there is no evidence of decreasing stroke incidence even though the mortality decreased in Malmo, Sweden. This study implies that the net post-stroke burden increased in the population, because of the increasing incidence of stroke and a decreasing case fatality.

Besides mortality and the incidence of stroke, prevalence of stroke risk factors in the population can be used as indicators to evaluate and predict the current and future burden of stroke. Derby et al. evaluated stroke risk factors and found that smoking is the only decreasing risk factor in the population, which declined from 45% to 37% (p=0.03) in men, and from 35% to 31% (p=0.05) in women. Other risk factors such as
hypertension, proportion of hypertensives on treatment, and the proportion of treated persons who were controlled remained stable from 1989 to 1993.\textsuperscript{6}

Besides smoking and hypertension, one of the most important risk factors for stroke is age. The Centers for Disease Control and Prevention (CDC) illustrated American’s age distribution using data from United States Bureau of Census. This presentation shows that the baby boomers will join the elderly group (over 65 years old) starting at 2010. The CDC predicts that longer life expectancy and aging baby boomers will dramatically change health care utilization, and it is expected that the stroke burden will also increase.\textsuperscript{7}

Besides aging in the population, the increasing trend of other stroke risk factors concern to stroke burden to the future society. Among the many risk factors of stroke, obesity is the most drastically increasing one in the population. According to Mokdad et al, the prevalence of obesity, which is defined as a body mass index $\geq 30$ kg/m$^2$, increased from 12\% in 1991 to 20.9\% in 2001 in the United States.\textsuperscript{8} Must and colleagues (1999) concluded in their publication titled ‘The disease burden associated with overweight and obesity’ that more than half of all US adults are considered to be overweight or obese.\textsuperscript{9} Cardiovascular disease, hypertension, and diabetes mellitus, which are highly correlated with obesity, also increase the stroke risk.\textsuperscript{10}

Considering prevalent stroke risk factors in the population, the overall burden of stroke may increase even though the stroke death rate has decreased. Actually, from a financial perspective, an increasing trend of overall stroke burden has been observed. The CDC projected the combined cost for heart disease and stroke to be $351$ billion in 2003, $209$ billion for health care expenditures and $142$ billion for lost productivity from death
and disability. Among $351$ billion, $45 – 60$ billion was estimated as stroke cost: $20 – 30$ billion for direct health care expenditure and $30 – 40$ billion for death and disability cost. Compared with year 1995 estimates that were $30$ billion for the total stroke burden and $17$ billion for death and disability, an increasing trend of the burden of stroke is clear. 11 In stroke, death and disability related cost makes up 57% of the total cost, and is much higher than heart disease.

Disability is prevalent after stroke and a serious consideration for stroke survivors and for society. The Department of Health and Human Services reported that ten to eleven million Americans are alive with disability resulting from stroke and heart disease in 1999, 2,12 and the American Heart Association stated that approximately 4.5 million stroke survivors were alive in 2000 with various degree of disability. 2 The high prevalence of residual disability after stroke event is a significant morbidity that should be properly evaluated and treated. Though mortality is definitely a final outcome measure for stroke more so than any other outcome measures, mortality does not provide information on survivors with disability.

In summary, prevalent risk factors of stroke in population, the aging population, and decreasing tendency of stroke mortality indicate that the burden of stroke of the stroke survivors will keep increasing in the future. For the existing 4.5 million stroke survivors and the expected future stroke survivors, health care practitioners, policy makers, and researchers need accurate assessments of long-term stroke outcomes in terms of residual disability.

This dissertation focuses on physical disability prognoses over time after stroke. The first part of the literature review introduces globally used instruments for physical
disability assessment after stroke. The second part of this chapter contains information on how long-term outcomes have been evaluated in stroke outcomes research from the population-level perspective. Since this dissertation focuses on a population level evaluation, economic and epidemiological aspects will be emphasized rather than the pathological or biological prognoses of individual stroke cases.

**Measuring Post Stroke Illness: Physical Functioning Instruments**

The Post-Stroke Rehabilitation Clinical Guidelines from the Agency for Health Care Policy and Research (AHCPR) recommends three instruments to evaluate post stroke physical disability: the Barthel Index, the Functional Independence Measure, and the Modified Rankin Scale, based on cumulated knowledge from rehabilitation and stroke outcomes literature. AHCPR recommends the usage of the Barthel Index and the Functional Independence Measure for screening, formal assessment, monitoring, and maintenance of stroke related disability. The Modified Rankin Scale is recommended for usage in acute hospitalization. Validity and reliability are well examined for all three instruments. The following subsection describes detail characteristics for each instrument respectively.

**Barthel Index**

The Barthel Index (BI) is composed of 10 items with varying weights. Two items regarding personal toileting (wash face, comb hair, shave, and clean teeth) and self bathing are evaluated on a two-score scale: 0 and 5 points; six items regarding feeding, getting on and off from the toilet, ascending and descending stairs, dressing, controlling bowels, and controlling bladders are evaluated on a three-score scale: 0, 5, and 10 points; and two items regarding moving from wheelchair to bed and returning, and walking on a level surface are evaluated with a four-score scale: 0, 5, 10, and 15 points. The Barthel
Index is a cumulative score calculated by summing each item score. The Barthel Indices are multiples of 5 with the range from 0 (completely dependent) to 100 (independent in the basic activities of daily living). Higher scores represent a higher degree of independence. The Barthel Index is widely used to measure stroke disability, however, a ceiling effect, detecting change at higher level functioning, is documented as a weakness of the Barthel Index.\textsuperscript{13,16}

**Functional Independence Measure, the Motor Component**

The Motor component of the Functional Independence Measure (Motor FIM) consists of 13 items\textsuperscript{17-19}: eating, grooming, bathing, dressing upper body, dressing lower body, toileting, bladder management, bowel management, transfer to bed/chair/wheelchair, transfer to toilet, transfer to tub/shower, locomotion on walk/wheelchair and locomotion on stairs. Each item is rated with a score from 1 to 7, on a Likert-type scale: 1 indicates that the patient needs complete assistance, 2 - maximal assistance, 3 - moderate assistance, 4 - minimal assistance, 5 - supervision, 6 - modified independence and 7 means that the patient is independent in this ADL.

The FIM Motor instrument has seven Likert scales, so compared with the Barthel Index, the FIM Motor provides greater differentiation of a person’s disability level. The FIM Motor, however, shows ceiling and floor effects at the upper and lower ends of physical functioning score ranges from 13 to 91 points.

**The Modified Rankin Scale**

The Modified Rankin Scale (MRS) defines six levels of disability and one for death: 0 indicates no symptom at all; 1 – no significant disability despite symptoms, able to carry out all usual duties and activities; 2 – slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance; 3 – moderate
disability; requiring some help, but able to walk without assistance; 4 – moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 – severe disability; bedridden, incontinent and requiring constant nursing care and attention; and 6 meaning dead.\textsuperscript{20,21} Individual scores in the Modified Rankin Scale describe clinically distinct functional states of the patient. Modified Rankin Scale is a simple overall assessment of disability, but sensitivity to change in disability has not been tested.

The three instruments discussed above are recommended by AHCPR: BI with the range of 0 to 100, FIM Motor with the range of 13 to 91, and MRS with the category range 0 to 5. These are all evaluated in terms of validity and reliability; however a crosswalk between/among measures to our best knowledge does not exist. The lack of a translation scheme can undermine the quality of patient care in the continuum of care. Even though those instruments are recommended measures of disability, if they do not allow cross interpretation between/among instruments, patients may not be accurately evaluated and treated based on their prognosis from facility to facility, that is, across the continuum of care. This dissertation, in part, will develop a translation scheme among those three widely used disability measures.

\textbf{Decision Analysis and Modeling}

\textbf{The Need for Modeling}

This dissertation focuses in evaluating long-term post stroke disability prognosis on the population level. Therefore, the literature review focuses on how stroke outcomes research has presented post-stroke residual disability in a population from an economic and epidemiological perspective.
Stroke outcomes research from the economic perspective is often based on pre-existing mortality and morbidity information cumulated by observational studies or clinical trials. It is not feasible to carry out a research of ‘N = total population’ or ‘N = total stroke survivor’ due to limited resources available. In addition, it may take too long to obtain timely information needed for decision and policy making. For these reasons, modeling methods are useful in the outcome evaluation of pharmaceuticals. Thus, the conclusions or estimates produced by economic studies using modeling are often challenged because of uncertainty, lack of generalizability, and internal or external validity. Such limitations, however, can be improved by sensitivity analysis. Thus, pharmacoeconomic modeling is a necessary tool to overcome the limited resources and provide the information needed immediately.

Modeling approaches are commonly used for decision making in the medical field including clinical practice and policy making. According to Briggs and Gray, 76% of cost-effectiveness studies adopted a modeling approach, and few economic evaluations are conducted alongside clinical trials. Instead, data are usually from several resources, such as literature, hospital records, or expert opinion or judgments.

Patient’s health state prognosis is structured as a model, often as a decision tree. In addition, computer based modeling with an established mathematical techniques, such as Markov modeling, is increasingly used in health and pharmacoeconomic evaluation. Briggs and Gray reported also that Markov and decision tree methods are dominantly utilized in modeling approach in health outcomes research. A brief introduction on the concept of decision analysis using modeling will be provided in the literature review section, to help understand the structure of this dissertation.
Decision analysis is a quantitative, probabilistic method to establish a model for problems under circumstances of uncertainty. For medical decision analysis, clinically important outcomes to make a decision are included in a model. Then, using knowledge from many sources regarding the problems, and the outcomes such as quality adjusted life year (QALYs), costs are computed.

To perform medical decision analysis, the following elements are necessary. The first element is **structuring the problem**, that is, structure a model to represent the clinical problem. This step requires understanding of decision alternatives for the specific problem, possible clinical outcomes, and sequence of events. Often, a series of assumptions for modeling are needed to structure a model. Second, **probabilities** for those sequences of events should be assigned. Thirdly, **utility** (or other value) should be assigned to those outcomes. Fourthly, after evaluating the expected utility of each strategy, a **sensitivity analysis** is necessary.

**Structuring the Problem**

To perform a decision analysis, a decision tree is usually adopted to structure the problem. Decision tree analysis puts decision alternatives and sequences of events into a structure via decision nodes, chance nodes and terminal nodes.

First, a decision node is a point in a decision tree at which several choices are possible. For example, when a person has a migraine headache (disease), if this person has two options of drug A and drug B, this situation can be presented as below.
Only two choices are assumed in this case, but it is possible to define more choices as long as they are mutually exclusive. A decision nodes are symbolized by square shapes.

Second, chance nodes are a point in a decision tree at which chance determines which outcome will occur. For example, if the person takes a drug, and there are two possible outcomes of ‘headache absent (disease absent)’ and ‘headache present (disease present)’, this situation can be illustrated as below.

In this example, only two outcomes are shown, but there is no limitation on the number of different outcomes as long as they are mutually exclusive and collectively exhaustive. A chance node is symbolized with a circle shape in the decision tree.

Thirdly, a terminal node presents the final outcome state associated with each possible pathway, and this node is symbolized with a triangle shape. Value or worth must be applied to the terminal node, for example, quality adjusted life years, costs, and so on.

To explain decision and chance nodes, two terms ‘mutually exclusive’ and ‘collectively exhaustive’ were used. The quality presented by the terminology is
important in structuring a decision tree. Mutually exclusive means that the intersection of the events is empty, so only one of the possible events can occur. Collectively exhaustive indicates that events that are taken from one chance node make up the entire outcome universe, which means a probability of one, and at least one of the events must occur.

**Probability and Conditional Probability**

Probabilities, by definition, range in value from 0.0 to 1.0. A probability of 0 means the event is impossible to happen, and a probability of 1.0 means the event is certain to occur. A probability of 0.5 indicates a chance event meaning it is equally likely and unlikely. The probability that event A occurs, given that event B has occurred, is called the conditional probability of event A, given event B, and denoted by

\[ P(A|B) \]

**Valuing Outcomes: Utilities**

Utilities are quantitative measures of the strength of a person’s preference for an outcome, that is, they reflect how a person values his/her state of health. Utilities are considered for medical decision making or policy making processes. Several methods have been used to collect utility data, which are the standard gamble approach, the time trade-off approach, rating scale, willingness-to-pay approach, and the equivalence measure. In Health Economics or Pharmacoeconomics, utility information has been used to determine the quality levels for the quality-adjusted life-year (QALY) model. The following five subsections introduce briefly how to establish utility by each method.
Standard gamble

The standard gamble approach is the classic method of measuring preferences in economics, first presented by von Neumann and Morgenstern in 1953. The standard gamble approach has been used to establish utility (preference) of a health state by determining the risk of death one would accept to improve a specific health state; that is, by asking a person to choose between life in a given clinical state and a gamble between death and perfect health. Then, the utility of the specific health state is given by the probability of perfect health in the gamble, which is the person did not find any difference between the gamble and the specific state of health.

This is an illustration of the standard gamble approach for the utility of disability. A person has a chronic pain problem around his knee that is partially relieved with NSAID medication. He needs an assistant when he walks, and cannot run at all because of this chronic pain. In this situation, he was told that a pill exists that would cure his chronic pain and completely relieve him from it forever with 50% probability. However, there is an adverse effect with a 50% of possibility to cause death. The illustration below explains the situation described.

If the person answers that he does not want to take this pill, a follow-up question is asked with a different probability: for example, 99% relief and 1% death. If the answer to this question is yes, then next question would be “Would you take this pill if the probability of relief is 75%, and the probability of the death is 25%?” This iterative
process is repeated until the person can not find any difference between taking and not taking the pill. The utility of the specific disease for this person for this specific disease will be the probability assigned to the ‘no chronic pain’ branch when the person cannot present his preference between the two options.

**Time trade-off (TTO)**

The utility for a specific health state is assessed by asking how much time a person would give up to improve the health state. This approach was developed as a simpler alternative to standard gamble. To find utility, choice of a set length of life in a given compromised health state and a shorter length of life in perfect health will be asked a person who carries the specific compromised health state.

For example, for the person who has chronic pain, the utility of this person can be identified by asking a series of questions;

Assume that your life expectancy is 20 more years with chronic pain. If there is a pill that relieves you completely from the chronic pain, but you will live only 10 more years, instead of 20 years, would you take this Pill?

If the answer is no, then

Would you take this Pill if you live 19 years without chronic pain, instead of 20 years with chronic pain?

This iterative process of questioning will be repeated until the person cannot find any difference. At this point, the utility of the person who has chronic pain will be the ratio of the length of life in perfect health to the length of life in the compromised health state; for example, if the person answers that there is no difference between 20 years with chronic pain and 16 years with perfect health, then the utility of this person is,
Utility (U) = \frac{\text{Length of life with compromised health}}{\text{Length of life with perfect health}}, \text{ therefore,}

\begin{align*}
U &= \frac{16}{20} = 0.8
\end{align*}

Rating scale

The rating scale is the simplest approach to measure a subject’s preference for a given state of health. A person is asked to choose what level would be the best representation of his current health, anchored to zero and hundred; zero represents death, and hundred indicates perfect health. The rating scale is easily explained to most of the people as compared with the other two approaches introduced above. <Figure 2.2>

Willingness to pay (contingent valuation)

This approach asks how much the person is willing to pay in financial terms to improve his health state (or to avoid a particular outcome, or to reduce the chance of death etc.). The willingness to pay method is usually used to perform a Cost-Benefit Analysis (CBA), which requires human lives and quality of life both to be valued in monetary units.

Equivalence measure (person trade-off)

The methods listed above are used to obtain preference in medical decision making processes at the individual level, but equivalence measure is applied to the policy making process. To get utility information with this method, for example, how many people cured in one health state to be equivalent to curing 100 people in another health states. Utility obtained from this method reflects social worth of alternative health-care interventions.

The concept of utility is clearly different from Quality of Life (QoL) measures. QoL measures, such as the Medical Outcomes Study Short-Form 36 or disease specific QoL instruments describe several domains in health states. However, QoL measures do
Figure 2.2. Rating scale, horizontal and vertical visual aid to elicit a utility score for the current state of health.
not provide the information about the person’s preference and due to this, the utility is fundamentally different from the QoL measures. Although there is apparent difference between QoL and utility, researchers tend to use QoL instrument to capture outcomes more often than utility measures. It is because the QoL is easier to be understood and administered by people compared to utility measures, which is dependent on the level of person’s understanding, cognitive ability to follow complex measurement task.

Researchers have expressed interest in converting QoL measures into utilities. Bosch and Hunink, in their article titled “The relationship between descriptive and valuational quality-of-life measures in patients with intermittent claudication” tried to correlate descriptive QoL measures and person’s utilities. They concluded that the QoL measure cannot reliably predict person’s utilities, which is measured by the time trade-off or standard gamble method.\textsuperscript{28} Apparently, translation between multi-domain descriptive QoL scale and utility is not an easy task, and moreover, they represent different concepts,\textsuperscript{29} researchers have interest in searching functions that conveniently predict utility from QoL scale since, as mentioned above, QoL scales are widely used in health outcomes research as patient reported outcomes measures.

**Sensitivity Analysis**

Sensitivity analysis is a method to examine the stability of the conclusion whether the conclusion of the economic evaluation is changed when one or more variables are varied under the assumption that all the other things are constant at their best estimate (or baseline case). If the conclusion is not changed throughout the range of variation of the variables, the conclusion is robust, but if the conclusion is changed, it is presented that the conclusion is sensitive to the value of the specific variable(s).
Sensitivity analysis can be compared to the confidence interval when statistical inferences are discussed to handle uncertainty in economic analysis. Instead of sensitivity analysis, extreme scenario analysis, and probabilistic sensitivity analysis methods are also used to deal with uncertainty. Extreme scenario analysis can be done by selecting simultaneously the most optimistic or pessimistic situation to examine a best or worst case.

Probabilistic sensitivity analysis is done by large numbers of Monte Carlo simulations. This examines the conclusion of the evaluation when the variables involved are allowed to vary simultaneously. Compared to sensitivity analysis and extreme scenario analysis, probabilistic sensitivity analysis is currently accepted as the most appropriate method to produce more realistic range values.

As shown above, decision analysis is used to solve problems under uncertainty in health care or medical practice, the decision tree method fits well, and is easily presented and understood by practitioners or patients to help decision making. However, some health states, which have recursive events for a long period of time, cannot easily be managed in decision tree. For example, person having chronic disease, such as heart disease, various cancers, diabetes, asthma etc., may be faced with multiple decisions involving events over his life span. It is necessary that the changed utility and probability over time be adjusted and accounted for in the decision analysis.

The Markov modeling method is useful when the problem involves recurrent events over time. The apparent difference between the decision tree method and Markov modeling is how uncertain events are treated. In decision trees, uncertain events are at the chance nodes, while the Markov modeling method put the uncertain health states
(instead of events), and transitions between health states are assumed to predict the future events.

The Markov modeling was developed by Andrei Andreyevich Markov (1856-1922), a Russian mathematician. Typically, Markov models are presented mathematically with matrix algebra.\textsuperscript{30} The Markov modeling technique has been used for problem solving in many areas mostly in Operational Research, and Engineering.

Health economics, epidemiology, and clinical practice have also utilized Markov modeling for clinical decision making.\textsuperscript{31-33} Sonnenberg and Beck, in their article titled, ‘Markov Models in Medical Decision Making’, stated that Markov models provide a convenient way of modeling prognosis of clinical problems with ongoing risk, such as when the event would occur, and/or how many times the specific event (i.e., health state) would occur.\textsuperscript{34} Especially, Health Economics and Pharmacoeconomics have been using this method to predict financial impact of long-term chronic diseases.

Details about how to use the Markov modeling technique for post-stroke long-term disability outcome will be discussed in the methodology section. In the next section of literature on how stroke outcomes studies evaluate long-term stroke outcomes and incorporate these outcome in the economic evaluation of the financial burden of stroke will be appraised.

**Long-term Disability Evaluation in Stroke Outcomes Research**

As mentioned in the previous section, taking a modeling approach is necessary to obtain information to make decisions based on limited resources. In this section, the quality of the current information from literature on long-term disability outcomes in stroke survivors will be appraised.
In spite that disability and quality of life are important measure to evaluate the impact of stroke, this information is often not collected in large scale epidemiological, observational or clinical trials. Lack of such information undermines the integrity of economic evaluations of stroke outcomes, and often leads inaccurate estimate of the burden of stroke. Considering that stroke turns into chronic state with residual disability, information on the residual disability among stroke survivors is needed.

It is helpful to characterize stroke as two distinct phases – acute and chronic – in order to understand the needs of long-term stroke outcome evaluation. The acute phase, a life-threatening phase, is characterized with high mortality rate, and the chronic phase with residual disability. Because of this, ideally stroke outcomes research can be defined as two distinct phases: short-term and long-term. Mortality information represents the outcome, and it is a straightforward and easy to collect. However, for long-term outcomes, the outcome indicators often do not have clear end points, and moreover, the information cannot easily be collected due to extended follow-up. For this reason, the short-term outcomes are comparatively well studied, but are not for the long-term outcomes. In this section of literature review, published original literature for long-term economic evaluation on stroke outcomes will be examined.

**Extracting Articles: Inclusion and Exclusion Criteria**

Articles that evaluated the economic outcomes of stroke with modeling approaches were included in this literature review. Medline searches were performed for the literature published until March 2003, with the search query: ‘economic*’ and ‘model*’ and ‘outcome*’ and ‘stroke’. One hundred and one articles were retrieved from the Medline database. Review articles and meta-analysis articles were excluded.
Table 2.3. Literature review: economic stroke outcomes evaluation using a modeling approach.

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Economic study type</th>
<th>intervention</th>
<th>prediction model/direct evaluation</th>
<th>time frame</th>
<th>patient cohort</th>
<th>disability</th>
<th>unit</th>
<th>regionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiliaru, 2003</td>
<td>CE</td>
<td>carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA)</td>
<td>markov</td>
<td>lifetime cost</td>
<td>70 year old patients undergoing either CEA or CAS</td>
<td>morbidity(?)</td>
<td>$/lifetime savings per patient</td>
<td>Scotland, Ireland, Netherland</td>
</tr>
<tr>
<td>Avorn, 2002</td>
<td>CE</td>
<td>lipid lowering therapy and placebo</td>
<td>markov</td>
<td>lifetime cost</td>
<td>70 yo +</td>
<td>functional status</td>
<td>$/QALY</td>
<td>USA</td>
</tr>
<tr>
<td>ALLHAT 2002</td>
<td>no stroke outcomes (hypertensive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simons, 2003</td>
<td>no stroke outcomes (hypertensive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sundberg, 2003</td>
<td>assess economic outcomes(cost)</td>
<td>three different policy options</td>
<td>computer model for estimating the costs of stroke services</td>
<td>not specified</td>
<td>not specified</td>
<td>handicap</td>
<td>$/stroke</td>
<td>Swedish data</td>
</tr>
<tr>
<td>van den Bos, 2002</td>
<td>not relevant (no economic study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flack, 2002</td>
<td>assess economic outcomes(cost)</td>
<td>none</td>
<td>model</td>
<td>not specified</td>
<td>pt who have BP control and no achieving control</td>
<td>morbidity(?)</td>
<td>$, national estimate</td>
<td>USA</td>
</tr>
<tr>
<td>Sabatine, 2002</td>
<td>Not relevant (stroke is considered as one of the outcomes of drug intervention)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoff, 2002</td>
<td>Not relevant – acute treatment only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capomolla, 2002</td>
<td>no stroke outcomes (heart failure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lai, 2002</td>
<td>assess clinical outcomes, compare disability</td>
<td>none</td>
<td>direct evaluation</td>
<td>90 days after stroke</td>
<td>stroke patients deemed recovered (Barthel Index &gt; or =95) with 2 stroke-free populations of community-dwelling elderly</td>
<td>Y</td>
<td>$/QALY</td>
<td>USA</td>
</tr>
<tr>
<td>Article Number</td>
<td>Economic study type</td>
<td>intervention</td>
<td>prediction model/direct evaluation</td>
<td>time frame</td>
<td>patient cohort</td>
<td>disability</td>
<td>unit</td>
<td>regionality</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-----------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>------------</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>Williams, 2002</td>
<td>no stroke outcomes (hyperglycemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coyle, 2002</td>
<td>no stroke outcomes (DM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNaughton, 2002</td>
<td>not relevant (no economic study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Najib, 2002</td>
<td>no stroke outcomes (CHD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chanbers, 2002</td>
<td>CU</td>
<td>none</td>
<td>markov</td>
<td>long-term (not specify time frame)</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>USA, Europe</td>
</tr>
<tr>
<td>Samsa, 2002</td>
<td>CE</td>
<td>ancrod treatment</td>
<td>Stroke Policy Model</td>
<td>short and long term (but not specify the time frame)</td>
<td>495 patients with data on functional status at the conclusion of follow-up</td>
<td>Y(rehab cost, rehab LOS, BI, MRS, but no staging approach)</td>
<td>$/QALY</td>
<td>USA</td>
</tr>
<tr>
<td>Jacobsson, 2001</td>
<td>no stroke outcomes (eating training)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post, 2002</td>
<td>CU</td>
<td>Routine duplex surveillance after carotid endarterectomy</td>
<td>Monte Carlo Markov</td>
<td>5yrs</td>
<td>not specified, use lit review data</td>
<td>Y(major disability, minor disability)</td>
<td>$/QALY</td>
<td>Netherland</td>
</tr>
<tr>
<td>Evans, 2002</td>
<td>not relevant (no economic study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tokunaga, 2002</td>
<td>not relevant - no patient outcomes evaluated in relation to hospital cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ottenbacher, 2001</td>
<td>no stroke outcomes (rehab satisfaction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams, 2002</td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Article Number</td>
<td>Economic study type</td>
<td>intervention</td>
<td>prediction model/ direct evaluation</td>
<td>time frame</td>
<td>patient cohort</td>
<td>disability</td>
<td>unit</td>
<td>regionality</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-------------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>------------</td>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>Chau, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (CHD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanders, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (MI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinclair, 2001, Pharmacoeconomics</td>
<td>CU</td>
<td>T-PA</td>
<td>markov</td>
<td>lifetime</td>
<td>patient after initial acute ischaemic stroke</td>
<td>rehabilitation cost, MRS (staging but no transition, )</td>
<td>$/QALY</td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (CHD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - no patient outcomes evaluated in relation to national wide cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowper, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (cardiology)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ottenbacher, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (compare two different statistical methods)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hochstenbach, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant (no economic study)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henderson, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - no patient outcomes evaluated in relation to GP-led community hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wexler, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (heart failure)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reed, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - no patient outcomes. Hospital cost and LOS oriented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grieve, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - no patient outcomes, compare regions in terms of hazard ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korn, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (arterial occlusion in the lower extremities)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>meta-analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tengs, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leyinson, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.3. (cont.)

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Economic study type</th>
<th>intervention</th>
<th>prediction model/direct evaluation</th>
<th>time frame</th>
<th>patient cohort</th>
<th>disability</th>
<th>unit</th>
<th>regionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diez-Tejedor, 2001</td>
<td>review article</td>
<td>none</td>
<td>multiple linear regression</td>
<td>not specified</td>
<td>1341 ischemic stroke patients, mean age=70.5</td>
<td>Y (used BI, MRS, European stroke scale) Staging BI → 0-45-70-95-100</td>
<td>$/stroke USA</td>
<td></td>
</tr>
<tr>
<td>Murray, 2001</td>
<td>no stroke outcomes (atrial fibrillation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinclair, 2001, J Clin Epidemiol</td>
<td>no stroke outcomes (methodology article)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stineman, 2001, Med Care</td>
<td>not relevant - acute hospital stay only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caro, 2001</td>
<td>assess cost</td>
<td>none</td>
<td>multiple linear regression</td>
<td>not specified</td>
<td>1341 ischemic stroke patients, mean age=70.5</td>
<td>Y (used BI, MRS, European stroke scale) Staging BI → 0-45-70-95-100</td>
<td>$/stroke USA</td>
<td></td>
</tr>
<tr>
<td>Sarasin, 2000</td>
<td>CE</td>
<td>antiplatelet regimens</td>
<td>markov</td>
<td>not specified</td>
<td>65yr</td>
<td>Y</td>
<td>$/QALY USA</td>
<td></td>
</tr>
<tr>
<td>Mayer, 2000</td>
<td>not relevant - assess only 30 day survivor rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kane, 2000</td>
<td>not relevant - only cost matter for different settings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmer, 2000, Schweiz Med Wochenschr</td>
<td>no stroke outcomes-DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson, 2000</td>
<td>no stroke outcomes - hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Article Number</td>
<td>Economic study type</td>
<td>intervention</td>
<td>prediction model/direct evaluation</td>
<td>time frame</td>
<td>patient cohort</td>
<td>disability</td>
<td>unit</td>
<td>regionality</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-----------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>------------</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>Derdeyn, 2000</td>
<td>CE</td>
<td>PET screening</td>
<td>markov</td>
<td>not specified</td>
<td>cohort of 45 symptomatic patients with carotid occlusion</td>
<td>Y (used lit: stroke free (0.9), BI &gt; 95 (0.76), BI &lt; 95 (0.39))</td>
<td>$/QALY</td>
<td>USA</td>
</tr>
<tr>
<td>Palmer, 2000, Diabetologia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes (DM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chambers, 1999</td>
<td>CE</td>
<td>antiplatelet regimens</td>
<td>decision analytical model</td>
<td>not specified</td>
<td>(ESPS-2, Oxfordshire Community Stroke Project and UK national statistics), in the model mean age=70</td>
<td>Y (disabled stroke survivor, using MRS 0-3-5)</td>
<td>$/QALY</td>
<td>UK</td>
</tr>
<tr>
<td>Hoenig, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel, 1999, J Vasc Surg 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes - carotid entarterectomy vs. events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramsey, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes - DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sloan, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - medicare payment oriented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wein, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shi, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - SES evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catherwood, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes - atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samsa, 1999, J Clin Epidemiol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not relevant - support methodology for long-term stroke impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grover, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no stroke outcomes - HMG-CoA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Article Number</td>
<td>Economic study type</td>
<td>intervention</td>
<td>prediction model/ direct evaluation</td>
<td>time frame</td>
<td>patient cohort</td>
<td>disability</td>
<td>unit</td>
<td>regionality</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-------------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>------------</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>Samsa, 1999,  Stroke</td>
<td>not relevant - epidemiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennett, 1999</td>
<td>not relevant - thrombocytopenia drug evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker, 1998</td>
<td>not relevant - case manager program evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvey, 1998</td>
<td>not relevant - rehab outcome only, not stroke outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goetzel, 1998</td>
<td>not relevant - expenditure risk factor evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crane, 1998</td>
<td>not relevant - formulary consideration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel, 1998</td>
<td>not relevant - duplex ultrasound surveillance after carotid endarterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanderstrom, 1998</td>
<td>not relevant - measuring instrument evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stineman, 1998</td>
<td>no stroke outcomes - oriented to rehab utilization pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelemans, 1998</td>
<td>no stroke outcomes - renal artery stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagan, 1998</td>
<td>CE, T-PA, markov, 30yrs, acute stroke patients, Y, mentioned rehabilitation, but not clear, $/QALY, USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancioli, 1998</td>
<td>not relevant - assess public knowledge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolf, 1998</td>
<td>no stroke outcomes - atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indredavik, 1997</td>
<td>not relevant - foreign language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lavender, 1998</td>
<td>no stroke outcomes - carotid endarterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoenig, 1997</td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parmigiani, 1997</td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porter, 1997</td>
<td>no stroke outcomes - surgery vs. stereotactic radiosurgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.3. (cont.)

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Economic study type</th>
<th>intervention</th>
<th>prediction model/ direct evaluation</th>
<th>time frame</th>
<th>patient cohort</th>
<th>disability</th>
<th>unit</th>
<th>regionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenthal, 1997</td>
<td>not relevant - compare different settings in terms of LOS……</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retchin, 1997</td>
<td>not relevant (no economic study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riviere, 1997</td>
<td>no stroke outcomes - Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrucci, 1997</td>
<td>not relevant - elderly peoples' utilizazion of different services when they were disabled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cronenwett, 1997</td>
<td>not relevant - carotid endarterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derdeyn, 1996</td>
<td>not relevant - screening intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor, 1996</td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schulzer, 1996</td>
<td>not relevant - brian and almut may have interest in this article</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pestana, 1991</td>
<td>no stroke outcomes - cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutton, 1996</td>
<td>review article</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gage, 1995</td>
<td>no stroke outcomes - atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanninen, 1995</td>
<td>not relevant - imaging of carotid artery stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tseyat, 1995</td>
<td>no stroke outcomes - captopril intervention for MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kent, 1995</td>
<td>not relevant - imaging of carotid artery stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalish, 1995</td>
<td>no stroke outcomes - thrombolitics for acute MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaste, 1995</td>
<td>not relevant - randomized clinical trial to evaluate two different intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowen, 1994</td>
<td>not relevant - only acute treatment phase, LOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Article Number</td>
<td>Economic study type</td>
<td>intervention</td>
<td>prediction model/direct evaluation</td>
<td>time frame</td>
<td>patient cohort</td>
<td>disability</td>
<td>unit</td>
<td>regionality</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-----------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>------------</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>Odderson, 1993</td>
<td>not relevant - acute treatment only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harada, 1987</td>
<td>not relevant - rehab outcome only, not stroke outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savage, 1987</td>
<td>not relevant - hypertension, no economic study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feigenson, 1979</td>
<td>not relevant - rehab oriented, not stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference 35-135
Articles were excluded if they were primarily evaluating other disease areas, such as diabetes mellitus, hypertension, myocardial infarction, heart failure, hyperlipidemia, hyperglycemia, cardiovascular disease, atrial fibrillation etc. Articles describing an intervention instead of stroke disease, and stroke outcome were not the main purpose of the study, those articles are also excluded. In addition, methodologies supporting studies for stroke are excluded because they do not directly evaluate economic outcomes in stroke patients. Through this procedure, fourteen articles were chosen for further review. Selected articles are highlighted using bold character in Table 2. Among these articles, the following questions will be reviewed.

- Economic analysis used in the study
- Time frame of the outcome evaluation
- Intervention involved
- Age of study subjects or cohort
- Evaluation of long-term residual disability

**Findings of the Literature Search**

In this section, the following information will be discussed based on the finding: economic analysis used in the study, time frame of outcome evaluation to estimate stroke long-term outcomes, whether the stroke long-term outcomes were evaluated as a tool to evaluate a specific intervention, age of study subjects that used to evaluate stroke long-term outcomes, whether and how the residual disability after stroke was included in the stroke long-term outcomes evaluation. This review is focusing on the methods, not on the results. Thus the results of individual studies are not presented.
Table 2.4. Summary of findings

<table>
<thead>
<tr>
<th>Article</th>
<th>Economic study type</th>
<th>intervention</th>
<th>prediction model</th>
<th>time frame</th>
<th>cohort characteristics</th>
<th>Disability (in outcome)</th>
<th>unit</th>
<th>regionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilaru, 2003</td>
<td>cost-effectiveness</td>
<td>surgery</td>
<td>Model, Markov</td>
<td>lifetime</td>
<td>65+</td>
<td>N</td>
<td>$/patients</td>
<td>Europe</td>
</tr>
<tr>
<td>Avorn, 2002</td>
<td>cost-effectiveness</td>
<td>drug, oral</td>
<td>Model, Markov</td>
<td>lifetime</td>
<td>65+</td>
<td>N</td>
<td>$/QALY</td>
<td>North America</td>
</tr>
<tr>
<td>Sundberg, 2003</td>
<td>assess cost</td>
<td>policy</td>
<td>model</td>
<td>not specified</td>
<td>not specified</td>
<td>N</td>
<td>$/stroke</td>
<td>Europe</td>
</tr>
<tr>
<td>Flack, 2002</td>
<td>assess cost</td>
<td>none</td>
<td>model</td>
<td>not specified</td>
<td>not specified</td>
<td>N</td>
<td>$, national estimate</td>
<td>North America</td>
</tr>
<tr>
<td>Lai, 2002</td>
<td>assess clinical outcomes</td>
<td>none</td>
<td>direct estimation from study result</td>
<td>&lt;=1yr</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>Europe</td>
</tr>
<tr>
<td>Chambers, 2002</td>
<td>cost-utility</td>
<td>none</td>
<td>Model, Markov</td>
<td>not specified</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>Europe and North America</td>
</tr>
<tr>
<td>Samsa, 2002</td>
<td>cost-effectiveness</td>
<td>drug, inj</td>
<td>model</td>
<td>not specified</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>North America</td>
</tr>
<tr>
<td>Post, 2002</td>
<td>cost-utility</td>
<td>imaging</td>
<td>Model, Markov</td>
<td>&gt;1yr</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>North America</td>
</tr>
<tr>
<td>Sinclair, Caro, 2001</td>
<td>cost-utility</td>
<td>drug, inj</td>
<td>Model, Markov</td>
<td>lifetime</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>North America</td>
</tr>
<tr>
<td>Sarasin, 2000</td>
<td>assess cost</td>
<td>none</td>
<td>model</td>
<td>not specified</td>
<td>not specified</td>
<td>Y</td>
<td>$/stroke</td>
<td>North America</td>
</tr>
<tr>
<td>Derdeyn, 2000</td>
<td>cost-effectiveness</td>
<td>screening</td>
<td>Model, Markov</td>
<td>not specified</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>Europe</td>
</tr>
<tr>
<td>Chambers, 1999</td>
<td>cost-effectiveness</td>
<td>drug, oral</td>
<td>model</td>
<td>&gt;1yr</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>Europe</td>
</tr>
<tr>
<td>Fagan, 1998</td>
<td>cost-effectiveness</td>
<td>drug, inj</td>
<td>Model, Markov</td>
<td>&gt;1yr</td>
<td>not specified</td>
<td>Y</td>
<td>$/QALY</td>
<td>North America</td>
</tr>
</tbody>
</table>
Economic analysis

As presented in table 2.4, cost-utility analysis (CU) was the most commonly used economic analysis in stroke economic outcomes research: nine out of fourteen articles (71%). Other studies used dollar spent per patient, dollar spent per stroke, or national estimate for burden of stroke.

Time frame

Seven out of the fourteen studies did not state the time frame of observation for their analyses. Of the studies that presented time frames, one assessed economic outcomes of stroke for less than one year, and three studies evaluate more than one year time frame (two are for five years and one for 30 years). Lifetime costs were considered in three out of fourteen articles. Time frames of stroke outcomes research tend to vary from study to study. Considering the chronic phase of stroke, which often last until death, the evaluation long-term (or life-time) residual disability would be important information in evaluating stroke outcomes.

Intervention

Ten studies were related to intervention evaluation: one article on surgery (carotid angioplasty and stenting and carotid endarterctomy), six articles on medications (one for anchrod, two for anti-platelet, one for lipid lowering, and two for t-PA), one article for imaging (Routine duplex surveillance after carotid endarterectomy), one article for screening (PET screening), and one article for policy. A considerable portion of stroke outcomes research was performed to evaluate medical intervention related to stroke prevention/improvement.
Age

The cohort age, which is the most important risk factor of stroke were diverse. Three studies put restrictions on age eligibility: two studies only considered 70 year old and older, one article 65 year old and above. Nine articles did not present age, and two articles showed mean age of 70.5 and 70 years old respectively. <Table 2.3 and Table 2.4>

Considering that age is the most important risk factor of stroke, clear statement on age is necessary in stroke outcomes research. Furthermore, for long-term evaluation of stroke outcomes, the estimates of outcomes highly depend on the patient age that she/he has stroke.

Residual disability

Terminology referring to post-stroke residual disability was not consistent across the fourteen articles. Studies presented disability outcomes as a part of overall outcomes with terminology such as, functional status, handicap, rehabilitation, major/minor disability, or morbidity. <Table 2.3>

Economic evaluation considers financial aspect of health outcomes, thus for long-term stroke outcomes, rehabilitation cost or disability related costs should be considered. Stroke long-term outcome studies consider the financial impact caused by residual disability, but often did not differentiate the severity of disability.

Post-stroke disability in survivors showed various degrees of disability. Without considering severity of disability, the information on rehabilitation costs or disability cost is only a crude estimate of the economic impact of residual disability. Detailed findings of disability evaluation will be provided below.
All the fourteen articles mentioned disability as a part of stroke burden, but only ten out of the fourteen articles included disability in outcome estimation. <Table 2.4>

Three out of the ten articles dichotomized disability categories. Post et al. used ‘major’, ‘minor’ disability; and Chambers et al. dichotomized disability using Modified Rankin Scale, 0 to 3, and 3 to 5. Derdeyn et al. used Barthel Index and dichotomized at the point, 95. This approach looks simple and concise, but there are weaknesses: (1) the evidence about where to establish the cutting point between two categories is not clear, and (2) the characteristics of two groups dichotomized with any criteria were not clearly presented, in other words, the dichotomization of disability was not supported with any reason.

Caro et al. used multiple instruments: the Modified Rankin Scale (MRS) and the Barthel index, but they used the Barthel Index scores to differentiate different levels of disability. The cutoffs, for the zero to one hundred scale of Barthel Index, were 45, 70 and 95; therefore four different levels of disability were categorized. However, similar to the dichotomization, this article also did not present any scientific reasoning on why their categorization system was appropriate.

Sinclair et al. used a six leveled Modified Rankin Scale (MRS), which has an ordinal scale from 0 to 5, and explains clinically distinct levels of disability in patients. Published utility information was used to match to each MRS level, and those utility values assigned were 0.9 for MRS0, 0.8 for MRS1, 0.46 for MRS2, 0.34 for MRS3, 0.3 for MRS4, and -0.02 for MRS5. Interestingly, utility and MRS did not have a linear relationship, and the difference between adjacent levels of MRS were not equal across the entire MRS scale.
Information linking utility and disability level does not appear possible with the other two widely used ADL disability measures: the Barthel index and the FIM Motor scores. Because they are continuous scales, appropriate categorization of the Barthel index score and FIM Motor component score is needed to link utility to these measures. A simple categorization scheme, such as equal intervals in the scale would not be appropriate, especially because these instruments show ceiling effects. For the MRS, the categorization does not seem to be a necessity unless the levels need further simplification. However, as cited above from Sinclair’s study, the patient perceived utility for each MRS level still needs further research to get a clear relationship.

Three of the fourteen studies used the Barthel Index. One of them did not differentiate disability levels, but two articles used their own categorization scheme: BI>=95 and BI<95, and 0-45, 45-70, 70-95, and 95-100.

Four articles among fourteen studies used the Modified Rankin Scale. Chamber et al simplified the six category scale into two level with the following dichotomization scheme: MRS0 to MRS2, and MRS3 to MRS5.

This finding shows that there is no standard method for evaluating long-term stroke outcomes or for interpreting various degrees of disability in stroke survivors. Considering that disability is one of the major components of health care cost after stroke, more specific evaluation of disability after stroke, and the survivor’s disability prognoses over time is needed. Currently, the stroke outcomes research literature does not provide sufficient information on the long-term outcomes of stroke including residual disability.
This dissertation focuses on evaluating disability outcomes after stroke using secondary data: (a) the Kansas City Stroke Study, an observational study without intervention, and (b) the Perindopril pROtection aGainst REcurrent Stroke Study, a clinical trial with oral antihypertensive for stroke prevention. Using these two datasets, the main purpose of this dissertation that is an analysis of post-stroke residual disability prognoses in survivors will be performed. This dissertation will achieve several objectives to reach the study purpose: (1) rational staging/level setting scheme of disability outcomes in patients, (2) long-term disability outcomes in stroke patients based on the stages, (3) appropriate utilities for distinct level of disability, and (4) to predict prognosis of disability in stroke patients based on short-term observation of patients, and (5) the effectiveness of antihypertensive medication intervention program to prevent recurrent stroke are interpreted in terms of a long-term time frame with including residual disability after stroke.
CHAPTER 3
CONCEPTUALIZATION OF A DISABILITY EVALUATION MODEL

As mentioned in the previous chapter, long-term residual disability of stroke survivors is an important issue nevertheless this has received little attention. The purpose of this chapter is to develop a methodology to evaluate stroke outcomes focusing on residual disability among stroke survivors.

Figure 3.1 shows the structure of a stroke outcome evaluation model in a drug intervention study. Since the outcome of interest is disability, disability is presented as outcome. For convenience, the Modified Rankin Scale (MRS) is used to express disability outcomes in study subjects.

![Diagram showing the structure of a stroke outcome evaluation model in a drug intervention study.]

Figure 3.1. Disability outcomes of drug and placebo intervention.

The model expresses the chronological order of intervention and outcomes of interventions. At the left end, a person who had a stroke is assigned to drug intervention.
or placebo intervention group. The disability outcomes are presented at right side with levels of disability. This model, however, evaluates the outcomes of the intervention only once at a specified measurement point, i.e., at one year post intervention or ten years after intervention. This model may not be able to appropriately evaluate patient’s disability outcome due to the lack of information about how subject’s experience (i.e., changes in disability condition) until he arrives to the specified measurement point. This is a simple representation to evaluate outcome in most acute disease states, but for certain disease states, such as chronic disability conditions in patients, this simple way does not reflect patient outcomes in a practical sense.

The impracticality arises because a person who has a chronic disability may experience changes of health status over time. Thus, ideally, the outcome measures in the people who have chronic disability conditions should be able to capture these changes and incorporate these into the overall outcome evaluation. From this point of view, figure 3.1 misses the changes in disability in subjects that may be important components in evaluating chronic disability.

Let’s assume that a cohort is followed yearly after enrollment for a four years time window. Figure 3.2 presents the disability outcomes of the two groups for a specific time period and at multiple outcome measuring points. Compared to model 3.1, this model retrieves more information on the effects of the intervention in terms of disability. Apparently, this model will provide stronger evidence if the results of comparisons at each measurement point are consistent. However, this does not provide information on ‘how’ or ‘through which pathway’ the patient arrived at the specific disability level. In other words, the transitions of patient conditions are ignored.
Figure 3.2. Disability outcome evaluation at specific point
Incorporating transitions of condition in evaluating chronic status, modeling long-term outcomes instead of focusing exclusively on final outcome measures, is important for two reasons. First, transitions provide detailed information on patient outcomes; transitions allow us to account for possible morbidity situations (or health status/conditions) that patient experienced through the course of time. Thus focusing on outcomes measured only once at a specified point may not appropriately evaluate the impact of chronic disease states. Such analysis disregards the morbidity that patient experiences and related health care services that patient may have consumed. Therefore, transition information is important for chronic disease, modeling such as disability, by the nature of disease.

Second, information on population level transition of disease condition will provide practitioners important clinical information in decision making and will aid the health care policy makers in establishing proper services and allocation of scarce resources. Especially, considering the lengthened life expectancy and predicted future societal burden resulting from an ageing population, the information on transitions of chronic disability will be important to plan health care services and provide appropriate care.

From this perspective, if we consider four year outcomes with yearly interval outcome measures, we can use this longitudinal information with the model presented in Figure 3.3. Patient starts therapy in either ACE inhibitor or placebo groups after randomization, and outcomes are measured at each planned time point.

Patients are assigned to one of MRS0 – MRS5 at the first year. Individuals in any of those levels have a chance to be in one of seven stages at the second evaluation: MRS0 – MRS5 or death. So, at the second evaluation point, a person who started in one of
either group has 43 options to be located. Thereafter at the third outcome evaluation points, there will be 260 branches, and 1,612 branches at the fourth outcome measuring point.

Figure 3.3. Prognoses of disability (Individual)

This presentation describes exhaustively all the possible pathways and final locations for a person enrolled in the intervention. However, this approach is not easy to analyze and interpret considering the required number of subjects. Moreover, the interest is on the ‘population level’ disability evaluation, not in the individual. Thus, the model was modified to Figure 3.4 to meet the purpose of the current study.
Figure 3.4. Prognoses of disability in the population

From Figure 3.4, the number of branches remains forty two (6x7=42). This population level transition between two outcome measuring points can be successfully and meaningfully described. For example,

*A stroke survivor who is in the MRS1 in the first year could be in MRS0 with a probability of 0.1; could be in MRS1 with the probability of 0.3; MRS2, 0.2; MRS3, 0.2; MRS4, 0.1; and MRS5, 0.1 for the second year.*
This dissertation will use the model illustrated in the Figure 3.4, and the disability prognoses in two drug intervention groups will be compared. Using appropriate utility information and assumptions, disability states will be described in two intervention groups. Since there is no cost information available from the data source, monetary benefits will not be considered in this dissertation.

Figure 3.5 illustrates the disability transition with hypothetical stages (Rankin0 to Rankin5) and all the possible transitions between stages are presented with dotted lines. Through the methods and results section, the procedure investigating the components of the model - stages of disability, utilities, and transition probabilities - will be explained and answered.
Figure 3.5. Exhaustive and exclusive pathways of disability transition in post-stroke population
CHAPTER 4
METHODS

The purpose of this study is to develop a methodology to evaluate stroke outcomes considering residual disability among stroke survivors. The developed methodology was used to examine disability outcomes and prognoses in a sample population enrolled in a multinational clinical trial, PROGRESS. In the previous chapter, chapter 3, disability outcome evaluation was described with a conceptual model. To investigate and determine the model components introduced in the chapter 3, in the current chapter, research questions are introduced, and statistical methods for individual research question addressed.

This chapter is organized and structured with five specific aims:

(1) to develop a categorization scheme based on the BI defining discrete disability states,

(2) to investigate representative utility (time trade-off) estimate in stroke survivors in relation to the BI,

(3) to examine the disability prognoses of stroke survivors in active drug and placebo intervention groups,

(4) to examine the disability prognoses among the people who experienced recurrent stroke, and

(5) to examine the effectiveness of drug intervention considering residual disability post stroke.
Two data sources were used to achieve these aims: the Kansas City Stroke Study data, and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). Study design, settings, inclusion criteria, randomization, and data collection methods are presented in this chapter.

**Study Design**

The Kansas City Stroke Study (KCSS) was a prospective cohort study designed to examine the patterns of recovery of stroke patients. KCSS started in October, 1995 and data collection was completed in 1999. The Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) was a randomized placebo controlled trial designed to resolve clinical uncertainty about the efficacy and safety of routine blood pressure lowering therapy with ACE inhibitor for individuals with a history of stroke or transient ischaemic attack. The PROGRESS study started in 1995 and completed data collection in February 2001.

**Setting**

The Kansas City Stroke Study was performed in 12 participating hospitals in the Greater Kansas City area: Baptist Hospital, Department of Veterans Affairs Medical Centers at Kansas City and Leavenworth, Liberty Hospital, Medical Center of Independence, Mid-American Rehabilitation Hospital, Rehabilitation Institute, Research Medical Center, St. Luke’s Hospital, St. Joseph Health Center, Trinity Lutheran Hospital, and the University of Kansas Medical Center.

The PROGRESS study included subjects from 172 centers in Asia, Australia and Europe. Twenty five hospitals from Australia and New Zealand, twenty six hospitals from China, twenty five hospitals from France and Belgium, eleven hospitals from Italy,
thirty three hospitals from Japan, and twenty three hospitals from United Kingdom and Ireland participated in the study.

**Sampling, Inclusion and Exclusion Criteria**

Eligible stroke patients in the Kansas City Stroke Study\textsuperscript{137} were identified by (1) a review of daily admission records, (2) referrals from physicians, clinical nurse specialists and therapist on medical, neurology, and rehabilitation units, and (3) review of discharge code. The World Health Organization (WHO) definition of stroke was adopted as the criteria for a stroke event. The WHO criteria for stroke is, ‘rapid onset and of vascular origin reflecting a focal disturbance of cerebral function, excluding isolated impairment of higher function and persisting longer than 24 hours’. Trained nurses or physical therapists reviewed medical records and interviewed both patients and clinicians to determine whether the patient was eligible for, then consented to enroll.

In the Kansas City Stroke Study, subjects were excluded if they were less than 18 years old; had stroke onset more than 14 days before the date of interview; had subarachnoid hemorrhage; had hepatic failure; had renal failure; had New York Heart Association functional grade 3 or 4 heart failure (patients with cardiac disease resulting in inability or marked limitation to carry on any physical activity without discomfort); were unable to take care of their own affairs prior to stroke; were lethargic, obtunded or comatose; and lived more than 70 miles from the participating hospital.

Patients with a history of stroke or transient ischaemic attack within the previous five years were eligible subjects for the Perindoprol Protection against Recurrent Stroke Study (PROGRESS)\textsuperscript{138}. The definition of stroke in PROGRESS was, ‘an acute disturbance of focal neurological function with symptoms lasting more than 24 hrs and thought to be due to intracerebral hemorrhage or ischaemia’, and the definition of
transient ischaemic attack was ‘an acute disturbance of focal neurological or monocular function with symptoms lasting less than 24 hrs and thought to be due to arterioembolic or thrombotic vascular disease’. Patients had to be clinically stable for at least 2 weeks after their most recent vascular event before their entry of study and had to consent to participate.

Subjects were excluded if they had a definite indication (e.g., heart failure) or contraindication (e.g., potential to be pregnant, renal artery stenosis) for treatment with ACE Inhibitor; had current clinical instability; had life threatening non-vascular illness; showed evidence of non-compliance with treatment or follow-up, and had a disability likely to prevent regular attendance at study clinics.

**Randomization**

PROGRESS trial was a placebo controlled randomized trial. Potentially eligible individuals entered a 4-week pre-randomization run-in period. During this period, they received open labeled perindopril 2 mg for 2 weeks and 4 mg for subsequent 2 weeks. During the 4-week run-in phase before randomization, subject’s adherence and tolerance of potentially eligible individuals were examined.

Treatment allocation was assigned by a central computer based randomization service, which was accessed by telephone or facsimile. Randomization of patients was stratified by the patient’s intension regarding treatment intensity (single therapy or combination therapy), study center, age, sex, entry systolic blood pressure and qualifying event.

The Kansas City Stroke Study was a prospective observational study, so randomization did not take place.
Data Collection

Patients in the Kansas City Stroke Study were evaluated at enrollment (within 14 days from stroke onset), one, three, and six month after stroke. Functional Independence Measure, Modified Rankin Scale, Barthel ADL index, and time trade-off were assessed and measured at each measurement point.

Patients in the PROGRESS were assessed annually after enrollment for four year follow-up period. Patient’s Barthel ADL index, recurrent vascular event and event date were collected.

Post-Stroke Disability Evaluation Model

In the literature review chapter, decision analysis and modeling in health outcomes research was briefly introduced, and in the previous chapter, disability transition model was conceptualized. In this section, several important terminologies are introduced. For reference, Figure 3.5 is copied to Figure 4.1. Figure 4.1 shows key components of the stroke outcome evaluation model. First, ‘stages’ presenting different degrees of disability are presented with solid-line circles in the figure; second, transitions from one to another stages or staying in the same disability levels are presented using dashed line with arrow. The arrow indicates direction of transition. Chance of the transitioning from one level to another is ‘transition probability’.

‘Utility’, is also an important component in the model. Utility represents how much this level of disability is valued by the people who have this disability level.

---

1 Only include the measurements, which will be used in this study from each database.
In this dissertation, stages and utilities are developed utilizing KCSS, and probabilities of disability transition are arrived from the PROGRESS data. These five aims are proposed to investigate these model components.

**Overview of Data Analysis**

Table 4.1 provides a brief summary for the overview of this dissertation. Individual research questions, hypotheses, and statistical tests are discussed later. Aim one and two used the KCSS data, and aim three and four used PROGRESS data.

![Disability Transition Diagram](image)
Table 4.1. Objectives, Aims and Research questions

<table>
<thead>
<tr>
<th>Objective</th>
<th>Aims</th>
<th>Data source</th>
<th>Research Questions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability Stage development</td>
<td>(1) to develop a categorization scheme, the Barthel Index, defining discrete disability states</td>
<td>KCSS</td>
<td>RQ1</td>
</tr>
<tr>
<td>Utility development</td>
<td>(2) to investigate representative time trade-off estimate in stroke survivors, in relation to Barthel Index</td>
<td>KCSS</td>
<td>RQ2s, 3s,</td>
</tr>
<tr>
<td>Transition Probability development</td>
<td>(3) to examine the disability prognoses of stroke survivors in active drug and placebo groups</td>
<td>PROGRESS</td>
<td>RQ4s, 5s</td>
</tr>
<tr>
<td>Transition Probability development</td>
<td>(4) to examine the disability prognoses among the people who experienced recurrent stroke</td>
<td>PROGRESS</td>
<td>RQ6s, 7s</td>
</tr>
<tr>
<td>Drug effectiveness Evaluation</td>
<td>(5) to examine the effectiveness of the drug intervention considering residual disability post stroke</td>
<td>KCSS, PROGRESS</td>
<td>RQ8s</td>
</tr>
</tbody>
</table>

Multiple research questions exist under RQ 2 – RQ 8.

Aim 1 & 2 (Research Question 1 to 3) using Kansas City Stroke Study

The categorization scheme for the Barthel Index was developed using the global disability scale, the Modified Rankin Scale by performing the research question 1. Disability categories served as disability stages in the model <Fig 4.1>.

From the research question 2 and 3, utility scores corresponding to individual stages were estimated.

Aim 3 & 4 (Research Question 4 to 7) using PROGRESS data

PROGRESS was a placebo controlled ACE inhibitor intervention clinical trial designed to investigate the effectiveness of ACE inhibitor in preventing recurrent strokes.

In this data, participant’s disability was recorded yearly with the Barthel Index.
In research question 4, patients’ disability outcome was compared between ACE inhibitor treated group and placebo group using Barthel Index and Categorized Barthel Index.

In research question 5, disability prognosis over time was addressed based on the Categorized Barthel. This information was utilized as transition probability in disability evaluation model. In research question 6 and 7, subpopulation that experienced recurrent stroke was extracted and the same procedure with research question 6 and 7 was applied.

Aim 5 (Research Question 8) using KCSS and PROGRESS data

Research question 8 was to examine the effectiveness of drug intervention in terms of disability among stroke survivors. The detailed research questions, hypotheses, and test methods are described below.

Aim 1. Stage Development

In this section, the hypotheses and statistical analysis methods for each research question is described.

Research Question 1

RQ1. What are the cut-off points in the Barthel index that match with the Modified Rankin Scale?

(No hypothesis test was performed. Logistic regression was used in the analysis.)

The Barthel Index was scored with ten basic Activities of Daily Living items with different weight attached. The ten ADL questions are (1) feeding, (2) transfer to chair from bed, (3) grooming, (4) toileting, (5) bathing, (6) walking without help (or use of wheelchair if the person cannot walk), (7) go up and down stairs, (8) dressing, (9) control of bowel movement, and (10) control of bladder. Transferring from bed to chair and
walking are evaluated on 0, 5, 10, or 15 point scale; feeding, toileting, walk up and down stairs, dressing, bowel control, and bladder control are evaluated on 0, 5, or 10 point scale. Grooming, bathing, and use of wheelchair items are evaluated on 0, or 5 point scale. The higher score represents better ability in performing basic ADLs.

Even though the Barthel Index is widely used to measure stroke survivor’s activities of daily living, with minimal interviewee burden, the score does not necessarily indicate the degree of disability. In addition, due to the reported ceiling effect in the Barthel Index, the categorization cannot be done with arithmetic cut-offs. For this reasons, in this study, by examining the relationship between the global disability measure (the Modified Rankin Scale, MRS), and the Barthel Index, meaningful disability category was developed from the Barthel Index.

The correlation between the Barthel Index and the MRS was examined and the distribution of the Barthel Index for each MRS level was illustrated. Descriptive method including box plot with inter-quartile ranges, mean, median, and percentile in the Barthel Index scores was examined for each MRS level. Logistic regression was used to develop probability density functions and generate potential cut-off points. Among several combinations of cut-off points, the one set that minimizes false positive responses was chosen for the categorization scheme. Combinations of cut-off points were chosen in a mutually exclusive and exhaustive way providing equal weights for individual records.

**Aim 2. Utility Development**

**Research Question 2**

Research Questions 2-1, 2-2, and 2-3 are about the relationship between utility and disability levels. The relationship between the Barthel Index and time trade-off (TTO) was examined. Descriptive methods such as mean, median, standard deviation, inter-
quartile range, and percentile in the TTO was examined respectively for each disability level using the categorization scheme. The correlation coefficient between TTO and Barthel Index (RQ2-1), the correlation coefficient between TTO and C-BI (RQ2-2) was examined. Analysis of Variance was performed examining at the differences in TTO among the disability levels defined with C-BI (RQ2-3).

RQ2-1. Is there a correlation between the Barthel Index and time-trade off?
Ho: There is no correlation between time-trade off and the Barthel Index.
Ha: There is a correlation between time-trade off and the Barthel Index.
Pearson or Spearman correlation ($\alpha = 0.05$)

RQ2-2. Is there a correlation between the Categorized Barthel and time-trade off?
Ho: There is no correlation between time-trade off and the Categorized Barthel.
Ha: There is a correlation between time-trade off and the Categorized Barthel.
Pearson or Spearman correlation ($\alpha = 0.05$)

RQ2-3. Is there a difference in time-trade off among the disability levels defined by the Categorized Barthel?
Ho: There is no difference in time-trade off among disability levels defined by Categorized Barthel.
Ha: There is a difference in time-trade off among disability levels defined by Categorized Barthel.
ANOVA ($\alpha = 0.05$), and post-hoc test when it is needed
Research Question 3

Research questions 3-1, 3-2, and 3-3, are about the relationship between the MRS and utility scores. First, descriptive information such as mean, median, standard deviation, inter-quartile range, and percentile of TTO was examined for each level of disability in the MRS.

The correlation coefficient between TTO and disability levels in the MRS (RQ3-1) was determined. Since the categorization scheme from the BI produce less number of disability categories due to the ceiling effect, the disability levels in the MRS was collapsed and defined as reduced MRS (rMRS), then the correlation between TTO and rMRS was determined (RQ3-2). Analysis of Variance was performed to examine at the difference in TTO among the disability levels defined by rMRS (RQ3-3).

RQ3-1. Is there a correlation between the Modified Rankin Scale (MRS) and Time Trade-Off (TTO)?

Ho: There is no correlation between TTO and the MRS.

Ha: There is a correlation between TTO and the MRS.

Spearman correlation test ($\alpha = 0.05$)

RQ3-2. Is there a correlation between the reduced Modified Rankin Scale (rMRS) and TTO?

Ho: There is no correlation between TTO and the rMRS.

Ha: There is a correlation between TTO and the rMRS.

Spearman correlation test ($\alpha = 0.05$)
RQ3-3. Is there a difference in TTO among the disability levels defined by the reduced Modified Rankin Scale (rMRS)?

Ho: There is no difference in TTO among the disability levels defined by rMRS.
Ha: There is a difference in TTO among the disability levels defined by rMRS. Kruskal-Wallis one way ANOVA ($\alpha = 0.05$), and post-hoc test when it is needed

**Aim 3. Transition Probabilities**

**Research Question 4**

The research question 4 is to examine whether there is a difference between ACE inhibitor treatment group and placebo treatment group in terms of disability outcome measured with BI. Barthel scores was categorized based on categorization schemes developed from the Research question 1. Frequencies of categorized disability level were examined for active and placebo treatment group to see the distributions of C-BI in two groups. Kruskal-Wallis one way analysis of variance test was performed to determine if a statistically significant difference exist between ACE inhibitor treatment group and placebo group. (RQ4-1 ~ RQ4-4)

RQ4-1. Based on the categorization scheme developed in RQ1, is there a significant difference in patient’s disability between ACE inhibitor and placebo groups with respect to the Barthel Index at year 1?

Ho: There is no difference in C-BI between ACE inhibitor intervention group and the placebo group at year 1.
Ha: There is a difference in C-BI between ACE inhibitor intervention group and the placebo group at 1 year.

Kruskal-Wallis test ($\alpha = 0.05$)

RQ4-2 ~ RQ4-4. Same procedures are applied for year 2, 3, and 4, respectively.

**Research Question 5**

This question is to determine the disability prognoses in ACE inhibitor and placebo groups. The categorization scheme from research question 1 was used and frequencies were recorded for the cells in table 4.2. Ten different transitions from five outcome collecting points were examined respectively, i.e., baseline $\rightarrow$ year1, year1 $\rightarrow$ year2, year2 $\rightarrow$ year3, and year3 $\rightarrow$ year4 (RQ5-1 ~ RQ5-4).

This information was used to obtain transition probabilities for the stroke disability evaluation model. No inferential statistic was used.

Table 4.2. Disability transition probability table

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>......</th>
<th>n-2</th>
<th>n-1</th>
<th>n</th>
<th>death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>......</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RQ5-1. Based on C-BI, is there a difference in the prognosis of disability in the ACE inhibitor and placebo group from baseline to year 1?

(No hypothesis)

RQ5-2 – RQ5-4. Same procedure was performed for:

- year 1 → year 2,
- year 2 → year 3, and
- year 3 → year 4.

**Research Question 6**

This question was to determine the disability prognoses in ACE inhibitor intervention group and placebo group when subjects experienced recurrent stroke. Barthel scores was categorized based on categorization schemes developed from the Research question 1. Frequencies of categorized disability level were examined for active and placebo treatment group to see the distributions of C-BI in two groups. Kruskal-Wallis tests were performed to determine if statistically significant difference exists between ACE inhibitor group and placebo group at first, second, third, and fourth outcome measuring point respectively (RQ6-1 ~ RQ6-4).

RQ6-1. Is there a significant difference in C-BI at the first year of recurrent stroke between active and placebo ACE inhibitor intervention groups when patient experienced recurrent stroke?

Ho: There is no difference in C-BI between ACE inhibitor and placebo groups at the first year of recurrent stroke.
Ha: There is a difference in C-BI between ACE inhibitor and placebo groups at the first year of recurrent stroke.

Kruskal-Wallis test ($\alpha = 0.05$)

RQ6-2 ~ RQ6-4. Same procedure was applied for the second year, the third year, and the fourth year after the recurrent stroke.

**Research Question 7**

This research question was to examine if statistically significant difference exists in Categorized Barthel between ACE inhibitor intervention group and placebo group at first, second, third, and fourth year after the recurrent stroke. The categorization scheme from research question 1 was used and frequencies for each cell (see Table 4.2) were recorded.

Four sets of transition probability tables arriving from five outcome collecting points were recorded respectively, that is, measure before recurrent stroke $\rightarrow$ first measure after recurrent stroke, first measure after recurrent stroke $\rightarrow$ second measure after recurrent stroke, second measure after recurrent stroke $\rightarrow$ third measure after recurrent stroke, and third measure after recurrent stroke $\rightarrow$ fourth measure after recurrent stroke (RQ7-1 ~ RQ7-4).

Study subjects may have recurrent stroke any time in the twelve month period between two measuring points. Thus in order to perform this analysis, an assumption was made that the recurrent stroke occurrence time are randomly distributed in yearly calendar, and no difference in intervention and placebo treatment group.
Figure 4.2. Recurrent stroke and measurement points

RQ7-1. For the subpopulation that had recurrent stroke - Based on the Categorized Barthel, is there a difference in the prognosis of disability between ACE inhibitor and placebo group between two time point: before and after the recurrent stroke?

(No hypothesis test)
RQ7-2 – RQ7-4. Same procedure was applied for: from ‘first year after stroke’ to ‘second year after stroke’, from ‘second year after stroke’ to ‘third year after stroke’, and ‘third year after stroke’ to ‘fourth year after stroke’ respectively.

**Aim 4. Effectiveness of the Intervention**

**Research Question 8**

The information obtained from the Research Question one through seven - disability stages, utilities, and transition probabilities - was used to answer research question 8. Figure 4.3 presents the disability transition model and illustrate how the individual research questions support the components of the model.

RQ8-1. What is the integrated benefit of ACEI (placebo) treatment compared to placebo (ACEI) treatment in terms of utility considering four year disability and the transitions?

RQ8-2. For the recurrent stroke victims, what is the integrated benefit of ACEI (placebo) treatment compared to placebo (ACEI) treatment in terms of utility considering four year disability and the transitions?

The research questions, hypotheses, and statistical tests are organized in the Table 4.3.
Figure 4.3. Illustration of how the information explored in this dissertation supports the suggested disability evaluation model

**Utility:** Utility (time trade-off) are assigned to each disability level (Aim 2, RQ2, 3)

**Transition Probability:** Transition probability is explored by examining disability prognosis in stroke survivors (Aim 3 and 4, RQ 4, 5, 6, and 7)

**Disability Stage:** Stages are developed using the Barthel Index and the Modified Rankin Scale from KCSS dataset. (Aim 1, RQ1)
Table 4.3. Summary of research questions, hypotheses, and statistical tests for each aim

<table>
<thead>
<tr>
<th>Categorization</th>
<th>RQ #</th>
<th>Research question</th>
<th>Hypothesis</th>
<th>Test, and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RQ1</td>
<td>What are the cut-off points in the Barthel index that match with the Modified Rankin Scale?</td>
<td>N/A</td>
<td>Logistic regression</td>
</tr>
<tr>
<td>RQ #</td>
<td>Research question</td>
<td>Hypothesis</td>
<td>Test, and significance</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>RQ2-1</td>
<td>Is there a correlation between the Barthel Index and time-trade off?</td>
<td>Ho: There is no correlation between time-trade off and the Barthel Index.</td>
<td>Pearson or Spearman correlation ($\alpha = 0.05$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ha: There is a correlation between time-trade off and the Barthel Index.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ2-2</td>
<td>Is there a correlation between the Categorized Barthel and time-trade off?</td>
<td>Ho: There is no correlation between time-trade off and the Categorized Barthel.</td>
<td>Pearson or Spearman correlation ($\alpha = 0.05$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ha: There is a correlation between time-trade off and the Categorized Barthel.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ2-3</td>
<td>Is there a difference in time-trade off among the disability levels defined by the Categorized Barthel?</td>
<td>Ho: There is no difference in time-trade off among the disability levels defined by Categorized Barthel.</td>
<td>Kruskal-Wallis test ($\alpha = 0.05$), and post-hoc test when it is needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ha: There is a difference in time-trade off among the disability levels defined by Categorized Barthel.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ3-1</td>
<td>Is there a correlation between the Modified Rankin Scale (MRS) and time-trade off?</td>
<td>Ho: There is no correlation between time-trade off and the MRS.</td>
<td>Spearman correlation ($\alpha = 0.05$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ha: There is a correlation between time-trade off and the MRS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ3-2</td>
<td>Is there a correlation between the reduced Modified Rankin Scale (rMRS) and time-trade off?</td>
<td>Ho: There is no correlation between time-trade off and the rMRS.</td>
<td>Spearman correlation ($\alpha = 0.05$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ha: There is a correlation between time-trade off and the rMRS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ3-3</td>
<td>Is there a difference in time-trade off among the disability levels defined by the reduced Modified Rankin Scale (rMRS)?</td>
<td>Ho: There is no difference in time-trade off among the disability levels defined by rMRS.</td>
<td>Kruskal-Wallis test ($\alpha = 0.05$), and post-hoc test when it is needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ha: There is a difference in time-trade off among the disability levels defined by rMRS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ #</td>
<td>Research question</td>
<td>Hypothesis</td>
<td>Test, and significance</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
<td>------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>disability evaluation, cross-sectional</td>
<td><strong>RQ4-1</strong></td>
<td>Based on the categorization scheme developed in RQ1, produce Categorized Barthel (CB). Is there a significant difference in patient’s disability between ACE inhibitor intervention group and placebo groups at year 1?</td>
<td>Ho: There is no difference in C-BI between ACE inhibitor intervention group and the placebo group at 1 year. Ha: There is a difference in C-BI between ACE inhibitor intervention group and the placebo group at 1 year.</td>
<td>Kruskal-Wallis test ($\alpha = 0.05$)</td>
</tr>
<tr>
<td></td>
<td><strong>RQ4-2</strong></td>
<td>Same procedures will be applied for year 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>RQ4-3</strong></td>
<td>Same procedures will be applied for year 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>RQ4-4</strong></td>
<td>Same procedures will be applied for year 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disability evaluation, prognosis over</td>
<td><strong>RQ5-1</strong></td>
<td>Based on the Categorized Barthel, is there a difference in the prognosis of disability in ACE inhibitor and placebo group from baseline to year 1?</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td><strong>RQ5-5</strong></td>
<td>Same procedure; year 1 $\rightarrow$ year 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>RQ5-8</strong></td>
<td>Same procedure; year 2 $\rightarrow$ year 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>RQ5-10</strong></td>
<td>Same procedure; year 3 $\rightarrow$ year 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ #</td>
<td>Research question</td>
<td>Hypothesis</td>
<td>Test and significance</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disability evaluation for the recurrent stroke population, cross-sectional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ6-1</td>
<td>Is there a significant difference in Categorized Barthel at the first year of recurrent stroke between active and placebo ACE inhibitor intervention groups when patient experienced recurrent stroke?</td>
<td>Ho: There is no difference in Categorized Barthel between ACE inhibitor and placebo groups at the first year of recurrent stroke. Ha: There is a difference in Barthel Index between ACE inhibitor and placebo groups at the first year of recurrent stroke.</td>
<td>Kruskal-Wallis test ($\alpha = 0.05$)</td>
<td></td>
</tr>
<tr>
<td>RQ6-2</td>
<td>Same procedure applied for the second year after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ6-3</td>
<td>the third year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ6-4</td>
<td>the fourth year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disability evaluation for the recurrent stroke population, prognosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ7-1</td>
<td>For the subpopulation that had recurrent stroke - Based on the Categorized Barthel, is there a difference in the prognosis of disability between ACE inhibitor and placebo group between two time point: before and after the recurrent stroke?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ7-2</td>
<td>Same procedure applied for: from ‘first year after stroke’ to ‘second year after stroke’</td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>RQ7-3</td>
<td>from ‘second year after stroke’ to ‘third year after stroke’</td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>RQ7-4</td>
<td>From ‘third year after stroke’ to ‘fourth year after stroke’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ #</td>
<td>Research question</td>
<td>Hypothesis</td>
<td>Test, and significance</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>RQ8-1</td>
<td>Effectiveness of intervention in terms of disability outcome&lt;br&gt;What is the integrated benefit of ACEI (placebo) treatment compared to placebo (ACEI) treatment in terms of utility considering four year disability and transitions of disability?</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>RQ8-2</td>
<td>For the recurrent stroke victims, what is the integrated benefit of ACEI (placebo) treatment compared to placebo (ACEI) treatment in terms of utility considering four year disability and transitions of disability?</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 5
RESULTS

The purpose of this study was to develop a methodology to evaluate stroke outcomes considering residual disability among stroke survivors. This methodology was used to examine disability outcomes and prognoses in a sample population enrolled in a multinational clinical trial, PROGRESS. In this chapter, results for the research questions are described below.

Aim 1. Disability Stage Development

The relationship between two instruments - the activities of daily living (BI) and the global disability measure (MRS) was the focus of disability stage development. The unit of analysis was defined by each pair of observations on the ‘BI and the MRS’. The study sample included 1,836 observations for 459 subjects. However, due to attrition, only 1,680 records were available for analysis. The reasons for attrition included death, moving into other state, withdrawal, and refusal. Details of missing and valid sample sizes for each month are listed in Table 5.1. Proportions of missing data were calculated based on the available sample sizes. Overall, the number of missing was minimal, 0.24% for the MRS and BI pairs. <Table 5.1>

Even though the loss increases over time, this should not be considered a potential bias factor, because the focus of this analysis is on the relationship between the instruments and not on the external validity of the instrument findings.
Table 5.1. Missing data for each month

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>freq</th>
<th>freq</th>
<th>freq</th>
<th>freq</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>expired</td>
<td>0</td>
<td>6</td>
<td>1.31</td>
<td>18</td>
<td>3.92</td>
<td>32</td>
<td>6.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>withdraw</td>
<td>0</td>
<td>3</td>
<td>0.65</td>
<td>4</td>
<td>0.87</td>
<td>5</td>
<td>1.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moved</td>
<td>0</td>
<td>3</td>
<td>0.65</td>
<td>5</td>
<td>1.09</td>
<td>12</td>
<td>2.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>refused</td>
<td>0</td>
<td>7</td>
<td>1.53</td>
<td>21</td>
<td>4.58</td>
<td>27</td>
<td>5.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other misc reasons</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>7</td>
<td>1.53</td>
<td>6</td>
<td>1.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>available pt record</td>
<td>459</td>
<td>440</td>
<td>95.86</td>
<td>404</td>
<td>88.02</td>
<td>377</td>
<td>82.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total no of patients</td>
<td>459</td>
<td>459</td>
<td>100</td>
<td>459</td>
<td>100</td>
<td>459</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of MRS-BI pairs available</td>
<td>459</td>
<td>439</td>
<td>99.77</td>
<td>402</td>
<td>99.50</td>
<td>375</td>
<td>99.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
<td>freq</td>
</tr>
</tbody>
</table>

Frequency distribution: Figure 5.1 illustrates the frequency distribution of BI scores compared to each MRS in 1,675 observations. It shows the mean, median, inter-quartile range, 5th and 95th percentile, minimum and maximum of the BI. In this illustration, ceiling effects are observed for BI scores as compared to the MRS. The BI scores did not differentiate disability well in higher ADL levels, which correspond to MRS 0, 1, and 2.

Correlation Coefficients: Correlations were examined between the BI and MRS. Spearman correlation coefficients calculated were -0.8856 (p<0.0001) between BI and MRS.

Kruskal-Wallis and Multiple comparison procedure- Dwass, Steel, Critchlow-Fligner: The Kruskal-Wallis tests were applied to determine whether there was a statistically significant difference (p<0.05) in mean scores of BI among MRS levels (Chisq=1338.29, df=5, P<0.0001). Kruskal-Wallis mean score for BI for each level of MRS were expected to be highest in MRS0, and lowest in MRS5: MRS0 > MRS1 > MRS2 >
MRS3 > MRS4 > MRS5. MRS0 and MRS1 did not statistically significant difference
and the actual order of the Kruskal-Wallis mean order scores was MRS1 > MRS0 >
MRS2 > MRS3 > MRS4 > MRS5.

Figure 5.1. Distribution of Barthel Index score for each Modified Rankin Scale level

Multiple comparison tests (Dwass, Steel, Critchlow-Fligner) were performed as a
follow-up to the Kruskal-Wallis tests. The BI did not differentiate MRS1 and MRS0, nor
MRS0 and MRS2 <Table 5.2>. The Kruskal-Wallis and follow-up multiple comparison
test can be summarized as below, where an underline indicates that the pair is not
significantly different:
Barthel Index: \( \text{MRS1} > \text{MRS0} > \text{MRS2} > \text{MRS3} > \text{MRS4} > \text{MRS5} \)

Table 5.2. Result of Kruskal-Wallis tests and Pairwise Comparisons (Dwass, Steel, Critchlow-Fligner)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Mean Order Score</th>
<th>Differences, (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRS0 vs. MRS1</td>
<td>-78.35 (p = 0.5136)</td>
<td></td>
</tr>
<tr>
<td>MRS0 vs. MRS2</td>
<td>57.52 (p = 0.5424)</td>
<td></td>
</tr>
<tr>
<td>MRS0 vs. MRS3</td>
<td>443.88*</td>
<td></td>
</tr>
<tr>
<td>MRS0 vs. MRS4</td>
<td>953.34*</td>
<td></td>
</tr>
<tr>
<td>MRS0 vs. MRS5</td>
<td>1240.76*</td>
<td></td>
</tr>
<tr>
<td>MRS1 vs. MRS2</td>
<td>135.88*</td>
<td></td>
</tr>
<tr>
<td>MRS1 vs. MRS3</td>
<td>522.23*</td>
<td></td>
</tr>
<tr>
<td>MRS1 vs. MRS4</td>
<td>1031.70*</td>
<td></td>
</tr>
<tr>
<td>MRS1 vs. MRS5</td>
<td>1319.11*</td>
<td></td>
</tr>
<tr>
<td>MRS2 vs. MRS3</td>
<td>386.35*</td>
<td></td>
</tr>
<tr>
<td>MRS2 vs. MRS4</td>
<td>895.82*</td>
<td></td>
</tr>
<tr>
<td>MRS2 vs. MRS5</td>
<td>1183.24*</td>
<td></td>
</tr>
<tr>
<td>MRS3 vs. MRS4</td>
<td>509.47*</td>
<td></td>
</tr>
<tr>
<td>MRS3 vs. MRS5</td>
<td>796.88*</td>
<td></td>
</tr>
<tr>
<td>MRS4 vs. MRS5</td>
<td>287.42*</td>
<td></td>
</tr>
<tr>
<td>All levels</td>
<td>KW test statistic = 1338.29*</td>
<td></td>
</tr>
</tbody>
</table>

* p-value <0.0001

KW = Kruskal Wallis

**Polytomous Logistic Regression Model - Model Appropriateness and Probabilistic distribution:** The probability distributions of MRS given the BI were derived using a polytomous logistic regression analysis method.\(^{140}\) The final model is selected by considering the model fit diagnostics.

The model is stated as:

\[
\text{logit} (\text{MRS} < i) = \alpha + \beta \times X
\]

MRS: \(i = 0, 1, 2, 3, 4, \text{and} \ 5\)

\(X = 0 – 100\) for BI score
\[ \alpha = \text{intercept} \]

\[ \beta = \text{estimate from polytomous logistic regression analysis} \]

\[
\text{Probability (MRS < i)} = \frac{e^{(\alpha + \beta X)}}{1 + e^{(\alpha + \beta X)}}
\]

Defining six levels for the MRS was not appropriate in the polytomous logistic model. Based on the model fit diagnostics, the BI score cannot differentiate six different levels of MRS, but is appropriate for five levels in the MRS. These are MRS 5, 4, 3, 2, and the collapsed level of MRS0 and MRS1 (MRS(0,1)).

The first graph of the Figure 5.2 shows the BI score distribution for five levels. Although a five level model was statistically appropriate, MRS(0,1) was completely included in the MRS2 probability distribution line, so no differentiation between the MRS2 and MRS(0,1) can be observed. The second graph in Figure 5.2 illustrates four level MRS-BI model: MRS(0,1,2), MRS3, MRS4, and MRS5. A four level MRS- BI model differentiates individual levels.

Categorization of Barthel Index: Based on the result of the polytomous logistic regression analysis, cutoffs in the BI were determined. Ideal cutoffs were defined as the corresponding scores at intersections of probabilistic distributions for two adjacent probability lines, which mean that these scores have an equal 50% probability of being located in either of two adjacent MRS levels. The ideal cutoff points, however, do not represent the real BI score because they are ideal values generated by the probability density function based on logistic regression estimates. Several scores around the ideal cutoffs were selected as potential cutoffs, and the combinations of potential cutoffs were
Figure 5.2. Probability Distribution of Modified Rankin Scale (MRS) given the Barthel Index Score
Figure 5.3. Probability Distribution of Modified Rankin Scale (MRS) given Barthel Index scores for each wave

Each colored line presents the probabilistic distribution of scores using corresponding time point data only. The black lines show the probabilistic distribution of the aggregated data.
selected to be mutually exclusive and exhaustive. Among combinations of potential
cutoffs, the one set minimizing the false positive response rate was selected for the BI
score. The false positive rate was minimized at 21.6% for the categorization scheme: C-
BI5 is $0 \leq BI < 15$, C-BI4 is $15 \leq BI < 70$, C-BI3 is $70 \leq BI < 95$, and C-BI1 is $95 \leq BI \leq 100$. With this categorization scheme, 603, 461, 484, and 128 records were categorized
to MRS(0,1,2), MRS3, MRS4 and MRS5 respectively in comparison to 606, 487, 459
and 127 from the MRS.

Time influence on Categorization scheme: The data from four waves were
collapsed to increase the sample size and obtain more robust analytical results. In order
to verify whether the categorization schemes behaved differently for each wave,
probability density functions were generated and examined for each time point. Figure
5.3 illustrates the probability distribution of each MRS level given BI score for baseline,
month 1, month 3, and month 6, respectively. Even when each wave’s data were
separated for logistic regression, the distribution presented similar trend and cutoff
points. <Figure 5.3>.

**Summary of Aim 1**

The purpose of aim 1 was to develop a categorization scheme for an ordinal ADL
measure, the Barthel Index. The Modified Rankin Scale, a global disability measure was
used as comparator. Four disability categories from BI were identified: $0 \leq BI < 15$,
$15 \leq BI < 70$, $70 \leq BI < 95$, and $95 \leq BI \leq 100$, and will be referred to in the following as
C-BI 1, 3, 4 and 5. These are comparable to MRS (0,1,2), MRS3, MRS4, and MRS5.
Definition of each level of C-BI is: C-BI1, Less than slight disability; unable to carry out
all previous activities but able to look after one’s own affairs without assistance; C-BI3,
Moderate disability requiring some help, but able to walk without assistance; C-BI4,
Moderate severe disability; Unable to walk without assistance and unable to attend to
own bodily needs without assistance; C-BI5, Severe disability; bedridden, incontinent,
and requiring constant nursing care and attention.

<table>
<thead>
<tr>
<th>rMRS</th>
<th>Modified Rankin Scale (MRS)</th>
<th>Barthel Index</th>
<th>Categorized BI (C-BI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MRS0</td>
<td>95 ≤ BI ≤ 100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MRS1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MRS3</td>
<td>70 ≤ BI &lt; 95</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>MRS4</td>
<td>15 ≤ BI &lt; 70</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>MRS5</td>
<td>0 ≤ BI &lt; 15</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 5.4. Relationship between Modified Rankin Scale and Barthel Index, and
categorized measures

Table 5.3. Result Summary of Research Question 1

<table>
<thead>
<tr>
<th>RQ #</th>
<th>Research question</th>
<th>Hypothesis</th>
<th>Test, and significance</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RQ1</td>
<td>What are the cut-off points in the Barthel index that match with the Modified Rankin Scale?</td>
<td>n/a</td>
<td>Logistic regression</td>
<td>Four disability levels were identified; C-BI1 ↔ 0≤BI≤15 C-BI3 ↔ 15≤BI≤70 C-BI4 ↔ 70≤BI≤95 C-BI5 ↔ 95≤BI≤100</td>
</tr>
</tbody>
</table>

**Aim 2. Utility Development**

Aim 2 is organized to develop utility estimates for individual disability levels. To do so, first, Time-Trade Off (TTO or expressed as YRSLIVE) score distributions were examined in the KCSS data. Second, correlations between employed measures: the
Barthel Index (BI), Categorized Barthel Index (C-BI), Modified Rankin Scale (MRS), reduced Modified Rankin Scale (rMRS), and TTO were examined. Third, Kruskal-Wallis analysis of variance tests were applied to examine if there were statistically significant differences in TTO among disability levels.

Time-Trade Off distribution: baseline, 1, 3, and 6 month post-stroke:

Figure 5.5 illustrates the TTO distribution at baseline, 1, 3, and 6 month post-stroke for the KCSS cohort. TTO scores distributions do not seem to be normally distributed, and a large proportion of patients reported that current health state with disability are equivalent to perfect health. For example, in the baseline, 1 month, 3 month, and 6 month measure, 24%, 33%, 36%, and 38% of patients reported that their current health has the same value as perfect health. Descriptive statistics and correlation coefficients are presented in table 5.4.

Categorization and correlations between employed measures after categorization: BI and MRS Scale were manipulated and four disability groups were categorized in the aim 1. Based on the categorization scheme, new variables, rMRS and C-BI were created. Correlations were examined between TTO and BI, TTO and C-BI, TTO and MRS, and TTO and rMRS. It appears that by categorizing established instruments, BI and MRS, information in BI and MRS is lost. Therefore, it is not unusual that the strength of the correlations is attenuated.

As reported in the results in table 5.4, the strength of the correlation of disability measures with TTO was consistently attenuated. However, the degree of attenuation was
small: that is, 3.6% (0.338 → 0.326), and 6% (0.345 → 0.324) decreases in correlations were observed as the result of the categorization.

Left above, baseline (n=256); right above, 1 month (n=274); left below, 3 month (n=259); right below, 6 month (n=240). YRSLIVE = the number of years with current health that the patient is willing to trade in for the perfect health.

Figure 5.5. TTO value distribution at baseline, 1, 3, and 6 month post-stroke.

The ultimate purpose of Aim 2 was to develop the utility estimates for disability levels, C-BI. For example, C-BI levels can be matched with TTO value X with range (or inter-quartile range) of (A, B).
Table 5.4. Correlations between employed measures: the Barthel Index, the Categorized Barthel Index, the Modified Rankin Scale, the reduced Modified Rankin Scale, and the Time-Trade Off Utilities (TTO) for the individual disability level:

Utilities (TTO) for the individual disability level:

One important assumption in developing the estimates was that the patient’s perception of their disability was not changed by a time factor, or maturation process. For example, stroke patients might develop coping strategies over time after the stroke event, and adapt or develop a coping with their new health condition. In this case, it is possible that the patient may perceive his/her utility as higher than that of before, even though their disability level or physical functioning level has not changed. Vise versa, if the patient feels hopeless or depressed about his/her new condition, this person may report decreased utility even though the disability or functioning level did not change. Due to the nature of the utility, a response shift over time is very possible. Even though this dissertation does not focus on response shift, it is important to be aware of a possible serious response shift.
If patients report significantly different utilities for level 1 disability in terms of time since stroke event, utility estimate should be examined and assigned for each time point, instead of assigning one universal utility estimate for a certain disability level regardless of time. Thus, before utility estimates were produced for C-BI levels, in the next subsection, an examination for systematic or significant differences in patient’s report of TTO across baseline, month 1, month 3, and month 6 was performed. Then in the following subsection, the TTO estimate for individual disability level was determined.

Patient perception on TTO over time: baseline to six month:

TTO scores for the same disability level extracted from the baseline, month 1, month 3, and month 6 were analyzed using Kruskal-Wallis analysis of variance test.

TTO data were descriptively examined and the distribution was reported in table 5.5. Table 5.6 shows four sets of comparisons. The numbers in the cells indicate the sample size; red and blue colors represent the number of cases defined by the rMRS, and C-BI respectively. Except the most disabled group that is level 5, the Kruskal-Wallis tests were performed with adequate sample size.

The result of Kruskal-Wallis ANOVA, at significance level 0.05, showed that patient’s TTO was not significantly different across baseline, 1, 3, and 6 month time points within disability level except level 5 defined by C-BI. However, considering the extremely small sample size (n= 16, 7, 2, and 1 for baseline, month 1, month 3, and month 6 respectively), further study is necessary to determine whether patients’ TTO are significantly different when the patients are severely disabled. (Table 5.7.)
Table 5.5. Descriptive information, TTO distribution

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>27 81 132 16</td>
<td>124 89 54 7</td>
<td>148 78 31 2</td>
<td>162 52 25 1</td>
</tr>
<tr>
<td>Mean</td>
<td>7.225 7.122 5.91 1.974</td>
<td>7.909 7.097 5.917 5.512</td>
<td>8.292 6.796 5.333 0.083</td>
<td>8.062 6.441 5.666 0.083</td>
</tr>
<tr>
<td>Median</td>
<td>8 9 7.25 1</td>
<td>9 8 7.5 6</td>
<td>9.5 7.5 5.5 0.083</td>
<td>9 7.5 6 0.083</td>
</tr>
<tr>
<td>Mode</td>
<td>10 10 9 0.083</td>
<td>10 10 10 3</td>
<td>10 10 7.5 0.083</td>
<td>10 10 8 0.083</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantile</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>10 10 10 8</td>
<td>10 10 10 10</td>
<td>10 10 10 0.83</td>
<td>10 10 10 0.83</td>
</tr>
<tr>
<td>99%</td>
<td>10 10 10 8</td>
<td>10 10 10 10</td>
<td>10 10 10 0.83</td>
<td>10 10 10 0.83</td>
</tr>
<tr>
<td>95%</td>
<td>10 10 10 8</td>
<td>10 10 10 10</td>
<td>10 10 10 0.83</td>
<td>10 10 10 0.83</td>
</tr>
<tr>
<td>90%</td>
<td>10 10 10 8</td>
<td>10 10 10 10</td>
<td>10 10 10 0.83</td>
<td>10 10 10 0.83</td>
</tr>
<tr>
<td>75% Q3</td>
<td>10 10 9 2.75</td>
<td>10 10 10 9</td>
<td>10 10 7.5 0.083</td>
<td>10 9 8 0.083</td>
</tr>
<tr>
<td>Median</td>
<td>8 9 7.25 1</td>
<td>9 8 7.5 6</td>
<td>9.5 7.5 5.5 0.083</td>
<td>9 7.5 6 0.083</td>
</tr>
<tr>
<td>25% Q1</td>
<td>5 5 3 0.083</td>
<td>6.5 6 2 3</td>
<td>7.5 5.5 2 0.083</td>
<td>7.5 4.75 3 0.083</td>
</tr>
<tr>
<td>10%</td>
<td>1 1 0.083 0.083</td>
<td>3 0.5 0.083 0.083</td>
<td>5 0.5 0.083 0.083</td>
<td>4 1 1.5 0.083</td>
</tr>
<tr>
<td>5%</td>
<td>0.5 0.083 0.083 0.083</td>
<td>1 0.083 0.083 0.083</td>
<td>3 0.083 0.083 0.083</td>
<td>1 0.083 0.083 0.083</td>
</tr>
<tr>
<td>1%</td>
<td>0.083 0.083 0.083 0.083</td>
<td>0.083 0.083 0.083 0.083</td>
<td>0.083 0.083 0.083 0.083</td>
<td>0.083 0.083 0.083 0.083</td>
</tr>
<tr>
<td>Min</td>
<td>0.083 0.083 0.083 0.083</td>
<td>0.083 0.083 0.083 0.083</td>
<td>0.083 0.083 0.083 0.083</td>
<td>0.083 0.083 0.083 0.083</td>
</tr>
</tbody>
</table>
Table 5.6. Comparison of disability levels for different time points

<table>
<thead>
<tr>
<th>Time point</th>
<th>baseline</th>
<th>month 1</th>
<th>month 3</th>
<th>month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>rMRS1, C-BI1, or C-BI1</td>
<td>46, 27</td>
<td>116, 124</td>
<td>148, 148</td>
<td>159, 162</td>
</tr>
<tr>
<td>rMRS3, C-BI3</td>
<td>70, 81</td>
<td>94, 89</td>
<td>77, 78</td>
<td>60, 52</td>
</tr>
<tr>
<td>rMRS4, C-BI4</td>
<td>120, 132</td>
<td>56, 54</td>
<td>32, 31</td>
<td>18, 25</td>
</tr>
<tr>
<td>rMRS5, C-BI5</td>
<td>20, 16</td>
<td>7, 7</td>
<td>2, 2</td>
<td>6, 1</td>
</tr>
</tbody>
</table>

Numbers in the cell indicate the sample size for relevant cases. Red: reduced Modified Rankin Scale; Blue: Categorized Barthel Index.

Table 5.7. Kruskal-Wallis test of TTO for four different time points: baseline, month 1, month 3, and month 6 (df = 3)

<table>
<thead>
<tr>
<th>Categorized Barthel Index</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruskal-Wallis statistic</td>
<td>1.8567</td>
<td>3.6402</td>
<td>1.2517</td>
<td>7.8422</td>
</tr>
<tr>
<td>p value</td>
<td>0.6027</td>
<td>0.303</td>
<td>0.7406</td>
<td>0.0494</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>reduced Modified Rankin Scale</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruskal-Wallis statistic</td>
<td>1.0506</td>
<td>0.7343</td>
<td>2.9286</td>
<td>5.606</td>
</tr>
<tr>
<td>p value</td>
<td>0.789</td>
<td>0.8651</td>
<td>0.4028</td>
<td>0.1324</td>
</tr>
</tbody>
</table>

TTO estimate as utility for each disability level:

TTO distribution was examined using boxplots displayed in figure 5.6 and 5.7, also corresponding estimates were displayed.

Mean, median, and quartiles were presented in the figures 5.6 and 5.7. TTO distribution does not follow normality as shown in figure 5.5, the median may be a better estimate to represent the results.
When stroke patients have severe disability, they are more willing to trade off life for perfect health. For example, patients with level 1 in C-BI were willing to trade 10 years of their life with 9 years of perfect health, and patients with level 5 in Categorized BI were willing to trade their 10 years of life with 1 year of perfect health.

Statistical difference in TTO estimate as utility among different levels of disability:

There were significant differences in TTO scores among four different levels of disability, and the Kruskal-Wallis statistics, p-value and mean order scores are summarized in Table 5.8.

To identify the location that the statistical differences occurred, pair wise comparison, the Dwass-Steel-Chritchlow-Fligner tests were performed using StatsDirect (Ver. 2.3.7.). Table 5.9 summarizes the result of pair wise comparison. All the pairs showed that TTO estimates are significantly different among the four disability levels.

**Summary of Aim 2:**

C-BI and rMRS were derived from BI and MRS. Lost information was observed but it appeared to be minimal in terms of correlation coefficients. Reduction in correlation coefficients was less than 7%, and statistical significance was maintained. No response shift was detected in TTO measured in stroke patients within 6 month post-stroke at four different time points: baseline, 1, 3, and 6 months. The TTO estimates for C-BI level 1, 3, 4, and 5 were 9, 8, 7, and 1. In other words, the utility for C-BI level 1 was 0.9, and the utility for C-BI level 5 was 0.1.
Figure 5.6. TTO distribution, mean, median, and quartiles by Categorized Barthel
Table 5.7: TTO distribution, mean, median, and quartiles by reduced Modified Rankin Scale

<table>
<thead>
<tr>
<th>Quantile</th>
<th>rMRS1</th>
<th>rMRS3</th>
<th>rMRS4</th>
<th>rMRS5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>469</td>
<td>301</td>
<td>226</td>
<td>32</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>8.005</td>
<td>7.006</td>
<td>5.687</td>
<td>3.156</td>
</tr>
<tr>
<td><strong>Std Deviation</strong></td>
<td>2.719</td>
<td>3.224</td>
<td>3.551</td>
<td>3.516</td>
</tr>
<tr>
<td><strong>Variance</strong></td>
<td>7.394</td>
<td>10.395</td>
<td>12.607</td>
<td>12.365</td>
</tr>
<tr>
<td><strong>Mode</strong></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0.083</td>
</tr>
<tr>
<td><strong>Quantile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%, Max</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>99%</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>95%</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>90%</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>75%, Q3</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>6.75</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>1.75</td>
</tr>
<tr>
<td>25%, Q1</td>
<td>7</td>
<td>5.5</td>
<td>2</td>
<td>0.083</td>
</tr>
<tr>
<td>10%</td>
<td>4</td>
<td>1</td>
<td>0.083</td>
<td>0.083</td>
</tr>
<tr>
<td>5%</td>
<td>1</td>
<td>0.083</td>
<td>0.083</td>
<td>0.083</td>
</tr>
<tr>
<td>1%</td>
<td>0.083</td>
<td>0.083</td>
<td>0.083</td>
<td>0.083</td>
</tr>
<tr>
<td>0%, Min</td>
<td>0.083</td>
<td>0.083</td>
<td>0.083</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Figure 5.7. TTO distribution, mean, median, and quartiles by reduced Modified Rankin Scale
Table 5.8. Statistical difference in TTO among four different disability levels

<table>
<thead>
<tr>
<th>disability levels</th>
<th>C-BI</th>
<th></th>
<th>rMRS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>KW mean order scores</td>
<td>N</td>
<td>KW mean order scores</td>
</tr>
<tr>
<td>1</td>
<td>461</td>
<td>606.54</td>
<td>469</td>
<td>601.72</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>497.13</td>
<td>301</td>
<td>503.44</td>
</tr>
<tr>
<td>4</td>
<td>242</td>
<td>397.33</td>
<td>226</td>
<td>389.69</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>193.4</td>
<td>32</td>
<td>221.77</td>
</tr>
</tbody>
</table>

KW statistic (p value) 117.61 (<0.0001) 116.27 (<0.0001)

KW = Kruskal-Wallis

Table 5.9. Pair wise comparisons

<table>
<thead>
<tr>
<th>Pairs</th>
<th>Mean Difference, (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YRSLIVE for rMRS1 – YRSLIVE for rMRS3</td>
<td>98.28 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for rMRS1 – YRSLIVE for rMRS4</td>
<td>212.03 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for rMRS1 – YRSLIVE for rMRS5</td>
<td>379.95 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for rMRS3 – YRSLIVE for rMRS4</td>
<td>113.75 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for rMRS3 – YRSLIVE for rMRS5</td>
<td>281.67 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for rMRS4 – YRSLIVE for rMRS5</td>
<td>167.92 (0.0028)</td>
</tr>
<tr>
<td>YRSLIVE for CBI1 – YRSLIVE for CBI3</td>
<td>109.31 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for CBI1 – YRSLIVE for CBI4</td>
<td>209.21 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for CBI1 – YRSLIVE for CBI5</td>
<td>413.14 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for CBI3 – YRSLIVE for CBI4</td>
<td>99.8 (0.0004)</td>
</tr>
<tr>
<td>YRSLIVE for CBI3 – YRSLIVE for CBI5</td>
<td>303.73 (&lt; 0.0001)</td>
</tr>
<tr>
<td>YRSLIVE for CBI4 – YRSLIVE for CBI5</td>
<td>203.93 (0.0005)</td>
</tr>
</tbody>
</table>

Level 1, 3, 4, and 5 in C-BI were significantly different in terms of the TTO scores.

C-BI1, Less than slight disability; unable to carry out all previous activities but able to look after own affairs without assistance; C-BI3, Moderate disability requiring some help, but able to walk without assistance; C-BI4, Moderate severe disability; Unable to walk without assistance and unable to attend to own bodily needs without assistance; C-BI5, Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.
Table 5.10. Utility estimates for C-BI disability levels.

<table>
<thead>
<tr>
<th></th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>8.046</td>
<td>6.912</td>
<td>5.812</td>
<td>2.708</td>
</tr>
<tr>
<td>Std Deviation</td>
<td>2.697</td>
<td>3.285</td>
<td>3.511</td>
<td>3.317</td>
</tr>
</tbody>
</table>

Quantile

- 100% Max: 10 10 10 10
- 95%: 10 10 10 9
- 90%: 10 10 10 8
- 75% Q3: 10 10 9 5
- 50% Median: 9 8 7 1
- 25% Q1: 7.5 5 2.5 0.083
- 10%: 4 0.5 0.083 0.083
- 5%: 1 0.083 0.083 0.083
- 0% Min: 0.083 0.083 0.083 0.083

Aim 3. Disability Evaluation & Transition Probability

Disability prognosis was evaluated in the two treatment groups: active ACE inhibitor and placebo. Categorized Barthel Index (C-BI) was used to evaluate the patient’s outcome in terms of disability.

Before evaluating disability in the sample population, missing percents in each group were compared in table 5.12 to see if there is any potential bias. There was no indication of bias in terms of missing rates in two groups.

Patient outcomes in terms of Categorized Barthel Index (C-BI): Comparison in active and placebo treatment groups:

Patient’s disability was categorized and disability outcomes were compared between active and placebo groups. The results are summarized in table 5.13. Up to the end of the first year after treatment started, the two treatment groups did not present statistical differences in C-BI. By the end of the second year, however, the two groups started to present difference in C-BI. During the third and fourth year, C-BI showed statistical differences; placebo treatment group tend to have more people in the severe disability range, C-BI 3, 4, and 5, than those in the active treatment group.
Table 5.11. Result Summary of Research Question 2 and 3

<table>
<thead>
<tr>
<th>RQ #</th>
<th>Research question</th>
<th>Hypothesis</th>
<th>Test, and significance</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>Is there a correlation between the BI and TTO?</td>
<td>Ho: There is no correlation between time-trade off and the Barthel Index. Ha: There is a correlation between time-trade off and the Barthel Index.</td>
<td>Spearman correlation ($\alpha = 0.05$)</td>
<td>Reject Ho; There is a significant correlation. (See Table 5.4.)</td>
</tr>
<tr>
<td>2-2</td>
<td>Is there a correlation between the CBI and TTO?</td>
<td>Ho: There is no correlation between time-trade off and the Categorized Barthel. Ha: There is a correlation between time-trade off and the Categorized Barthel.</td>
<td>Spearman correlation ($\alpha = 0.05$)</td>
<td>Reject Ho; There is a significant correlation. (See Table 5.4.)</td>
</tr>
<tr>
<td>2-3</td>
<td>Is there a difference in TTO among the levels defined by C-BI?</td>
<td>Ho: There is no difference in time-trade off among the disability levels defined by Categorized Barthel. Ha: There is a difference in time-trade off among the disability levels defined by Categorized Barthel.</td>
<td>Kruskal Wallis ($\alpha = 0.05$)</td>
<td>Reject Ho; There is a significant difference in TTO among four levels of C-BI. (See Table 5.7)</td>
</tr>
<tr>
<td>3-1</td>
<td>Is there a correlation between the MRS and TTO?</td>
<td>Ho: There is no correlation between time-trade off and the MRS. Ha: There is a correlation between time-trade off and the MRS.</td>
<td>Spearman correlation ($\alpha = 0.05$)</td>
<td>Reject Ho; There is a significant correlation. (See Table 5.4.)</td>
</tr>
<tr>
<td>3-2</td>
<td>Is there a correlation between the rMRS and TTO?</td>
<td>Ho: There is no correlation between time-trade off and the rMRS. Ha: There is a correlation between time-trade off and the rMRS.</td>
<td>Spearman correlation ($\alpha = 0.05$)</td>
<td>Reject Ho; There is a significant correlation. (See Table 5.4.)</td>
</tr>
<tr>
<td>3-3</td>
<td>Is there a difference in TTO among the levels defined by rMRS?</td>
<td>Ho: There is no difference in time-trade off among the disability levels defined by rMRS. Ha: There is a difference in time-trade off among the disability levels defined by rMRS.</td>
<td>Kruskal Wallis ($\alpha = 0.05$)</td>
<td>Reject Ho; There is a significant difference in TTO among four levels of rMRS. (See Table 5.7)</td>
</tr>
</tbody>
</table>
Table 5.12. Missing data over four year time period

<table>
<thead>
<tr>
<th>time point</th>
<th>treatment</th>
<th>number of observation</th>
<th>death frequency</th>
<th>death %</th>
<th>missing, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomization</td>
<td>Active</td>
<td>3047</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3052</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>baseline</td>
<td>Active</td>
<td>3043</td>
<td>N/A</td>
<td>N/A</td>
<td>0.13%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3050</td>
<td>N/A</td>
<td>N/A</td>
<td>0.07%</td>
</tr>
<tr>
<td>~1 year</td>
<td>Active</td>
<td>2842</td>
<td>51</td>
<td>1.67%</td>
<td>5.05%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2861</td>
<td>58</td>
<td>1.90%</td>
<td>4.36%</td>
</tr>
<tr>
<td>~2 year</td>
<td>Active</td>
<td>2747</td>
<td>71</td>
<td>2.33%</td>
<td>7.52%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2747</td>
<td>74</td>
<td>2.42%</td>
<td>7.57%</td>
</tr>
<tr>
<td>~3 year</td>
<td>Active</td>
<td>2646</td>
<td>78</td>
<td>2.56%</td>
<td>10.60%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2653</td>
<td>79</td>
<td>2.59%</td>
<td>10.48%</td>
</tr>
<tr>
<td>~4 year</td>
<td>Active</td>
<td>2071</td>
<td>90</td>
<td>2.95%</td>
<td>29.08%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2064</td>
<td>90</td>
<td>2.95%</td>
<td>29.42%</td>
</tr>
<tr>
<td>total</td>
<td>Active</td>
<td>N/A</td>
<td>290</td>
<td>9.52%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>N/A</td>
<td>301</td>
<td>9.86%</td>
<td>N/A</td>
</tr>
<tr>
<td>~5 year</td>
<td>Active</td>
<td>58</td>
<td>15</td>
<td>0.49%</td>
<td>97.60%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>53</td>
<td>17</td>
<td>0.56%</td>
<td>97.71%</td>
</tr>
<tr>
<td>~6 year</td>
<td>Active</td>
<td>---</td>
<td>1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>---</td>
<td>1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>total</td>
<td>Active</td>
<td>N/A</td>
<td>306</td>
<td>10.04%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>N/A</td>
<td>319</td>
<td>10.45%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Death% = (death frequency/baseline number of observation) x 100
Missing% = ((baseline number of observation – death frequency) – number of observation of that year)/baseline number of observation x 100.

Disability Transition Probability:

Disability evaluation in stroke patients was illustrated using C-BI. One of the weaknesses identified in the previous section is that mortality was not included. Ignoring mortality outcome in evaluating survivor’s disability may facilitate several competing hypotheses. For example, if the severely disabled people might have died early in active treatment group compared with the patients in the placebo group, disability outcome might look better in the active group, but it may not be correct conclusion to evaluate treatment effectiveness. Thus, even though the focus is disability evaluation among
survivors, it is important to carry the mortality information in the evaluation of the study population.

Table 5.13. Kruskal-Wallis test: Categorized Barthel Index outcome in active and placebo treatment groups

<table>
<thead>
<tr>
<th>TREAT</th>
<th>N</th>
<th>Frequency of C-BI (%)</th>
<th>Kruskal-Wallis test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>3047</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>Placebo</td>
<td>3052</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>2842</td>
<td>9</td>
<td>69</td>
</tr>
<tr>
<td>Placebo</td>
<td>2861</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>2747</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>Placebo</td>
<td>2747</td>
<td>18</td>
<td>80</td>
</tr>
<tr>
<td>Year 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>2646</td>
<td>7</td>
<td>79</td>
</tr>
<tr>
<td>Placebo</td>
<td>2653</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>Year 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>2071</td>
<td>8</td>
<td>66</td>
</tr>
<tr>
<td>Placebo</td>
<td>2064</td>
<td>18</td>
<td>71</td>
</tr>
</tbody>
</table>

To address this issue, first, the proportion of missing and death rates in each group were examined. Based on the PROGRESS investigator group’s report in Lancet, the death rate was not significantly different in two groups. As presented in the table 5.12, there is approximately a 0.34% difference in mortality between active and placebo groups.
The attrition in the two groups was evaluated after removing the death records. Table 5.12 shows that the rates of missing were not different in two groups, but between 3rd and 4th year, there was a large number of missing in the BI measure.

One year disability transition probabilities were identified for active and placebo treatment groups. Four probabilities for one year cycle: baseline vs. first year outcome, first year vs. second year, second year vs. third year, and the third year vs. the fourth year outcomes, were identified for possible transitions: CBI1 → CBI1, CBI1 → CBI3, CBI1 → CBI4, CBI1 → CBI5, CBI1 → death, CBI3 → CBI1, CBI3 → CBI3, CBI3 → CBI4, CBI3 → CBI5, CBI3 → death, CBI4 → CBI1, CBI4 → CBI3, CBI4 → CBI4, CBI4 → CBI5, CBI4 → death, CBI5 → CBI1, CBI5 → CBI3, CBI5 → CBI4, CBI5 → CBI5, and CBI5 → death. These transition probabilities were summarized in table 5.14a and b. The structure of the transition probability matrix was introduced in the methodology chapter, table 4.2. Since each transition has four different probabilities, the weighted average was calculated. Table 5.14a shows active treatment group’s transition probabilities, and table 5.14b shows placebo treatment group’s transition probabilities.

Summary of Aim 3:

Aim 3 has two research question sets, RQ 4s and RQ5s. Four research questions RQ4-1 to 4-4 examined yearly disability outcome in two groups with C-BI. Statistical significances were observed in the C-BI after second year throughout the fourth year.

RQ 5s were organized to develop transition probabilities in active and placebo treatment groups. The probability set was provided in table 5.14a and 5.14b for active
and placebo treatment groups respectively. The research question 4 and 5, test method and results are summarized in the table 5.15.

**Aim 4. Disability Evaluation & Transition Probability in Recurrent Stroke**

In the PROGRESS cohort, 727 recurrent strokes events were reported. In the active treatment group, there were 307 cases of recurrent strokes, and in the placebo treatment group, 420 cases were reported. Cumulative recurrent stroke frequencies are summarized in table 5.16. Approximately 10% of the active treatment group and 14% of the placebo treatment group had recurrent strokes during the study period.

Table 5.17 shows the frequency and proportion of death among the subjects who had recurrent stroke. Overall, 27% and 25% of the subjects who experienced recurrent stroke died in the same year in the active and the placebo group respectively.

Patient’s disability measures were collected at the planned follow-up dates: 1, 2, 3, and 4 year from the randomization date (index date). Thus, in order to address research question 6 adequately, data were reconstructed based on individual patient’s stroke event date and measurement date, for example, new variables such as ‘baseline for recurrent stroke event’, ‘first measure after recurrent event’, ‘second measure after recurrent event’, ‘third measure after recurrent event’, and ‘fourth measure after recurrent event’ were identified and assigned as new variables for the people who experienced recurrent stroke. <See figure 4.2>.

For example, if a patient had a recurrent stroke during the first year after randomization, this patient’s baseline for the recurrent stroke is equal to the actual baseline measure that the person had at the randomization point. Then the first measure
after recurrent stroke will be the 1-year point measure. In this manner second, third, and fourth disability measurement after the recurrent stroke was assigned.

If a patient had a recurrent stroke at 32 months after randomization, a 24-month point measure of disability is assigned as baseline for the recurrent stroke, 36-month measure as ‘first measure after recurrent stroke’, and 48-month measure as ‘second measure after recurrent stroke’. In this specific case, due to the data collection timeframe of PROGRESS, the third and fourth measure after the recurrent stroke could not be obtained. The frequencies of those variables are summarized in the table 5.18.

Categorized Barthel Index score after recurrent stroke in two treatment groups:

In this subsection, disability outcome in the two groups (ACE treatment versus placebo) were compared using categorized Barthel Index (C-BI). Table 5.19 summarized the disability outcome after recurrent stroke. There was no statistical difference detected using Kruskal-Wallis tests except the baseline measure for the recurrent stroke. Similar as above, this comparison might lead to a biased result due to a selection bias by not considering deceased subjects.

Disability transitions after recurrent stroke:

To include the missing data due to death, and attrition, disability transitions among the people who had recurrent stroke were examined and summarized in the table 5.20a and 5.20b. Due to the small sample size, the transition probability table for recurrent stroke could not be completed.

**Summary of Aim 4:**

In aim 4, disability after recurrent stroke in the active and placebo treatment population did not show any statistical difference in C-BI. Transitions of disability levels
were examined for the people who experienced recurrent stroke, but due to the small sample size the transition probability tables could not be completed. Table 5.21 presents the summary result for Aim 4.

**Aim 5. Disability Evaluation for Stroke Preventive Intervention**

In the previous four subsections, the three components in disability evaluation model were examined disability stages (Aim 1), utilities for each disability level (Aim 2), and transition probability (Aim 3). The key results, that is, the disability evaluation model parameters, are summarized in the table 5.22, and the complete model for active treatment group is presented in figure 5.8. Not all the probabilities could be listed. The placebo treatment group can be presented with the same structured model with the placebo group’s transition probabilities.

The current section is focused on population level utility differences between active and placebo treatment groups.

Based on the transition probabilities, morbidity and mortality outcomes in the active treatment cohort were calculated and displayed in figure 5.9a. The predicted frequency of each disability level and death are shown for one year interval transition probability sets, which are baseline → year 1, year 1 → year 2, year 2 → year 3, year 3 → year 4; and weighted transition probabilities produced from four sets of yearly transition probabilities. The actual frequencies of each category in the cohort at each cycle are also presented for each cycle for comparison to the predicted frequency. Figure 5.9b illustrates the placebo cohort behavior for four cycles.

Weighted transition probabilities were used and the ten year disability outcome for each treatment group was predicted. This dissertation focused on the comparison of treatment effectiveness between active and placebo groups, so a person’s life expectancy
was not considered. Two graphs in figure 5.10 illustrated the active and placebo treatment cohorts’ behavior separately for the ten years time window. Actual frequencies during the four years of data collection time period were presented with the predicted frequencies. Actual cohort information was collected during the four year study period, so predicting lines were used to project beyond the four-year time period.

Between year 3 and 4, large differences were observed in the C-BI1. As shown in table 5.13, and described in figure 5.9a and 5.9b, 4th year data had a large amount of missing data as compared to the previous years. Based on the major PROGRESS publication, 3,049 in active and 3,053 in placebo subject’s vital status were able to be retrieved at the scheduled end of the follow-up. It is not clear why this amount of missing data occurred especially for the Barthel Index measure.

In the data illustration in the figure 5.9a and 5.9b, it seemed a large number of subjects moved from C-BI1 to the missing category. However, it may be because C-BI1 carried the biggest weight among all groups, so simply C-BI1 category had biggest impact by the large number of missing records. Because of the large drop in the real frequency in C-BI1, the transition probabilities and prediction lines, apparently were influenced and moved down. It is uncertain how the prediction line and transition probability changes if the abnormally large number of missing records did not happen at the 4th year data collection point.

Figure 5.11 illustrated the predicted disability in the cohort of active and placebo treatment groups. Active treatment groups showed favorable disability outcomes and mortality: more people in C-BI1 and less in C-BI3 and death. For the C-BI 4, and C-BI 5, active and placebo groups, no difference was observed.
The utility outcome was calculated based on the predicted disability and presented in the table 5.23. The active treatment group presents slightly higher utilities compared to those in the placebo group.

**Summary of Aim 5:**

In aim 5, the effectiveness of active and placebo treatment in the population was compared in terms of disability and utility. Slightly better disability outcomes were observed in the active treatment compared to the placebo treatment. Research question 8-2 was not completed due to the lack of transition probability information after the recurrent stroke, and remains for the further research.
Table 5.14a. Transition probabilities for active treatment group

<table>
<thead>
<tr>
<th>Categories</th>
<th>Baseline --&gt; Year 1</th>
<th>Categories</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-BI1</td>
<td>C-BI3</td>
<td>C-BI4</td>
</tr>
<tr>
<td>C-BI1</td>
<td>0.9147</td>
<td>0.0137</td>
<td>0.0044</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.3986</td>
<td>0.4722</td>
<td>0.0397</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.1098</td>
<td>0.2073</td>
<td>0.5488</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.5000</td>
</tr>
<tr>
<td></td>
<td>0.7500</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2590</td>
<td>173</td>
<td>69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>Year 1 --&gt; Year 2</th>
<th>Categories</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-BI1</td>
<td>C-BI3</td>
<td>C-BI4</td>
</tr>
<tr>
<td>C-BI1</td>
<td>0.9340</td>
<td>0.0139</td>
<td>0.0031</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.1618</td>
<td>0.6994</td>
<td>0.0694</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0435</td>
<td>0.1159</td>
<td>0.7246</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.1250</td>
</tr>
<tr>
<td>missing</td>
<td>0.2875</td>
<td>0.0438</td>
<td>0.0188</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2496</td>
<td>172</td>
<td>74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>Year 2 --&gt; Year 3</th>
<th>Categories</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-BI1</td>
<td>C-BI3</td>
<td>C-BI4</td>
</tr>
<tr>
<td>C-BI1</td>
<td>0.9267</td>
<td>0.0184</td>
<td>0.0036</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.1163</td>
<td>0.7035</td>
<td>0.0523</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0000</td>
<td>0.0135</td>
<td>0.7703</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>missing</td>
<td>0.2772</td>
<td>0.0326</td>
<td>0.0217</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2384</td>
<td>174</td>
<td>79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>Year 3 --&gt; Year 4</th>
<th>Categories</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-BI1</td>
<td>C-BI3</td>
<td>C-BI4</td>
</tr>
<tr>
<td>C-BI1</td>
<td>0.7550</td>
<td>0.0159</td>
<td>0.0029</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.0805</td>
<td>0.5690</td>
<td>0.0690</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0000</td>
<td>0.1279</td>
<td>0.5696</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>missing</td>
<td>0.1932</td>
<td>0.0242</td>
<td>0.0097</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Total (N)</td>
<td>1854</td>
<td>143</td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>Weighted Average</th>
<th>Categories</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-BI1</td>
<td>C-BI3</td>
<td>C-BI4</td>
</tr>
<tr>
<td>C-BI1</td>
<td>0.8852</td>
<td>0.0154</td>
<td>0.0035</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.2101</td>
<td>0.5966</td>
<td>0.0558</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0395</td>
<td>0.0888</td>
<td>0.6480</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.1364</td>
</tr>
<tr>
<td>missing</td>
<td>0.2522</td>
<td>0.0325</td>
<td>0.0162</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
</tbody>
</table>
Table 5.14b. Transition probabilities for placebo treatment group

**Baseline --> Year 1**

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI1</th>
<th>C-BI3</th>
<th>C-BI4</th>
<th>C-BI5</th>
<th>missing</th>
<th>death</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI1</td>
<td>0.9123</td>
<td>0.0222</td>
<td>0.0056</td>
<td>0.0004</td>
<td>0.0422</td>
<td>0.0174</td>
<td>2702</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.3440</td>
<td>0.5400</td>
<td>0.0480</td>
<td>0.0000</td>
<td>0.0440</td>
<td>0.0240</td>
<td>250</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.1474</td>
<td>0.2000</td>
<td>0.5053</td>
<td>0.0211</td>
<td>0.0947</td>
<td>0.0316</td>
<td>95</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.2000</td>
<td>0.0000</td>
<td>0.4000</td>
<td>0.2000</td>
<td>0.2000</td>
<td>5</td>
</tr>
<tr>
<td>missing</td>
<td>0.5000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.5000</td>
<td>2</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
<td>0</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2566</td>
<td>215</td>
<td>75</td>
<td>5</td>
<td>135</td>
<td>58</td>
<td>3054</td>
</tr>
</tbody>
</table>

**Year 1 --> Year 2**

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI1</th>
<th>C-BI3</th>
<th>C-BI4</th>
<th>C-BI5</th>
<th>missing</th>
<th>death</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI1</td>
<td>0.9201</td>
<td>0.0218</td>
<td>0.0039</td>
<td>0.0016</td>
<td>0.0339</td>
<td>0.0187</td>
<td>2566</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.1349</td>
<td>0.7070</td>
<td>0.0791</td>
<td>0.0093</td>
<td>0.0326</td>
<td>0.0372</td>
<td>215</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0133</td>
<td>0.0533</td>
<td>0.7067</td>
<td>0.0667</td>
<td>0.0667</td>
<td>0.0933</td>
<td>75</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.8000</td>
<td>0.2000</td>
<td>0.0000</td>
<td>5</td>
</tr>
<tr>
<td>missing</td>
<td>0.3111</td>
<td>0.0296</td>
<td>0.0000</td>
<td>0.0222</td>
<td>0.5556</td>
<td>0.0815</td>
<td>135</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
<td>58</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2433</td>
<td>216</td>
<td>80</td>
<td>18</td>
<td>175</td>
<td>132</td>
<td>3054</td>
</tr>
</tbody>
</table>

**Year 2 --> Year 3**

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI1</th>
<th>C-BI3</th>
<th>C-BI4</th>
<th>C-BI5</th>
<th>missing</th>
<th>death</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI1</td>
<td>0.9277</td>
<td>0.0148</td>
<td>0.0056</td>
<td>0.0004</td>
<td>0.0337</td>
<td>0.0177</td>
<td>2433</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.1157</td>
<td>0.7176</td>
<td>0.0648</td>
<td>0.0046</td>
<td>0.0556</td>
<td>0.0417</td>
<td>216</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0125</td>
<td>0.0875</td>
<td>0.7500</td>
<td>0.0250</td>
<td>0.0500</td>
<td>0.0750</td>
<td>80</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0556</td>
<td>0.0000</td>
<td>0.0556</td>
<td>0.5000</td>
<td>0.0556</td>
<td>0.3333</td>
<td>18</td>
</tr>
<tr>
<td>missing</td>
<td>0.2914</td>
<td>0.0514</td>
<td>0.0286</td>
<td>0.0114</td>
<td>0.5314</td>
<td>0.0857</td>
<td>175</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
<td>132</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2335</td>
<td>207</td>
<td>94</td>
<td>15</td>
<td>192</td>
<td>211</td>
<td>3054</td>
</tr>
</tbody>
</table>

**Year 3 --> Year 4**

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI1</th>
<th>C-BI3</th>
<th>C-BI4</th>
<th>C-BI5</th>
<th>missing</th>
<th>death</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI1</td>
<td>0.7448</td>
<td>0.0184</td>
<td>0.0017</td>
<td>0.0013</td>
<td>0.2128</td>
<td>0.0210</td>
<td>2335</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.0560</td>
<td>0.6280</td>
<td>0.0483</td>
<td>0.0097</td>
<td>0.2029</td>
<td>0.0531</td>
<td>207</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0106</td>
<td>0.0319</td>
<td>0.5532</td>
<td>0.0426</td>
<td>0.2660</td>
<td>0.0957</td>
<td>94</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.5333</td>
<td>0.2000</td>
<td>0.2667</td>
<td>15</td>
</tr>
<tr>
<td>missing</td>
<td>0.2188</td>
<td>0.0260</td>
<td>0.0260</td>
<td>0.0052</td>
<td>0.6354</td>
<td>0.0885</td>
<td>192</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
<td>211</td>
</tr>
<tr>
<td>Total (N)</td>
<td>1794</td>
<td>181</td>
<td>71</td>
<td>18</td>
<td>689</td>
<td>301</td>
<td>3054</td>
</tr>
</tbody>
</table>

**Weighted Average**

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI1</th>
<th>C-BI3</th>
<th>C-BI4</th>
<th>C-BI5</th>
<th>missing</th>
<th>death</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI1</td>
<td>0.8791</td>
<td>0.0194</td>
<td>0.0043</td>
<td>0.0009</td>
<td>0.0777</td>
<td>0.0186</td>
</tr>
<tr>
<td>C-BI3</td>
<td>0.1712</td>
<td>0.6441</td>
<td>0.0597</td>
<td>0.0056</td>
<td>0.0811</td>
<td>0.0383</td>
</tr>
<tr>
<td>C-BI4</td>
<td>0.0494</td>
<td>0.0959</td>
<td>0.6192</td>
<td>0.0378</td>
<td>0.1250</td>
<td>0.0727</td>
</tr>
<tr>
<td>C-BI5</td>
<td>0.0233</td>
<td>0.0233</td>
<td>0.0233</td>
<td>0.5349</td>
<td>0.1396</td>
<td>0.2558</td>
</tr>
<tr>
<td>missing</td>
<td>0.2698</td>
<td>0.0357</td>
<td>0.0198</td>
<td>0.0119</td>
<td>0.5754</td>
<td>0.0873</td>
</tr>
<tr>
<td>death</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
Table 5.15. Result summary of research question 4 and 5

<table>
<thead>
<tr>
<th>RQ #</th>
<th>Research question</th>
<th>Hypothesis</th>
<th>Test, and significance</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-1</td>
<td>Is there a significant difference in patient’s disability between ACE inhibitor and placebo groups in respect to the C-BI at 1 year?</td>
<td>Ho: There is no difference in Barthel Index between ACE inhibitor intervention group and the placebo group at 1 year. Ha: There is a difference in Barthel Index between ACE inhibitor intervention group and the placebo group at 1 year.</td>
<td>Kruskal-Wallis test ($\alpha = 0.05$)</td>
<td>Accept Ho: there is no difference.</td>
</tr>
<tr>
<td>4-2</td>
<td>Same procedures will be applied for year 2</td>
<td></td>
<td></td>
<td>Accept Ho: there is no difference.</td>
</tr>
<tr>
<td>4-3</td>
<td>Same procedures will be applied for year 3</td>
<td></td>
<td></td>
<td>Reject Ho: there is significant difference.</td>
</tr>
<tr>
<td>4-4</td>
<td>Same procedures will be applied for year 4</td>
<td></td>
<td></td>
<td>Reject Ho: there is significant difference.</td>
</tr>
<tr>
<td>5-1</td>
<td>Based on the Categorized Barthel, is there a difference in the prognosis of disability in ACE inhibitor and placebo group from baseline to year 1?</td>
<td>No hypothesis test</td>
<td></td>
<td>Table 5.14a &amp; 5.14b</td>
</tr>
<tr>
<td>5-2</td>
<td>Same procedure applied for year 1 $\rightarrow$ year 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-3</td>
<td>Same procedure applied for year 2 $\rightarrow$ year 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-4</td>
<td>Same procedure applied for year 3 $\rightarrow$ year 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5.16. Recurrent stroke time in the sample population

<table>
<thead>
<tr>
<th>year of recurrent stroke</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
</tr>
<tr>
<td>1</td>
<td>108</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>total</td>
<td>298</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.17. Recurrent stroke and death in the sample population

<table>
<thead>
<tr>
<th>year</th>
<th>recurrent stroke</th>
<th>death</th>
<th>death among recurrent stroke</th>
<th>recurrent stroke</th>
<th>death</th>
<th>death among recurrent stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108</td>
<td>13</td>
<td>0.12</td>
<td>125</td>
<td>12</td>
<td>0.10</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>18</td>
<td>0.22</td>
<td>125</td>
<td>26</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>23</td>
<td>0.37</td>
<td>91</td>
<td>26</td>
<td>0.29</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>27</td>
<td>0.59</td>
<td>55</td>
<td>32</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td><strong>four year subtotal</strong></td>
<td><strong>81</strong></td>
<td><strong>0.27</strong></td>
<td><strong>125</strong></td>
<td><strong>26</strong></td>
<td><strong>0.24</strong></td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>3</td>
<td>0.33</td>
<td>23</td>
<td>6</td>
<td>0.26</td>
</tr>
<tr>
<td>6</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td><strong>total</strong></td>
<td><strong>605</strong></td>
<td><strong>165</strong></td>
<td><strong>816</strong></td>
<td><strong>199</strong></td>
<td><strong>0.24</strong></td>
</tr>
</tbody>
</table>

Odd Ratio, four year subtotal 1.1665 (0.8144, 1.6679), p=0.4286
Table 5.18. Frequency of disability category after recurrent stroke

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th></th>
<th>% among available observation</th>
<th>Placebo</th>
<th></th>
<th>% among available observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basemfor2ndsecat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>232</td>
<td>75.57</td>
<td>80.56</td>
<td>363</td>
<td>86.43</td>
<td>87.89</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>42</td>
<td>13.68</td>
<td>14.58</td>
<td>37</td>
<td>8.81</td>
<td>8.96</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>13</td>
<td>4.23</td>
<td>4.51</td>
<td>9</td>
<td>2.14</td>
<td>2.18</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>1</td>
<td>0.33</td>
<td>0.35</td>
<td>4</td>
<td>0.95</td>
<td>0.97</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8888</td>
<td>19</td>
<td>6.19</td>
<td>7</td>
<td>1.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FiMafter2ndsecat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>143</td>
<td>46.58</td>
<td>67.77</td>
<td>206</td>
<td>49.05</td>
<td>68.44</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>42</td>
<td>13.68</td>
<td>19.91</td>
<td>56</td>
<td>13.33</td>
<td>18.60</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>21</td>
<td>6.84</td>
<td>9.95</td>
<td>32</td>
<td>7.62</td>
<td>10.63</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>5</td>
<td>1.63</td>
<td>2.37</td>
<td>7</td>
<td>1.67</td>
<td>2.33</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>8888</td>
<td>49</td>
<td>15.96</td>
<td>19.6</td>
<td>59</td>
<td>14.05</td>
<td></td>
</tr>
<tr>
<td>9999</td>
<td>47</td>
<td>15.31</td>
<td>19.05</td>
<td>59</td>
<td>14.05</td>
<td></td>
</tr>
<tr>
<td>SMafter2ndsecat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>107</td>
<td>34.85</td>
<td>68.15</td>
<td>162</td>
<td>38.57</td>
<td>66.39</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>29</td>
<td>9.45</td>
<td>18.47</td>
<td>47</td>
<td>11.19</td>
<td>19.26</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>18</td>
<td>5.86</td>
<td>11.46</td>
<td>26</td>
<td>6.19</td>
<td>10.66</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>3</td>
<td>0.98</td>
<td>1.91</td>
<td>9</td>
<td>2.14</td>
<td>3.69</td>
</tr>
<tr>
<td>7777</td>
<td>7</td>
<td>2.28</td>
<td>4.71</td>
<td>24</td>
<td>5.71</td>
<td></td>
</tr>
<tr>
<td>8888</td>
<td>77</td>
<td>25.08</td>
<td>21.5</td>
<td>73</td>
<td>17.38</td>
<td></td>
</tr>
<tr>
<td>9999</td>
<td>66</td>
<td>21.5</td>
<td>21.5</td>
<td>79</td>
<td>18.81</td>
<td></td>
</tr>
<tr>
<td>TMafter2ndsecat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>69</td>
<td>22.48</td>
<td>61.06</td>
<td>94</td>
<td>22.38</td>
<td>62.67</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>24</td>
<td>7.82</td>
<td>21.24</td>
<td>28</td>
<td>6.67</td>
<td>18.67</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>18</td>
<td>5.86</td>
<td>15.93</td>
<td>20</td>
<td>4.76</td>
<td>13.33</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>2</td>
<td>0.65</td>
<td>1.77</td>
<td>8</td>
<td>1.9</td>
<td>5.33</td>
</tr>
<tr>
<td>7777</td>
<td>45</td>
<td>14.66</td>
<td>64</td>
<td>64</td>
<td>15.24</td>
<td></td>
</tr>
<tr>
<td>8888</td>
<td>73</td>
<td>23.78</td>
<td>114</td>
<td>27.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9999</td>
<td>76</td>
<td>24.76</td>
<td>92</td>
<td>21.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FoMafter2ndsecat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>34</td>
<td>11.07</td>
<td>62.96</td>
<td>42</td>
<td>10</td>
<td>60.87</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>13</td>
<td>4.23</td>
<td>24.07</td>
<td>14</td>
<td>3.33</td>
<td>20.29</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>6</td>
<td>1.95</td>
<td>11.11</td>
<td>10</td>
<td>2.38</td>
<td>14.49</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>1</td>
<td>0.33</td>
<td>1.85</td>
<td>3</td>
<td>0.71</td>
<td>4.35</td>
</tr>
<tr>
<td>7777</td>
<td>87</td>
<td>28.34</td>
<td>135</td>
<td>32.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8888</td>
<td>82</td>
<td>26.71</td>
<td>118</td>
<td>28.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9999</td>
<td>84</td>
<td>27.36</td>
<td>98</td>
<td>23.33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Basemfor2ndse, baseline BI measure for recurrent stroke; FiMafter2ndse, first BI measure after the recurrent stroke; SMafter2ndse, second measure; TMafter2ndse, third measure; FoMafter2ndse, fourth measure; FiMafter2ndse, fifth measure 7777=missing, due to the study time frame, 8888=missing with no reason, 9999=missing due to death
Table 5.19. Comparison of disability outcome after recurrent stroke event in active and placebo treatment groups with Categorized Barthel Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>TREAT</th>
<th>N</th>
<th>mean score</th>
<th>KW statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basemfor2ndsecat</td>
<td>Active</td>
<td>288</td>
<td>366.03</td>
<td>6.9570</td>
<td>0.0083</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>413</td>
<td>340.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FImafter2ndsecat</td>
<td>Active</td>
<td>211</td>
<td>257.10</td>
<td>0.0088</td>
<td>0.9253</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>301</td>
<td>256.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMafter2ndsecat</td>
<td>Active</td>
<td>157</td>
<td>198.50</td>
<td>0.1744</td>
<td>0.6762</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>244</td>
<td>202.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMafter2ndsecat</td>
<td>Active</td>
<td>113</td>
<td>132.25</td>
<td>0.0028</td>
<td>0.9578</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>150</td>
<td>131.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FoMafter2ndsecat</td>
<td>Active</td>
<td>54</td>
<td>60.55</td>
<td>0.2130</td>
<td>0.6444</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>69</td>
<td>63.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FifMafter2ndsecat</td>
<td>Active</td>
<td>2</td>
<td>60.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1</td>
<td>60.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Basemfor2ndsecat, baseline C-BI measure for recurrent stroke; FImafter2ndsecat, first C-BI measure after the recurrent stroke; SMafter2ndsecat, second C-BI measure after the recurrent stroke; TMafter2ndsecat, third C-BI measure after the recurrent stroke; FoMafter2ndsecat, fourth C-BI measure after the recurrent stroke; FifMafter2ndsecat, fifth C-BI measure after the recurrent stroke
Table 5.20a. Transitions in active treatment group for recurrent stroke

### Baseline for RS --> First Measure after the RS

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI 1</td>
<td>0.5862</td>
<td>0.0819</td>
<td>0.0474</td>
<td>0.0172</td>
<td>7777</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.0238</td>
<td>0.5238</td>
<td>0.119</td>
<td>0.0238</td>
<td>8888</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0</td>
<td>0.3846</td>
<td>0</td>
<td>9999</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8888</td>
<td>0.3158</td>
<td>0.0526</td>
<td>0</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
<td>42</td>
<td>21</td>
<td>5</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI 1</td>
<td>0.7203</td>
<td>0.014</td>
<td>0.007</td>
<td>0</td>
<td>7777</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.0952</td>
<td>0.5714</td>
<td>0.0476</td>
<td>0.0238</td>
<td>8888</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0</td>
<td>0.619</td>
<td>0.0476</td>
<td>9999</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8888</td>
<td>0</td>
<td>0.0408</td>
<td>0.0204</td>
<td>0.1429</td>
<td>49</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>29</td>
<td>18</td>
<td>3</td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI 1</td>
<td>0.5794</td>
<td>0.0374</td>
<td>0.028</td>
<td>0</td>
<td>7777</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.1034</td>
<td>0.6552</td>
<td>0.1034</td>
<td>0</td>
<td>8888</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0</td>
<td>0.6111</td>
<td>0</td>
<td>9999</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.6667</td>
<td>3</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>8888</td>
<td>0.0519</td>
<td>0.013</td>
<td>0.013</td>
<td>0.4935</td>
<td>77</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>24</td>
<td>18</td>
<td>2</td>
<td>76</td>
</tr>
</tbody>
</table>

### First Measure --> Second Measure

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI 1</td>
<td>0.4348</td>
<td>0.0145</td>
<td>0</td>
<td>0</td>
<td>7777</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.0833</td>
<td>0.4583</td>
<td>0.0833</td>
<td>0</td>
<td>8888</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0</td>
<td>0.2222</td>
<td>0</td>
<td>9999</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>8888</td>
<td>0.0274</td>
<td>0.0137</td>
<td>0</td>
<td>0.5479</td>
<td>73</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
<th>Total</th>
</tr>
</thead>
</table>
| Basemfor2ndsecat, baseline C-BI measure for recurrent stroke; FiMafter2ndsecat, first C-BI measure after the recurrent stroke; SMafter2ndsecat, second C-BI measure after the recurrent stroke; TMafter2ndsecat, third C-BI measure after the recurrent stroke; FoMafter2ndsecat, fourth C-BI measure after the recurrent stroke; FifMafter2ndsecat, fifth C-BI measure after the recurrent stroke; 7777=missing, due to the study time frame, 8888=missing with no reason, 9999=missing due to death
Table 5.20b. Transitions in placebo treatment group for recurrent stroke

<table>
<thead>
<tr>
<th>Categories</th>
<th>C-BI 1</th>
<th>C-BI 3</th>
<th>C-BI 4</th>
<th>C-BI 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BasemforRS</td>
<td>0.5565</td>
<td>0.1212</td>
<td>0.0606</td>
<td>0.0165</td>
<td>0.0028</td>
</tr>
<tr>
<td>First Measure --&gt; Second Measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.1081</td>
<td>0.3243</td>
<td>0.1622</td>
<td>0.027</td>
<td>0.0216</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0</td>
<td>0.4444</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8888</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>56</td>
<td>32</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Second Measure --&gt; Third Measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>0.7476</td>
<td>0.0534</td>
<td>0.0049</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.1071</td>
<td>0.5357</td>
<td>0.0536</td>
<td>0.0357</td>
<td>0</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0</td>
<td>0.6625</td>
<td>0.5625</td>
<td>0.125</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1429</td>
<td>0.1429</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8888</td>
<td>0.0339</td>
<td>0.0678</td>
<td>0.0508</td>
<td>0.0339</td>
<td>0.3559</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>47</td>
<td>26</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Third Measure --&gt; Fourth Measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-BI 1</td>
<td>0.5432</td>
<td>0.0247</td>
<td>0.0062</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C-BI 3</td>
<td>0.0851</td>
<td>0.4681</td>
<td>0.0851</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C-BI 4</td>
<td>0</td>
<td>0.0769</td>
<td>0.5385</td>
<td>0.0385</td>
<td>0</td>
</tr>
<tr>
<td>C-BI 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.6667</td>
<td>0</td>
</tr>
<tr>
<td>7777</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8888</td>
<td>0.0274</td>
<td>0</td>
<td>0</td>
<td>0.0137</td>
<td>0.0137</td>
</tr>
<tr>
<td>9999</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>28</td>
<td>20</td>
<td>8</td>
<td>64</td>
</tr>
</tbody>
</table>

Baseline for RS --> First Measure after the RS

BasemforRS, baseline C-BI measure for recurrent stroke; FiMafter2ndsecat, first C-BI measure after the recurrent stroke; SMafter2ndsecat, second C-BI measure after the recurrent stroke; TMafter2ndsecat, third C-BI measure after the recurrent stroke; FoMafter2ndsecat, fourth C-BI measure after the recurrent stroke; FifMafter2ndsecat, fifth C-BI measure after the recurrent stroke; 7777=missing, due to the study time frame, 8888=missing with no reason, 9999=missing due to death.


Table 5.21. Result summary of research question 6 and 7

<table>
<thead>
<tr>
<th>RQ #</th>
<th>Research question</th>
<th>Hypothesis</th>
<th>Test, (α)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-1</td>
<td>Is there a significant difference in Categorized Barthel at the first year of recurrent stroke between active and placebo ACE inhibitor intervention groups for patient experienced recurrent stroke?</td>
<td>Ho: There is no difference in Categorized Barthel between ACE inhibitor and placebo groups at the first year of recurrent stroke. Ha: There is a difference in Barthel Index between ACE inhibitor and placebo groups at the first year of recurrent stroke.</td>
<td>Kruskal Wallis (α = 0.05)</td>
<td>Significant difference</td>
</tr>
<tr>
<td>6-2</td>
<td>Same procedure will be applied for the second year after the recurrent stroke.</td>
<td></td>
<td></td>
<td>No Significant difference</td>
</tr>
<tr>
<td>6-3</td>
<td>the third year</td>
<td></td>
<td></td>
<td>No Significant difference</td>
</tr>
<tr>
<td>6-4</td>
<td>the fourth year</td>
<td></td>
<td></td>
<td>No Significant difference</td>
</tr>
<tr>
<td>7-1</td>
<td>For the subpopulation that had recurrent stroke - Based on the Categorized Barthel, is there a difference in the prognosis of disability between ACE inhibitor and placebo group between two time point: before and after the recurrent stroke?</td>
<td></td>
<td></td>
<td>Table 5.20a &amp; 5.20b</td>
</tr>
<tr>
<td>7-2</td>
<td>Same procedure will be applied for: from ‘first year after stroke’ to ‘second year after stroke’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-3</td>
<td>from ‘second year after stroke’ to ‘third year after stroke’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-4</td>
<td>From ‘third year after stroke’ to ‘fourth year after stroke’</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5.22. Summary of model parameters, stages, utility and transition probabilities

<table>
<thead>
<tr>
<th>Disability level</th>
<th>Barthel Index range</th>
<th>Utility (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-BI1</td>
<td>0&lt;=BI&lt;15</td>
<td>9 (10, 7.5)</td>
</tr>
<tr>
<td>C-BI3</td>
<td>15&lt;=BI&lt;70</td>
<td>8 (10, 5)</td>
</tr>
<tr>
<td>C-BI4</td>
<td>70&lt;=BI&lt;95</td>
<td>7 (9, 2.5)</td>
</tr>
<tr>
<td>C-BI5</td>
<td>95&lt;=BI&lt;=100</td>
<td>1 (5, 0.083)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8888</th>
<th>9999</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0.8852</td>
<td>0.0154</td>
<td>0.0035</td>
<td>0.0006</td>
<td>0.0790</td>
<td>0.0163</td>
<td>0.9999</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>0.2101</td>
<td>0.5966</td>
<td>0.0558</td>
<td>0.0039</td>
<td>0.0791</td>
<td>0.0545</td>
<td>1.0000</td>
</tr>
<tr>
<td>1</td>
<td>8888</td>
<td>0.0395</td>
<td>0.0888</td>
<td>0.6480</td>
<td>0.0230</td>
<td>0.1086</td>
<td>0.0921</td>
<td>1.0000</td>
</tr>
<tr>
<td>1</td>
<td>9999</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.1364</td>
<td>0.3636</td>
<td>0.2727</td>
<td>0.2273</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8888</th>
<th>9999</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>0.2522</td>
<td>0.0325</td>
<td>0.0162</td>
<td>0.0036</td>
<td>0.6072</td>
<td>0.0883</td>
<td>1.0001</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>0.8791</td>
<td>0.0194</td>
<td>0.0043</td>
<td>0.0009</td>
<td>0.0777</td>
<td>0.0186</td>
<td>1.0001</td>
</tr>
<tr>
<td>3</td>
<td>8888</td>
<td>0.1712</td>
<td>0.6441</td>
<td>0.0597</td>
<td>0.0056</td>
<td>0.0811</td>
<td>0.0383</td>
<td>1.0000</td>
</tr>
<tr>
<td>3</td>
<td>9999</td>
<td>0.0494</td>
<td>0.0959</td>
<td>0.6192</td>
<td>0.0378</td>
<td>0.1250</td>
<td>0.0727</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>5</th>
<th>8888</th>
<th>9999</th>
<th>9999</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5</td>
<td>0.0233</td>
<td>0.0233</td>
<td>0.0233</td>
<td>0.5349</td>
<td>0.1396</td>
</tr>
<tr>
<td>4</td>
<td>8888</td>
<td>0.2698</td>
<td>0.0357</td>
<td>0.0198</td>
<td>0.0119</td>
<td>0.5754</td>
</tr>
<tr>
<td>4</td>
<td>9999</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

1=C-BI1, 3=C-BI3, 4=C-BI4, 5=C-BI5, 8888=missing with no reason, 9999=missing due to death
Figure 5.8. Complete disability evaluation model, active treatment group.
Figure 5.9a. Predicted and actual disability outcomes in active treatment group for the study period
Figure 5.9b. Predicted and actual disability outcomes in placebo treatment group for the study period.

1 = C-BI1; 3 = C-BI3; 4 = C-BI4; 5 = C-BI5;

p1 = transition probabilities for baseline → year1; p2 = transition probabilities for year1 → year2;
p3 = transition probabilities for year2 → year3; p4 = transition probabilities for year3 → year4;
weighted = weighted probabilities;

1yr real = disability frequency at the 1st year measuring point; 2yr real = disability frequency at the
2nd year measuring point; 3yr real = disability frequency at the 3rd year measuring point; 4yr real =
disability frequency at the 4th year measuring point;
Figure 5.10. Predicted and actual disability levels for a ten years of observation period
Figure 5.11. Predicted disability comparison between active and placebo groups for the extended time period.
Table 5.23. Ten year outcome projection in terms of utility in active and placebo treatment groups

<table>
<thead>
<tr>
<th></th>
<th>active 3051</th>
<th></th>
<th>placebo 3054</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>basecase</td>
<td>L</td>
<td>H</td>
</tr>
<tr>
<td>start</td>
<td>9.97</td>
<td>8.85</td>
<td>7.15</td>
<td>9.97</td>
</tr>
<tr>
<td>cycle1</td>
<td>9.75</td>
<td>8.59</td>
<td>6.83</td>
<td>9.74</td>
</tr>
<tr>
<td>cycle2</td>
<td>9.48</td>
<td>8.32</td>
<td>6.55</td>
<td>9.46</td>
</tr>
<tr>
<td>cycle3</td>
<td>9.19</td>
<td>8.05</td>
<td>6.30</td>
<td>9.16</td>
</tr>
<tr>
<td>cycle4</td>
<td>8.90</td>
<td>7.78</td>
<td>6.07</td>
<td>8.85</td>
</tr>
<tr>
<td>cycle5</td>
<td>8.60</td>
<td>7.51</td>
<td>5.86</td>
<td>8.54</td>
</tr>
<tr>
<td>cycle6</td>
<td>8.31</td>
<td>7.26</td>
<td>5.65</td>
<td>8.24</td>
</tr>
<tr>
<td>cycle7</td>
<td>8.03</td>
<td>7.01</td>
<td>5.45</td>
<td>7.95</td>
</tr>
<tr>
<td>cycle8</td>
<td>7.76</td>
<td>6.77</td>
<td>5.26</td>
<td>7.67</td>
</tr>
<tr>
<td>cycle9</td>
<td>7.49</td>
<td>6.53</td>
<td>5.08</td>
<td>7.39</td>
</tr>
<tr>
<td>cycle10</td>
<td>7.24</td>
<td>6.31</td>
<td>4.90</td>
<td>7.13</td>
</tr>
</tbody>
</table>

Utility values presented are per person.
L= averaged utility for the entire cohort when utility estimate Q1 is applied;
H= averaged utility for the entire cohort when utility estimate Q3 is applied.
basecase= averaged utility for the entire cohort when median utility estimate is applied.

Table 5.24. Result summary of research question 8

<table>
<thead>
<tr>
<th>RQ #</th>
<th>Research question</th>
<th>Hypothesis</th>
<th>Test, and significance</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-1</td>
<td>What is the integrated benefit of ACEI (placebo) treatment compared to placebo (ACEI) treatment in terms of utility</td>
<td>N/A</td>
<td>N/A</td>
<td>See Table 5.23</td>
</tr>
<tr>
<td>8-2</td>
<td>For the recurrent stroke patients, what is the integrated benefit of ACEI (placebo) treatment compared to placebo (ACEI) treatment in terms of utility considering four year disability and transitions of disability?</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
The purpose of this study was to evaluate the effectiveness of ACE inhibitor in terms of long-term disability in post-stroke patients. PROGRESS found that recurrent stroke incidence was significantly lower in ACE inhibitor treatment group as compared to placebo. Mortality rates, however, were not significantly different. Long-term disability evaluation was not a part of their major publication. This dissertation complemented the PROGRESS findings by considering both long-term disability post-stroke and mortality.

In order to model the progression of stroke disability over time in a population, a global categorization scheme is needed to identify different stages of stroke disability. Modified Rankin Scale is a well accepted global disability measure that was used to categorize the Barthel index in this study. Four of the six MRS stages of functional disability were identified in the Barthel index. That is, the Barthel index was not able to discriminate two of the MRS disability stages. The MRS spans the entire spectrum of human physical functioning, while the Barthel index appears to only cover lower levels of physical functioning. This was observed in the ceiling effect of the instrument.

Even though the C-BI was not able to differentiate all levels of the MRS, the categorization scheme is useful for the evaluation of population level disability and transitions among disability levels because these stages represent distinct and clinically meaningful characteristics of disability. Because of the inability of the C-BI to capture higher levels of physical functioning, future research is needed to determine the level of disability distinction that is most appropriate for modeling stroke related outcomes. This
should be based on the theoretical understanding of post stroke disability and the practical ability to measure those levels.

Patient reported outcomes are an important way of gauging patient’s health status. The time-trade off method was used to assess health state preferences. Utility estimates for the four levels of disability were 1, 7, 8, and 9. Which means the people who had less than slight disability valued their 10 years equal to 9 years of perfect health; the people who had moderate disability perceive their 10 years of life equal to 8 years of perfect health, and so on.

People in C-BI5 valued their lives much less than those in other stages. C-BI1 through C-BI4 stages showed a linear relationship in utility and disability. However, when C-BI5 was included the relationship between utility and disability changed, the utility level dropped drastically between level C-BI4 and C-BI5, which was from 7 to 1.

The disability stage categorization scheme and utility estimates were used to compare and interpret the long term outcomes in terms of mortality and disability between treatment and placebo groups. Four year outcomes were compared without modeling, while long-term outcomes were modeled.

During the four year of data collection, 9.52% of active ACE inhibitors and 9.86% of placebo treatment group subjects died, there were 0.3% more death in the active treatment group. This difference, however, was not statistically significant. Compared to mortality, disability presented differences in the two groups: the placebo group presented more severe disability. By the end of the second year, 90.1% of active treatment subjects stayed in C-BI1, but only 88.1% of placebo treatment group subjects were in the C-BI1 (p<0.06). This trend was maintained for the third and fourth year showing statistically
significant differences in disability at 3 years post-stroke and 4 years post-stroke (p<0.001). In summary, during the four year study time window, the ACE inhibitor treatment group showed more favorable disability, that is less severe disability, but no difference in mortality compared to placebo treatment.

Prediction modeling showed a higher proportion of placebo group patients were in the more severe disability levels (C-BI3, C-BI4, and C-BI5) and death stage. Approximately, 0.56 – 0.80 year of utility was gained per person, with ten year of ACE inhibitor treatment.

Since patients were randomized in the PROGRESS study, no other factors were considered to predict mortality and disability. In reality, however, numerous patient related factors and other factors may affect the results of treatment on mortality and disability, for example, patient’s life style change, new co-morbidity developed access to medical treatment. For more precise models and predictions, the effects of these factors on mortality and morbidity need to be studied in the future.

One of the most important limitations of the ten year prediction model was the uncertainty whether the prediction slope maintains the same slope or changes if treatment regimen are discontinued or continued beyond the four year trial window. This study unfortunately could not provide an answer because these outcomes can be affected with treatment withdrawal or the use of treatment beyond four years. This is an inherent limitation in modeling and predicting long-term outcomes from clinical trial data.

ACE inhibitors are known for their effectiveness in preventing recurrent stroke, and multiple large clinical trials have reported this phenomenon. The mechanism of
this phenomenon has not been clearly identified yet, but it has been proposed that ACE inhibitors prevent artery remodeling, and increase blood circulation of the brain.\textsuperscript{143-145}

If ACE inhibitors reduce recurrent stroke incidence via the above mentioned mechanism, it is also theoretically plausible that ACE inhibitor therapy benefits residual disability. This dissertation showed that ACE inhibitor treatment reduced disability. However, the benefit of ACE inhibitor use compared to placebo use in terms of disability is not dramatically large. That is, even though there was a tendency of better disability outcomes in the ACE treatment group, due to small differences. It is difficult to make a strong argument for ACE inhibitor use for improving disability after stroke.

When interpreting the results of this dissertation, it is necessary to consider the limitations. First, the PROGRESS trial used the Barthel Index as a measure of physical functioning. The disability evaluation with the Barthel Index may not be an optimal choice because of its’ well known ceiling effect for higher functioning people.

Second, the PROGRESS excluded subjects who might not be able to attend follow-up visits due to their lower functioning, so, it is very likely that PROGRESS did not select a representative population of stroke survivors. The selection of participants in PROGRESS should be taken into account in generalizing the findings of this study to the entire stroke population.

Third, PROGRESS only used the Barthel Index to measure functional disability, without any other instruments, such as quality of life or utility of patients. Thus, the disability categorization scheme and the utility estimates for each categorized disability level were developed using the Kansas City Stroke Study data. Developing a categorization scheme based on another population may introduce bias. That is, KCSS
study cohort data ended at six month post-stroke of the enrolled stroke patients, so the utility estimates for disability levels may not represent the utility of the people in the different time frame.

In this dissertation, statistical tests were performed to examine if there is a response shift in utility within the six month window. There was no response shift observed, so the utility estimates for individual disability levels were applied to interpret the PROGRESS data. For more accurate evaluation of PROGRESS, however, response shift should have been examined in the PROGRESS study population for the same time window of Barthel Index data collection time. As mentioned earlier, this is one of the limitation related using two different datasets.

In terms of response shift, it is possible that patients develop better coping skills over the four year time window than over a six month time window. If this is the case, utility estimates need to be adjusted appropriately according to the period that the model evaluates. This was not accounted for in this dissertation due to the lack of information. Future research will need to evaluate response shifts in the population.

Fourth, the BI is not a disability measure; rather it is designed to measure activities of daily living. In this study, via paring the BI scores and MRS, BI was translated into disability levels. Even though it is a logical procedure, information losses may have occurred. For example, not all six disability levels defined by MRS were identified in the BI scores, only four levels were identified. Thus, for the people in higher functioning levels, such as MRS0, 1, and 2, was not differentiated in this dissertation.

Fifth, the BI scores in patients might have been attributed to other diseases or the natural process of ageing, but this study did not differentiated by attributing causes of
disability. Instead, the study assumed that two treatment groups are randomized in all variables, which included that the attributing causes of disability are even in two groups. With this assumption, this study focused on the difference in disability between ACE inhibitor treatment group and placebo treatment group.

Sixth, the ethnic/racial selection is different from American population. For example, African Americans were not represented in PROGRESS. Outcomes may differ by ethnic groups and this should be considered when applying these results to the US population. Further research is needed to examine the variation of effectiveness due to ethnic and racial variation on disability post-stroke.

Seventh, it is well documented in the medical literature that other factors, that is, person’s life style and co-morbidities affects disease outcomes. Due to the lack of information, however, this dissertation could not control these factors in the analysis. It would have been more informative if this dissertation tested the effects of these factors on outcomes.

Eighth, the transition probability matrix for recurrent stroke patients was not completed. This task was planned under the hypothesis that people who had recurrent stroke may have different disability transitions. If this is the case, the recurrent stroke patients should be modeled using an appropriate transition matrix. However, in the PROGRESS study, ten and fourteen percent of active and placebo treatment groups who had experienced recurrent stroke during the study period were selected, and this sample size was not enough to establish a transition matrix. Further research is necessary to evaluate the ACE inhibitor in terms of disability after recurrent stroke.
As mentioned in the second chapter, the review of literature, residual disability after stroke has been rarely investigated compared to other major stroke outcomes, such as mortality and recurrent stroke incidence. The lack of research on recurrent stroke is understandable considering the limited resources, difficulties of data collection, and long time period required for collecting the disability information. However, it is important to appreciate that stroke related disability is one of the most important outcomes that should be included in stroke outcome evaluation. Appropriate modeling technology may elevate the resource constraints. For an ageing society, disability and stroke will be more and more important from a public health perspective.

In this dissertation, the disability evaluation was performed using data that was already collected. Ideally, modeling and evaluation should be planned and designed before the initiation of a trial with consideration of important components of the evaluation model, such as selecting an appropriate disability measure, and selecting appropriate time intervals for the outcome measure.

This dissertation simulated how stroke outcome could be evaluated including residual disability, but other aspects of stroke could be evaluated appropriately as well with the cooperation of different disciplines of health professions. Further studies are necessary to understand stroke outcomes and prepare for the future needs of public health.
APPENDIX A
INSTRUMENTS

Modified Rankin Scale

0  No symptom at all
1  No significant disability despite symptoms; able to carry out all usual duties and activities
2  Slightly disability; unable to carry out all previous activities but able to look after own affairs without assistance
3  Moderate disability requiring some help, but able to walk without assistance
4  Moderate severe disability; Unable to walk without assistance and unable to attend to own bodily needs without assistance
5  Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
Barthel Index

1. Today, are you able to feed yourself?

10 Independent; feeds self from tray or table; can put in assistive device if needed; accomplishes feeding in reasonable time
5 Assistance necessary with cutting food, etc.
0 Cannot meet criteria
88 Contraindicated due to________________________

2. Today, are you able to get out of bed or into a chair?

15 Independent in all phases of this activity
10 Minimal help needed or patient needs to be reminded or supervised for safety of 1 or more parts if this activity
5 Patient can come to sitting position without help of second person but need to be lifted out of bed and assisted with transfers
0 Cannot meet criteria
88 Contraindicated due to________________________

3. Today, are you able to wash your face, brush your teeth, brush your hair etc?

5 Can wash hands, face; comb hair, cleans teeth. Can shave (males) or apply makeup (females) without assistance; females need not braid or style hair.
0 Cannot meet criteria
88 Contraindicated due to________________________

4. Today are you able to get on and off the toilet?

10 Able to get on and off the toilet, fastens/unfastens clothes; can use toilet paper without assistance. May use wall bar or other support if needed; if bedpan is necessary, patient can place it on chair, empty, and clean it.
5 Needs help because of imbalance or other problems with clothes or toilet paper
0 Cannot meet criteria
88 Contraindicated due to________________________
5 Today, are you able to bathe yourself?

5 May use bath tub, shower or sponge bath. Patient must be able to perform all functions without another person being present.
0 Cannot meet criteria
88 Contraindicated due to __________________________

6 Today, are you able to walk without help?

15 Patient can walk at least 50 yards without assistance or supervision; may use braces, prostheses, crutches, canes, or walker, but not a rolling walker. Must be able to lock/unlock braces, assume standing or seated position, get mechanical aids into position for use and dispose of the mechanical aids when seated (putting on and off braces should be scored under dressing).
10 Assistance needed to perform above activities, but can walk 50 yards with little help
0 Cannot meet criteria
88 Contraindicated due to __________________________

7 Today, are you able to use a wheelchair?
*(Do not score this item if patient completes score for walking.)*

5 Patient cannot ambulate, but can propel wheelchair independently; can go around corners, turn around maneuver chair to table, bed, toilet, etc., must be able to push chair 50 yards.
0 Cannot meet criteria
88 Contraindicated due to __________________________

8 Today, are you able to walk up and down stairs?

10 Able to go up and down flight of stairs safely without supervision; using canes, handrails, or crutches when needed and can carry these items as ascending/descending.
5 Needs help or supervision of any of the above items
0 Cannot meet criteria
88 Contraindicated due to __________________________

9 Today, are you able to dress and undress yourself?
10 Able to put on, fasten and remove all clothing; ties shoelaces unless necessary adaptations used. Activity includes fastening braces and corsets when prescribed; suspenders, loafer shoes and dresses opening in the front may be used when necessary.

5 Needs help putting on, fastening, or removing clothing; must accomplish at least half of task alone within reasonable time; women need not be scored on use of brassiere or girdle unless prescribed

0 Cannot meet criteria

88 Contraindicated due to________________________

10 Today, are you able to control your bowels?

10 Able to control bowels and have no accidents. Can use a suppository or take an enema when necessary (as for spinal cord injury patients who have had bowel training).

5 Needs help in using a suppository or taking an enema or has occasional accidents

0 Cannot meet criteria

88 Contraindicated due to________________________

11 Today, are you able to control your bladder?

10 Able to control bladder day and night. Spinal injury patients must be able to put on external devices and leg bags independently, clean and empty bag, and must stay dry day and night.

5 Occasional accidents occur, cannot wait for bed pan, does not get to toilet in time or needs help with external device.

0 Cannot meet criteria

88 Contraindicated due to________________________
Functional Independence Measure (FIM)

MOTOR

SELF-CARE

A. Eating

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

B. Grooming

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

C. Bathing

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

D. Dressing-Upper Body

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
E. Dressing-Lower Body

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

F. Toileting

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

SPHINCTER CONTROL

G. Bladder Management

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

H. Bowel Management
TRANSFERS

I. Bed, Chair, Wheelchair

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

J. Toilet

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

K. Tub, Shower

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance
LOCOMOTION

L. Walk/Wheelchair

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance

M. Stairs

7 Complete Independence
6 Modified Independence
5 Supervision
4 Minimal Assistance
3 Moderate Assistance
2 Maximal Assistance
1 Total Assistance
APPENDIX B
SAS PROGRAMMING FOR CONSTRUCTING DATASETS

Programming for AIM2

```sas
options ps=10000 NODATE NUMBER PAGENO=1;
/*
*****************************************************************************
** AIM 2. To investigate representative utility **
** (time trade-off) estimate in stroke survivors **
** in relation to Barthel Index **
*****************************************************************************
*/

/* PREPARATION WORK start
*****************************************************************************
DATA kcsstemp.tbarthel_rankin_timetr (keep= id month ranktday tbarthel yrslive);
MERGE kcss.barthel kcss.rankin kcss.timetr;
BY id month;
RUN;

DATA a;
set kcsstemp.tbarthel_rankin_timetr;
run;

PROC NPAR1WAY wilcoxon data=a wilcoxon;
   class month;
   var yrslive;
RUN;
options nodate ls=80 ps=10000;
run;

DATA b0;
set a;
if ranktday=0;
run;

PROC NPAR1WAY wilcoxon data=b0 wilcoxon;
   class month;
   var yrslive;
```
RUN;

DATA b1;
  SET a;
  IF ranktday=1;
RUN;

PROC NPAR1WAY WILCOXON DATA=b1 WILCOXON;
  CLASS month;
  VAR yrslive;
RUN;

DATA b2;
  SET a;
  IF ranktday=2;
RUN;

PROC NPAR1WAY WILCOXON DATA=b2 WILCOXON;
  CLASS month;
  VAR yrslive;
RUN;

DATA b3;
  SET a;
  IF ranktday=3;
RUN;

PROC NPAR1WAY WILCOXON DATA=b3 WILCOXON;
  CLASS month;
  VAR yrslive;
RUN;

DATA b4;
  SET a;
  IF ranktday=4;
RUN;

PROC NPAR1WAY WILCOXON DATA=b4 WILCOXON;
  CLASS month;
  VAR yrslive;
RUN;

DATA b5;
  SET a;
  IF ranktday=5;
RUN;

PROC NPAR1WAY WILCOXON DATA=b5 WILCOXON;
  CLASS month;
  VAR yrslive;
RUN;

DATA c;
  SET a;
  IF (95<=tbarthel<=100) THEN tbarthelcat=1;
  IF (70<=tbarthel<95) THEN tbarthelcat=3;
  IF (15<=tbarthel<70) THEN tbarthelcat=4;
IF (0<=tbarthel<15) THEN tbarthelcat=5;

IF (0<=ranktday<=2) THEN ranktdaycat=1;
ELSE ranktdaycat=ranktday;
run;
/* subject effect*/

proc glm data=c;
    class tbarthelcat id;
    model yrslive = tbarthelcat id tbarthelcat*id ;
    random  id id*tbarthelcat /test;
run;
quit;

proc mixed data=c covtest;
    class tbarthelcat id;
    model yrslive = tbarthelcat ;
    random  id ;
run;

proc genmod data=c;
    class tbarthel;
    model yrslive = tbarthelcat / dist=multinomial
                        link=cumlogit
                        aggregate=tbarthelcat
                        type1
    ;
run;

proc genmod data=c;
    class id ;
    model yrslive=tbarthelcat / type3 dist=MULTINOMIAL link=cumlogit;
    repeated  subject=id / corrw;
run;

proc genmod data=c;
    class id ;
    model yrslive=tbarthelcat / type3 dist=MULTINOMIAL link=cumlogit;
    * repeated  subject=id / corrw;
run;

data c1;
set c;
if tbarthelcat=1;
group=1;
run;

PROC NPAR1WAY wilcoxon data=c1 wilcoxon;
    class month;
    var yrslive;
RUN;

data c3;
set c;
if tbarthelcat=3;
group=1;
run;
PROC NPAR1WAY wilcoxon data=c3 wilcoxon;
    class month;
    var yrslive;
RUN;

data c4;
set c;
if tbarthelcat=4;
group=1;
run;
PROC NPAR1WAY wilcoxon data=c4 wilcoxon;
    class month;
    var yrslive;
RUN;

data c5;
set c;
if tbarthelcat=5;
group=1;
run;
PROC NPAR1WAY wilcoxon data=c5 wilcoxon;
    class month;
    var yrslive;
RUN;

data d1;
set c;
if ranktdaycat=1;
group=2;
run;
PROC NPAR1WAY wilcoxon data=d1 wilcoxon;
    class month;
    var yrslive;
RUN;

data d3;
set c;
if ranktdaycat=3;
group=2;
run;
PROC NPAR1WAY wilcoxon data=d3 wilcoxon;
    class month;
PROC NPAR1WAY wilcoxon data=d4 wilcoxon;
   class month;
   var yrslive;
RUN;

PROC NPAR1WAY wilcoxon data=d5 wilcoxon;
   class month;
   var yrslive;
RUN;

PROC NPAR1WAY wilcoxon data=c1d1 wilcoxon;
   class group;
   var yrslive;
RUN;

PROC NPAR1WAY wilcoxon data=c3d3 wilcoxon;
   class group;
   var yrslive;
RUN;

PROC NPAR1WAY wilcoxon data=c4d4 wilcoxon;
   class group;
   var yrslive;
RUN;

PROC NPAR1WAY wilcoxon data=c5d5 wilcoxon;
   class group;
   var yrslive;
RUN;

/* Preparation work done
here***************************************************************************/

/*
******************************************************************************
RQ2-1 Is there a correlation between the Barthel Index and time-trade off?
RQ2-2 Is there a correlation between the Categorized Barthel and time-trade off?
RQ3-1 Is there a correlation between the Modified Rankin Scale (MRS) and time-trade off?
RQ3-3 Is there a correlation between the reduced Modified Rankin Scale (rMRS) and time-trade off?
*******************************************************************************/

options ls=80 ps=10000 nodate nonumber;
run;

data a1;
set kcsstemp.tbarthel_rankin_timetr;
IF (95<=tbarthel<=100)THEN tbarthelcat=1;
IF (70<=tbarthel<95)THEN tbarthelcat=3;
IF (15<=tbarthel<70)THEN tbarthelcat=4;
IF (0<=tbarthel<15)THEN tbarthelcat=5;
IF (0<=ranktday<=2)THEN ranktdaycat=1;
ELSE ranktdaycat=ranktday;
run;

proc corr data=a1 pearson spearman;
var yrslive tbarthel tbarthelcat ranktday ranktdaycat;
title1 'correlation coefficients';
run;

proc sort data=a1;
by ranktday;

proc means data=a1;
var yrslive;
by ranktday;
title1 'PROC MEANS output - before categorization';
run;

proc univariate data=a1;
var yrslive;
by ranktday;
output out=a
mean=Mean mode=Mode median=Median
q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
min = Min max=Max;
run;

proc means data=a2;
var yrslive;
by ranktdaycat;
run;
proc univariate data=a2 ;
var yrslive;
by ranktdaycat ;
output out=a
mean=Mean mode=Mode median=Median
q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
min = Min max=Max;
run;

proc boxplot data=a2;
plot yrslive*ranktdaycat / boxstyle = skeletal
nohlable
cboxes = dagr
cboxfill = ywh
cframe = vligb
vaxis = axis1;
run;
```sas
proc sort data=a2;
  by tbarthelcat;
run;
proc means data=a2;
  var yrslive;
  by tbarthelcat;
  title1 'PROC MEANS output - Categorized Barthel';
run;
proc univariate data=a2;
  var yrslive;
  by tbarthelcat;
  output out=a
    mean=Mean mode=Mode median=Median
    q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
    min = Min max=Max;
  title1 'PROC UNIVARIATE output - after categorization';
run;

symbol v=plus c=salmon;
axis1 minor=none color=black label=(angle=90 rotate=0);
title 'boxplot yrslive*tbarthelcat (AFTER CATEGORIZATION)';
title2 '';
proc boxplot data=a2;
  plot yrslive*tbarthelcat / boxstyle = skeletal
    nohlable =
    cboxes = dagr
    cboxfill = ywh
    cframe = vligb
    vaxis = axis1;
run;
```

```*/
******************************************************************************
RQ2-3 Is there a difference in time-trade off among the disability levels defined by the Categorized Barthel?
RQ3-2 Is there a difference in time-trade off among the disability levels defined by the Modified Rankin Scale (MRS)?
RQ3-4 Is there a difference in time-trade off among the disability levels defined by the reduced Modified Rankin Scale (rMRS)?
*******************************************************************************/
```

```sas
Data a1;
  set kcstemp.tbarthel_rankin_timetr;
  IF (95<=tbarthel<=100) THEN tbarthelcat=1;
  IF (70<=tbarthel<95) THEN tbarthelcat=3;
  IF (15<=tbarthel<70) THEN tbarthelcat=4;
```
IF (0<=tbarthel<15) THEN tbarthelcat=5;

IF (0<=ranktday<=2) THEN ranktdaycat=1;
ELSE ranktdaycat=ranktday;
run;

PROC NPAR1WAY wilcoxon data=a1 wilcoxon;
  class tbarthelcat;
  var yrslive;
  TITLE1 'ONE WAY ANOVA - AFTER CATEGORIZATION OF BARTHEL';
RUN;

PROC NPAR1WAY wilcoxon data=a1 wilcoxon;
  class ranktdaycat;
  var yrslive;
  TITLE1 'ONE WAY ANOVA - AFTER CATEGORIZATION OF RANKIN';
RUN;

PROC NPAR1WAY wilcoxon data=kcsstemp.tbarthel_rankin_timetr wilcoxon;
  class ranktday;
  var yrslive;
  TITLE1 'ONE WAY ANOVA - BEFORE CATEGORIZATION';
RUN;

/* manipulation of the data to move to StatsDirect for pairwise comparison after Kruskal Wallis test*/
proc sort data=a1 out=sortbytbarthelcat;
  by tbarthelcat;
run;

proc sort data=a1 out=sortbyranktdaycat;
  by ranktdaycat;
run;

/* just curious......what is the agreement of the patient's disability level, in tbarthelcat and ranktdaycat*/
proc freq data=sortbytbarthelcat;
  tables tbarthelcat*ranktdaycat;
run;

/*POST-HOC TEST*/

/*Done by using StatsDirect software (Acknowledge Brian Sauer , Jan 29 2004)*/

/*NEED STATDIRECT OR STATEXACT SOFTWARE FOR ACCURATE ANALYSIS, BUT NONE OF THEM ARE AVAILABLE FOR ME. SO, ANALYSIS IS DONE IN THE SAS BY CHOOSING TWO LEVELS THAT NEED TO BE COMPARED*/
data a2;
set a1;
if ranktday in (0,1);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
class ranktday;
var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR RANKIN 0 AND 1';
RUN;

data a2;
set a1;
if ranktday in (1,2);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
class ranktday;
var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR RANKIN 1 AND 2';
RUN;

data a2;
set a1;
if ranktday in (2,3);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
class ranktday;
var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR RANKIN 2 AND 3';
RUN;

data a2;
set a1;
if ranktday in (3,4);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
class ranktday;
var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR RANKIN 3 AND 4';
RUN;

data a2;
set a1;
if ranktday in (4,5);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
class ranktday;
var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR RANKIN 4 AND 5';
RUN;

data a2;
set a1;
if ranktday in (0, 2);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
   class ranktday;
   var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR RANKIN 0 AND 2';
RUN;

/**/
data a2;
set a1;
if ranktdaycat in (1, 3);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
   class ranktdaycat;
   var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR CATEGORIZED RANKIN (0+1+2) AND 3';
RUN;

data a2;
set a1;
if ranktdaycat in (3, 4);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
   class ranktdaycat;
   var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR CATEGORIZED RANKIN 3 AND 4';
RUN;

data a2;
set a1;
if ranktdaycat in (4, 5);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
   class ranktdaycat;
   var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR CATEGORIZED RANKIN 4 AND 5';
RUN;
/**/
data a2;
set a1;
if tbarthelcat in (1, 3);
run;

PROC NPAR1WAY wilcoxon data=a2 wilcoxon;
   class tbarthelcat;
   var yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR CATEGORIZED BARTHEL 1 AND 3';
RUN;
DATA a2;
SET a1;
IF tbarthelcat IN (3,4);
RUN;

PROC NPAR1WAY wilcoxon DATA=a2 wilcoxon;
   CLASS tbarthelcat;
   VAR yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR CATEGORIZED BARTHEL 3 AND 4';
RUN;

DATA a2;
SET a1;
IF tbarthelcat IN (4,5);
RUN;

PROC NPAR1WAY wilcoxon DATA=a2 wilcoxon;
   CLASS tbarthelcat;
   VAR yrslive;
   TITLE1 ' TTO K-W ANOVA TEST FOR CATEGORIZED BARTHEL 4 AND 5';
RUN;

PROC SORT DATA=a1;
BY tbarthelcat;
RUN;

OPTIONS NODATE PAGENO=1 LINESIZE=80 PAGESIZE=60;
GOPTIONS HTITLE=2 HTEXT=2.5 FTEXT=SWISSB FTITLE=SWISSB;

PROC UNIVARIATE DATA=a1 NOPRINT;
   VAR yrslive;
   BY tbarthelcat;
   HISTOGRAM YRSLIVE /NORMAL(NOPRINT) CBARLINE=GREY;
RUN;

DATA a2;
SET a1;
IF tbarthelcat=5;
RUN;

* every measuring points-seperately calculate yrslive univariate*/
OPTIONS LS=80 PS=10000 NODATE;
RUN;
DATA a;
SET kcsstemp.tbarthel_rankin_timetr;
IF (95<=tbarthel<=100) THEN tbarthelcat=1;
IF (70<=tbarthel<95) THEN tbarthelcat=3;
IF (15<=tbarthel<70) THEN tbarthelcat=4;
IF (0<=tbarthel<15) THEN tbarthelcat=5;
RUN;
data amonth0;
set a;
if month=0;
run;

data amonth1;
set a;
if month=1;
run;

data amonth3;
set a;
if month=3;
run;

data amonth6;
set a;
if month=6;
run;

proc sort data=amonth0;
by tbarthelcat;
run;
proc means data=amonth0;
var yrslive;
by tbarthelcat;
title1 'month 0 yrslive for tbarthelcat';
run;
proc univariate data=amonth0;
var yrslive;
by tbarthelcat;
output out=a
mean=Mean mode=Mode median=Median
q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
min = Min max=Max;
title1 'month 0 yrslive for tbarthelcat';
run;
symbol v=plus c=salmon;
axis1 minor=none color=black label=(angle=90 rotate=0);
title 'month 0 yrslive for tbarthelcat';

proc boxplot data=amonth0;
plot yrslive*tbarthelcat / boxstyle = skeletal
nohlabel
cboxes = dagr
cboxfill = ywh
cframe = vligb
vaxis = axis1;
proc sort data=amonth1;
by tbarthelcat;
run;
proc means data=amonth1;
var yrslive;
by tbarthelcat;
title1 'month 1 yrslive for tbarthelcat';
run;
proc univariate data=amonth1;
var yrslive;
by tbarthelcat;
output out=a
  mean=Mean mode=Mode median=Median
  q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
  min = Min max=Max;
title1 'month 1 yrslive for tbarthelcat';
run;
symbol v=plus c=salmon;
axis1 minor=none color=black label=(angle=90 rotate=0);
title 'month 1 yrslive for tbarthelcat';
proc boxplot data=amonth1;
plot yrslive*tbarthelcat /
  boxstyle = skeletal
  nohlabel
  cboxes   = dagr
  cboxfill = ywh
  cframe   = vligb
  vaxis    = axis1;
run;
proc sort data=amonth3;
by tbarthelcat;
run;
proc means data=amonth3;
var yrslive;
by tbarthelcat;
title1 'month 3 yrslive for tbarthelcat';
run;
proc univariate data=amonth3;
var yrslive;
by tbarthelcat;
output out=a
  mean=Mean mode=Mode median=Median
  q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
  min = Min max=Max;
title1 'month 3 yrslive for tbarthelcat';
run;

symbol v=plus c=salmon;
axis1 minor=none color=black label=(angle=90 rotate=0);
title 'month 3 yrslive for tbarthelcat';

proc boxplot data=amonth3;
   plot yrslive*tbarthelcat  / boxstyle = skeletal
      noblabel
         cboxes = dagr
         cboxfill = ywh
         cframe  = vligb
         vaxis   = axis1;
run;

proc sort data=amonth6;
   by tbarthelcat;
run;
proc means data=amonth6 ;
   var yrslive;
   by tbarthelcat;
   title1 'month 6 yrslive for tbarthelcat';
run;
proc univariate data=amonth6 ;
   var yrslive;
   by tbarthelcat;
   output out=a
      mean=Mean mode=Mode median=Median
      q1=Q1 q3=Q3 p5=P5 p10=P10 p90=P90 p95=P95
      min = Min max=Max;
   title1 'month 6 yrslive for tbarthelcat';
run;

symbol v=plus c=salmon;
axis1 minor=none color=black label=(angle=90 rotate=0);
title 'month 6 yrslive for tbarthelcat';

proc boxplot data=amonth6;
   plot yrslive*tbarthelcat  / boxstyle = skeletal
      noblabel
         cboxes = dagr
         cboxfill = ywh
         cframe  = vligb
         vaxis   = axis1;
run;
Programming for AIM3

OPTIONS LS=80 PS=10000 nodate number pageno=1;
run;

*****************************************
*****************PROGRESS ***************
*****MERGE BARTHEL file & DEMO file *****
*****************************************

DATA Barthel (keep= treat pid bsb bs12 bs24 bs36 bs48 bs60);
SET PROGRESS.BARTHEL;
run;
PROC SORT DATA=Barthel;
BY PID;
RUN;
DATA Demo;
SET PROGRESS.DEMO;
run;
PROC SORT DATA=Demo;
BY PID;
RUN;
Data randate (keep=pid randate);
set progress.randate;
run;
PROC SORT DATA=randate;
BY PID;
RUN;
DATA sassessment (keep=pid me medate);
SET PROGRESS.SASSESSMENT;
RUN;
PROC SORT DATA=sassessment;
BY PID;
RUN;

DATA C;
MERGE Barthel Demo randate sassessment;
BY PID;
RUN;
Data d1;
set c;
if treat='Active' then treatno=1;
else if treat='Placebo' then treatno=0;
else treatno=.;
*/
proc freq data=d1;
tables treatno;
run;
*

IF (95<=BSB<=100) THEN BSBcat=1 /*'95<=BSB<=100'*/;
IF (70<=BSB<95) THEN BSBcat=3 /*'70<=BSB<95'*/;
IF (15<=BSB<70) THEN BSBcat=4 /*'15<=BSB<70'*/;
IF (0<=BSB<15) THEN BSBcat=5 /*'0<=BSB<15'*/;

IF (95<=BS12<=100) THEN BS12cat=1 /*'95<=BSB<=100'*/;
IF (70<=BS12<95) THEN BS12cat=3 /*'70<=BSB<95'*/;
IF (15<=BS12<70) THEN BS12cat=4 /*'15<=BSB<70'*/;
IF (0<=BS12<15) THEN BS12cat=5 /*'0<=BSB<15'*/;

IF (95<=BS24<=100) THEN BS24cat=1 /*'95<=BSB<=100'*/;
IF (70<=BS24<95) THEN BS24cat=3 /*'70<=BSB<95'*/;
IF (15<=BS24<70) THEN BS24cat=4 /*'15<=BSB<70'*/;
IF (0<=BS24<15) THEN BS24cat=5 /*'0<=BSB<15'*/;

IF (95<=BS36<=100) THEN BS36cat=1 /*'95<=BSB<=100'*/;
IF (70<=BS36<95) THEN BS36cat=3 /*'70<=BSB<95'*/;
IF (15<=BS36<70) THEN BS36cat=4 /*'15<=BSB<70'*/;
IF (0<=BS36<15) THEN BS36cat=5 /*'0<=BSB<15'*/;

IF (95<=BS48<=100) THEN BS48cat=1 /*'95<=BSB<=100'*/;
IF (70<=BS48<95) THEN BS48cat=3 /*'70<=BSB<95'*/;
IF (15<=BS48<70) THEN BS48cat=4 /*'15<=BSB<70'*/;
IF (0<=BS48<15) THEN BS48cat=5 /*'0<=BSB<15'*/;

IF (95<=BS60<=100) THEN BS60cat=1 /*'95<=BSB<=100'*/;
IF (70<=BS60<95) THEN BS60cat=3 /*'70<=BSB<95'*/;
IF (15<=BS60<70) THEN BS60cat=4 /*'15<=BSB<70'*/;
IF (0<=BS60<15) THEN BS60cat=5 /*'0<=BSB<15'*/;

IF (AGE<35) THEN AGECAT='AGE<35';
IF (35<=AGE<45) THEN AGECAT='35<=AGE<45';
IF (45<=AGE<55) THEN AGECAT='45<=AGE<55';
IF (55<=AGE<65) THEN AGECAT='55<=AGE<65';
IF (65<=AGE<75) THEN AGECAT='65<=AGE<75';
IF (75<=AGE<85) THEN AGECAT='75<=AGE<85';
IF (85<=AGE) THEN AGECAT='85<=AGE';

IF (HEIGHT<140) THEN HEIGHTCAT='HEIGHT<140';
IF (140<=HEIGHT<150) THEN HEIGHTCAT='140<=HEIGHT<150';
IF (150<=HEIGHT<160) THEN HEIGHTCAT='150<=HEIGHT<160';
IF (160<=HEIGHT<170) THEN HEIGHTCAT='160<=HEIGHT<170';
IF (170<=HEIGHT<180) THEN HEIGHTCAT='170<=HEIGHT<180';
IF (180<=HEIGHT<190) THEN HEIGHTCAT='180<=HEIGHT<190';
IF (190<=HEIGHT) THEN HEIGHTCAT='190<=HEIGHT';

IF (WEIGHT<40) THEN WEIGHTCAT='WEIGHT<40';
IF (40<=WEIGHT<50) THEN WEIGHTCAT='40<=WEIGHT<50';
IF (50<=WEIGHT<60) THEN WEIGHTCAT='50<=WEIGHT<60';
IF (60<=WEIGHT<70) THEN WEIGHTCAT='60<=WEIGHT<70';
IF (70<=WEIGHT<80) THEN WEIGHTCAT='70<=WEIGHT<80';
IF (80<=WEIGHT<90) THEN WEIGHTCAT='80<=WEIGHT<90';
IF (90<=WEIGHT<100) THEN WEIGHTCAT='90<=WEIGHT<100';
IF (100<=WEIGHT<110) THEN WEIGHTCAT='100<=WEIGHT<110';
IF (110<=WEIGHT<120) THEN WEIGHTCAT='110<=WEIGHT<120';
IF (120<=WEIGHT) THEN WEIGHTCAT='120<=WEIGHT';

IF (BMI<19) THEN BMICAT='BMI<19';
IF (19<=BMI<25) THEN BMICAT='19<=BMI<25';
IF (25<=BMI<27) THEN BMICAT='25<=BMI<27';
IF (27<=BMI<29) THEN BMICAT='27<=BMI<29';
IF (29<=BMI<32) THEN BMICAT='29<=BMI<32';
IF (32<=BMI<35) THEN BMICAT='32<=BMI<35';
IF (35<=BMI<40) THEN BMICAT='35<=BMI<40';
IF (40<=BMI) THEN BMICAT='40<=BMI';

IF (EDU<9) THEN EDUCAT='EDU<9';
IF (9<=EDU<12) THEN EDUCAT='9<=EDU<12';
IF (12<=EDU<16) THEN EDUCAT='12<=EDU<16';
IF (16<=EDU) THEN EDUCAT='16<=EDU';
run;

data d2;
set d1;
if treatno in (0, 1);
run;

data d3;
set d2;
day1=substr(randate,1,2);
month1=substr(randate,4,2);
year1=substr(randate,7,4);
format newrandate mmmddyy10.;
newrandate=mdy(month1,day1,year1);
RUN;

data d4;
set d3;
day2=substr(medate,1,2);
month2=substr(medate,4,2);
year2=substr(medate,7,4);
format newmedate mmmddyy10.;
newmedate=mdy(month2,day2,year2);
RUN;
/*
proc print data=d4;
var randate newrandate medate newmedate me;
run;
*/

DATA d5;
SET d4;
MRDIFDATE=NEWMEDATE-NEWRANDATE;
RUN;
/*
proc freq data=d5;
tables mrdifdate;
run;
*/

Data d6;
Set d5;
if (0<=mrdifdate<365) then deathwithinyr=1;
if (365<=mrdifdate<730) then deathwithinyr=2;
if (730<=mrdifdate<1095) then deathwithinyr=3;
if (1095<=mrDIFDATE<1460) then deathwithinyr=4;
IF (1460<=mrDIFDATE<1825) then deathwithinyr=5;
IF (1825<=mrDIFDATE<2190) then deathwithinyr=6;
run;

/*
proc freq data=d6;
tables deathwithinyr;
run;
*/

/*
proc sort data=d6;
by treat;
run;

proc freq data=d6;
tables deathwithinyr;
by treat;
title1 '  ';
run;
*/

data d7;
set d6;
if bsbcat=.' then bsbcatwM_=8888;
else bsbcatwM_=bsbcat;
if bs12cat=.' then bs12catwM_=8888;
else bs12catwM_=bs12cat;
if bs24cat=.' then bs24catwM_=8888;
else bs24catwM_=bs24cat;
if bs36cat=.' then bs36catwM_=8888;
else bs36catwM_=bs36cat;
if bs48cat=.' then bs48catwM_=8888;
else bs48catwM_=bs48cat;
if bs60cat=.' then bs60catwM_=8888;
else bs60catwM_=bs60cat;
run;
/*
proc sort data=d7;
by treat;
run;

proc freq data=d7;
tables bsbcatwM_ bs12catwM_ bs24catwM_ bs36catwM_ bs48catwM_ bs60catwM_; 
by treat;
run;
*/
data d8;
set d7;
bsbcatwM=bsbcatwM_; 
bs12catwM=bs12catwM_; 
bs24catwM=bs24catwM_; 
bs36catwM=bs36catwM_; 
bs48catwM=bs48catwM_; 
bs60catwM=bs60catwM_; 
   if deathwithinyr=1 then do;
    bs12catwM=9999; bs24catwM=9999; bs36catwM=9999; bs48catwM=9999;
    bs60catwM=9999;
   end;
   
   else if deathwithinyr=2 then do;
    bs24catwM=9999; bs36catwM=9999; bs48catwM=9999; bs60catwM=9999;
   end;
   
   else if deathwithinyr=3 then do;
    bs36catwM=9999; bs48catwM=9999; bs60catwM=9999;
   end;
   
   else if deathwithinyr=4 then do;
    bs48catwM=9999; bs60catwM=9999;
   end;
   
   else if deathwithinyr=5 then do;
    bs60catwM=9999;
   end;
run;
*/
proc sort data=d8;
by treat;
run;

proc freq data=d8;
tables bsbcatwM bs12catwM bs24catwM bs36catwM bs48catwM bs60catwM;
by treat;
run;
*/
proc freq data=d8;
tables bsbcatwm bs12catwm bs24catwm bs36catwm bs48catwm bs60catwm;
run;
data readyforaim3;
set d8;
run;

/*
DATA e_ (KEEP= TREAT THERAPY COUNTRY BSBCAT BS6CAT BS12CAT BS24CAT
BS36CAT BS48CAT BS60CAT);
SET e;
PROC freq DATA=e_;
table treat*(BSBCAT BS12CAT BS24CAT BS36CAT BS48CAT BS60CAT)/ NOPERCENT
NOCOL NOROW;
RUN;
*/

/*
DATA e_ (keep=TREAT EDUCAT BMICAT WEIGHTCAT HEIGHTCAT AGECAT GENDER
RACE);
SET e;
run;

PROC FREQ DATA=e_;
;
RUN;
*/

********************************************************************************
**********PROGRESS **************
******ANALYSIS FOR RESEARCH AIM 3******
**ANALYSIS FOR RESEARCH QUESTION 4, 1-4**
********************************************************************************

Is there a significant difference in patient's disability between ACE inhibitor
and placebo groups in respect to the Barthel Index at 1 year?
********************************************************************************
Same procedures will be applied for each year data
********************************************************************************

;/* REPEATED MEASURE ANALYSIS OF VARIANCE*/
proc glm DATA=readyforaim3;
class TREAT;
model BSB--BS48 =  
   TREAT / nouni;
   repeated Time 5 (0 12 24 36 48) polynomial / summary printe;
run;
quit;

/*INDIVIDUAL TIME POINT T-TEST / ANOVA */
PROC SORT DATA=readyforaim3;
   BY TREAT;
RUN;
PROC MEANS DATA = readyforaim3 MEAN CLM STD;
   VAR BSB BS12 BS24 BS36 BS48;
   BY TREAT;
   TITLE 'DESCRIPTION -- BARTHEL SCORE AT EACH DATA POINT';
RUN;
PROC NPAR1WAY wilcoxon data=readyforaim3 wilcoxon;
   class treat;
   var BSB BS12 BS24 BS36 BS48;
   TITLE 'Kruskal Wallis test: BARTHEL SCORE AT EACH DATA POINT';
RUN;
/*
PROC ANOVA DATA=readyforaim3 ;
CLASS TREAT;
MODEL BSB=TREAT;
MEANS TREAT ;
TITLE 'BASELINE BARTHEL SCORE T-TEST';
RUN;
PROC ANOVA DATA=readyforaim3 ;
CLASS TREAT;
MODEL BS6=TREAT;
MEANS TREAT ;
TITLE '6 MONTH BARTHEL SCORE T-TEST';
RUN;
PROC ANOVA DATA=readyforaim3 ;
CLASS TREAT;
MODEL BS12=TREAT;
MEANS TREAT ;
TITLE '12 MONTH BARTHEL SCORE T-TEST';
RUN;
PROC ANOVA DATA=readyforaim3;
CLASS TREAT;
MODEL BS24=TREAT;
MEANS TREAT ;
TITLE '24 MONTH BARTHEL SCORE T-TEST';
RUN;
PROC ANOVA DATA=readyforaim3;
CLASS TREAT;
CLASS TREAT;
MODEL BS36=TREAT;
MEANS TREAT ;
TITLE '36 MONTH BARTHEL SCORE T-TEST';
RUN;

PROC ANOVA DATA=readyforaim3;
CLASS TREAT;
MODEL BS48=TREAT;
MEANS TREAT ;
TITLE '48 MONTH BARTHEL SCORE T-TEST';
RUN;
*/

********************************************************************************
******ANALYSIS FOR RESEARCH AIM 3******
**ANALYSIS FOR RESEARCH QUESTION 4, 5-8**
********************************************************************************
Based on the categorization scheme developed in RQ1, produce Categorized Barthel(CB).
Is there a significant difference in patient's disability between ACE inhibitor and placebo groups in respect to the Barthel Index at 1 year?
********************************************************************************
Same procedures will be applied for each year data
********************************************************************************
;
proc freq data=readyforaim3;
tables treat*bsbcatwM/cmh;
title1 'baseline C-BI ';
run;

proc freq data=readyforaim3;
tables treat*bsl2catwM/cmh;
title1 '12 month C-BI ';
run;

proc freq data=readyforaim3;
tables treat*bs24catwM/cmh;
title1 '24 month C-BI ';
run;

proc freq data=readyforaim3;
tables treat*bs36catwM/cmh;
title1 '36 month C-BI ';
run;

proc freq data=readyforaim3;
tables treat*bs48catwM/cmh;
title1 '48 month C-BI ';
run;
run;

proc freq data=readyforaim3;
tables treat*bs60catwM/cmh;
title1 '60 month C-BI ';
run;

proc freq data=readyforaim3;
tables deathwithinyr;
by treat;
run;

PROC SORT DATA=readyforaim3;
BY TREAT;
RUN;
PROC NPAR1WAY wilcoxon data=readyforaim3 wilcoxon;
class treat;
var BSBcatwM BS12catwM BS24catwM BS36catwM BS48catwM;
title 'Kruskal Wallis test: Categorized BARTHEL ';
RUN;

/*
****************************************************
RQ5-1 Based on the Categorized Barthel, is there a difference in the prognosis of disability in ACE inhibitor and placebo group from baseline to year 1?
RQ5-2 Same procedure will be performed for baseline ' year 2
RQ5-3 Same procedure; baseline'year 3
RQ5-4 Same procedure; baseline' year 4
RQ5-5 Same procedure; year 1 ' year 2
RQ5-6 Same procedure; year 1' year 3
RQ5-7 Same procedure; year 1 ' year 4
RQ5-8 Same procedure; year 2' year 3
RQ5-9 Same procedure; year 2' year 4
RQ5-10 Same procedure; year 3' year 4
****************************************************
*/

proc freq data=readyforaim3;
tables treat*bsbcatwM*bs12catwM/cmh nocol nopercent;
title1 'disability: from baseline to year 1';
run;

proc freq data=readyforaim3;
tables treat*bsbcatwM*bs24catwM/cmh nocol nopercent;
title1 'disability: from baseline to year 2';
run;

proc freq data=readyforaim3;
data readyforaim3a;
set progress.readyforaim3;
if treatno=1 /*'1=Active'*/;
run;
proc freq data=readyforaim3a;
tables bsbcatwM*bs12catwM bs12catwM*bs24catwM bs24catwM*bs36catwM
bs36catwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in active treatment group : one year cycle';
run;
proc freq data=readyforaim3a;
tables bsbcatwM*bs24catwM bs12catwM*bs36catwM bs24catwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in active treatment group : two year cycle';
run;

proc freq data=readyforaim3a;
tables bsbcatwM*bs36catwM bs12catwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in active treatment group : three year cycle';
run;

proc freq data=readyforaim3a;
tables bsbcatwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in active treatment group : four year cycle';
run;

data readyforaim3p;
set progress.readyforaim3;
if treatno=0 /*'Placebo'*/;
run;

proc freq data=readyforaim3p;
tables bsbcatwM*bs12catwM bs12catwM*bs24catwM bs24catwM*bs36catwM bs36catwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in placebo treatment group : one year cycle';
run;

proc freq data=readyforaim3p;
tables bsbcatwM*bs24catwM bs12catwM*bs36catwM bs24catwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in placebo treatment group : two year cycle';
run;

proc freq data=readyforaim3p;
tables bsbcatwM*bs36catwM bs12catwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in placebo treatment group : three year cycle';
run;

proc freq data=readyforaim3p;
tables bsbcatwM*bs48catwM / cmh nocol nopercent;
title1 'disability transition in placebo treatment group : four year cycle';
run;
Programming for AIM4

OPTIONS LS=80 PS=10000 nodate number pageno=1;

*******************************
**************      AIM 4     **************
**disability prognoses among the people who**
**    experienced the recurrent stroke    **
***************************************;

/* Sort and Merge*/

DATA passessment (keep=pid se sedate);
SET PROGRESS.PASSESSMENT;
RUN;

PROC SORT DATA=passessment;
BY PID;
RUN;

data a;
set progress.readyforaim3;
run;

proc sort data=a;
by pid;
run;

DATA aim4;
MERGE passessment a;
BY PID;
RUN;

data aim4a;
set aim4;
if se=1;
run;

DATA aim4b;
SET aim4a;
day=substr(sedate,1,2);
month=substr(sedate,4,2);
year=substr(sedate,7,4);
format newsedate mmdy10.;
newsedate=mdy(month,day,year);
RUN;
/*
proc print data=aim4b;
var sedate day month year newsedate;
run;
*/
/*Calculation of date difference*/

DATA aim4c;
SET aim4b;
SRDIFDATE=NEWSEDATE-NEWRANDATE;
RUN;

/*
PROC PRINT DATA=aim4c;
VAR NEWSEDATE NEWRANDATE SRDIFDATE;
RUN;
*/

DATA aim4d;
SET aim4c;
IF (0<=SRDIFDATE<365) THEN SEinC=1 /*'0<se<=1yr'*/;
IF (365<=SRDIFDATE<730) THEN SEinC=2 /*'1yr<se<=2yr'*/;
IF (730<=SRDIFDATE<1095) THEN SEinC=3 /*'2yr<se<=3yr'*/;
IF (1095<=SRDIFDATE<1460) THEN SEinC=4 /*'3yr<se<=4yr'*/;
IF (1460<=SRDIFDATE<1825) THEN SEinC=5 /*'4yr<se<=5yr'*/;
IF (1825<=SRDIFDATE<2190) THEN SEinC=6 /*'5yr<se<=6yr'*/;
RUN;

/*
PROC SORT DATA=aim4d;
BY treat;
RUN;
PROC freq DATA=aim4d;
tables SEinC ;
by treat;
run;
*/

DATA aim4e;
SET aim4d;
if bsb=. then bsbwM_=_8888_;
else bsbwM_=bsb;
if bs12=. then bs12wM_=_8888_;
else bs12wM_=bs12;
if bs24=. then bs24wM_=_8888_;
else bs24wM_=bs24;
if bs36=. then bs36wM_=_8888_;
else bs36wM_=bs36;
if bs48=. then bs48wM_=_8888_;
else bs48wM_=bs48;
if bs60=. then bs60wM_=_8888_;
else bs60wM_=bs60;
run;

DATA aim4f;
set aim4e;
bsbwM=bsbwM_;
bs12wM=bs12wM_;
bs24wM=bs24wM_;
bs36wM=bs36wM_;
bs48wM=bs48wM_;
bs60wM=bs60wM_;
run;
data aim4g;
set aim4f;
if deathwithinyr=1 then do;
bs12wM=9999; bs24wM=9999; bs36wM=9999; bs48wM=9999; bs60wM=9999;
end;
else if deathwithinyr=2 then do;
bs24wM=9999; bs36wM=9999; bs48wM=9999; bs60wM=9999;
end;
else if deathwithinyr=3 then do;
bs36wM=9999; bs48wM=9999; bs60wM=9999;
end;
else if deathwithinyr=4 then do;
bs48wM=9999; bs60wM=9999;
end;
else if deathwithinyr=5 then do;
bs60wM=9999;
end;
run;
data aim4h;
set aim4g;
if SEinC=1 THEN DO;
basemfor2ndse=bsbwM; FiMafter2ndse=bs12wM; SMAfter2ndse=bs24wM;
TMAfter2ndse=bs36wM; FoMafter2ndse=bs48wM; fifMafter2ndse=bs60wM;
end;
if SEinC=2 THEN do;
if bs60wM=9999 then do;
basemfor2ndse=bs12wM; FiMafter2ndse=bs24wM;
SMAfter2ndse=bs36wM;
TMAfter2ndse=bs48wM; FoMafter2ndse=bs60wM;
fifMafter2ndse=9999;
end;
else do;
basemfor2ndse=bs12wM; FiMafter2ndse=bs24wM;
SMAfter2ndse=bs36wM;
TMAfter2ndse=bs48wM; FoMafter2ndse=bs60wM;
fifMafter2ndse=7777;
end;
end;

IF SEinC=3 THEN do;
    if bs60wM=9999 then do;
        basemfor2ndse=bs24wM; FImafter2ndse=bs36wM;
        SImafter2ndse=bs48wM;
        TImafter2ndse=bs60wM; PoMafter2ndse=9999;
        fifMafter2ndse=9999;
    end;
    else do;
        basemfor2ndse=bs24wM; FImafter2ndse=bs36wM;
        SImafter2ndse=bs48wM;
        TImafter2ndse=bs60wM; PoMafter2ndse=7777;
        fifMafter2ndse=7777;
    end;
end;

IF SEinC=4 THEN do;
    if bs60wM=9999 then do;
        basemfor2ndse=bs36wM; FImafter2ndse=bs48wM;
        SImafter2ndse=bs60wM;
        TImafter2ndse=9999; PoMafter2ndse=9999; fifMafter2ndse=9999;
    end;
    else do;
        basemfor2ndse=bs36wM; FImafter2ndse=bs48wM;
        SImafter2ndse=bs60wM;
        TImafter2ndse=7777; PoMafter2ndse=7777; fifMafter2ndse=7777;
    end;
end;

IF SEinC=5 THEN do;
    if bs60wM=9999 then do;
        basemfor2ndse=bs48wM; FImafter2ndse=bs60wM;
        SImafter2ndse=9999;
        TImafter2ndse=9999; PoMafter2ndse=9999; fifMafter2ndse=9999;
    end;
    else do;
        basemfor2ndse=bs48wM; FImafter2ndse=bs60wM;
        SImafter2ndse=7777;
        TImafter2ndse=7777; PoMafter2ndse=7777; fifMafter2ndse=7777;
    end;
end;

IF SEinC=6 THEN do;
    if bs60wM=9999 then do;
        basemfor2ndse=bs60wM; FImafter2ndse=9999; SImafter2ndse=9999;
        TImafter2ndse=9999; PoMafter2ndse=9999; fifMafter2ndse=9999;
    end;
    else do;
        basemfor2ndse=bs60wM; FImafter2ndse=7777;
        SImafter2ndse=7777;
        TImafter2ndse=7777; PoMafter2ndse=7777; fifMafter2ndse=7777;
    end;
end;
run;
data aim4i;
set aim4h;

IF SEinC=1 THEN DO;
basemfor2ndsecat=bsbcatwM; FiMafter2ndsecat=bs12catwM;
SMafter2ndsecat=bs24catwM;
TMafter2ndsecat=bs36catwM; FoMafter2ndsecat=bs48catwM;
fifMafter2ndsecat=bs60catwM;
end;

IF SEinC=2 THEN do;
  if bs60catwM=9999 then do;
    basemfor2ndsecat=bs12catwM; FiMafter2ndsecat=bs24catwM;
    SMafter2ndsecat=bs36catwM;
    TMafter2ndsecat=bs48catwM; FoMafter2ndsecat=bs60catwM;
    fifMafter2ndsecat=9999;
  end;
  else do;
    basemfor2ndsecat=bs12catwM; FiMafter2ndsecat=bs24catwM;
    SMafter2ndsecat=bs36catwM;
    TMafter2ndsecat=bs48catwM; FoMafter2ndsecat=bs60catwM;
    fifMafter2ndsecat=7777;
  end;
end;

IF SEinC=3 THEN do;
  if bs60catwM=9999 then do;
    basemfor2ndsecat=bs24catwM; FiMafter2ndsecat=bs36catwM;
    SMafter2ndsecat=bs48catwM;
    TMafter2ndsecat=bs60catwM; FoMafter2ndsecat=9999;
    fifMafter2ndsecat=9999;
  end;
  else do;
    basemfor2ndsecat=bs24catwM; FiMafter2ndsecat=bs36catwM;
    SMafter2ndsecat=bs48catwM;
    TMafter2ndsecat=bs60catwM; FoMafter2ndsecat=7777;
    fifMafter2ndsecat=7777;
  end;
end;

IF SEinC=4 THEN do;
  if bs60catwM=9999 then do;
    basemfor2ndsecat=bs36catwM; FiMafter2ndsecat=bs48catwM;
    SMafter2ndsecat=bs60catwM;
    TMafter2ndsecat=9999; FoMafter2ndsecat=9999;
    fifMafter2ndsecat=9999;
  end;
  else do;
    basemfor2ndsecat=bs36catwM; FiMafter2ndsecat=bs48catwM;
    SMafter2ndsecat=bs60catwM;
    TMafter2ndsecat=7777; FoMafter2ndsecat=7777;
    fifMafter2ndsecat=7777;
  end;
end;

IF SEinC=5 THEN do;
if bs60catwM=9999 then do;
  basemfor2ndsecat=bs48catwM; FiMafter2ndsecat=bs60catwM;
  SMafter2ndsecat=9999;
  TMafter2ndsecat=9999; FoMafter2ndsecat=9999;
  fifMafter2ndsecat=9999;
end;
else do;
  basemfor2ndsecat=bs48catwM; FiMafter2ndsecat=bs60catwM;
  SMafter2ndsecat=7777;
  TMafter2ndsecat=7777; FoMafter2ndsecat=7777;
  fifMafter2ndsecat=7777;
end;
end;

IF SEinC=6 THEN do;
  if bs60catwM=9999 then do;
    basemfor2ndsecat=bs60catwM; FiMafter2ndsecat=9999;
    SMafter2ndsecat=9999;
    TMafter2ndsecat=9999; FoMafter2ndsecat=9999;
    fifMafter2ndsecat=9999;
  end;
  else do;
    basemfor2ndsecat=bs60catwM; FiMafter2ndsecat=7777;
    SMafter2ndsecat=7777;
    TMafter2ndsecat=7777; FoMafter2ndsecat=7777;
    fifMafter2ndsecat=7777;
  end;
end;
run;

proc sort data=aim4i;
  by treat;
run;

proc freq data=aim4i;
  tables /*basemfor2ndse FiMafter2ndse SMafter2ndse TMafter2ndse
  FoMafter2ndse FifMafter2ndse*/
  basemfor2ndsecat FiMafter2ndsecat SMafter2ndsecat TMafter2ndsecat
  FoMafter2ndsecat FifMafter2ndsecat;
  by treat;
run;
data readyforaim4;
set aim4i;
run;
data progress.readyforaim4;
set readyforaim4;
run;

/*
/*
**************************************************************************
RQ6-1 Is there a significant difference in Barthel Index score at the first year of recurrent stroke between active and placebo ACE inhibitor intervention groups when patient experienced recurrent stroke?
RQ6-2 Same procedure applied for:
  the second year
RQ6-3 the third year
RQ6-4 the fourth year

******************************************
*/

data a (keep= basemfor2ndse FiMafter2ndse SMAfter2ndse TMafter2ndse FoMafter2ndse FifMafter2ndse treat);
set progress.readyforaim4;
run;
	only
options ps=10000 ls=80 nonumber nodate;
run;

data ab a1 a2 a3 a4 a5;
set a;
if basemfor2ndse not in (7777, 8888, 9999) then output ab;
if FiMafter2ndse not in (7777, 8888, 9999) then output a1;
if SMAfter2ndse not in (7777, 8888, 9999) then output a2;
ifTMafter2ndse not in (7777, 8888, 9999) then output a3;
if FoMafter2ndse not in (7777, 8888, 9999) then output a4;
if FifMafter2ndse not in (7777, 8888, 9999) then output a5;
run;
%macro ttest (in=, var=);
proc ttest data = &in;
class treat;
var &var;
   TITLE '';
RUN;
%mend ttest;
	ttest (in= ab, var=basemfor2ndse);
	ttest (in= a1, var=FiMafter2ndse);
	ttest (in= a2, var=SMAfter2ndse);
	ttest (in= a3, var=TMafter2ndse);
	ttest (in= a4, var=FoMafter2ndse);
	ttest (in= a5, var=FifMafter2ndse);
run;

data a;
set readyforaim4;
run;

PROC SORT DATA = a;
BY TREAT;
RUN;

PROC MEANS DATA = a lclm mean uclm q1 median q3;
VAR basemfor2ndse FiMafter2ndse SMAfter2ndse TMafter2ndse FoMafter2ndse;
/*
 *********************************************
 RQ6-5 Is there a significant difference
 in Categorized Barthel at the first year
 of recurrent stroke between active and
 placebo ACE inhibitor intervention groups
 when patient experienced recurrent stroke?
 RQ6-6 Same procedure will be applied for
 the second year after the recurrent stroke
 RQ6-7 the third year
 RQ6-8 the fourth year
 *********************************************
 */

/*CATEGORIZATION OF BARTHEL SCORE (FOR THE SECOND STROKE EVENT)*/

data a (keep= basemfor2ndsecat FiMafter2ndsecat SMafter2ndsecat TMafter2ndsecat FoMafter2ndsecat FifMafter2ndsecat treat);
set progress.readyforaim4;
run;

data ab a1 a2 a3 a4 a5;
set a;
if basemfor2ndsecat not in (7777, 8888, 9999) then output ab;
if FiMafter2ndsecat not in (7777, 8888, 9999) then output a1;
if SMafter2ndsecat not in (7777, 8888, 9999) then output a2;
if TMafter2ndsecat not in (7777, 8888, 9999) then output a3;
if FoMafter2ndsecat not in (7777, 8888, 9999) then output a4;
if FifMafter2ndsecat not in (7777, 8888, 9999) then output a5;
run;

%macro ttest (in=, var=);
proc npar1way wilcoxon data = &in wilcoxon;
class treat;
var &var;
TITLE '';
RUN;
%mend ttest;
%ttest (in= ab, var=basemfor2ndsecat);
%ttest (in= a1, var=FiMafter2ndsecat);
%ttest (in= a2, var=SMafter2ndsecat);
%ttest (in= a3, var=TMafter2ndsecat);
%ttest (in= a4, var=FoMafter2ndsecat);
%ttest (in= a5, var=FifMafter2ndsecat);
run;

PROC SORT DATA=a;
BY TREAT;
RUN;

PROC FREQ DATA=a;
TABLES basemfor2ndsecat FiMafter2ndsecat SMafter2ndsecat TMafter2ndsecat FoMafter2ndsecat /NOCOL NOPERCENT;
by treat;
TITLE1 'after 2nd stroke disability category and mortality outcome';
RUN;

PROC MEANS DATA=a lclm mean uclm q1 median q3;
VAR MRDIFDATE;
by treat;
title1 'date difference b/w mortality event and randomization date';
RUN;

/*
*********************************************
RQ7-1 For the subpopulation that had recurrent stroke - Based on the Categorized Barthel, is there a difference in the prognosis of disability between ACE inhibitor and placebo group between two time point: before and after the recurrent stroke?
RQ7-2 Same procedure will be applied for: from 'first year after stroke' to 'second year after stroke'
RQ7-3 from 'second year after stroke' to 'third year after stroke'
RQ7-4 From 'third year after stroke' to 'fourth year after stroke'
**********************************************/

PROC FREQ DATA=progress.readyforaim4;
TABLE treat*basemfor2ndsecat*FiMafter2ndsecat treat*FiMafter2ndsecat*SMafter2ndsecat treat*SMafter2ndsecat*TMafter2ndsecat treat*TMafter2ndsecat*FoMafter2ndsecat / NOCOL NOPERCENT CMH;
TITLE1 'TABLE FOR RQ7';
RUN;

proc freq data=progress.readyforaim4;
tables seinc;
run;

proc freq data=progress.readyforaim4;
tables /*basemfor2ndse FiMafter2ndse SMafter2ndse TMafter2ndse FoMafter2ndse FifMafter2ndse*/
basemfor2ndsecat FiMafter2ndsecat SMafter2ndsecat TMafter2ndsecat FoMafter2ndsecat FifMafter2ndsecat;
by treat;
run;

proc sort data=progress.readyforaim4;
by treat;
run;
proc freq data = progress.readyforaim4;
tables seinc;
by treat;
run;
LIST OF REFERENCES


2. American Heart Association; Heart disease and stroke statistics; 2003; Dallas, TX


7. Centers for Disease Control and Prevention; Healthy aging: Preventing disease and improving quality of life among older Americans; 2003


12. Department of Health and Human Services; Preventing chronic diseases: Investing wisely in health-preventing heart disease and stroke

175
13. Agency for Health Care Policy and Research; Post-stroke rehabilitation, clinical guideline number 16; 1995; Rockville, MD


44. Caro JJ, Huybrechts KF, Kelley HE. Predicting treatment costs after acute ischemic stroke on the basis of patient characteristics at presentation and early dysfunction. *Stroke*. 2001;32:100-106


49. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997


76. Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke a comprehensive review. *Stroke*. 2001;32:964-972


80. Sinclair JC, Cook RJ, Guyatt GH, Pauker SG, Cook DJ. When should an effective treatment be used? Derivation of the threshold number needed to treat and the minimum event rate for treatment. *J Clin Epidemiol*. 2001;54:253-262


110. Indredavik B. [Treatment in the stroke unit reduces mortality, disability and need for institutional care]. *Nord Med*. 1997;112:313-316


118. Ferrucci L, Guralnik JM, Pahor M, Corti MC, Havlik RJ. Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. *JAMA*. 1997;277:728-734


135. Feigenson JS, Gitlow HS, Greenberg SD. The disability oriented rehabilitation unit—a major factor influencing stroke outcome. *Stroke*. 1979;10:5-8


BIOGRAPHICAL SKETCH

Sooyeon Kwon was born and raised in Seoul, Korea. She attended Ewha Womans University for her pharmacy degree and Seoul National University for her master’s degree in pharmaceutics. After graduating in 1996 with her master’s degree, she worked for a company, Hanmi Pharmaceutical Inc., in the foreign marketing and licensing, and domestic marketing and sales department. Sooyeon moved to the United States as a graduate student in 1999. She started graduate study in the department of Pharmaceutical Policy and Evaluative Science, School of Pharmacy, at the University of North Carolina, Chapel Hill. She finished three semesters in UNC and transferred to the University of Florida in January 2001, when Dr. Abraham Hartzema, her primary advisor, moved to Gainesville as an Eminent Scholar of Pharmacoeconomics, in the College of Pharmacy, University of Florida.

In the graduate program in the College of Pharmacy, University of Florida, Sooyeon performed pharmacoeconomic evaluation on migraine medications and stroke outcomes research. She had poster and podium presentations in the year 2001 – 2004 College of Pharmacy Showcase, and won four prizes: a first prize for poster presentation; two first prizes, and one finalist in podium presentations. In addition, for the Annual Graduate Forum held by the Graduate Council in the University of Florida, she got a first prize in 2001. She received a Foreign Student Academic Achievement Award in 2002 from University of Florida.
Sooyeon is a member of the International Society of Pharmaceutical Outcomes Research (ISPOR), International Society of Pharmaco-Epidemology (ISPE), American Society of Health-system Pharmacist (ASHP), American Pharmaceutical Association (APhA) and American College of Clinical Pharmacy (ACCP). She presented her research actively in the academic conferences. She is currently working at the Rehabilitation Outcomes Research Center of Excellence (RORC) under the Department of Veterans Affairs.

Sooyeon’s interest in health outcomes research and pharmacoeconomics started from her work experience which involved medication registration processes to European Union and the United States for the exportation of medicines. In 2001, Sooyeon worked at the head office of GlaxoSmithKline in Research Triangle Park in North Carolina. During this internship, she worked on the topic of the burden of diabetes in Europe. This internship experience facilitated her interests for the Pharmacoeconomics and Health Outcomes area.

While she attended graduate school she also completed her clinical pharmacy internship required from the State of Florida to be a registered pharmacist (R.Ph.) in the State of Florida.

She is currently far away from her family, relatives and friends, but she has been enjoying her graduate life here in the United States. Sooyeon is confident that she chose the right field to which to dedicate her life.