THE UTILIZATION AND TIMING OF NEUROIMAGING AND THE ROLE OF NEUROPHYSIOLOGICAL TECHNIQUES IN THE DIAGNOSTIC EVALUATION OF TRANSIENT ISCHEMIC ATTACK

by

Jodi Dawn Edwards

BA, University of Calgary, 2001
MA, University of Calgary, 2003

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

The Faculty of Graduate and Postdoctoral Studies
(Health Care and Epidemiology)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

April 2014

©Jodi Dawn Edwards, 2014
Abstract

**Background:** Transient ischemic attack (TIA) is an episode of transient focal neurological deficit with an ischemic vascular cause. Neuroimaging can detect ischemia, determine etiologic mechanisms, and identify stroke risk after TIA, and early assessment reduces stroke risk. Despite guidelines recommending imaging, Canadian hospital-based studies have reported underutilization and delays in the use of imaging procedures after TIA. However, as many TIA patients are not evaluated in hospital, population-based studies are required to determine whether imaging use increased after guideline implementation and characterize trends in imaging timing after TIA. Although administrative databases enable population-based studies of procedure utilization and timing, previous studies have been restricted to hospital-based cohorts, as physician claims data lack validity for TIA ascertainment. Further, as many patients are not evaluated acutely, the assessment of alternative techniques may inform the subacute effects of transient ischemia.

**Methods:** In Chapter 2, sensitivity, specificity, and positive predictive value were used to evaluate the validity of multiple algorithms for TIA case ascertainment from physician claims data. Chapters 3 and 4 provided estimates of imaging utilization before and after guideline implementation and trends in imaging timing in population-based TIA cohorts. Chapter 5 used transcranial magnetic stimulation to measure thresholds for intracortical inhibition and facilitation subacutely after TIA and assessed the relationship of these thresholds with clinical features of TIA.

**Summary of Findings:** The algorithms for TIA ascertainment using physicians claims data evaluated in Chapter 2 were not valid, informing the case definition for subsequent population-based analyses. Chapter 3 showed increases in neuroimaging use but overall poor utilization
after the implementation of practice guidelines, with differences by modality and diagnostic setting. In Chapter 4, no changes in imaging timing after TIA were observed over the study period. In Chapter 5, alterations in intracortical thresholds after TIA on transcranial magnetic stimulation were observed and correlated with clinical risk scores.

**Conclusions:** This dissertation contributes new knowledge of population-based practices of the use and timing of neuroimaging after TIA and has implications for future research examining barriers for timely access to imaging techniques and the utility of alternative techniques in the diagnostic evaluation of individuals with TIA.
Preface

This statement is to certify that the work in this dissertation was conceived, conducted, and written by Jodi Edwards. All research described in this dissertation was approved by the University of British Columbia’s (UBC) Clinical Research Ethics Board: H08-00797, H10-00820, H09-02638.

Jodi Edwards is entirely responsible for the work in Chapters 1 and 6.

Chapter 2 is based on work conducted by Jodi Edwards, and Drs. Adrian Levy and Mieke Koehoorn. Jodi Edwards was responsible for the conception of the study, the study design, data analyses and interpretation, and writing and revising the manuscript. Drs. Levy and Koehoorn participated in designing the study, data interpretation, and editing the manuscript.

Chapter 3 is based on work conducted by Jodi Edwards, and Drs. Adrian Levy, Mieke Koehoorn and Boris Sobolev. Jodi Edwards was responsible for the conception of the study, the study design, data analyses and interpretation, and writing and revising the manuscript. Drs. Levy, Koehoorn and Sobolev contributed to the study design and to editing the manuscript.

Chapter 4 is based on work conducted by Jodi Edwards, and Drs. Adrian Levy and Mieke Koehoorn. JE was responsible for the conception of the study, the study design, data analyses and interpretation, and writing and revising the manuscript. Drs. Levy and Koehoorn contributed to the study design and to editing the manuscript.

Chapter 5 is based on work conducted by Jodi Edwards and Drs. Lara Boyd and Adrian Levy. Jodi Edwards was responsible for conception of the study, study design, data acquisition, data
analysis, writing the manuscript, and revising the manuscript. Dr. Boyd contributed to the conception and design of the study, assisted in data interpretation and edited the manuscript and Dr. Levy contributed to the conception and design of the study and edited the manuscript.

A version of Chapter 5 has been published: Edwards JD, Meehan SK, Levy AR, Teal PA, Linsdell MA, Boyd LA. Changes in intracortical excitability after transient ischemic attack are associated with ABCD² score. Stroke. 2011 Mar;42(3):728-33. Chapters of this dissertation that have been published may include additional details than presented in the published work to increase clarity and continuity across the chapters of this combined dissertation work.
Table of Contents

Abstract .............................................................................................................................................. ii
Preface ................................................................................................................................................ iv
Table of Contents .............................................................................................................................. vi
List of Tables ........................................................................................................................................ xi
List of Figures ....................................................................................................................................... xiii
Acknowledgements .......................................................................................................................... xiv
Dedication ............................................................................................................................................. xvi

1 Introduction ......................................................................................................................................... 1

1.1. Background .................................................................................................................................. 1

1.1.1. Context ...................................................................................................................................... 1

1.1.2. The Burden of Stroke and Transient Ischemic Attack ................................................................. 2

1.1.3. Diagnostic Evaluation of TIA ..................................................................................................... 5

1.1.3.1. The Clinical Assessment of TIA ............................................................................................... 6

1.1.3.2. Challenges for the Clinical Assessment of TIA ....................................................................... 10

1.1.3.3. Neuroimaging Assessment of TIA ............................................................................................ 13

1.1.3.4. Identifying Ischemia ............................................................................................................... 13

1.1.3.5. Pathophysiologic Mechanisms of Ischemia .......................................................................... 15

1.1.3.6. Identifying Prognostic Categories after TIA .......................................................................... 16

1.2. Clinical Practice Guidelines for Imaging in the Diagnostic Evaluation of TIA ......................... 18

1.3. Summary of Background ............................................................................................................. 20

1.4. Literature Review: Knowledge Gaps and Research Questions ..................................................... 21

1.4.1. The Utilization of Imaging in the Diagnostic Evaluation of TIA .............................................. 21

1.4.2. Primary Care Evaluation of Individuals with TIA .................................................................... 23

1.4.3. Variation in Adherence and Impact of Clinical Guidelines ....................................................... 24
1.5. The Timing of Imaging after TIA ................................................................. 26
1.6. The Use and Challenges of Administrative Health Data for Population-Based
Research ........................................................................................................... 28
1.7. The Role of Transcranial Magnetic Stimulation in the Evaluation of TIA .......... 32
1.8. Dissertation Overview .................................................................................. 35

2 Assessing the Validity of Physician’s Billing Data for the Ascertainment of Cases of
Transient Ischemic Attack .................................................................................. 37

2.1 Introduction .................................................................................................. 37
2.2 Methods ....................................................................................................... 39

2.2.1 Data Sources and Permissions .................................................................. 39
2.2.1.1. The Consolidation File ........................................................................ 40
2.2.1.2. The Hospital Separations File .............................................................. 40
2.2.1.3. The MSP Payment Information File .................................................. 41
2.2.1.4. The PharmaCare File ........................................................................ 42
2.2.2. Study Design .......................................................................................... 42
2.2.2. Algorithm Generation ............................................................................. 42
2.2.4. Base Population ...................................................................................... 43
2.2.5. Reference Standard Cohort ...................................................................... 44
2.2.6. Classification Algorithms ......................................................................... 44
2.2.7. Statistical Analyses ................................................................................ 46

2.3. Results ........................................................................................................ 47
2.4. Discussion .................................................................................................. 49
2.5. Strengths and Limitations .......................................................................... 51
2.5. Conclusions ............................................................................................... 52

3 Practice Differences for the Utilization of Neuroimaging Procedures in the Evaluation
of Transient Ischemic Attack Before and After the Implementation of Clinical Practice

Guidelines: A Population-Based Study................................................................. 54

3.1 Introduction ................................................................................................. 54

3.2 Methods ..................................................................................................... 56

3.2.1 Study Design ........................................................................................ 56

3.2.2 Data Sources ......................................................................................... 57

3.2.3. Target Population and Cohort Definition ......................................... 57

3.2.4. Study Variables .................................................................................. 58

3.2.4.1. Primary Outcome ......................................................................... 58

3.2.4.2. Explanatory Variable ................................................................... 60

3.2.4.3. Censoring Events ........................................................................ 60

3.2.4.4. Demographic and Clinical Variables ............................................ 61

3.2.5. Statistical Analysis ............................................................................. 64

3.3. Results ..................................................................................................... 65

3.3.1. Analysis of Primary Outcome ............................................................ 68

3.3.2. Secondary Analyses .......................................................................... 70

3.4. Discussion ............................................................................................... 72

3.5. Strengths and Limitations ...................................................................... 82

3.6. Conclusions ............................................................................................. 84

4 Temporal Trends in the Timing of Imaging Procedures in Individuals with Transient

Ischemic Attack ............................................................................................... 85

4.1 Introduction ............................................................................................... 85

4.2 Methods .................................................................................................... 87

4.2.1 Study Design ....................................................................................... 87

4.2.2. Data Sources ...................................................................................... 87
4.2.3. Target Population and Cohort Definition .................................................. 87
4.2.4. Primary Outcome .................................................................................... 87
4.2.5. Censoring Events .................................................................................. 88
4.2.6. Demographic and Clinical Characteristics ............................................. 88
4.2.7. Statistical Analysis ................................................................................ 89
4.3. Results .......................................................................................................... 90
4.4. Discussion ..................................................................................................... 96
4.5. Strengths and Limitations .......................................................................... 101
4.6. Conclusions .................................................................................................. 102

5 Intracortical Inhibition and Facilitation are altered after Transient Ischemic Attack and are Associated with ABCD² Score ............................................................... 103

5.1 Introduction .................................................................................................... 103
5.2 Methods .......................................................................................................... 105
  5.2.1. Participants ............................................................................................ 105
  5.2.2. Clinical Evaluations .............................................................................. 106
  5.2.3. Measurement of Intracortical Excitability ............................................. 107
  5.2.4. Data Analyses and Statistical Evaluations ............................................ 108
5.3 Results ........................................................................................................... 110
5.4. Discussion .................................................................................................... 112
5.5. Limitations .................................................................................................... 117
5.6. Conclusions .................................................................................................. 118

6 Conclusion ....................................................................................................... 119

6.1. Summary ....................................................................................................... 119
6.2. Methodological Contributions ..................................................................... 121
6.3. Contributions to Guideline Development and Dissemination ................. 122
6.4. Clinical Contributions ................................................................. 124
6.5. Strengths and Limitations ............................................................. 126
6.6. Future Research ................................................................. 129

References ..................................................................................... 131
List of Tables

Table 1. Population-based rates of TIA occurrence ................................................................. 3
Table 2. Population-based estimates for risk of stroke after TIA ............................................. 4
Table 3. Anterior circulation syndromes .................................................................................. 7
Table 4. Posterior circulation syndromes .................................................................................. 7
Table 5. Distribution of stroke etiology in four population-based studies .............................. 8
Table 6. Sensitivity and specificity of classification algorithms for the ascertainment of TIA cases from physician billing data compared to a reference standard of cases of ischemic stroke with prior TIA ............................................................................................................................ 48
Table 7. Diagnostic codes and description of study cohort definition .................................. 58
Table 8. Procedure codes for all categories of the primary study outcome ............................ 59
Table 9. Diagnostic codes and death codes for censoring events ............................................ 61
Table 10. Codes, data sources, and description of demographic and clinical variables ......... 62
Table 11. Characteristics of 1583 individuals with transient ischemic attack within 90 days prior to stroke in British Columbia from 1992 to 2007, by calendar period ......................... 66
Table 12. Proportion of individuals with TIA who underwent a neuroimaging procedure prior to stroke, by calendar period ......................................................................................... 68
Table 13. Relationship between calendar prior (pre and post clinical guidelines) and rate of neuroimaging prior to stroke among individuals with TIA patients, multivariate Poisson log-linear regression model .............................................................................................................. 70
Table 14. Relationship between guideline period and average rate of CT and carotid ultrasound imaging in individuals with TIA, multivariate Poisson log-linear regression models ............ 71
Table 15. Characteristics of 1018 individuals diagnosed with transient ischemic attack within 90 days and prior to stroke by year during the period from 1998 to 2007 ........................................... 91
Table 16. Characteristics of time to the first recorded imaging procedure among those that underwent neuroimaging within 90 days after TIA across years from 1998 to 2007 ............... 93
Table 17. Demographic characteristics for participants in stroke and healthy age-matched control groups .................................................................................................................................................. 105
List of Figures

Figure 1. Short intracortical inhibition (SICI) induced by a test pulse (TP) after an inhibitory conditioning pulse (CP) and intracortical facilitation (ICF) induced after a facilitatory CP during paired-pulse TMS .......................................................... 33

Figure 2. Description of base population, reference cohort, and classification algorithms used in the validation of physicians billing data for the identification of TIA diagnoses ................. 45

Figure 3. 2 x 2 Table for analyses of sensitivity, specificity, and positive predictive value ...... 47

Figure 4. Estimated probability of undergoing a neuroimaging procedure prior to stroke in individuals with TIA, before and after implementation of clinical practice guidelines .......... 69

Figure 5. Percent of individuals with TIA that underwent early (≤ 7 days) and late (8-90 days) imaging among those that underwent an imaging procedure within 90 days of TIA from 1998 to 2007 (N=306) ........................................................................................................ 94

Figure 6. Percent of individuals with TIA diagnosed in the a) primary care setting (N=210) and b) hospital setting (N=96) that underwent early (≤ 7 days) and late (8-90 days) imaging among those that underwent imaging within 90 days after TIA in 1998 to 2007 imaging among those that underwent imaging within 90 days after TIA in 1998 to 2007 ................................. 95

Figure 7. Mean threshold for ICI and ICF in (A) the affected and unaffected hemispheres after TIA and (B) the dominant and nondominant hemispheres in healthy participants ............... 110

Figure 8. Relationship between ABCD² score and asymmetry in thresholds for a) ICI and b) ICF .................................................................................................................................................. 111
Acknowledgements

First, I would like to thank my doctoral supervisor, Dr. Mieke Koehoorn. Her dedicated mentoring, guidance, and belief in my abilities made completing this dissertation a possibility. I am incredibly grateful to Mieke for taking me on as a student and dedicating her time and expertise to this work, despite our different research interests. Mieke’s professionalism and work ethic are truly an example for her students and I can’t say how happy I am that I had the opportunity to work with her. I would also like to extend my deepest gratitude to my committee member, Dr. Lara Boyd. During the time I have spent at UBC, Lara has involved me in her research program as she would for one of her own students, and has become one of my greatest supporters. Her mentorship has been an invaluable part of my academic growth and I am honored to have had the opportunity to know Lara both professionally and personally. I am also incredibly grateful to my committee member, Dr. Adrian Levy for undertaking the, at times not easy, job of making me think like an epidemiologist; for his time and dedication to this project, even from a distance; and for always looking out for my best interests. I would also like to thank my committee member, Dr. Boris Sobolev, for his invaluable input and assistance. The guidance and time he has offered for this dissertation are greatly appreciated.

I would like to thank my colleagues in the Brain Behaviour Laboratory, Stroke Prevention Clinic, and CHSPR, who all contributed to various aspects of this work. My labmates in the Brain Behaviour Laboratory were always there to provide assistance and moral support and are the best group of people I can imagine having spent so much time with in a lab with no windows. Specifically, the guidance of Drs. Sean Meehan and Michael Borich was integral to my understanding of transcranial magnetic stimulation and neurophysiology and I am incredibly grateful to them for their time and willingness to provide advice. Jeanie Zabukovec, Meghan Linsdell, and Elizabeth Dao provided help with patient recruitment, data collection, and life in
general. Eric Cheng and Keivan Anbarani provided help with the development of programs for data analysis. I am incredibly appreciative of my colleagues at the Stroke Prevention Clinic for allowing me access to their clinic and patients, and for all of their support with study recruitment. In particular, I am grateful to Dr. Philip Teal for his support and clinical guidance throughout this project. Finally, from CHSPR, I would also like to thank Fan Xu and Yan Wang for their invaluable help in data management and to Lillian Tamburic for her advice on the use of SAS macros.

I must also extend my gratitude to the agencies that have provided me with generous funding support throughout my degree: The Michael Smith Foundation for Health Research (MSFHR), The Canadian Institutes for Health Research (CIHR), and the Philanthropic Educational Organization (PEO) International.

Last, but certainly not least, I would like to thank my family and friends for all of their love and support throughout this entire process. To my parents, who have always believed I could do anything I set out to do and my sister, who always listens and helps me remember what is truly important. Thank you all for your unyielding support. To my friends, who have always been interested in my research and are also always willing to provide a welcome distraction. Finally and most importantly, to my amazing husband Pierre-Luc and my son Joshua. Pierre-Luc, you are the most understanding and supportive partner anyone could ask for. Thank-you for your calming influence during the tough times, for keeping me focused when my motivation wavered, and most of all, for always being my biggest supporter. And for my Joshua, who came into this world near the end of this project and has shown me more joy than I ever thought possible.
Dedication

Pour mon amour

Qui a eu foi en nous et qui continue de le faire jour après jour
1 Introduction

1.1. Background

1.1.1. Context

Acute stroke has a devastating impact on the health and quality of life of patients and their families (1). Over the past two decades, advances in the prevention, diagnosis, and treatment of cerebrovascular disease have dramatically improved the management and outcomes of individuals with acute stroke and transient ischemic attack (TIA) (2). However, stroke still accounts for 6% of all deaths in Canada (3) and up to 80% of Canadian stroke survivors are left with a disability that restricts their daily activities (4). In a recent audit of the Quality of Stroke Care in Canada by the Canadian Stroke Strategy, the authors stated “far fewer Canadians should die or be disabled from stroke when we know how to prevent, treat, and enhance recovery. The knowledge exists – we need to use it” (page 6) (5). Increased knowledge that neuroimaging can help identify individuals at increased risk of stroke, such as those with TIA, has led to the development and implementation of clinical practice guidelines recommending the use of imaging procedures in the assessment of these individuals. Although the use of neuroimaging may offer important information to guide preventive management that can reduce stroke risk and decrease rates of death and disability due to stroke, recent evidence also suggests that gaps may remain between clinical guidelines and practice of recommended procedures in the diagnostic evaluation of individuals with TIA in Canada. The studies in this dissertation examine the use and timing of currently available brain and vascular neuroimaging techniques in Canadians with TIA and explore the role of potential alternative techniques for the diagnostic evaluation of individuals with TIA.
1.1.2. The Burden of Stroke and Transient Ischemic Attack

Stroke is the cause of nearly 10% of all deaths worldwide (6) and is the third most common cause of death in Canada (7). There are an estimated 50,000 strokes in Canada each year and over 14,000 Canadians die annually from stroke (8). Almost one third of stroke survivors are functionally dependent within one year of their stroke (9), making it the leading cause of adult long-term disability in North America and worldwide (10, 11). In Canada, approximately 300,000 individuals are living with a stroke-related disability (12) and stroke-related disability is one of the main contributors to reduced disability-adjusted-life years (11). In high-income nations, stroke accounts for almost 4% of direct health-care expenditures (13). In Canada, the annual cost of stroke, including healthcare expenditures and lost economic output, is estimated at approximately $3.5 billion (14). Thus, the importance of prevention to reduce the health and economic impact of stroke is clear and identifying individuals at high risk of stroke, such as those with TIA, is an essential first step in preventing stroke and ultimately lessening the burden of stroke-related disability (15).

Cerebral ischemia is a reduction of blood flow to the brain that, below a threshold of approximately 20ml/100g brain per min, results in a series of neurophysiological and metabolic changes that in turn lead to neurological deficits and ultimately irreversible cell death (infarction) (16). TIA is an episode of transient focal neurological deficit with an ischemic vascular cause (17). Each year in Canada, approximately 15,000 individuals are diagnosed as having an occurrence of TIA (18) and, in the United States, an estimated 200,000 to 500,000 individuals are diagnosed with TIA annually (6, 19). In prospective population-based studies both within North America and abroad, reported rates of first-ever TIA occurrence range from 0.20 to 1.1 per 1000 population per year (Table 1). One study estimating TIA occurrence from 1985 to 1989 in the United States (US) reported age- and sex-adjusted rates of 0.68 per 1000 (20). More recently, rates of TIA occurrence as high as 0.83 (21) (22) and 1.1 per 1000 have
been shown (19). In Canada, TIA occurrence rates are lower than in the US, with estimates based on emergency room diagnoses from 1999 to 2000 reported as 0.44 per 1000 for first-ever occurrences of TIA and 0.68 per 1000 for all (including recurrent) occurrences of TIA (22). However, the true population-based occurrence of TIA is likely much higher than these estimates suggest as, in many individuals, transient neurological events go undiagnosed or unreported until after a major stroke occurs (5).

Table 1. Population-Based Rates of TIA Occurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study N</th>
<th>Incidence Rate per 1000 (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giroud et al. (1991)</td>
<td>Dijon, France</td>
<td>984</td>
<td>0.20 (0.15-0.24)</td>
</tr>
<tr>
<td>Brown et al. (1998)</td>
<td>Minnesota, USA</td>
<td>202</td>
<td>0.68 (0.51-0.74)</td>
</tr>
<tr>
<td>Hill et al. (2004)</td>
<td>Alberta, Canada</td>
<td>2285</td>
<td>0.68 (0.65-0.71)</td>
</tr>
<tr>
<td>Rothwell et al. (2004)</td>
<td>Oxford, UK</td>
<td>426</td>
<td>0.47 (0.39-0.56)</td>
</tr>
<tr>
<td>Kleindorfer et al. (2005)</td>
<td>Kentucky, USA</td>
<td>927</td>
<td>0.83 (0.78-0.88)</td>
</tr>
<tr>
<td>Edlow et al. (2006)</td>
<td>USA</td>
<td>769</td>
<td>1.10 (0.90-1.30)</td>
</tr>
<tr>
<td>Cancelli et al. (2011)</td>
<td>Udine, Italy</td>
<td>178</td>
<td>0.52 (0.45-0.61)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval
†adjusted rates per 1000 population

Despite the rapid resolution of clinical symptoms in individuals with TIA, these events are important predictors of recurrent cerebrovascular events, such as acute stroke (22-26). Individuals with TIA are five times more likely to have a stroke over the next two years than the general population (5) and, across studies, up to 20% of strokes recurrent to TIA have been shown to occur within 90 days of the index event (21, 23, 27, 28) (Table 2). In Canada, the cumulative risk of stroke after TIA has been reported as 1.4% at 2 days, 6.7% at 30 days, 9.5% at 90 days, 14.5% at 1 year, and 30.0% at 5 years (22). Other prospective studies have reported even higher stroke risk, with estimates ranging from 8.0% at 7 days, 11.5% at 30 days, and 17.3% at 90 days in the Oxford Vascular Study (29); to 3.9% at 2 days, 7.0% at 7 days, and 14.6% at 90 days in the Greater Cincinnati/Northern Kentucky Stroke Study (21). A recent
meta-analysis of 18 prospective studies reporting stroke risk for independent cohorts involving over 10,000 individuals with TIA across North America and Europe showed pooled estimates of 3.1% for 2 day and 5.2% for 7 day stroke risk (25). Among those presenting with an acute stroke, estimates for the occurrence of prior TIA have ranged from 7% to 40%, depending on whether included individuals were population-based or hospital-based samples (30). In Canada, more than one third of individuals with stroke have experienced a prior TIA (5). However, the extent of the relationship between TIA and stroke may not be fully appreciated, as prior studies have shown that approximately 70% of individuals do not correctly recognize the symptoms of TIA or minor stroke (31) and only half of individuals with symptoms of TIA or stroke seek medical attention (32). Thus, the true occurrence of TIA prior to stroke remains unknown. However, it is well established that, once an individual experiences a TIA, both the likelihood of a recurrent cerebrovascular event, such as stroke, and the likelihood of having a poor outcome after this event are increased.

Table 2. Population-Based Estimates for Risk of Stroke after TIA †

<table>
<thead>
<tr>
<th>Study N</th>
<th>Mean age (years)</th>
<th>Stroke Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 days</td>
</tr>
<tr>
<td>Johnston et al.(27)</td>
<td>1707</td>
<td>72.0</td>
</tr>
<tr>
<td>OCSP(33)</td>
<td>209</td>
<td>69.4</td>
</tr>
<tr>
<td>Gladstone et al.(33)</td>
<td>265</td>
<td>71.0</td>
</tr>
<tr>
<td>Hill et al.(23)</td>
<td>2285</td>
<td>71.4</td>
</tr>
<tr>
<td>BASIC(26)</td>
<td>362</td>
<td>72.3</td>
</tr>
<tr>
<td>Kleindorfer et al.(22)</td>
<td>1023</td>
<td>70.4</td>
</tr>
<tr>
<td>ABCD(34)</td>
<td>190</td>
<td>73.7</td>
</tr>
<tr>
<td>Correia et al.(35)</td>
<td>141</td>
<td>69.9</td>
</tr>
<tr>
<td>Cucchiara et al.(36)</td>
<td>117</td>
<td>63.0</td>
</tr>
<tr>
<td>Tsivgoulis et al.(37)</td>
<td>226</td>
<td>63.9</td>
</tr>
<tr>
<td>Johnston et al.(36)</td>
<td>1084</td>
<td>--</td>
</tr>
<tr>
<td>Bray et al.(37)</td>
<td>98</td>
<td>73.0</td>
</tr>
<tr>
<td>Purroy et al.(38)</td>
<td>345</td>
<td>71.4</td>
</tr>
<tr>
<td>Calvet et al.(41)</td>
<td>201</td>
<td>61.2</td>
</tr>
<tr>
<td>EXPRESS(42)</td>
<td>160</td>
<td>71.4</td>
</tr>
</tbody>
</table>
Recurrent cerebrovascular events are a significant predictor of adverse clinical outcomes and disability in both individuals with acute stroke and TIA (39-41). Prior studies have shown that, after an index stroke, recurrent strokes are typically more severe (42), and associated with higher mortality (43, 44) and poorer functional outcomes (40, 45). In a study of 1,138 individuals with acute stroke, mortality was almost double for those with recurrent compared to first-ever stroke (43) and recurrent stroke also significantly increased the risk of disability and institutionalization (39, 40). Previous studies have also shown that, even for transient index events (i.e. TIA), the occurrence of a recurrent cerebrovascular event is predictive of poor outcomes. In one study, up to one third of individuals admitted to hospital for a TIA suffered a disabling stroke during their stay that left them functionally dependent at discharge (46). Further, a recent prospective study showed that, in individuals with TIA and minor stroke left with a disability after their index event, the likelihood of a poor clinical outcome after a recurrent event was very high (41). Thus, the accurate and timely diagnosis of TIA is crucial for the prevention of stroke and stroke-related disability, given current estimates for the number of Canadians each year that experience a TIA, the high risk of future stroke in individuals with TIA, and the increased likelihood that individuals with a history of TIA will have a poor clinical outcome or permanent disability if they experience a recurrent cerebrovascular event.

1.1.3. The Diagnostic Evaluation of TIA

Unlike some conditions, there is currently no test that can definitively diagnose a TIA. As a result, TIA is a clinical assessment, based largely on information from individuals’ recollections of their symptoms during the episode of neurological deficit, provided during the
The purpose of the assessment of TIA are to: 1) establish an ischemic origin for the event; 2) exclude non-vascular causes of the event; 3) ascertain the underlying vascular mechanism to guide therapeutic strategy; and 4) identify prognostic categories for the risk of future cerebrovascular events. Although accurately attributing transient neurological symptoms to an ischemic origin and identifying the presumed vascular mechanism of ischemia are essential for determining acute management and estimating stroke risk in individuals with TIA, there are a number of challenges associated with obtaining this information solely from the clinical assessment of TIA. The following section describes the clinical features and pathophysiologic mechanisms of TIA and how this information affects acute treatment and risk profile after TIA, and outlines some of the challenges for the clinical evaluation of presenting symptoms.

1.1.3.1. The Clinical Assessment of TIA

The clinical presentation of TIA can vary widely, depending on the vascular territory affected by the event. In the anterior circulation, TIA symptoms are unilateral and are commonly characterized by motor impairment (hemiparesis or weakness), visual or sensory loss, neglect, or aphasia (speech impairment) when the dominant hemisphere is involved. Posterior circulation TIAs are less common, but may present with visual impairment, facial numbness, vertigo, nausea, vomiting, or ataxia (with or without dysarthria). Basilar artery syndromes may involve hemianopia (visual impairment) or cortical blindness, memory impairment and, in severe cases, a decreased level of consciousness or coma. Although, clinically, the presenting symptoms can provide information about the potential location of the affected vascular territory, they do not give any indication of the pathophysiologic mechanisms responsible for producing the symptoms of TIA.
### Table 3. Anterior Circulation Syndromes†

<table>
<thead>
<tr>
<th>Artery</th>
<th>Branch</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>Ophthalmic artery</td>
<td>Critical stenosis may lead to ‘limb-shaking transient ischemic attacks’ and watershed infarctions (variable presentations) ± MCA symptoms</td>
</tr>
<tr>
<td>MCA</td>
<td>M1: proximal MCA</td>
<td>Left M1: Global aphasia, right hemiparesis with face and arm more affected than leg, right hemisensory loss, right homonymous hemianopia&lt;br&gt;Right M1: Left-side neglect, left hemiparesis with face and arm more affected than leg, left hemisensory loss, left homonymous hemianopia</td>
</tr>
<tr>
<td></td>
<td>M2: MCA, superior division</td>
<td>Left M2 superior: Expressive aphasia and hemiparesis with face and arm more affected than leg&lt;br&gt;Right M2 superior: Left-side neglect and hemiparesis with face and arm more affected than leg</td>
</tr>
<tr>
<td></td>
<td>M2: MCA, inferior division</td>
<td>Left M2 inferior: Receptive aphasia with right hemisensory loss and minimal weakness&lt;br&gt;Right M2 inferior: Left hemisensory loss and minimal weakness</td>
</tr>
<tr>
<td>ACA</td>
<td></td>
<td>Contralateral hemiparesis with leg more affected than arm and face, incontinence</td>
</tr>
<tr>
<td>Small Vessel Disease (Lacunar)</td>
<td>Sensorimotor syndrome</td>
<td>Contralateral hemiparesis and sensory loss</td>
</tr>
<tr>
<td></td>
<td>Pure motor syndrome</td>
<td>Contralateral hemiparesis</td>
</tr>
<tr>
<td></td>
<td>Ataxic-hemiparesis syndrome</td>
<td>Contralateral hemiparesis and dysmetria</td>
</tr>
</tbody>
</table>

Abbreviations: ICA=internal carotid artery; MCA=middle cerebral artery; ACA=anterior cerebral artery<br>†Reprinted with permission from Lewandowski et al. 2008(48)

### Table 4. Posterior Circulation Syndromes†

<table>
<thead>
<tr>
<th>Artery</th>
<th>Syndrome</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>Lateral medullary syndrome</td>
<td>Vertigo, nausea, vomiting, hoarseness, hiccupping, ipsilateral Horner syndrome, ipsilateral dysmetria, ipsilateral facial sensory loss to pain and temperature, and contralateral arm/leg sensory loss to pain and temperature</td>
</tr>
<tr>
<td>Posterior cerebral</td>
<td>Cortical blindness</td>
<td>Contralateral hemianopia (note: with right homonymous hemianopia, check reading ability for the alexia without agraphia syndrome)</td>
</tr>
<tr>
<td>Basilar</td>
<td>Locked-in syndrome (when occlusion complete)</td>
<td>Symptoms vary but may include diminished level of consciousness, visual hallucinations, disconjugate gaze,</td>
</tr>
</tbody>
</table>
Artery Syndrome Symptoms

Small vessel disease (Lacunar) Weber syndrome alternating hemiparesis, and coma
Benedikt syndrome Ipsilateral third nerve palsy and contralateral/Hemiparesis
Claude syndrome Ipsilateral third nerve palsy and contralateral tremor or dysmetria
Millard-Gubler syndrome Ipsilateral third nerve palsy and contralateral weakness, tremor, and ataxia
Ipsilateral eye abduction palsy (sixth cranial nerve), ipsilateral facial weakness (seventh cranial nerve), and contralateral arm and leg weakness

†Reprinted with permission from Lewandowski et al. 2008(48)

The pathophysiologic mechanisms of stroke and TIA are typically classified according to the following five major categories: 1) large-artery atherosclerosis (LAA), including large-artery thrombosis and artery-to-artery embolism; 2) cardioembolism (CE); 3) small artery occlusion (SAO); 4) other causes (OC), including rare events (e.g., hypercoaguable states); and 5) undetermined causes (UND) (51). Prior studies reporting the population-based distribution of these mechanisms in both Britain and North America have indicated that, in these populations, the most common pathophysiologic categories were LAA and SAO, with approximately 50% of acute ischemic stroke and TIA events originating from large-artery or small-vessel disease (20, 29)(Table 5). A further 20% of acute ischemic events are attributable to CE, 5% to OC, and the remainder to UND.

Table 5. Distribution of Stroke Etiology in Four Population-based Studies†

<table>
<thead>
<tr>
<th>Artery</th>
<th>OXVASC Study (Britain; n=102)</th>
<th>OCSP Study (Britain; n=545)</th>
<th>Rochester (USA; n=454)</th>
<th>Erlangen (Germany; n=531)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>77</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>16.7 (0.4-23.9)</td>
<td>14.1 (11.2-17.1)</td>
<td>16.3 (12.9-19.7)</td>
<td>13.4 (10.5-16.3)</td>
</tr>
<tr>
<td>Small Vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>119</td>
<td>72</td>
<td>120</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>19.6 (11.9-27.3)</td>
<td>21.8 (18.4-25.3)</td>
<td>15.9 (12.5-19.2)</td>
<td>22.6 (19.0-26.2)</td>
</tr>
</tbody>
</table>
Identifying the underlying vascular mechanisms of ischemia is a crucial component of the diagnostic evaluation of TIA, as both estimated stroke risk and acute treatment strategies differ based on the etiologic subtype of the event. TIAs associated with a high-grade stenosis or occlusion (i.e. 70–99%) due to large-artery atherosclerosis (LAA) have previously been shown to carry the greatest risk of subsequent stroke, with studies reporting an estimated 20% risk of stroke at 90 days post-TIA in individuals with high-grade lesions (52). As a result, surgical intervention (i.e., carotid endarterectomy) is recommended after TIA in these individuals (30).

Three major prospective randomized trials demonstrated the benefit of surgery and medical therapy over medical therapy alone for reducing recurrent stroke risk among patients with either ischemic stroke or TIA and a symptomatic high-grade (>70%) carotid occlusion (53-55). Carotid stenting has been evaluated as a potential alternative to endarterectomy for individuals with high surgical risk (56) and benefits have also been reported with the use of short-term intensive antiplatelet therapy in subgroups of individuals with TIA due to LAA mechanisms (57-59).

Oral anti-coagulation therapy has been shown to reduce stroke risk in individuals with TIA or minor stroke due to cardioembolic mechanisms, such as atrial fibrillation (60, 61). For hypertensive individuals with stroke or TIA due to small vessel disease, a 43% reduction in

<table>
<thead>
<tr>
<th></th>
<th>OXVASC Study (Britain; n=102)</th>
<th>OCSP Study (Britain; n=545)</th>
<th>Rochester (USA; n=454)</th>
<th>Erlangen (Germany;n=531)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardioembolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>127</td>
<td>132</td>
<td>143</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>18.6 (11.1-26.2)</td>
<td>23.3 (19.8-26.9)</td>
<td>29.1 (24.9-33.3)</td>
<td>26.9 (23.2-30.7)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>33</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>2.9 (0.06-8.4)</td>
<td>6.1 (4.2-8.4)</td>
<td>2.6 (1.4-4.6)</td>
<td>1.7 (0.8-3.2)</td>
</tr>
<tr>
<td><strong>Undetermined</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>43</td>
<td>189</td>
<td>164</td>
<td>188</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>42.2 (32.6-51.7)</td>
<td>34.7 (30.7-38.7)</td>
<td>36.1 (31.7-40.5)</td>
<td>35.4 (31.3-39.5)</td>
</tr>
</tbody>
</table>

Abbreviations: OXVASC=Oxford Vascular Study; OCSP=Oxford Community Stroke Project; CI=confidence interval; N=number; †Reprinted with permission from Schulz and Rothwell, 2003(57)
stroke risk has been associated with combination anti-hypertensive treatment (62). For individuals with stroke or TIA associated with noncardioembolic mechanisms, including small vessel atherosclerotic occlusions and lacunar or cryptogenic events, several trials have also reported benefit for different combinations of antiplatelet therapies (57, 63-66). Although aspirin is the established first-line therapy for stroke prevention after cerebral ischemia (67), with previous studies reporting that aspirin monotherapy resulted in a 23% risk reduction for recurrent vascular events (68), recent clinical trial data have also demonstrated an incremental benefit for dual antiplatelet therapy, combining aspirin with extended-release dipyridamole (65). Despite the importance of confirming the ischemic origin of TIA and identifying the underlying mechanisms to determine risk and inform the selection of appropriate acute therapies, there are several challenges associated with obtaining this information from the clinical assessment of TIA (69-71).

1.1.3.2. Challenges for the Clinical Assessment of TIA

One of the major challenges for the clinical assessment of TIA is that the presenting symptoms of the event are often resolved by the time of evaluation (17). In the majority of cases, clinical signs of TIA last less than 1 hour, and often less than 30 minutes (72) and, according to traditional definitions of TIA, do not exceed 24 hours (30). In a pooled analysis of TIA symptom duration, 60% of events lasted <1 hour, 11% lasted <2 hours, and only 14% lasted >6 hours (73). As a result, it has been shown that less than 10% of individuals with TIA are examined by a physician when they are fully symptomatic (74). The clinical assessment of TIA thus frequently relies on the patient’s recall of information regarding the episode of neurological impairment after the symptoms have resolved. This reliance on historical information introduces the potential for recall bias, leading to a high degree of variability in the accuracy of TIA diagnoses (17). Previous studies have shown that there is a significant lack of agreement regarding TIA diagnosis among emergency physicians and neurologists, with inter-
observer agreement among diagnosing physicians reported to be as low as 50% (75). Even among stroke specialists, whose judgment is often considered to be the gold standard, agreement regarding whether a clinical event can be diagnosed as TIA has been shown to be poor (70).

During the clinical assessment, it may also be challenging to localize patient’s symptoms to a specific vascular territory. The reliability of the clinical classification of the affected vascular territory in individuals with a recent TIA or minor stroke has previously been shown to be only moderate, with inter-observer agreement on vascular territory ranging from 0.46 to 0.60 (76). Further, even if the presenting symptoms appear clinically consistent with a specific vascular territory, it does not necessarily indicate an ischemic origin for the event. There are a number of neurological conditions of non-ischemic origin that may also present with symptoms localized to a specific vascular territory and may have similar signs and duration to TIA. These ‘TIA-mimics’ can include migraine, seizure, headache, syncope, hypoglycemia, subarachnoid hemorrhage, or space-occupying lesions, such as subdural or epidural hematomas (72, 77). Previous cohort studies have shown that 25% to 50% of individuals referred for suspicion of TIA from their clinical assessment have a final diagnosis of a non-ischemic event (78, 79), contributing to the variability in the accuracy of TIA diagnoses based solely on clinical findings. However, prior studies have also indicated that, although the occurrence of recurrent vascular events, including stroke, recurrent TIA, and myocardial infarction is high within 90 days in individuals with definite TIA, these events are absent in TIA mimics, suggesting that the occurrence of a subsequent clinical vascular event may be a useful criterion to retrospectively distinguish TIA from TIA mimic (80).

A final challenge with the clinical assessment of TIA is the ability to accurately stratify individuals into risk categories based on clinical features of the presenting event. Although several clinical risk-scoring systems have been developed (34, 36), studies assessing the ability of these systems to reliably classify individuals with TIA into prognostic categories for risk of
stroke have shown variable results. The first of these systems, the California prognostic score, was validated for the estimation of 90-day stroke risk and consisted of five factors, including: age greater than 60 years; the presence of diabetes mellitus; symptom duration exceeding 10 minutes; motor weakness; and speech impairment (36). The ABCD score encompassed the same five features, with the addition of a blood pressure threshold of >140/90 mmHg at the initial assessment and a more detailed breakdown of symptom duration, with different points for the categories of <10 minutes, 10-59 minutes, and >60 minutes (34). The ABCD² score has since become one of the most widely used clinical scores and has been validated for the estimation of 2-day, 7-day and 90-day stroke risk (81). This score is recommended as part of the TIA diagnostic work-up in several clinical guidelines (72), and recent revisions to this score (e.g., ABCD²-I) extend beyond clinical features to incorporate findings from brain and vascular imaging (82). However, despite widespread use of the ABCD² score, previous studies assessing its predictive utility have been inconsistent. Results from previous retrospective studies and one small prospective hospital-based study (83) have shown that the ABCD² score demonstrates good (84) to modest (85) predictive value and good discriminatory utility for distinguishing TIA from non-vascular diagnoses (86). Yet, more recently, a prospective study assessing the accuracy of the ABCD² score for predicting stroke at 7 and 90 days demonstrated that ABCD² scores of > 5 had less than 50% sensitivity and scores of > 2 showed poor specificity (12.5%), classifying almost all individuals as high risk. These data suggest that the ABCD² is inaccurate as a predictor of recurrent stroke at 7 and 90 days and that its discriminative value is clinically unacceptable, with only limited utility to identify prognostic risk categories in individuals with TIA (87).

Recent advances in neuroimaging technologies provide the opportunity to address some of the challenges facing the clinical assessment of TIA and have led to an increased role for the use of imaging in the diagnostic evaluation of TIA (30). Imaging investigations can provide
important information to complement the clinical evaluation of TIA and inform the identification of ischemic changes and vascular mechanisms that may be used to help guide acute management strategies and improve risk stratification after TIA.

1.1.3.3. Neuroimaging Assessment of TIA

Over the past two decades, advances in neuroimaging technology have revolutionized the ability to visualize the brain and cerebrovasculature (88). Brain and vascular imaging provide important insights into the pathophysiology of cerebral ischemia (89) and, given the challenges associated with the clinical assessment of TIA, have the potential to be particularly beneficial in individuals with TIA. During the diagnostic evaluation of TIA, brain and vascular imaging can provide information to confirm the presence of ischemic changes and determine the mechanisms underlying these changes that may offer evidence to support the diagnosis of TIA. Importantly, as the risk profile of individuals with TIA and strategies for acute management differ based on this information (30, 90), the use of imaging during the diagnostic assessment can ultimately help clinicians initiate appropriate preventive interventions to reduce the risk of recurrent cerebrovascular events. The following section describes currently available imaging techniques and outlines how each of these techniques may benefit the diagnostic evaluation of TIA.

1.1.3.4. Identifying Ischemia

Investigating the presence of ischemic changes on structural brain imaging is important to help identify an ischemic origin for events with transient neurological symptoms (91) and provide support for the clinical diagnosis of TIA. This information may also be used to help rule out hemorrhage or alternative diagnoses of neurological conditions with symptoms that mimic TIA. In individuals with acute stroke, conventional non-contrast computed tomography (CT) is the most commonly used imaging modality for the identification of ischemic infarction (92). CT rapidly differentiates between ischemic infarction and acute intracerebral hemorrhage (93) and provides essential information to guide the urgent treatment of individuals with acute stroke,
particularly in the time-sensitive context of thrombolytic therapy (94). However, although non-contrast CT is a widely available and inexpensive imaging tool for the detection of hemorrhage, it has poor sensitivity to detect acute ischemic changes not associated with infarction or small areas of ischemic infarct (95). Evidence for ischemic changes on non-contrast CT in individuals with TIA varies widely across studies, with reported frequencies ranging from <1% to 34% (96). One large prospective study of 606 individuals with TIA reported relevant infarcts on CT in only 13% of individuals (97) and, in a more recent prospective study, acute ischemic changes were detected on CT in only 4% of individuals (98). Thus, although the ability to link acute ischemic changes with a transient clinical event is crucial to provide evidence supporting a clinical TIA diagnosis, detection of these changes with non-contrast CT is limited and, thus, the primary utility of CT in the assessment of TIA is to eliminate hemorrhage as the source of presenting symptoms.

Conventional magnetic resonance imaging (MRI) is more sensitive than non-contrast CT for the detection of acute cerebral ischemia (99). Previous work has demonstrated that the presence of clinically relevant acute lesions on standard MRI occurs in approximately 30% of individuals with TIA (100). Further, multimodal diffusion-weighted MRI (DWI) measures the diffusibility of water in brain tissue and offers even greater sensitivity for the detection of acute ischemic changes than both standard CT and MRI (99, 101-103), capturing cytotoxic injury within minutes of onset (104). Thus, the presence of a restricted diffusion lesion on DWI provides evidence to confirm a diagnosis of ischemia (105), enabling the clinician to focus acute management decisions on strategies appropriate for events of ischemic origin.

Several previous studies have demonstrated DWI positivity in samples of individuals with TIA. Although the proportion of individuals with TIA that show DWI abnormalities varies considerably across studies, some studies have reported that up to two-thirds of TIA patients may demonstrate focal abnormalities on DWI (100, 106-108). However, data from a recent large
multicenter, pooled analysis indicated that DWI positive findings were present in only 33% of individuals with TIA (73). It is also important to note that, although positive DWI findings offer confirmation of an ischemic origin for a transient neurological event, prior work has also demonstrated that a negative DWI investigation does not rule out the diagnosis of TIA and may, in fact, be predictive of increased risk for recurrent TIA (109). In one study of 85 individuals presenting to the emergency department within 12 hours of TIA, those without a DWI lesion on the baseline MRI were 4.6 times more likely to have a subsequent TIA at 1 year than those with a DWI lesion, but 4.3 times less likely to have a subsequent stroke. Thus, although MRI, and specifically advanced diffusion-weighted MR imaging techniques, offer improved sensitivity for the detection of ischemic changes in individuals with TIA and may provide evidence to support an ischemic origin for transient neurological symptoms, these changes are not necessarily present in all individuals with TIA.

1.1.3.5. Pathophysiologic Mechanisms of Ischemia

Identifying the pathophysiologic mechanisms of TIA is important to guide preventive management, as the acute treatment and risk profile of individuals with TIA differ based on the mechanisms that caused the TIA symptoms. Several non-invasive vessel imaging techniques, including carotid ultrasound, transcranial doppler (TCD), CT angiography (CTA), and MR angiography (MRA) are currently available for the visualization of the intra- and extracranial vasculature (99) and the identification of potential mechanisms related to the clinical event. Findings of a systematic review and meta-analysis of studies examining the utility of vascular imaging techniques for the detection of internal carotid artery stenose indicated that carotid ultrasound demonstrates 98% sensitivity and 88% specificity for the detection of atherosclerotic occlusions exceeding 50% in the internal carotid artery (ICA), and a sensitivity and specificity of 94% and 90% respectively for ICA stenoses exceeding 70% (110). Prior work has also shown that MRA is 82% sensitive and 97% specific for the identification of occlusions exceeding 50%
and that large-artery stenoses may also be readily identified using CTA (112). TCD has previously demonstrated utility for the detection of microembolic signals that can be present with extracranial or cardiac mechanisms of embolism and holter cardiac monitoring may also be used to detect cardiac embolic sources (30).

Previous studies using carotid ultrasound reported that 8% to 31% of individuals with TIA or minor stroke show evidence of an occlusion exceeding 50% in the extracranial ICA (113, 114). In recent prospective studies using CTA, large-vessel occlusions were present in 13% of individuals with TIA or stroke (115) and 34% of individuals with TIA or minor stroke demonstrated intracranial or extracranial vessel occlusions or stenosis exceeding 50% ipsilateral to the clinically relevant ischemic tissue (112). Further, prior studies combining vessel imaging with structural brain imaging have shown convergence between these measures, with almost 50% of individuals with TIA with acute DWI lesions also showing evidence of large artery occlusive disease (116). Although less common in individuals with TIA than stroke, approximately 11% of individuals admitted for TIA have atrial fibrillation detected on cardiac monitoring (117). Given the divergent management strategies for each of the different sources of ischemia, information on the underlying mechanisms of TIA from vascular imaging and other investigations can provide important information to guide the management of these individuals and may help identify those at highest risk for recurrent cerebrovascular events (70, 118).

1.1.3.6. Identifying Prognostic Categories after TIA

Although all individuals with TIA are at risk of future stroke, several factors may contribute to an increased risk for some, including factors such as the duration and type of clinical symptoms (36), and the etiological mechanism of the presenting event (119). It is thus important to identify prognostic categories for individuals presenting with TIA, as this information may influence the type and/or timing of acute management and determine whether hospitalization is required (120, 121). The addition of information from imaging findings has
been shown to significantly improve the predictive value of the ABCD² clinical risk score (74, 122, 123), suggesting that the use of imaging is an important complement to the clinical evaluation of TIA. Numerous previous studies have also demonstrated the predictive value of brain and vascular imaging information alone for the estimation of stroke risk after TIA. For instance, individuals with large artery occlusions detected on vascular imaging have been shown to be at highest risk of early stroke recurrence (53). Abnormalities on CT/CTA and MRI have also been shown to be predictive of recurrent events, or symptom progression, in individuals with TIA and minor stroke (41, 124); and the presence of DWI lesions or intracranial occlusions on vascular imaging have been associated with increased stroke risk in individuals with TIA or minor stroke (125). Further, it has also been suggested that the combination of brain and vascular imaging might incrementally improve prognostic accuracy in individuals with TIA, with results from one study demonstrating that the presence of a large artery atherosclerotic lesion on vascular imaging in combination with positive findings on DWI brain imaging independently predicted stroke recurrence at 90-day follow-up (90).

This increase in evidence for the benefits of imaging information in management decisions for individuals at high risk of stroke over the past thirty years (99) and the increased availability of brain and vascular imaging technologies across practice settings over this period (126) led to the development of clinical practice guidelines specific to the use of neuroimaging in individuals with TIA (127). Clinical practice guidelines, typically developed by health organizations or professional associations, are evidence-based recommendations on the best practices and standards of care for use by healthcare providers in the diagnosis, management, and treatment of specific clinical conditions (128). Clinical guidelines are an increasingly important tool to reduce practice variation, support efficient use of available health resources, and improve quality of care (129). Numerous dissemination strategies may be used to facilitate the uptake of guideline recommendations and promote practice change, including continuing
medical education, conferences, websites and other mass media distribution strategies, educational outreach, and financial incentives (130). The following section describes the first set of clinical practice guidelines developed for the use of imaging in individuals with TIA.

1.2. Clinical Practice Guidelines for the Use of Imaging in the Diagnostic Evaluation of TIA

In 1997, the Stroke Council of the American Heart Association (AHA) implemented the first set of clinical practice guidelines specific to the use of neuroimaging in the diagnostic evaluation of TIA (127). Prior to these guidelines, AHA recommendations for the management of TIA indicated that neuroimaging investigations for patients presenting with symptoms of TIA were only indicated if diagnosis and strategy remained uncertain after the initial clinical assessment (131). Canadian Best Practice Recommendations for Stroke Care were not developed until 2006 (14), thus the AHA guidelines were considered to be the North American practice standard until the Canadian standards became available. Although active dissemination strategies for these guidelines may have been limited in Canada, conventional dissemination of guideline recommendations to Canadian practitioners through scientific publications, continuing education, and conferences may still have influenced practice for the use of imaging.

Based on increased evidence for the benefit of neuroimaging information, the 1997 AHA guidelines recommended that individuals with TIA symptoms should be promptly evaluated and that the initial diagnostic evaluation of TIA should involve CT and vascular imaging, particularly for those individuals presenting with a clinical history suggestive of hemispheric TIA and/or high risk vascular causes (127). Specifically, recommendations for brain imaging included: 1) individuals with manifestations suggestive of hemispheric TIA receive a CT scan of the head in the initial diagnostic evaluation to exclude a rare lesion such as a subdural hematoma or brain tumor responsible for symptoms (Class III, type C); 2) despite a slight advantage of MRI over CT in detection of brain infarction appropriate to hemispheric symptoms of ischemia,
substitution of MRI for CT in initial evaluation of individuals with TIA is not warranted. MRI may be considered when a CT scan fails to substantiate the clinical diagnosis or if additional diagnoses require confirmation or exclusion (Class III); 3) CT of the head has a limited role in evaluation of individuals with vertebrobasilar TIAs, as subdural hematoma or brain tumor are not known to present with transient symptoms resembling posterior circulation ischemia (Class III). CT can detect areas of appropriate cerebellar or, less commonly, brain stem infarction; a finding that in selected instances may alter clinical management. In addition, CT may show evidence of severe atherosclerotic disease in the vertebrobasilar system, such as dolichoectasia of the basilar artery, as a potential mechanism of TIAs (Class III); and 4) the routine use of MRI in evaluation of individuals with vertebrobasilar TIAs is not justified (Class III) vis-à-vis general management, despite its advantages over CT in detection of lesions potentially related to the mechanism of posterior circulation TIAs, such as atherosclerotic tortuosity, stenosis, or occlusion of the basilar artery (Class III)(pg. 1483)(127).

For vascular imaging, recommendations included: 1) a non-invasive vessel screening technique is indicated as an initial diagnostic test in individuals with TIA symptoms, in particular for the study of vessels involved in causing symptoms of carotid hemispheric or retinal ischemia. MRA provides noninvasive imaging of extracranial carotid, vertebrobasilar, and major intracranial vessels but leads to overestimation of degree of arterial stenosis so that its role in evaluation of individuals with TIA has limitations (Class II). Contrast-enhanced CT scanning of the cervical vessels with helical methodology, in particular images of the arterial wall as well as the lumen, may be helpful as a screening tool in centers where it is available (Class III); and 2) radiographic arteriography best defines surgically remediable lesions in the accessible, extracranial segment of the carotid artery. Radiographic arteriography is generally recommended for a symptomatic patient when non-invasive tests indicate 70% occlusion in the appropriate carotid artery and exclusions do not apply (pg. 1485) (127).
1.3. Summary of Background

In summary, the preceding section described stroke as a major cause of morbidity and mortality in Canada and outlined evidence for TIA as an important predictor of stroke risk. This section also summarized current evidence on the utility of available neuroimaging techniques to detect ischemia, determine ischemic mechanisms, and identify prognostic categories and ultimately help inform the diagnostic evaluation and guide acute management strategies in individuals with TIA. This evidence helped to inform the development and implementation of clinical practice guidelines for neuroimaging in the evaluation of TIA, with specific recommendations for the use of brain and vascular imaging individuals presenting with TIA, as outlined above.

Despite the implementation of guidelines for the use of imaging after TIA in 1997 and continued scientific support for the benefits of brain and vascular imaging in the diagnostic evaluation of TIA since that time, evidence from recent hospital-based studies suggests that gaps may remain between evidence and practice for the use and timing of these techniques in the assessment of TIA individuals in Canada. The evaluation of population-based practice changes for the utilization and timing of available imaging procedures associated with the implementation of these guidelines is required to identify potential practice gaps and inform the development and implementation of future evidence-based recommendations for the diagnostic evaluation of TIA across all practice settings where individuals with TIA present for care. Further, the assessment of alternative techniques for the detection of ischemic changes after TIA may offer additional tools to help address existing practice gaps and optimize the diagnosis and management of individuals with TIA. The following section provides a rationale for further research on the use and timing of neuroimaging in individuals with TIA that may contribute to the understanding of the impact of clinical practice guidelines on the population-based utilization of imaging procedures, provide information to characterize current practice for the
timing of imaging after TIA, and advance current knowledge regarding the potential of neurophysiological techniques for the evaluation of the short term effects of transient ischemia on the brain in individuals with TIA.

1.4. Literature Review: Knowledge Gaps and Research Questions

1.4.1. The Utilization of Imaging in the Diagnostic Evaluation of TIA

Previous studies evaluating the use of imaging in the diagnostic evaluation of individuals with TIA have indicated that, despite guideline recommendations and evidence for the benefit of imaging information, utilization rates for imaging procedures after TIA remain low. In a retrospective study identifying TIA cases from a national survey of ambulatory care in the United States (US), CT scans were performed within 90 days of the presenting TIA in only 56% of cases (132). Another emergency department-based study found that, across 16 tertiary care centers in the US, CT was obtained in only 67% of eligible cases (98). In addition, a population-based study of individuals with TIA evaluated in primary care practices across the US reported that only 23% of cases were referred for imaging investigations, including both CT and MRI, on the day of the index event, confirming that utilization of neuroimaging procedures in the primary care setting is also low (133). These studies suggest that, in both hospital and primary care settings, gaps remain between practice recommendations and the use of imaging procedures for the evaluation of TIA.

Although fewer studies have evaluated the utilization of imaging procedures after TIA in Canada, results from two previous hospital-based studies indicated that imaging procedures are also underutilized in the emergency department assessment of Canadians with TIA. In one study, individuals with TIA presenting to four different emergency departments in Ontario from May to December 2000 were prospectively identified from a stroke registry (134). Most individuals with TIA in this cohort were discharged from the emergency department and, of
those discharged, only 31% received neuroimaging (CT or MRI) prior to discharge. Further, in
the 30 days following the index TIA, only 58% underwent an outpatient CT procedure, 44% a
carotid ultrasound, 3% an MRI, 5% cerebral angiography and 19% echocardiography, indicating
the underuse of both urgent and outpatient imaging procedures for individuals evaluated in the
emergency department setting (134). In another study, individuals with TIA presenting to the
emergency department of a tertiary care center in Alberta in 1997 were retrospectively identified
and evaluated for in-hospital imaging from chart review (135). Although results indicated that
the majority of individuals presenting with TIA in this cohort underwent a CT scan in the
emergency department (81%), vascular imaging procedures were underutilized, with only 16%
receiving a carotid ultrasound in the emergency department and an additional 26% receiving
outpatient referral for this procedure (135).

Evidence from the preceding studies suggests that clinical practice guidelines
recommending imaging in the diagnostic evaluation of individuals with TIA may have had
minimal impact on practice in Canada. However, these studies were restricted to TIA cases
presenting to emergency department practice settings only and did not examine potential
changes in imaging practices over time, following the implementation of clinical practice
guidelines for individuals with TIA. As many individuals with TIA are not evaluated in
hospital-based practice settings, it is difficult to determine whether these findings represent
population-based practices for the use of imaging after TIA in Canada. In addition, as no
previous population-based studies have evaluated longitudinal practices for the use of imaging
procedures after TIA in Canada, there are no available data on whether practice changes
occurred in relation to the implementation of clinical guidelines for imaging in this population.
The following section reviews the literature on the primary care evaluation and management of
TIA and the variation in the uptake of stroke clinical practice guidelines across care settings,
providing additional rationale for the importance of population-based studies to determine
whether clinical guidelines influenced practice for the use of imaging in the diagnostic evaluation of TIA.

1.4.2. Primary Care Evaluation of Individuals with TIA

Several previous studies have demonstrated that, rather than presenting to hospital with TIA symptoms, many individuals with TIA are evaluated and managed on an outpatient basis by their primary care provider (133). In population-based studies of patient’s behaviour in seeking medical attention in the United Kingdom (UK), 77% of individuals with TIA or minor stroke first sought medical attention for their symptoms through their primary care physician (31) and only 9.9% of TIA cases presented to the emergency department (136). General practice opening hours in the UK have also been shown to have a significant impact on the median time to seek medical attention after TIA. Individuals experiencing events after their general practitioner’s regular hours were significantly less likely to seek medical attention within 24 hours (137). Recent qualitative data examining global trends in management approaches for individuals with TIA showed a more even distribution, as approximately half of individuals in France, Germany, Spain and the UK initially sought medical care from their general practitioner or primary care practice; while approximately 70% of individuals with TIA in Italy and the US entered the clinical path via the emergency department (138). Similarly, in a recent comparative study of patient behaviour in Canada, approximately 65% of Canadians presented with TIA symptoms to the emergency department (139). A practice audit of primary care medical practices in the US also showed that only 2% of individuals presenting to their family physician with a first TIA were admitted to hospital for evaluation on the day of the index visit, 31% had no hospitalization or evaluations during the first 30 days, and only 45% were sent for specialist referral (133). Similarly, in a survey of primary care physicians in Germany, 50.9% of general practitioners preferred the outpatient management of TIA (140). Thus, in addition to initially presenting to primary care, a significant proportion of individuals with TIA may also be
managed entirely on an outpatient basis by their family physician. Findings of these studies indicated that, across countries, individuals with TIA are evaluated and managed on both an urgent and outpatient basis and suggest that population-based studies assessing the utilization of guideline recommended services in the TIA population should include individuals diagnosed and managed in both care settings.

1.4.3. Variation in Adherence and Impact of Clinical Guidelines

The potential impact of clinical guidelines on health outcomes depends on the successful implementation of guideline recommendations into practice (141, 142) and evidence for observable practice changes resulting from guideline implementation is varied (143-145). Although adherence to clinical guidelines is lower in the primary care setting (146), some studies have shown that, across various clinical populations and care settings, clinical guidelines reduce inequities in access to services and improve patient outcomes and quality of care (147-149). However, other studies have demonstrated that the uptake of clinical guidelines results in only moderate improvements in health indicators (150-153).

For individuals with stroke and TIA, evidence for the impact of clinical guidelines on management across different care settings is inconsistent. Several previous studies evaluating the impact of clinical guidelines on the management of individuals with stroke and TIA have shown improved patient outcomes associated with adherence to clinical guidelines, including mortality (154), diagnosis and treatment (155), functional recovery (154, 156), and patient satisfaction (157). In one study, compliance with general AHA guidelines for individuals admitted with acute ischemic stroke resulted in a 15% reduction in mortality and a 13% increase in treatment effectiveness at a 6 month follow-up (154). Compliance with AHA guidelines specific to in-hospital treatment with systemic thrombolysis has also been shown to decrease mortality rates (158), while non-compliance with recommendations has been associated with increased rates of intracerebral hemorrhage (159). Further, one prospective study in the US
showed that participation in a ‘Get With the Guidelines’ national quality improvement program for treatment of individuals hospitalized with stroke or TIA was associated with sustained improvements in several performance measures over a five year program period (160). In the primary care setting, one previous study demonstrated that the implementation of evidence-based guidelines resulted in a 36% increase in the diagnosis of atrial fibrillation and improved quality of treatment for individuals with TIA (155). Another study evaluating the implementation of a quality improvement program in primary care clinics showed a 41% increase in specialist referral rates and improved early treatment and preventive advice for individuals with TIA (161).

By contrast, other studies evaluating clinical guidelines have shown that recommendations have had a minimal impact on specific care outcomes for individuals with stroke and TIA. Previous studies assessing adherence to recommendations for the use of lipid-lowering agents in hospitalized stroke and TIA individuals with low-density lipoprotein levels have reported the underuse of lipid treatment, indicating that those at greatest risk of cardiovascular events were least likely to be at guideline-recommended levels (162). Conversely, the overuse of anti-hypertensive therapies compared to AHA guidelines in individuals admitted for acute ischemic stroke has also been shown (163). Prior work has demonstrated that rates of in-hospital screening for mood and cognitive dysfunctions and access to psychological services in post-stroke individuals are suboptimal compared to guideline recommendations (164) and, despite published recommendations describing 11 major criteria for the establishment of primary stroke centres (165) none of these criteria have been shown to improve measured outcomes, including in-hospital mortality or frequency of discharge home (166). Adherence to recommended protocols for use of oral anticoagulation in individuals with atrial fibrillation has been shown to be low among general practitioners (167) and, in a survey of over 800 family physicians in the US regarding their practices for cardiovascular risk management, significant gaps were observed
between guideline recommendations and treatment practices for both antiplatelet and lipid lowering therapies (168).

This variation in findings for adherence to clinical guidelines for the management of individuals with stroke and TIA in different care settings highlights the need for continued research on the effects of guideline implementation on clinical practice in these populations. The evaluation of practice patterns in relation to clinical guidelines is an important measure of practice change and may help identify potential gaps in evidence-based care. Although prior hospital-based studies have suggested that imaging procedures are underutilized in the diagnostic evaluation of TIA in Canada, no previous studies have examined whether changes in practice for the use of imaging in individuals with TIA occurred after the implementation of clinical guidelines. Further, given the number of TIA cases that may be diagnosed and managed through the primary care system, population-based studies examining utilization for individuals evaluated in both hospital and outpatient settings are warranted to determine the impact of clinical guidelines on imaging procedure utilization in individuals with TIA.

Thus, to determine whether clinical practice guidelines for imaging after TIA influenced population-based practices for the utilization of neuroimaging procedures in individuals presenting with TIA in Canada, the following Research Question was investigated in this dissertation (Chapter 3): **Did population-based utilization of neuroimaging procedures in individuals presenting with TIA increase after the implementation of the American Heart Association imaging practice guidelines in 1997 and did utilization vary by care setting (primary care versus hospital setting) or type of neuroimaging procedure?**

1.5. The Timing of Neuroimaging Investigations after TIA

In recent years, there has been an increased recognition that much of the risk of stroke after TIA is accrued very early after the index event (169, 170). Previous work evaluating the
The timing of stroke after TIA has demonstrated that almost half of ischemic strokes occur within 48 hours of the index TIA (23, 27-29). Thus, the timing of the diagnostic assessment, including the timing of imaging investigations that contribute to the overall clinical picture, may play an important role in effective preventive management after TIA.

Recent studies have shown that the risk of stroke after TIA is reduced when rapid diagnostic assessment and initiation of preventive treatments are performed in individuals with TIA (78, 171, 172). Two previous prospective observational studies that compared the assessment and treatment of individuals with TIA in rapid access clinics with standard clinic-based assessment and primary-care-initiated treatment reported significant reductions in stroke risk associated with rapid assessment (within 48 hours) protocols (42, 43). Further, results from a recent randomized controlled pilot trial assessing the impact of the initiation of antiplatelet or statin therapy within 24 hours after TIA or minor stroke on recurrent stroke risk showed a potential role for urgent treatment in reducing recurrent events, underscoring the need for continued investigation of the potential benefits of intervention in the hyper-acute phase of TIA (65). Delays to imaging and intervention in TIA patients have also previously been associated with an increased risk of preventable early recurrent stroke (60). Thus, given the evidence for the high risk of stroke after TIA and increasing evidence to support the benefits of urgent evaluation in reducing this risk, there is an evolving consensus that rapid diagnosis and treatment are important factors in optimizing management strategies for the prevention of stroke in individuals with TIA.

A recent audit of the quality of stroke care in Canada provided an evaluation of hospital-based practices on the use and timing of imaging after TIA (5). This audit consisted of data representing 38,210 patients admitted to 295 Canadian hospitals from 2008-2009, including 6,510 admitted for TIA. Results revealed that only 13% had undergone imaging within one hour of their arrival to the emergency department, and only 69% within 24 hours, suggesting that the
timing of imaging procedures performed in individuals admitted to hospital for TIA may be suboptimal. There are no currently available population-based studies evaluating the timing of imaging procedures performed in individuals diagnosed with TIA across care settings (hospital and primary care) in Canada. However, data characterizing population-based trends in the timing of imaging procedures performed in individuals with TIA in different care settings may offer important insights into how quickly Canadians presenting with symptoms of TIA to both inpatient and outpatient care are undergoing neuroimaging investigations and whether the timing of these procedures has decreased in recent years.

To determine whether the timing of imaging procedures performed in individuals presenting with TIA in Canada has decreased over time, the following Research Question was investigated in this dissertation (Chapter 4): Among individuals that underwent imaging within 90 days of TIA diagnosis, has the timing of neuroimaging procedures performed after TIA decreased over time?

1.6. The Use and Challenges of Administrative Health Data for Population-Based Research

Administrative health data are longitudinal population-based data sources that provide detailed individual-level information on diagnoses, procedures, and medications for entire populations over several years. These data are an increasingly valuable resource for research on health service utilization and outcomes (173) and are potentially well-suited for the investigation of imaging procedure utilization and timing in the Canadian TIA population. However, one limitation of these data for population-based studies is the ability to reliably ascertain TIA cases from certain types of administrative records.

In Canada, administrative health data are obtained from multiple sectors, including inpatient facilities, medical services plans, vital statistics, and prescription drug systems (174). Canada’s universal medicare system ensures almost complete population coverage for the
majority of services administered within these sectors (175). Administrative health data used in this dissertation were obtained from the British Columbia Ministry of Health via Population Data British Columbia (henceforth Population Data BC) and the extract used in the studies in Chapters 2 to 4 included records from the following databases: 1) the Consolidation file (medical service plan (MSP) registration); 2) the Hospital Separations file; 3) the MSP Master Payment Information file (physician and health professional outpatient services); and 4) the PharmaCare file (comprehensive prescriptions for those 65 and older), for the fiscal period of April 1, 1989 to March 31, 2008 (176). These administrative data are routinely collected at the time of the health services encounter for the purposes of diagnostic classification and physician or procedural billing (177) and consist of detailed individual-level information on diagnoses, procedures, and medications for the population over several years. These databases are useful for system-level health service planning, performance reporting and evaluation, and clinical decision-making (178) and are also increasingly used for research on health service utilization and health outcomes (173). However, as they are not designed for research purposes, the validity of using these administrative data for research relies directly with the data quality.

Data quality has previously been defined as “the whole of planned and systematic procedures that take place before, during, and after data collection to guarantee the quality of data in a database for it’s intended use” (179). One of the main indicators used to evaluate the quality of administrative data is whether the data are valid compared to an external data source (178). Several potential threats to validity need to be considered and addressed when conducting research using administrative health databases. A number of steps are involved for the diagnosis or procedure to be accurately captured in the administrative record and errors at any of these steps can significantly influence the completeness and validity of the data (180). Missing or incomplete data are frequently encountered in large databases and can bias study results, particularly if the missing data are not randomly distributed (177). Inaccuracies in the data also
have the potential to introduce bias into the results of a study (180). Further, the quality of recorded information may vary substantially between physicians and hospitals, or across jurisdictions (181). In Canada, national hospital databases developed by the Canadian Institute for Health Information (CIHI), including the Discharge Abstract Database, use a standard abstraction form and quality evaluation methodology, increasing the validity of these data (174).

A well-documented issue for the use of administrative databases is the validity of coding of information on diagnoses and procedures (181-183). The degree to which the coded information measures the actual patient diagnosis or procedure performed (i.e., measurement validity) is a major concern for researchers using administrative data, as invalid data can result in the misclassification of diagnoses or procedures and bias the interpretability and generalizability of study findings (181). Data validity varies substantially across different diagnostic classes and care providers and, as a result, there is an increasing recognition of the importance of using validated algorithms for the identification of diagnostic records to minimize the potential for misclassification and bias (182).

Hospitalization data from the Canadian Institute of Health Information (CIHI) discharge abstract database demonstrate high validity for the ascertainment of stroke diagnoses (183-187). Prior studies evaluating International Classification of Diseases, Ninth Revision (ICD-9) codes for Cerebrovascular Diseases (in the range of 430.x-438.x) for the ascertainment of stroke diagnoses have shown the highest sensitivity and positive predictive value for algorithms using codes 430.x, 431.x for hemorrhagic stroke and 434.x and 436.x for ischemic stroke. In general, these studies also indicated that the primary discharge position, denoting the diagnosis primarily responsible for admission from among multiple potential diagnostic codes related to an individual’s hospital stay, is associated with higher positive predictive values (PPVs) (184). Studies using algorithms with combinations of codes from hospital discharge data have also reported PPV’s of 85% or higher (184) for the identification of stroke. Although fewer studies
have assessed the validity of TIA diagnostic coding, validated algorithms for the identification of TIA diagnoses from hospital discharge data are also available (184). Previous studies evaluating the ICD9 code 435.x for the identification of TIA cases from hospital discharge records or emergency department visits have reported PPVs of 70% or higher associated with these data and, similar to ischemic stroke, records from the primary discharge position show greater sensitivity (183, 187-189).

By contrast, physicians billing data have demonstrated reduced validity for the ascertainment of TIA diagnoses. A major challenge with the use of physicians billing data is that primary care diagnoses of TIA are subject to poor diagnostic accuracy (183, 190) and high rates of misclassification (191), and variation across providers has rendered these data difficult to validate at the population-based level. For instance, two previous studies examined the validity of ascertaining TIA cases using algorithms involving both inpatient and outpatient data and reported lower PPVs than studies where cases ascertainment was based on hospital discharge data alone (192, 193). As a result, the majority of studies to date using administrative data to evaluate TIA populations have been restricted to the use of hospital discharge administrative data for TIA case ascertainment. However, given the number of individuals with TIA that may be diagnosed and managed through the primary care system (133), validated algorithms for TIA cohorts that include cases ascertained from physician billing data would enable the population-based analyses of individuals diagnosed and managed across different care settings. In an effort to validate information across different administrative population-based data sets (194-196), Roos et al assessed the concordance and validity of data elements from linked hospital discharge abstracts and physician claims databases (195). This comparative quality assessment technique was subsequently used to examine the validity of hospital coding and physician claim submissions for surgical procedures (197).
As an essential step in addressing the above described knowledge gaps regarding population-based practices for imaging utilization (Chapter 3) and timing (Chapter 4) in individuals with TIA, a methodological study was used to address the following Research Question (Chapter 2): **Can a valid algorithm for the ascertainment of TIA cases from physician billing administrative health be identified?**

1.7. The Role of Transcranial Magnetic Stimulation in the Evaluation of TIA

Although prior evidence indicates that early assessment and intervention after TIA are important factors for the reduction of stroke risk in this population, it has also been established that many individuals delay seeking medical care after experiencing TIA symptoms (31, 198) and are not assessed within the highest risk window for stroke. In addition, although prior studies have indicated that available imaging techniques, such as DWI, have high sensitivity to detect ischemic changes acutely after TIA (101), only a small proportion of individuals show abnormalities on diffusion imaging in the subacute phase after TIA (199) and previous work has also shown that negative DWI findings do not rule out a diagnosis of TIA (109). It is thus important to evaluate the potential of alternative techniques to provide information about the short-term effects of transient ischemia on the brain. Transcranial magnetic stimulation (TMS) is a neurophysiological stimulation technique that measures the excitability of the brain’s cortical pathways (200-202). TMS has been widely used to measure the impact of ischemia on the cortical motor networks in individuals with acute and subacute ischemic stroke (203, 204); however, few studies have examined its ability to detect changes in excitability after TIA. The following section describes TMS and reviews the literature on the use of TMS in individuals with stroke and TIA.

TMS is a non-invasive method of stimulating the cerebral cortex that has been widely used to measure the impact of ischemia on the cortical motor networks in individuals with acute
and subacute ischemic stroke (203, 204). TMS delivers a brief (<1 ms) electromagnetic pulse that activates cortical motor neurons (205, 206) and produces a motor evoked potential (MEP) in the contralateral musculature, which provides a measure of the excitability of the corticomotor pathway (207). The minimal stimulator intensity required to induce an MEP in the target muscle represents the (resting or active) motor threshold for an individual.

TMS also enables the excitability of intracortical inhibitory and facilitatory interneurons to be measured using paired-pulse stimulation techniques (208, 209) (202, 203) (Figure 1). Past work employing paired pulse TMS measures has shown that, in the acute phase of stroke recovery, excitability in intracortical circuits is altered in both the ipsi- and contralesional cerebral hemispheres (203, 204, 210-214). These studies have generally demonstrated reductions in short intracortical inhibition (SICI) in ipsilesional (211, 213) and contralesional intracortical networks after acute stroke (203, 204, 210). The physiological mechanisms underlying altered intracortical excitability relate to the intracortical transmission of gamma-aminobutyric acid (GABA) and glutamate (215, 216).

†Figure reprinted with permission from Goss et al. 2012(217)

Figure 1. Short intracortical inhibition (SICI) induced by a test pulse (TP) after an inhibitory
conditioning pulse (CP) and intracortical facilitation (ICF) induced after a facilitatory CP during paired-pulse TMS†

Post-ischemic alterations in the cortical neurophysiology, measured with TMS, are emerging as an important predictive measure of functional outcome after acute ischemic stroke. Prior work has demonstrated that, in the first week after stroke, the presence or absence of MEPs in the paretic limb in response to stimulation of the affected hemisphere predicts post-stroke functional recovery (218-221). The excitability of intracortical neurons is also altered in both ipsilesional and contralesional cortices following acute stroke and these changes have been shown to have predictive value for functional outcomes post-stroke (222, 223). Despite prior evidence for the prognostic utility of neurophysiological changes following ischemic stroke, the nature of intracortical excitability and potential predictive value of these measures in individuals with TIA has not been well characterized.

Few studies have examined whether alterations in intracortical excitability are present after episodes of transient ischemia. One study using single-pulse TMS in individuals whose motor symptoms persisted for > 1 hour reported an increase in resting motor thresholds after TIA (224). However, a separate paired-pulse TMS study demonstrated significant shifts in ipsilateral intracortical inhibition in a subset of individuals with very brief TIA (< 10 minutes); a trend for altered intracortical facilitation (ICF) was also observed and these effects were observed in the absence of structural changes on CT or MRI (225). These data suggest that, similar to acute stroke, TIA may have an impact on GABAergic and glutamatergic neurotransmission. Thus, post-ischemic alterations in cortical excitability may be present, even after transient episodes of ischemia and in the absence of abnormalities on structural brain imaging.

The assessment of TMS technologies in TIA is in its infancy and there are several unanswered questions about the potential value of TMS measures in this clinical population.
Although previous data suggest that short-term alterations in intracortical excitability are present after TIA (224, 225), these studies involved the use of methodologies potentially limited in their ability to detect post-ischemic changes in intracortical excitability (226), did not include comparisons with healthy age-matched adults, and reported inconsistent findings with respect to symptom duration. Further studies are required to characterize the nature of changes in intracortical excitability after TIA and identify potential relationships between altered excitability and clinical features previously shown to be associated with an increased risk of stroke after TIA.

To determine whether intracortical excitability is altered after TIA and evaluate the potential clinical relevance of TMS for the diagnostic evaluation of TIA, the following research question was investigated (Chapter 5): Are changes in intracortical excitability on paired-pulse transcranial magnetic stimulation observed after TIA and do they relate to clinical features of increased stroke risk after TIA?

1.8. Dissertation Overview

This dissertation is divided into six chapters with a focus on health service utilization and alternative health technologies in the diagnostic evaluation of TIA. Chapter 2 reports the results of a study that assessed the validity of classification algorithms for the ascertainment of TIA cases from a physicians billing database. Chapter 3 presents differences in the utilization of imaging procedures before and after the implementation of imaging practice guidelines in a population-based cohort of individuals with TIA. Chapter 4 describes the timing of imaging procedures performed in a population-based cohort of individuals with TIA across years from 1998 to 2007, and trends in imaging timing across this study period. Chapter 5 describes an experimental TMS study that investigated whether changes in intracortical excitability were present in individuals with TIA and related these changes to the clinical features of the event, as
measured by the ABCD\textsuperscript{2} score. Chapter 6 provides a summary of the findings of these studies, describes the overall contributions, strengths and limitations of this work, and outlines recommendations for future research in this area.

Chapters include additional detail to that of published articles to increase clarity and continuity across the dissertation work. While I have primary responsibility for all of the research in this thesis, a detailed description of my contributions and the contributions of my coauthors is provided at the beginning of this dissertation.
2 Assessing the Validity of Physicians Billing Administrative Data for the Ascertainment of Transient Ischemic Attack

2.1. Introduction

Administrative health data are increasingly used in studies of health service utilization and health outcomes (173). As administrative data are collected at the time of the health care encounter for the purposes of diagnostic classification and physician or procedural billing, the validity of administrative records is an important consideration when using these data for research purposes (177). The extent to which records coded in an administrative database accurately reflect patient diagnosis or procedure performed may vary considerably across different clinical populations and care settings (181-183, 227). For acute cerebrovascular events, such as stroke and transient ischemic attack (TIA), the validity of records coding diagnostic information is influenced by the fact that these events may be diagnosed and recorded in various care settings (e.g. hospital versus primary care) (227) and that diagnoses may vary by subtype (e.g., ischemic versus hemorrhagic) (184, 185, 190). As a result, there is an increasing recognition of the importance of using validated algorithms for the ascertainment of cases from administrative diagnostic records to minimize the potential for misclassification and bias (182).

Previous studies evaluating algorithms for TIA case ascertainment involving codes from both inpatient and outpatient databases have reported reduced validity when physicians billing data are included, as compared to the use of hospital discharge data alone (192, 193). These data are challenging to validate, as primary care diagnoses of TIA may be subject to poor diagnostic accuracy (183, 190) and high rates of misclassification (191), and individuals with TIA may follow several different care pathways after an initial encounter with a primary care physician, (133). As a result, the majority of previous studies using administrative data to evaluate TIA populations have been limited to the use of TIA cohorts ascertained from emergency department
or hospital discharge databases (184). However, as several studies have shown that a significant proportion of individuals with TIA may be diagnosed and managed by their primary care physician and not evaluated or admitted to hospital (31, 133, 140, 228), it is important to identify a validated algorithm for the ascertainment of TIA cases from physician billing data to enable population-based analyses of individuals with TIA.

One of the main indicators used to evaluate the quality of administrative data is whether the information is valid compared to an independent “gold standard” (178). A number of recent studies have used a combination of linked, population-based datasets to validate administrative health information (194, 197). For example, Roos et al. (2005) assessed the concordance and validity of data elements across linked hospital discharge abstracts and physician claims databases (195) and this methodology was then also used to examine the validity of physician claims submissions for surgical procedures in Ontario (197). One challenge in using data from multiple administrative databases to examine the validity of algorithms for physicians billing diagnoses of TIA is in identifying an administrative reference standard that most accurately reflects true TIA diagnoses. A previous population-based study addressed this concern using a clinically based criterion for the retrospective identification of TIA, where all TIA diagnoses occurring within 90 days prior to ischemic stroke were considered to be a definite TIA (171). To our knowledge, no previous studies have explicitly compared multiple algorithms involving diagnostic records from different administrative databases, and representing different potential clinical pathways, to evaluate the validity of physicians billing data for the identification of TIA cases.

The purpose of the present study was to determine whether an algorithm could be validated for the ascertainment of TIA cases from physicians billing administrative health data. Using multiple administrative databases, a set of algorithms for the identification of TIA cases from physicians billing records was evaluated in relation to a reference standard of individuals
with a TIA diagnosis occurring within 90 days prior to a hospital admission for ischemic stroke. The identification of a valid algorithm for outpatient TIA case ascertainment would enable population-based studies of TIA inclusive of individuals diagnosed in both hospital and primary care settings.

2.2. Methods

2.2.1. Data Sources and Permissions

The British Columbia (BC) Ministry of Health approved access to and use of the data facilitated by Population Data British Columbia (henceforth Population Data BC) for this study. Access to health data for the population of BC is provided to students and researchers who have received institutional ethics approval and whose proposed research has undergone both peer review and review by relevant data stewards. Ethical approval for all studies included in this dissertation was obtained from the Clinical Research Ethics Board at the University of British Columbia (Appendix A). All studies also underwent peer review as part of doctoral research funding from the Michael Smith Foundation for Health Research and the Canadian Institutes of Health Research, and as part of the proposal defense for the Thesis Screening Panel, a requirement for PhD candidacy in the School of Population and Public Health at the University of British Columbia. In addition, permission was obtained from data stewards at the BC Ministry of Health Services to access anonymized physician and hospital data for research purposes.

The data extract used in the present study and in subsequent studies in Chapters 3 and 4 of this dissertation included records from the following databases: 1) the Consolidation file (medical service plan (MSP) registration); 2) the Hospital Separations file; 3) the MSP Master Payment Information file (physician and health professional outpatient services); and 4) the PharmaCare file (comprehensive prescriptions for those 65 and older), for the fiscal period of
April 1, 1989 to March 31, 2008 (176). Data were linkable across these databases using individual-specific Personal Health Numbers (PHN) assigned to all permanent residents of BC. Prior to providing researchers access to the data, Population Data BC used this identification number to link individuals across datasets and then replaced it with an anonymized, project-specific study identification number (ID) (176). All databases are maintained by Population Data BC and regularly undergo cleaning by Population Data BC programming staff (176).

2.2.1.1. The Consolidation File

The Consolidation file contains detailed demographic and regional information for all individuals eligible for insured health services in BC (176), which includes all residents of the province of BC, with the exception of individuals covered by federal health care funding, including First Nations, veterans, and those residing in federal detention institutions. This database includes annual data files of insured individuals with birth year and month; sex; geographic location, including information on health service delivery area (HSDA) and neighbourhood-level income deciles; and plan registration dates.

2.2.1.2. The Hospital Separations File

The Hospital Separations file contains demographic, administrative, and clinical data on all hospital discharges (inpatient acute, chronic, rehabilitation), transfers, and deaths from acute care hospitals in BC (176). This database consists of detailed information, including admission and discharge dates, dates of death where relevant, and diagnostic and procedure codes, for the entire hospital stay for any patient admitted to hospital for inpatient or same-day surgical care, and not including emergency department coding (176).

In the hospital discharge abstracts, diagnostic information is recorded as ICD diagnostic codes (229) and includes 16 to 25 diagnoses per patient (16 prior to 2002), including the primary diagnosis and diagnosis most responsible for the hospital stay. Until 2001/02, all diagnostic codes in this database used ICD Revision 9 (ICD-9) (229), after which Revision 10
(ICD-10) was adopted for the coding of diagnostic information (230). This classification system has been validated at the population-level and has been shown to have good specificity and completeness for multiple health outcomes (231-233)(226-228), including the identification of stroke. Both the ICD-9 and ICD-10 systems demonstrate high positive predictive value for the ascertainment of stroke, particularly when records are limited to the primary diagnosis position (234).

Until 2002, the procedural classification used by hospitals in BC to record all in-hospital diagnostic and therapeutic procedures was the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) (235). After 2002, the Canadian Classification of Health Interventions (CCI) (236) was adopted for all data within the hospital separations database, as the companion procedural classification system to the ICD-10. Previous reabstraction studies evaluating the agreement between hospital records and procedure codes from hospital discharge data range from 88% to 96% agreement for these codes (237, 238).

2.2.1.3. The MSP Payment Information File

The MSP Payment Information File contains data on all medically necessary services, including laboratory and diagnostic procedures (e.g., CT, MRI) that are provided on a fee-for-service basis by practitioners to individuals covered by MSP (176). In this database, practitioners are separated into physicians and supplementary benefit practitioners (e.g., physiotherapists) and specialty codes are included to identify practitioners (176). Each billing record contains the date of service, a fee item for the service provided, and a single diagnosis. Diagnostic information in the MSP physicians’ billings database is recorded using only ICD-9 diagnostic code formatting, truncated to the three-digit level (176). In British Columbia, during the period of this data extract, approximately 90% of physicians operated on a fee for service payment basis within the MSP (239). Previous work has also demonstrated that procedures identified via physicians billing data have high levels of agreement when compared to those
identified from hospital discharge data (89%-94%) (240, 241), and the use of physician billing data in combination with other administrative health data sources to identify procedures has also been shown to improve the identification of relevant procedures (242).

2.2.1.4. The PharmaCare File

The PharmaCare file contains data on prescription drugs paid for under the PharmaCare program, including the date of purchase, type and quantity of medication purchased. This database is comprehensive for prescriptions for those aged 65 and older in the province, beginning in 2003. In this database, Canadian Drug Identity Codes (CDIC) are used to uniquely identify a particular drug according to its chemical, dosage, form, and manufacturer (176). For the present study, CDIC’s were used to identify prescription drug information for adjustment purposes in all multivariable analytic models.

2.2.2. Study Design

The present study was a validation study, comparing multiple algorithms for the ascertainment of TIA cases from physicians billing data to a reference standard algorithm of cases with a hospital admission for stroke with a prior diagnosis of TIA.

2.2.3. Algorithm Generation

Prior to defining the algorithms for the identification of TIA, it was important to characterize the processes underlying the generation of diagnostic records within these administrative databases, to determine how TIA diagnoses from patient encounters were captured and identify potential sources of variability and bias in these data. A previous qualitative study characterizing the clinical referral and management pathways for individuals with TIA in Europe and the United States (US) based on interviews with physicians and operational managers indicated that more general practitioners refer TIA cases to a neurologist or hospital specialist in the US, compared to European systems (138). To confirm the coding procedures involved in the generation of the administrative data used in the present study,
informal interviews were conducted with clinicians practicing in BC, including a stroke neurologist and a general practitioner (GP), billing clerks from a random sample of 20 general practice offices across BC, and billing administrators from the Vancouver Coastal Health, Northern Health, and Interior Health Authorities.

Based on these interviews, it was determined that, in BC, the main clinical care pathways for individuals with suspected TIA initially presenting within the primary care system included: 1) follow-up with the same general practitioner within 60 to 90 days, 2) referral to a neurology specialist, and 3) referral to hospital. In addition, it was apparent that there was variability in coding practices for TIA across general practice offices. Specifically, although the majority of offices reported using ICD9 code 435.x for suspected TIA, the use of alternate codes was also reported and some offices indicated that a suspected event would only be coded as TIA if confirmed at the time of a follow-up encounter. Thus, the most likely source of bias in these data involved the potential for misclassification arising from errors in disease classification for TIA from the initial presentation/visit. This information was incorporated into the design of the algorithms for TIA case ascertainment evaluated in the present study.

2.2.4. Base Population

The base population included all residents of BC eligible for health services during the study period from 1992 to 2007 with a diagnosis of TIA, identified from either: 1) the hospital discharge abstract database using ICD-9 code 435.x or ICD-10 code G45.x in the primary diagnosis position, and not including emergency department coding, or 2) the physician’s billing database using ICD-9 code 435 or ICD-10 code G45, with a corresponding specialist code for general practice [00], neurology [02], or cardiology [26].
2.2.5. Reference Standard Cohort

The reference standard cohort consisted of all individuals with a first recorded occurrence of ischemic stroke within the study period and a diagnosis of TIA within 90 days prior to the stroke. Stroke cases were ascertained using a previously validated algorithm for ischemic stroke from the discharge abstract database, involving ICD-9 codes 434.x and 436.x or ICD-10 codes I63.x and I64.x in the primary diagnosis position (186, 187). This stroke cohort was then restricted to cases that had a diagnosis of TIA within 90 days prior to the stroke diagnosis, ascertained from the base population, including all individuals with an ICD-9 code 435.x or ICD-10 code G45.x identified from either the physician billing (single code) or discharge abstract databases (inpatient codes in the primary diagnosis position).

2.2.6. Classification Algorithms

Based on the potential for bias associated with TIA diagnoses recorded at the initial primary care physician encounter, the present analysis required that each of the algorithms for the ascertainment of TIA cases include TIA diagnoses from two consecutive encounters, where encounters could include the following clinical pathways (Figure 2):

1. General Practitioner (GP) Diagnosis and GP Follow-Up: all individuals with two diagnostic records for TIA, defined using ICD-9 code 435 or ICD-10 code G45, with an associated specialist code for general practice (00), occurring within a 90-day period in the physician billing database.

2. GP Diagnosis and Specialist Referral Follow-Up: all individuals with two diagnostic records for TIA, defined using ICD-9 code 435 or ICD-10 code G45, with an associated specialist code for general practice (00) for the first record, and ICD-9 code 435 or ICD-10 code G45 with associated specialist codes for neurology (02) or cardiology (26) for the second record, occurring within a 90-day period in the physician billing database.
3. GP Diagnosis and Hospital Admission: all individuals with two diagnostic records for TIA, defined using ICD-9 code 435 or ICD-10 code G45, with an associated specialist code for general practice (00) for the first record, and ICD-9 code 435.x or ICD-10 code G45.x as the primary or most responsible diagnosis for the subsequent hospital admission record, occurring within a 90-day period in the physician billing and discharge abstract databases.

Figure 2. Description of base population, reference cohort, and classification algorithms used in the validation of physicians billing data for the identification of TIA diagnoses

Abbreviations: ICD9/10=International classification of diseases 9th and 10th revisions; TIA=transient ischemic attack; GP=general practitioner; SP=specialty practitioner (neurology and cardiology)
2.2.7. Statistical Analyses

TIA cases identified using the above described classification algorithms were compared with cases ascertained from the reference standard algorithm using measures of sensitivity, specificity, and positive predictive value (PPV) (243). Sensitivity is an estimation of the probability that the test algorithm will identify a TIA diagnosis in someone with TIA (true positives), while specificity is an estimation of the probability that the test algorithm will not identify a TIA diagnosis in someone that did not have a TIA (true negatives) (243). The PPV is an estimation of the probability that someone identified as having a TIA actually has a TIA (243). For the purposes of the present study, the PPV was the primary measure of interest, as it indexed the number of false positive cases identified by each of the classification algorithms. Estimates of sensitivity, specificity, and PPV for each of the TIA algorithms were based on a 2x2 comparison of TIA cases (yes/no) identified from physician billing data using each of the classification algorithms versus TIA cases (yes/no), where the TIA diagnosis were identified from either the physician billing or hospital discharge database as occurring within 90 days prior to an admission for ischemic stroke, ascertained from the hospital discharge database (reference standard) (Figure 3).
2.3. Results

A total of 102,492 individuals with a diagnostic record of TIA from the physicians billing or discharge abstract databases were identified for the base population. The reference cohort consisted of 2,473 individuals with a first recorded admission for ischemic stroke with a diagnosis of TIA within 90 days prior to stroke admission. TIA cohorts for each of the classification algorithm were then identified from the base population. Algorithm one (GP diagnosis and GP follow-up) identified a total of 23,300 TIA cases, algorithm two (GP and specialist referral) identified a total of 3931 TIA cases, and algorithm three (GP and hospital admission) identified a total of 1384 TIA cases (Figure 2).

Results revealed that, although specificity for each of the classification algorithms was high, ranging from 77% for the algorithm where TIA cases were identified from an initial GP diagnosis and GP follow-up, to 98% for the algorithm classifying TIA from an initial GP diagnosis and hospital admission, the sensitivity of these algorithms was poor, with the highest

<table>
<thead>
<tr>
<th>Classification Algo</th>
<th>TIA+</th>
<th>TIA-</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Positives (TP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Positives (FP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True Negatives (TN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Negatives (FN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total With TIA</td>
<td>TP + FN</td>
<td></td>
</tr>
<tr>
<td>Total Without TIA</td>
<td>FP + TN</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Table for analyses of sensitivity, specificity, and positive predictive value

Sensitivity = TP/(TP + FN)
Specificity = TN/(FP + TN)
Positive Predictive Value = TP/(TP + FP)
observed sensitivity at 37% for the algorithm where TIA cases were ascertained from an initial GP diagnosis and a GP follow-up encounter (Table 6). PPVs for each of the algorithms were also very low, with the algorithm for TIA cases ascertained from an initial GP diagnosis with a subsequent hospital admission demonstrating the highest PPV at 10%. The false positive rate (1-specificity) was particularly high for the algorithm where TIA cases were ascertained from an initial GP diagnosis, with a GP follow-up encounter (22.4%), resulting in the lowest observed PPV (4.0%) for this TIA case definition.

Table 6. Sensitivity and specificity of classification algorithms for the ascertainment of TIA cases from physician billing data compared to a reference standard of cases of ischemic stroke with prior TIA

<table>
<thead>
<tr>
<th>Algorithm 1: GP + GP Follow-Up</th>
<th>Reference Standard (Stroke with Prior TIA)</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIA+</td>
<td>TIA-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA+</td>
<td>926</td>
<td>22374</td>
<td>23300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA-</td>
<td>1547</td>
<td>77645</td>
<td>79192</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2473</td>
<td>100019</td>
<td>102492</td>
<td>37.4%</td>
<td>77.6%</td>
</tr>
<tr>
<td>Algorithm 2: GP + SP Follow-Up</td>
<td>TIA+</td>
<td>TIA-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA+</td>
<td>205</td>
<td>3726</td>
<td>3931</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA-</td>
<td>2268</td>
<td>96293</td>
<td>98561</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2473</td>
<td>100019</td>
<td>102492</td>
<td>8.2%</td>
<td>96.3%</td>
</tr>
<tr>
<td>Algorithm 3: GP + Hospital Admission</td>
<td>TIA+</td>
<td>TIA-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA+</td>
<td>138</td>
<td>1246</td>
<td>1384</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA-</td>
<td>2335</td>
<td>98773</td>
<td>101108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2473</td>
<td>100019</td>
<td>102492</td>
<td>5.6%</td>
<td>98.8%</td>
</tr>
</tbody>
</table>

GP=general practitioner; SP=specialist practitioner; PPV=positive predictive value
2.4. Discussion

The purpose of this study was to assess the validity of a set of algorithms designed to identify TIA cases from a physicians billing administrative health database. Based on the comparison of three different outpatient algorithms for TIA with a reference standard of TIA cases, derived from a cohort of individuals with a hospital admission for stroke after TIA, results showed that the validity of case definitions using physicians billing data to ascertain TIA was very low. Specifically, sensitivities of these algorithms ranged from 5% to 37% and none of the algorithms evaluated in the present study had a PPV exceeding 10%. These findings indicate that the algorithms derived from physicians billing data have insufficient sensitivity and PPV for the purposes of ascertaining TIA cases and suggest that population-based studies of individuals with TIA require alternative case definitions than those based solely on the use of physician billing records.

The results of this study are consistent with previous validation studies that demonstrated low predictive values for the ascertainment of TIA cases using outpatient data (184). One prior study using data from both inpatient and patient encounters to ascertain TIA as a comorbid diagnosis in individuals with diabetes reported a PPV of only 33% (192), while another study evaluating TIA case ascertainment in a pediatric population demonstrated a reduction in PPV from 67% to 52% when case ascertainment involved outpatient coding (193). Consistent with these findings, the algorithms for the ascertainment of TIA cases from outpatient data evaluated in the present study had limited validity, with observed PPVs ranging from 4% to 10%. Findings of the present study contribute to the evidence that case definitions based solely on physicians billing diagnostic records are not valid for the identification of TIA. Further, as this study explicitly compared multiple different algorithms defined according to the various clinical pathways by which TIA diagnoses may be captured after an initial outpatient encounter, this
study represents a comprehensive evaluation of the validity of outpatient data for the identification of TIA.

The PPVs associated with the algorithms evaluated in the present study were substantially lower than those reported in previous validation studies that included outpatient records for the identification of TIA cases (192, 193). As PPV is dependent on the prevalence of the disease in the population being tested (244), a potential explanation for this finding relates to the definition of the reference standard cohort employed in the present study. The reference cohort used in the present study included cases ascertained using a previously validated algorithm for the identification of ischemic stroke from hospital discharge data and limited these cases only to those with prior TIA, which increased the likelihood that the cases included in this cohort represented definite TIA. However, as the occurrence of stroke after TIA in the base population was low (2.4%), the use of this case definition for the reference standard cohort may have resulted in the overestimation of false positives detected by each of the classification algorithms, producing lower estimates of PPV. For instance, although the algorithm that selected TIA cases based on the presence of diagnostic records from two consecutive GP encounters showed the highest sensitivity (37%), the false positive rate for this algorithm was also very high (22.4%), resulting in a low PPV (4%) for this case definition. Another potential factor in the low number of TIA cases validated may have been the underestimation of true positives identified using each of the classification algorithms, due to the criteria requiring the identification of cases with two consecutive physician encounters. Despite these findings, as many individuals with TIA are diagnosed and managed by their primary care provider (132, 133), case definitions that include individuals evaluated in both hospital and outpatient settings are required for population-based research on health service utilization in the Canadian TIA population. However, it is challenging to retrospectively identify a population-based cohort of individuals with TIA in the absence of a validated algorithm for physicians billing data.
One potential strategy to address this issue involves the use of information on clinical outcomes to decrease the potential for misclassification in retrospective TIA case definitions. Previous studies have shown that recurrent cerebrovascular events, such as stroke, occur after definite TIA but are absent in individuals with transient neurological episodes that mimic TIA (80), suggesting that clinical outcome (i.e., stroke secondary to TIA) may be a useful criterion to retrospectively distinguish definite TIA from TIA mimic. This methodology was also employed in a previous population-based study to retrospectively identify TIA cases and minimize potential biases due to inaccurate clinical diagnoses and changes in diagnostic practices over time (171). Given the importance of capturing TIA cases across diagnostic settings for conducting population-based analyses of health services utilization in TIA, subsequent studies in this dissertation employ the identification of population-based TIA cohorts that include cases diagnosed in both hospital and primary care settings.

2.5. Strengths and Limitations

The main strength of this study included the use of data from longitudinal, population-based administrative databases to define the reference cohort and validation algorithms. As these databases are comprised of individual-level information on diagnoses for the entire population of British Columbia over several years, the use of these data ensured that all TIA diagnoses recorded from hospital admissions and physician encounters were captured and eligible for inclusion in the validation cohorts evaluated in this study and thus increased the generalizability of these findings. The use of another linked population-based database (i.e., the hospital discharge database) to derive the reference standard in the present study also enabled us to evaluate the validity of the physicians billing data for identifying TIA across the entire population. Another strength of this study was related to the use of multiple algorithms derived from physicians billing data to define the TIA cohorts for validation. In prior validation studies
that included outpatient diagnoses, algorithms for the ascertainment of TIA have been limited to a single case definition (184), thus the comparison of multiple potential case definitions in the present study enabled a more comprehensive assessment of the validity of physicians billing records for the identification of TIA. Further, as individuals presenting to a primary care provider with symptoms of TIA may engage the health care system along several potential clinical pathways, the use of information obtained from care providers and administrators regarding common care pathways for individuals with TIA increased the face validity of the algorithms used to define the validation cohorts evaluated in the present study.

The present study also had a number of limitations. One challenge with the use of administrative data to define the reference standard cohort was ensuring that the TIA cases included in this cohort represented definite TIA. Although the reference standard cohort used in the present study was based on the clinical criterion of having a stroke secondary to TIA and stroke cases were ascertained using a previously validated algorithm for the identification of stroke from hospital admissions records, which reduced the potential for misclassification in the reference standard, it is possible that some cases in this cohort did not represent true TIA. Further, as estimates of PPV are heavily influenced by disease prevalence, the use of a reference cohort of individuals with stroke secondary to TIA also likely resulted in the overestimation of false positives identified for each of the physician billing classification algorithms and ultimately limited the ability to validate these algorithms for TIA case ascertainment.

2.6. Conclusion

The present study sought to validate an algorithm for the ascertainment of TIA cases from physician billing administrative health data. Comparing multiple cohorts based on algorithms representing different clinical pathways of care for individuals with TIA presenting initially to their primary care provider to a reference cohort, results from this study indicated that it was not
possible to validate an algorithm for the ascertainment of TIA cases from physician billing data. As issues remain with the validity of identifying TIA cases directly from physician billing records, alternative methods for capturing outpatient cases are required. Given the importance of capturing TIA cases diagnosed across care settings for the population-based evaluation of health services in individuals with TIA, subsequent studies in this dissertation used population-based cohorts of individuals with TIA identified from a combination of hospital and outpatient data.
3.1. Introduction

Approximately 14,000 Canadians die annually from stroke (8). Stroke is the leading cause of adult long-term disability in North America and worldwide (7, 10), with one third of stroke survivors becoming functionally dependent within a year of their event (9). A transient ischemic attack (TIA) is an episode of transient focal neurological deficit with an ischemic vascular cause (17) and TIAs are an important risk factor for future stroke (22, 23, 25). Previous population-based studies have shown that up to 40% of individuals will suffer a stroke subsequent to TIA (22, 23, 25) and, in Canada, more than one third of stroke patients have experienced a prior TIA (5). There are a number of treatments available to reduce the risk of secondary stroke both in individuals with TIA and stroke (53-55, 57, 63-66). However, initiation of the most appropriate preventive management after TIA depends on the accurate diagnosis of the transient event as an episode of ischemic origin and the identification of the mechanisms underlying the TIA (30).

As TIA symptoms are often resolved by the time of presentation (17), information about the clinical features of the event is frequently based on patient’s recall of their symptoms at the time of the transient episode (47) and there are also several neurological conditions of non-ischemic origin that present with symptoms mimicking TIA (72, 77). As a result, previous work has shown that the reliability of TIA diagnoses based solely on clinical information is poor among both non-specialist diagnosing physicians and stroke sub-specialists (70, 118). Over the past two decades, there has been increasing evidence that brain and vascular imaging can provide valuable information to complement the clinical assessment of TIA and help to: 1)
confirm an ischemic origin for the event; 2) identify the underlying vascular mechanisms; and, 3) guide management for the prevention of stroke (30). In 1997, based on this evidence, the American Heart Association (AHA) implemented the first set of clinical practice guidelines specifically recommending the use of brain and vascular imaging investigations in the initial evaluation of individuals presenting with TIA (see Chapter 1, Section 1.2. for a detailed description of these guidelines) (127). As Canadian Best Practice Recommendations for Stroke Care were not developed until 2006, the AHA guidelines were considered to be the North American practice standard during the period following their implementation. Although active dissemination strategies for these guidelines may have been limited in Canada, conventional dissemination of guideline recommendations to Canadian practitioners through scientific publications, continuing education, and conferences may still have influenced practice for the use of imaging.

Despite these recommendations, recent studies assessing the use of imaging in individuals presenting to Canadian emergency departments with TIA have shown that imaging procedures remain underutilized in the evaluation of individuals with TIA (134, 135). In one study of individuals with TIA presenting to four emergency departments across Ontario, only 31% received in-hospital structural neuroimaging (CT or MRI scanning) prior to discharge, while only 58% underwent an outpatient CT procedure, 44% a carotid carotid ultrasound, 3% an MRI, 5% cerebral angiography and 19% echocardiography in the 30 days following the index TIA (134). Another study that evaluated imaging utilization in the emergency department of a tertiary care center in Alberta showed that use of vascular imaging techniques in the ED evaluation of TIA was particularly low, as only 16% of individuals received a carotid ultrasound prior to discharge and an additional 26% received an outpatient referral for this procedure (135).

These findings suggest that AHA clinical guidelines may have had a limited impact on practice for the utilization of imaging procedures after TIA in Canada. However, these studies
were restricted to individuals with TIA presenting to emergency department practice settings, and did not examine longitudinal changes in imaging practices in relation to the implementation of clinical practice guidelines for individuals with TIA. As many individuals with TIA are evaluated and managed on an outpatient basis by their primary care provider (132, 133), it is difficult to determine whether previous reports of imaging underutilization from hospital-based studies are representative of population-based practices for the use of imaging in individuals with TIA and whether changes in practice occurred in relation to the implementation of guidelines for imaging use.

To our knowledge, no previous population-based studies have examined the effect of guideline implementation on the utilization of imaging procedures after TIA. Thus, the primary objectives of this study were to: 1) characterize differences in the utilization of neuroimaging after TIA in individuals evaluated in both hospital and outpatient care settings in the Canadian province of British Columbia (BC) between two calendar periods, before and after the implementation of the 1997 American Heart Association clinical practice guidelines for imaging in the diagnostic evaluation of TIA, and 2) determine whether an increase in the use of imaging procedures in individuals with TIA was associated with the implementation of these guidelines. Secondary objectives were to assess differences in imaging practices based on care setting and imaging modality.

3.2. Methods

3.2.1. Study Design

This was a before and after retrospective cohort study designed to describe and compare utilization of neuroimaging procedures in a population-based cohort of individuals with TIA in the periods before and after the implementation of clinical practice guidelines for the use of imaging in the evaluation of TIA.
3.2.2. Data sources

All administrative databases used in the present study were previously described in Chapter 2 (Section 2.2.1.).

3.2.3. Target Population and Cohort Definition

The target population for the present study was individuals with TIA. The study cohort was identified retrospectively as individuals with TIA prior to stroke. As the results of Chapter 2 confirmed that diagnostic data from physicians billing data cannot be used alone to reliably ascertain TIA cases, the cohort for the present study was defined using clinically based criterion from both hospital discharge and physicians billing records that included all TIA cases occurring within 90 days prior to a hospital admission for stroke (171). All cases with a hospital admission for ischemic stroke from the calendar period 1992 to 2007 were identified using a previously validated algorithm for stroke diagnoses (187) and then restricted to those cases with a first occurrence of a TIA diagnosis within 90 days prior to the stroke, identified from either the hospital discharge or physicians billing databases (Table 7). All TIA cases identified via the physicians billing database were further limited to those seen by a sub-set of specialists (Table 7) and, for all cases identified via the hospital discharge database, only diagnostic codes for stroke and TIA in the primary or most responsible position were included in the study cohort. Cohort entry was defined as the date of presentation to medical care where the initial diagnosis of TIA was recorded (i.e. date of physician encounter or date of admission). The study cohort was followed for a period of 90 days, according to the commonly used clinical window of increased risk for stroke after TIA (36). All individuals with a diagnosis of stroke prior to or on the same day as the TIA diagnosis were excluded from the study cohort.
Table 7. Diagnostic codes and description of study cohort definition

<table>
<thead>
<tr>
<th>Classification</th>
<th>Code</th>
<th>Data Source (years)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-9 ICD-10</td>
<td>434.x, 436.x I63.x, I64.x</td>
<td>Discharge Abstracts Database (1992-2007)</td>
<td>Diagnostic record for ischemic stroke in the primary or most responsible diagnosis field</td>
</tr>
<tr>
<td>ICD-9 ICD-10</td>
<td>435.x G45.x</td>
<td>MSP Physician Billing Database Discharge Abstracts Database (1992-2007)</td>
<td>Diagnostic record for the first occurrence of TIA and occurring within 90 days prior to the diagnosis of ischemic stroke. Records for the occurrence of TIA from MSP database restricted to those associated with specialist codes 00 (GP), 02 (Neurology) or 26 (Cardiology). Records from the discharge abstract database restricted to in the primary or most responsible diagnostic field.</td>
</tr>
</tbody>
</table>

3.2.4. Study Variables

3.2.4.1. Primary Outcome

The primary outcome was defined as the first recorded neuroimaging procedure performed after the TIA diagnosis but prior to stroke (yes versus no). In BC, neuroimaging procedures are billable to the Medical Services Plan (MSP) on a fee-for-service basis that includes all procedures performed in emergency departments, inpatient procedures for CT imaging, and all diagnostic procedures performed on an outpatient basis. Procedures were identified using procedural fee item codes from the MSP billing database and using Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) and Canadian Classification of Health Interventions (CCI) procedure codes from the hospital separations database, previously shown to have high agreement (240, 241). All procedures were categorized and analyzed according to
imaging modality (i.e. yes/no for procedures from each modality) for the first procedure as
follows: computed tomography (CT), echocardiography, angiography, carotid ultrasound (US),
and magnetic resonance imaging (MRI) (Table 8). For individuals that underwent multiple
different procedures on the date of the first procedure, the outcome was categorized as “multiple
modality”.

Table 8. Procedure codes for all categories of the primary study outcome

<table>
<thead>
<tr>
<th>Imaging Procedure</th>
<th>Data Codes</th>
<th>Data Source</th>
<th>Description</th>
</tr>
</thead>
</table>
| Computed Tomography      | MSP procedure fee items: 08690, 08691, 08692 | MSP Physician Billing Database (1992-2007) | CT, head scan without contrast  
|                          |            |                          | CT, head  
|                          |            |                          | CT, aorta  
|                          |            |                          | CT and CT angiogram, heart and coronary arteries  
|                          |            |                          | CT, carotid artery  
|                          |            |                          | CT, other vessels head neck and spine  
|                          |            |                          | Cerebral angiography, bilateral  
|                          |            |                          | Doppler echocardiography  
|                          |            |                          | US, heart coronary arteries  
|                          |            |                          | US, carotid artery  
|                          |            |                          | US, intracranial vessels  

<table>
<thead>
<tr>
<th>Imaging Procedure</th>
<th>Data Codes</th>
<th>Data Source (years)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic Resonance Imaging</td>
<td>3.JX.30.xx</td>
<td>US, other vessels head neck</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2761</td>
<td>MRI, brain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2762</td>
<td>MRI, head</td>
<td></td>
</tr>
<tr>
<td>3.AN.40.xx</td>
<td>MRI, brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.ER.40.xx</td>
<td>MRI, head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.ID.40.xx</td>
<td>MRI, aorta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.IP.40.xx</td>
<td>MRI, heart coronary arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.JE.40.xx</td>
<td>MRI, carotid artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.JX.40.xx</td>
<td>MRI, other vessels head neck</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2.4.2. Explanatory Variable

The explanatory variable was calendar period, defined as the periods before (1992 to 1997) and after (1998 to 2007) the implementation of clinical practice guidelines for the use of imaging in the evaluation of TIA.

3.2.4.3. Censoring Events

For the present study, censoring events were stroke, death, or administrative censoring at the end of follow-up (90 days). Stroke was defined using a previously validated algorithm for the identification of stroke cases from ICD-9 and ICD-10 diagnostic codes (187) (Table 9). Death was identified using ICD-9 diagnostic codes for death from the physician billing database and death codes from the hospital separations database (Table 9). All observations were censored where the first recorded imaging procedure occurred within 90 days subsequent to the date of TIA diagnosis and prior to the date of stroke or death. To ensure that imaging procedures were related to the TIA and not the stroke event, observations were censored at the date of stroke if and only if the first recorded imaging procedure occurred subsequent to the date of TIA diagnosis and either on or after the date of stroke. Observations were censored at the date of death if there was no imaging post-TIA and death occurred within the 90-day follow-up
window. Remaining observations were administratively censored at the end of study follow-up (90 days).

Table 9. Diagnostic and death coding for censoring events

<table>
<thead>
<tr>
<th>Censoring Event</th>
<th>Data Codes</th>
<th>Data Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>ICD-9: 434.x, 436.x, ICD-10: I63.x, I64.x</td>
<td>Discharge Abstracts Database (1992-2007)</td>
<td>Diagnostic record for ischemic stroke in the primary or most responsible diagnosis field</td>
</tr>
<tr>
<td>Death</td>
<td>ICD-9: 348.8, 798.1, 798.2, 798.9</td>
<td>MSP Physician Billing Database</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>Hospital Exit: 1-9</td>
<td>Discharge Abstracts Database (1992-2007)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital Operative: 1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital Supplemental: 1-7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2.4.4. Demographic and Clinical Variables

Demographic and clinical variables identified as potential confounding variables for the effect of calendar period on the use of imaging procedures included the following: age, sex, fiscal year, income, health service delivery area (HSDA), comorbid clinical conditions, and prescription drug class (Table 10). Age was identified from the birth month and year in the Consolidation file and was categorized into 10-year age groups, with the final group including all individuals 65 years of age and older. Sex, fiscal year and neighbourhood-level income decile, based on Census income data, were also identified from the Consolidation file. Fiscal year was used as an indicator variable to account for baseline increases in imaging use over time and income decile was used as an indicator of socioeconomic status (SES).

For the purposes of the present study, the 16 health service delivery areas (HSDA) in BC were categorized into ‘urban’ and ‘rural’ service regions, where urban included all regions with a population greater than 250,000 and rural included all regions with a population less than this (240). The geographic variable was included to index access to available resources for imaging
procedures, with the assumption that individuals in urban health service areas would have increased access to neuroimaging services than those in rural regions (245).

The following clinical conditions were identified as comorbid risk factors related to both the use and type of imaging procedures performed in the diagnostic evaluation of TIA and as indicators of TIA severity: diabetes, heart disease, hypertension, and atrial fibrillation (246, 247). Previous work has demonstrated that ICD diagnostic coding in hospital separations data shows high sensitivity for the identification of the preceding comorbid conditions (187). ICD-9 and ICD-10 diagnostic codes from the MSP physician billing and Hospital Separations databases were used to identify the presence or absence (yes/no) of comorbid conditions in the present study (Table 11). Individuals in the study cohort were considered to have the condition if they had records for two physician visits or one hospital admission within a one year period at any point up to 2 years prior to the date of the TIA diagnosis.

Information on prescribed medications at the time of TIA diagnosis included the following classes of drugs: 1) blood formation and coagulation, 2) cardiovascular, 3) central nervous system, and 4) electrolytic, caloric, water balance (Table 10). This variable was categorized for each of the four prescription classifications (yes versus no), with a yes defined as a prescription record for any of the identified drug classes in the two-year period prior to TIA diagnosis. As medication status may be related to neuroimaging investigations (248), adjustment for drug class was performed where possible for all individuals with complete prescription information (those aged 65 and older).

Table 10. Codes, data sources, and description of demographic and clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data Codes</th>
<th>Data Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Year/Month</td>
<td>Registry</td>
<td>Patient age at the date of TIA diagnosis (date of diagnosis minus date of birth)</td>
</tr>
</tbody>
</table>

62
<table>
<thead>
<tr>
<th><strong>Variable</strong></th>
<th><strong>Data Codes</strong></th>
<th><strong>Data Source</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male/Female</td>
<td>Registry</td>
<td>Gender of resident eligible for health services in BC</td>
</tr>
<tr>
<td>Fiscal Year</td>
<td>Year</td>
<td>Registry</td>
<td>Fiscal year at the date of TIA diagnosis</td>
</tr>
<tr>
<td>Income Decile</td>
<td>1-10</td>
<td>Census Geodata</td>
<td>Neighbourhood level income from Census data as an indicator of socioeconomic status (SES)</td>
</tr>
<tr>
<td>Health Service Delivery Area</td>
<td>11, 12, 13, 14, 21, 22, 23, 31, 32, 33, 41, 42, 43, 51, 52, 53</td>
<td>Registry HAS Code</td>
<td>Location of access to health services</td>
</tr>
<tr>
<td>Drug Class</td>
<td>20, 24, 28, 40</td>
<td>Pharmacare CDIC Code</td>
<td>Prescription for one or more medications from these drug classes at the time of TIA diagnosis or at any point up to 2 year prior to TIA diagnosis.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ICD-9: 250.x</td>
<td>MSP and Hospital discharge data</td>
<td>Diagnosis of diabetes defined as yes if records for 2 physician visits or 1 hospitalization occurred within a one year period at any point up to 2 years prior to the first occurrence of TIA (study entry)</td>
</tr>
<tr>
<td></td>
<td>ICD-10: E10.x, E11.x, E13.x, E14.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>ICD-9: 401.x, 402.x</td>
<td>MSP and Hospital discharge data</td>
<td>Diagnosis of hypertension defined as yes if records for 2 physician visits or 1 hospitalization occurred within a one year period at any point up to 2 years prior to the first occurrence of TIA (study entry)</td>
</tr>
<tr>
<td></td>
<td>ICD-10: I10.x, I11.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>ICD-9: 410.x, 411.x, 412.x, 413.x, 414.x</td>
<td>MSP and Hospital discharge data</td>
<td>Diagnosis of heart disease defined as yes if records for 2 physician visits or 1 hospitalization occurred within a one year period at any point up to 2 years prior to the first occurrence of TIA (study entry)</td>
</tr>
<tr>
<td></td>
<td>ICD-10: I21.x, I25.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>ICD-9: 427.3</td>
<td>MSP and Hospital discharge data</td>
<td>Diagnosis of atrial fibrillation defined as yes if records for 2 physician visits or 1 hospitalization occurred within a one year period at any point up to 2 year prior to</td>
</tr>
<tr>
<td>Variable</td>
<td>Data Codes</td>
<td>Data Source</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the first occurrence of TIA (study entry)</td>
</tr>
</tbody>
</table>

### 3.2.5. Statistical Analyses

Frequency statistics were generated to characterize the study cohort with respect to all study variables in the periods before and after the implementation of clinical guidelines for the use of imaging in the diagnostic evaluation of TIA. Chi-square testing was used to compare characteristics of individuals with TIA across the two calendar periods.

Imaging utilization was evaluated descriptively by calculating the proportion of TIA cases that underwent a neuroimaging procedure between the recorded date of TIA diagnosis and prior to the date of stroke, by calendar period. The cumulative probabilities of undergoing an imaging procedure after TIA during each period were estimated using the product-limit method (249) and differences in access to imaging across calendar periods were examined using the log-rank test.

The average rate of imaging procedures performed prior to recurrent stroke was calculated for periods before and after the implementation of clinical guidelines. The effect of the implementation of practice guidelines on the average imaging rate before and after guideline implementation was estimated using a multivariable Poisson log-linear model, yielding a rate ratio (RR), adjusted for significant demographic and clinical variables identified in bivariate analyses (250).

Secondary analyses to characterize potential differences in imaging proportions and rates, by imaging modality and the care setting of the TIA diagnosis (primary care versus hospital), were also performed. For the analysis of imaging by modality, the outcome was the first recorded procedure from a different modality performed after the date of TIA diagnosis and prior to the date of stroke. As there were insufficient data to investigate differences in utilization...
for MRI, echocardiography, and angiography procedures, secondary analyses evaluated utilization for CT and carotid ultrasound procedures only. Imaging modalities that showed significant increases in utilization were then evaluated to determine whether these increases differed across diagnostic setting, comparing utilization between calendar periods for TIA cases ascertained from the physicians billing versus hospital discharge databases. The effect of calendar period on imaging rates by modality and diagnostic setting was determined using separate Poisson log-linear models for each imaging modality and setting of diagnosis.

All multivariable models included adjustment for demographic and clinical variables identified as significant potential confounding variables from bivariate analyses and, for all models, chi-squared goodness-of-fit tests were conducted to evaluate the model fit and test for over-dispersion in the data.

3.3. Results

Demographic and clinical characteristics of the study cohort are presented in Table 11. Among the 1583 individuals with TIA, the majority of individuals with TIA were aged 65 or older (82.9%), with no significant differences in age distribution between calendar periods (pre and post guideline implementation). The overall proportion of males and females with TIA across calendar periods was similar, but the proportion of females diagnosed with TIA increased significantly in the period after the implementation of clinical guidelines ($p=0.02$). Similar proportions of TIA cases resided in both urban and rural health service delivery areas across calendar periods. The proportion of individuals with TIA was highest in the lowest two income deciles (12.6% and 12.1%) across calendar periods and no significant differences between periods were observed for either HSDA or income. Across calendar periods, the majority of individuals were diagnosed in the primary care setting (80.1%) compared to hospital setting (19.9%), with no differences in setting of diagnosis between periods. Among those aged 65 and
older, significantly more individuals with TIA had been prescribed medications from the blood formation and coagulation and central nervous system drug classes at the time of TIA diagnoses in the period after the implementation of guidelines (p<.001), with no differences observed for either the cardiovascular, or the electrolytic, caloric and water balance drug classes. Across calendar periods, hypertension was the most commonly identified co-morbid clinical condition (42.6%). A significant increase in the proportion of individuals diagnosed with atrial fibrillation was observed from the pre- to post-guideline calendar period (p=.0001), although the number of individuals with TIA with comorbid atrial fibrillation was small. No differences in the proportion of individuals diagnosed with diabetes or heart disease were observed between calendar periods.

Table 11. Characteristics of 1583 individuals with transient ischemic attack within 90 days prior to stroke in British Columbia from 1992 to 2007, by calendar period

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>n (%)</td>
</tr>
<tr>
<td>20-34</td>
<td>4</td>
<td>57.1</td>
<td>3</td>
<td>42.9</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>35-44</td>
<td>7</td>
<td>33.3</td>
<td>14</td>
<td>66.7</td>
<td>21 (1.3)</td>
</tr>
<tr>
<td>45-54</td>
<td>27</td>
<td>39.7</td>
<td>41</td>
<td>60.3</td>
<td>68 (4.3)</td>
</tr>
<tr>
<td>55-64</td>
<td>61</td>
<td>35.1</td>
<td>113</td>
<td>64.9</td>
<td>174 (11.0)</td>
</tr>
<tr>
<td>65+</td>
<td>466</td>
<td>35.5</td>
<td>847</td>
<td>64.5</td>
<td>1313 (82.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>314</td>
<td>38.3</td>
<td>505</td>
<td>61.7</td>
<td>819 (51.7)</td>
</tr>
<tr>
<td>F</td>
<td>251</td>
<td>32.9</td>
<td>513</td>
<td>67.2</td>
<td>764 (48.3)</td>
</tr>
<tr>
<td>Health Service Delivery Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>273</td>
<td>38.1</td>
<td>444</td>
<td>61.9</td>
<td>717 (45.3)</td>
</tr>
<tr>
<td>Urban</td>
<td>292</td>
<td>33.7</td>
<td>574</td>
<td>66.3</td>
<td>866 (54.7)</td>
</tr>
<tr>
<td>Income Decile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>61</td>
<td>31.8</td>
<td>131</td>
<td>68.2</td>
<td>192 (12.1)</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>30.2</td>
<td>139</td>
<td>69.9</td>
<td>199 (12.6)</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>34.2</td>
<td>106</td>
<td>65.8</td>
<td>161 (10.2)</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>n=565</td>
<td>n=1018</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>33.3</td>
<td>98</td>
<td>66.7</td>
<td>147 (9.3)</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>44.2</td>
<td>96</td>
<td>55.8</td>
<td>72 (10.9)</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>41.2</td>
<td>91</td>
<td>58.3</td>
<td>156 (9.9)</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>37.0</td>
<td>92</td>
<td>63.0</td>
<td>146 (9.2)</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>39.2</td>
<td>90</td>
<td>60.8</td>
<td>148 (9.4)</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>31.4</td>
<td>83</td>
<td>68.6</td>
<td>121 (7.6)</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>34.8</td>
<td>92</td>
<td>65.3</td>
<td>141 (8.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Setting</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GP</td>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>447</td>
<td>35.3</td>
<td>821</td>
<td>64.8</td>
<td>1268 (80.1)</td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>37.5</td>
<td>197</td>
<td>62.5</td>
<td>315 (19.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Class</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>148</td>
<td>57.1</td>
<td>111</td>
<td>42.9</td>
<td>259 (16.4)</td>
</tr>
<tr>
<td>N</td>
<td>417</td>
<td>31.5</td>
<td>907</td>
<td>68.5</td>
<td>1324 (83.6)</td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>351</td>
<td>37.2</td>
<td>592</td>
<td>62.8</td>
<td>640 (40.4)</td>
</tr>
<tr>
<td>N</td>
<td>214</td>
<td>33.4</td>
<td>426</td>
<td>66.6</td>
<td>943 (59.6)</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>362</td>
<td>40.5</td>
<td>531</td>
<td>59.5</td>
<td>893 (56.4)</td>
</tr>
<tr>
<td>N</td>
<td>203</td>
<td>29.4</td>
<td>487</td>
<td>70.6</td>
<td>690 (43.6)</td>
</tr>
<tr>
<td>ECWB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>214</td>
<td>34.5</td>
<td>406</td>
<td>65.5</td>
<td>620 (39.2)</td>
</tr>
<tr>
<td>N</td>
<td>351</td>
<td>36.5</td>
<td>612</td>
<td>63.6</td>
<td>963 (60.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>99</td>
<td>33.1</td>
<td>200</td>
<td>66.9</td>
<td>299 (18.9)</td>
</tr>
<tr>
<td>No</td>
<td>466</td>
<td>36.3</td>
<td>818</td>
<td>63.7</td>
<td>1284 (81.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>232</td>
<td>34.4</td>
<td>443</td>
<td>65.6</td>
<td>675 (42.6)</td>
</tr>
<tr>
<td>No</td>
<td>333</td>
<td>36.7</td>
<td>575</td>
<td>63.3</td>
<td>908 (57.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Disease</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>134</td>
<td>38.6</td>
<td>213</td>
<td>61.4</td>
<td>347 (21.9)</td>
</tr>
<tr>
<td>No</td>
<td>431</td>
<td>34.9</td>
<td>805</td>
<td>65.1</td>
<td>1236 (78.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atrial Fibrillation</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2</td>
<td>4.8</td>
<td>42</td>
<td>95.6</td>
<td>44 (2.7)</td>
</tr>
<tr>
<td>No</td>
<td>563</td>
<td>36.6</td>
<td>976</td>
<td>63.4</td>
<td>1539 (97.3)</td>
</tr>
</tbody>
</table>

Abbreviations: GP=general practitioner, BFC=blood formation and coagulation, CV=cardiovascular, CNS=central nervous system, ECWB=electrolytic, caloric, water balance

‡Fisher’s Exact Test
3.3.1. Analysis of Primary Outcome

Overall, across calendar periods, 448 (28.3%; 95% CI=25.8-30.2) individuals with TIA underwent a neuroimaging procedure subsequent to TIA diagnosis and prior to stroke or death within the 90-day study follow-up period. The proportion of individuals with TIA that underwent a neuroimaging procedure prior to stroke increased from 25.1% (95%CI=21.6-28.7) before the implementation of practice guidelines to 30.1% (95%CI=27.2-32.9) in the period after the implementation of practice guidelines (Table 12). Results also showed that there was a significant increase in the cumulative probability of undergoing an imaging procedure prior to stroke in the period after the implementation of clinical guidelines (test statistic=4.49, df=1, \( p=0.03 \))(Figure 4).

Table 12. Proportion of individuals with TIA who underwent a neuroimaging procedure prior to stroke, by calendar period

<table>
<thead>
<tr>
<th>Calendar Period</th>
<th>TIA Cases</th>
<th>Total Events (Yes to Imaging)</th>
<th>Event Proportion</th>
<th>SE</th>
<th>95% CI</th>
<th>Log Rank</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Guideline†</td>
<td>565</td>
<td>142</td>
<td>25.1</td>
<td>1.8</td>
<td>(21.6-28.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>After Guideline</td>
<td>1018</td>
<td>306</td>
<td>30.1</td>
<td>1.4</td>
<td>(27.2-32.9)</td>
<td>4.49</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Abbreviations: SE=standard error; CI=confidence interval
†Reference category
Figure 4. Estimated probability of undergoing a neuroimaging procedure prior to stroke in individuals with TIA, before and after implementation of clinical practice guidelines

Multivariable Poisson regression analysis, comparing the average rate of imaging before and after the implementation of clinical practice guidelines, showed a trend towards increased utilization of imaging from the pre- to the post- clinical guideline period, with a 20% increase in the rate of imaging procedures performed in individuals with TIA after the implementation of the guidelines, adjusted for significant demographic and clinical characteristics. This trend was not statistically significant (RR=1.2, 95%CI: 0.9-1.5, \( p<0.08 \)) (Table 13). The chi-squared goodness-of-fit test was also not statistically significant (\( p=0.71 \)), indicating a good model fit for these data.
Table 13. Relationship between calendar prior (pre and post clinical guidelines) and rate of neuroimaging prior to stroke among individuals with TIA patients, multivariate Poisson log-linear regression model

<table>
<thead>
<tr>
<th>Guideline Period</th>
<th>TIA Cases</th>
<th>Total Time at Risk (days)</th>
<th>Event Rate</th>
<th>95% CI</th>
<th>Adjusted RR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Guideline</td>
<td>565</td>
<td>2006</td>
<td>7.1</td>
<td>(5.9-8.2)</td>
<td></td>
</tr>
<tr>
<td>After Guideline</td>
<td>1018</td>
<td>3432</td>
<td>8.9</td>
<td>(7.9-9.9)</td>
<td>1.2 (0.9-1.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; RR=rate ratio
†Reference category
‡Adjusted for age, sex, diagnostic setting, and presence of atrial fibrillation

3.3.2. Secondary Analyses

Secondary analyses evaluating the effect of guideline implementation on the utilization of imaging for CT and carotid ultrasound procedures separately indicated that, across diagnostic settings, the proportion of individuals with TIA that underwent a CT imaging procedure prior to stroke increased from 17.5% (95%CI=14.4-20.7) to 23.9% (95%CI=21.2-26.5) after the implementation of the guidelines, while the proportion of individuals that underwent a carotid ultrasound imaging procedure prior to stroke decreased from 14.7% (95%CI=11.8-17.6) to 12.8% (95%CI=10.7-14.8). The cumulative probability that individuals with TIA underwent a CT imaging procedure prior to stroke increased significantly in the period after the implementation of clinical guidelines (test statistic=8.33, df=1, \( p=0.003 \)), while the cumulative probability that individuals with TIA underwent a carotid ultrasound procedure prior to stroke remained unchanged (test statistic=2.21, df=1, \( p=0.21 \)).

Results also showed that there was a 30% increase in the rate of CT procedures following TIA in the period after the implementation of practice guidelines as compared to before, adjusted for demographic and clinical variables, and that this increase was statistically
significant (RR=1.3, 95%CI=1.1-1.6, \( p=0.04 \)). However, observed increases in the rate of carotid ultrasound procedures between calendar periods were not significant in the adjusted model (RR=0.9, 95%CI=0.7-1.2, \( p=0.36 \)) (Table 14). Chi-squared testing indicated that both models displayed a good fit to the data (CT: \( p=0.78 \), US: \( p=0.87 \)).

Table 14. Relationship between guideline period and average rate of CT and carotid ultrasound imaging in individuals with TIA, multivariate Poisson log-linear regression models

<table>
<thead>
<tr>
<th>Guideline Period</th>
<th># of Events</th>
<th>Total Time at Risk (days)</th>
<th>Event Rate</th>
<th>95% CI</th>
<th>Adjusted RR(\dagger) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Guideline</td>
<td>99</td>
<td>1304</td>
<td>7.6</td>
<td>(6.1-9.1)</td>
<td>--</td>
</tr>
<tr>
<td>After Guideline</td>
<td>243</td>
<td>2940</td>
<td>8.3</td>
<td>(7.2-9.3)</td>
<td>1.3 (1.1-1.6)(\dagger)</td>
</tr>
<tr>
<td>Carotid ultrasound Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Guideline</td>
<td>83</td>
<td>1469</td>
<td>5.6</td>
<td>(4.4-6.9)</td>
<td>--</td>
</tr>
<tr>
<td>After Guideline</td>
<td>130</td>
<td>1857</td>
<td>7.0</td>
<td>(5.7-8.2)</td>
<td>0.9 (0.7-1.2)(\dagger)</td>
</tr>
</tbody>
</table>

Abbreviations: CT-computed tomography; CI=confidence interval; RR=rate ratio
\(\dagger\) Adjusted for age, sex, diagnostic setting, presence of atrial fibrillation and prescriptions for blood formation and coagulation and central nervous system medications
\(\dagger\) Adjusted for age, sex, health service delivery area, and presence of heart disease

Further descriptive analyses to evaluate whether observed increases in the use of CT procedures varied by diagnostic setting revealed that the proportion of individuals with TIA who were diagnosed by their primary care physician that underwent a CT imaging procedure after TIA increased from 13.9% (95%CI=10.7-17.1) to 20.0% (95%CI=17.2-22.7) in the period after the implementation of the clinical guidelines, while the proportion of individuals diagnosed during a hospital admission that underwent a CT imaging procedure after TIA increased from 31.4% (95%CI=23.0-39.7) to 40.1% (95%CI=33.3-47.0). For those diagnosed in the primary
care setting, the cumulative probability of undergoing a CT imaging procedure prior to stroke or death increased significantly in the period after the implementation of clinical guidelines (test statistic=7.86, df=1, \( p=0.008 \)); however, no significant change in the cumulative probability of undergoing a CT imaging procedure prior to stroke or death was observed for those diagnosed during a hospital admission (test statistic=2.70, df=1, \( p=0.10 \)). By contrast, significant increases in the rate of CT imaging procedures performed after TIA in individuals diagnosed in a hospital setting were observed from before (7.3\% (95\%CI: 4.9-9.6) to after guideline implementation (14.7\% (95\%CI: 11.4-17.9) (test statistic=6.43, df=1, \( p=0.01 \)); while the rate of CT imaging procedures performed in those diagnosed in the primary care setting remained unchanged from before (4.1\% (95\%CI: 3.1-5.2)) to after guideline implementation (5.7\% (95\%CI: 4.8-6.5); test statistic=1.26, df=1, \( p=0.26 \)).

3.4. Discussion

The purpose of this study was to characterize and compare population-based differences in the utilization of brain and vascular imaging procedures in the diagnostic evaluation of individuals with TIA before and after the implementation of clinical practice guidelines. Results demonstrated a significant increase in the probability that individuals with TIA would undergo an imaging procedure prior to stroke or death within 90 days of TIA after the implementation of clinical guidelines, and a trend towards an increase in the rate of imaging procedures performed after TIA in the period after guideline implementation, as compared to before. However, despite these increases, overall utilization of imaging procedures in this population-based cohort remained low, with results indicating that only approximately 30\% of TIA cases underwent any type of imaging procedure prior to stroke or death within the 90-day follow-up period. Further, secondary analyses revealed that changes in practice for the use of imaging were limited to specific imaging modalities and varied based on diagnostic setting. Although both the
probability of undergoing a CT imaging procedure prior to stroke and the rate of CT procedures performed after TIA increased after the implementation of clinical guidelines, the probability and rate of carotid ultrasound remained unchanged. Practice patterns for the use of CT imaging procedures also appeared to vary across diagnostic settings, as descriptive analyses indicated that increases in the probability of undergoing a CT imaging procedure were limited to those individuals diagnosed within the primary care setting, while increases in the rate of CT procedures performed after TIA were limited to those diagnosed in the hospital setting. Overall, the findings of this study showed that the implementation of clinical practice guidelines had an impact on population-based utilization of imaging in the diagnostic evaluation of TIA, specifically for the recommended use of CT procedures. However, results also indicated that imaging remained underutilized in this cohort, particularly for carotid ultrasound procedures and that the guidelines had a differential impact on utilization based on care setting. These findings highlight practice changes that occurred with respect to the uptake of clinical guidelines for the utilization of neuroimaging procedures after TIA and also provide insight into potential gaps that remain between guideline recommendations and practice for the evaluation of individuals with TIA.

Although clinical guidelines are increasingly used to disseminate current scientific evidence and considerable resources are dedicated to the development and implementation of guidelines for evidence-based practice (251), there is substantial variability in the extent to which the implementation of clinical guidelines effects an observable change in practice (143-145). The significant increase in overall utilization of imaging procedures after TIA following the implementation of clinical guidelines observed in the present study suggests that clinical guidelines had an effect on the use of imaging in this population-based TIA cohort. This finding is consistent with prior work that demonstrated that clinical guidelines can result in sustained practice changes in the management of individuals with stroke and TIA. In one prospective
study evaluating national quality improvement guidelines for the in hospital treatment of stroke or TIA in the United States (US), adherence to these guidelines was associated with sustained improvements in several specific performance measures over the five-year follow-up period (160). Another study of practice in primary care demonstrated that the implementation of evidence-based guidelines resulted in a 36% increase in the diagnosis of atrial fibrillation and improved quality of treatment for individuals with TIA (155). Similar to these findings, results of the present study indicated that the implementation of practice guidelines recommending the use of imaging in the diagnostic assessment of TIA resulted in the increased utilization of these procedures in the evaluation of individuals with TIA. These findings contribute to the evidence that clinical guidelines can improve practice for the management of individuals with TIA and also suggest that guidelines can have an impact at the population-based level in individuals diagnosed with TIA across different care settings.

Despite the observed increase in the utilization of imaging procedures after guideline implementation, results of the present study revealed that the overall utilization of imaging after TIA remained low, as the probability that individuals with TIA underwent an imaging investigation prior to stroke increased to only 30% after the implementation of clinical guidelines. Secondary analyses also indicated that the effect of the clinical guidelines differed by imaging modality, with increases in imaging utilization observed for CT but not carotid ultrasound imaging procedures. These findings suggest that, despite evidence for the uptake of clinical guidelines for imaging use after TIA, the majority of individuals with TIA in this population-based cohort were not investigated with imaging prior to stroke and that the utilization of carotid ultrasound procedures was particularly low. These results are similar to previous hospital-based reports of underutilization of imaging procedures in the emergency-department assessment of individuals with TIA in Canada (134), where only 31% of individuals underwent CT or MRI imaging prior to discharge (134) and low rates of inpatient carotid
doppler imaging in the emergency department investigation of TIA were observed (135). Findings of the present study indicated that the underutilization of recommended imaging procedures extended to population-based practices for the evaluation of individuals with TIA and occurred even among high-risk patients (i.e. those that had a stroke within 90 days). Thus, although the present study demonstrated that clinical guidelines improved population-based practice for the use of imaging after TIA, the uptake of guideline recommendations was not sufficient to address an overall pattern of underutilization for imaging in the diagnostic evaluation of TIA, particularly for carotid ultrasound imaging.

Secondary analyses also revealed differential increases in the utilization of CT procedures by diagnostic setting. While increases in the probability that individuals with TIA underwent CT imaging after the implementation of clinical guidelines were present for those diagnosed in the primary care setting, increases in the rate of CT procedures performed after TIA were also observed, but limited to those diagnosed in hospital. This finding suggests that there was an uptake of guideline recommendations for CT imaging across settings, but that the guidelines impacted practice in different ways, with an increase in the number of individuals recommended for imaging investigations after TIA associated with primary care assessment and an increase in the number of imaging procedures per TIA patient associated with assessment in hospital. The uptake and adherence to clinical guidelines has previously been shown to be limited in the primary care setting (144, 145) and prior studies assessing utilization of imaging procedures for individuals evaluated by primary care providers have reported low rates of imaging utilization associated with primary care assessment (135) (133). Although findings of the present study indicated that the implementation of clinical guidelines was associated with an the increased use of CT procedures in individuals presenting to their primary care provider, the overall underutilization of CT and other imaging procedures observed in the present study suggests that
the underuse of imaging investigations in individuals presenting with TIA symptoms persists in this setting.

The population-based cohort examined in the present study represents a high-risk subset of the TIA population, as all individuals had a stroke within 90 days subsequent to TIA. However, as 80% of TIA cases included in the study cohort were diagnosed in the primary care setting, there may be several differences between this cohort and other high-risk cases from the general TIA population. Specifically, previous studies have shown that severe or higher-risk TIA patients more often present to hospital than to their family physician (135). Thus, the present cohort is unique in that it represents a high-risk cohort that was assessed primarily within the primary care setting. As a result, it is possible that the results of the present study may have underestimated current practices for imaging use in TIA cases assessed in other settings, such as those admitted to hospital. To assess this possibility, we conducted a sensitivity analysis, where utilization was evaluated only in those TIA cases within the study cohort that were diagnosed during a hospital admission. This analyses showed that, in the period after the implementation of clinical guidelines, 74% (95%CI=72.8-76.3) of cases underwent imaging post-TIA prior to stroke, indicating that the utilization of imaging procedures after TIA was in fact higher when considering only those individuals admitted to hospital for TIA. As such, these findings suggest that the gap between imaging guidelines and practice may be primarily associated with the primary care evaluation of individuals with TIA. In addition, by examining imaging utilization in this unique population-based cohort, the present study provided potentially important insights into the failure of stroke prevention in these individuals. Specifically, as 70% of individuals with TIA in the study cohort had no brain or vascular imaging work-up prior to stroke, a potential factor in the failure to prevent stroke subsequent to TIA in these individuals may have been insufficient information about the origin or mechanism of the event at assessment. These findings suggest that the evaluation of imaging utilization
represents a potential quality indicator for secondary stroke prevention in individuals with TIA, although prospective studies are required to determine whether imaging use at assessment has an impact on selected preventive management strategies and outcomes in individuals with TIA.

The underutilization of imaging investigations in the diagnostic evaluation of TIA may have important implications for the prevention of recurrent stroke in the TIA population. The underuse of imaging procedures at the time of assessment in the present study may have contributed to misclassification in the diagnosis of TIA or identification of etiological mechanisms and ultimately impacted management for the prevention of stroke after TIA (134). Of particular concern is the underuse of carotid ultrasound procedures, as occlusions exceeding 50% have been shown to occur in up to 34% number of patients with TIA (114) and TIA associated with a high-grade stenosis or occlusion due to a large-artery atherosclerotic (LAA) mechanism carries the greatest risk of subsequent stroke (52). Based on these estimates, if 34% of individuals in the present study had a LAA mechanism and the probability of undergoing carotid ultrasound imaging was only 12% after the implementation of clinical guidelines, approximately 300 individuals may have had a LAA occlusion that was not investigated with carotid ultrasound imaging over the study period. Given previous population-based data indicating delays in the use of carotid imaging and intervention after TIA are associated with a high risk of early preventable recurrent stroke (252), the lack of adherence to guideline recommendations for the use of vascular imaging may result in the under detection of individuals at highest risk for recurrent stroke and represent a missed opportunity for stroke prevention. However, it is important to note that the present findings do not indicate whether there was a lack of adherence to guidelines recommending carotid ultrasound imaging procedures or whether delays in the time to imaging after TIA prevented imaging prior to stroke. Further population-based studies are required to characterize the timing of imaging use in the evaluation of individuals with TIA.
Several factors may influence health professionals’ adherence to clinical guidelines and prior work has shown that a number of potential barriers may limit the uptake of guideline recommendations. Previous studies have shown that practitioner experience and perceptions play an important role in guideline adherence (253), while other potential barriers include the guidelines themselves, the dissemination strategy, the complexity of recommendations influencing guideline uptake (141), resource availability, and the organizational culture of the practice context (130, 254, 255). It is possible that some of these factors may be related to the low utilization rates and differential improvement in utilization for CT compared to carotid ultrasound procedures observed in the present study. As individuals with TIA are frequently neurologically healthy at the time of presentation (17), TIA has a history of being perceived as a benign condition and previous studies have shown that the evaluation and management of patients with TIA has traditionally lacked the urgency of acute stroke (256, 257). Although recent evidence for the high, immediate risk of stroke in individuals with TIA (36, 170) has resulted in an increased awareness that TIA is a medical emergency, it is possible that practitioner’s experience and perceptions of the severity of TIA was a factor in the low utilization of imaging procedures observed over the calendar periods evaluated in the present study, particularly as, in the majority of cases, the diagnosis of TIA was made by a primary care provider. Several previous studies have reported a lack of knowledge of TIA among primary care providers (140, 258-260). In one study surveying general practitioner’s (GP) knowledge of TIA symptoms and preferred strategies for investigation and management, 23% of GPs underestimated the risk of stroke after TIA and only 5–10% thought that a carotid ultrasound was an appropriate investigation (259). Other studies have reported good knowledge among primary care providers that TIA is a medical emergency (140, 260), but a lack of knowledge of clinical symptoms. One study showed only 14% of physicians recognized all clinical symptoms of TIA (260); a lack of awareness of relevant clinical guidelines (258); and low preferences for
urgent neuroimaging (133, 259, 260) and admission to hospital (133). It is thus possible that practitioner experience and perceptions contributed to the underutilization of recommended imaging procedures after TIA observed in the present study.

Another potential factor that may have influenced the uptake of guidelines in the present study relates to the dissemination of guideline information. Previous studies have shown that active dissemination strategies, including multifaceted interventions and interactive education result in the increased uptake of guidelines compared to passive approaches (130, 261). As the present study evaluated utilization of imaging in relation to the 1997 AHA imaging guidelines for TIA, it is possible that active dissemination activities for these guidelines were not implemented in Canada and, as a result, this version of the AHA guidelines may have had a limited impact on Canadian practices. Although the Canadian Neurological Society (CNS) endorses current AHA guidelines, the internal committee designed to review practice guidelines for endorsement by the CNS was not developed until 2010, thus the AHA guidelines evaluated in the present study were not formally endorsed by the CNS during the calendar periods included in this study. Similarly, the first reference to AHA practice recommendations for stroke to appear in the BC Medical Association guidelines specific to practice in BC was in 2009, indicating that earlier AHA recommendations were also not incorporated into provincial guidelines during the period evaluated in this study. In 2006, the Canadian Stroke Strategy implemented Canadian Best Practice Recommendations for Stroke Care, incorporating evidence from 14 sets of previous clinical guidelines from North America and abroad (14). These guidelines aligned with the 1997 AHA imaging practice guidelines in recommending immediate brain imaging and carotid artery imaging within 24 hours after TIA and also specifically incorporated a comprehensive dissemination strategy that included provincial and local consultations with clinicians and decision-makers and teaching materials, learning modules, and point-of-care tools targeted towards different clinical settings. Given the multifaceted approach
to the development and implementation of these guidelines, it is possible that greater changes in practice for the use of imaging in Canada would be observed in relation to these guidelines than those evaluated in the present study.

The complexity of guideline recommendations has also been shown to influence uptake, with guidelines that involve more specialized knowledge of a condition associated with reduced uptake and adherence (143). Given the complexity of factors involved in the diagnosis of TIA, it is possible that the complexity of the recommendations included in the AHA practice guidelines evaluated in this study affected uptake for imaging use, particularly among practitioners with less experience in the diagnosis and evaluation of TIA, such as primary care providers (260). Previous work has also demonstrated that guidelines are unlikely to effect a rapid change on practice (262). As the present study evaluated the utilization of imaging in relation to the first set of guidelines with specific recommendations for imaging use in individuals presenting with TIA (127), it is also possible that these guidelines were associated with a slower rate of practice change and that higher levels of utilization would be observed if evaluated with respect to subsequent guidelines.

Resource availability has also been shown to be a barrier to the uptake of clinical guidelines (254). Imaging-related resources, including the availability of after hours radiology services and wait times for outpatient tests, have been identified as potential factors in the underutilization of imaging after TIA (134). However, data from the Canadian Institute of Health Information (CIHI) indicate there was an increase in the availability of CT scanners in Canada over the calendar period evaluated in the present study (126), and previous work has identified carotid ultrasound as an optimal screening tool for carotid stenosis, due in part to the widespread availability of this technique (263). Another possible explanation for modality specific findings for the underuse of carotid ultrasound procedures in this study is that the use of vessel imaging techniques other than carotid ultrasound (e.g., CT and MR angiography, or
conventional arterial or venous angiography) may have been performed to evaluate vessel status in individuals with TIA (30). There were insufficient data on MRI and conventional angiography procedures performed after TIA in the present study population for the analysis of these modalities, suggesting either that these procedures were not performed in individuals included in the study cohort, or that these imaging procedures were not captured by the methodology for identifying procedural codes employed in the present study. However, it is important to note that the CT imaging category employed in the present study did not distinguish between non-contrast CT and CT involving angiography and, it is thus possible that some of the CT procedures performed after TIA also involved a vessel imaging sequence. Future population-based studies characterizing the utilization of imaging after TIA would benefit from a more detailed analysis of imaging subtypes to evaluate this possibility.

Findings of the present study have implications for the development and implementation of clinical guidelines related to the use of brain and vascular imaging after TIA and also for current practices for the use of these procedures in the assessment of individuals presenting with TIA. These findings demonstrated that clinical guidelines can effect observable practice changes with regard to the utilization of imaging procedures, but also highlighted an overall underuse of recommended procedures in the assessment of individuals with TIA. Based on prior literature identifying potential barriers to the uptake of clinical guidelines, future guidelines for imaging use after TIA may benefit from the development of recommendations that are accessible to clinicians with varying levels of experience in the assessment of acute ischemia, to potentially increase the uptake of recommendations the various care settings where individuals with TIA may be assessed and diagnosed, including both primary care and subspecialty settings. Further, to promote adherence to recommendations, the implementation of future imaging guidelines may also benefit from dissemination strategies involving active educational interventions targeting a range of care providers, including emergency department, neurology, and primary
care physicians. Although this literature offers insight into some potential barriers that may have influenced the uptake of imaging guideline recommendations evaluated in the present study, additional studies are required to identify specific barriers for the use of imaging procedures in the diagnostic assessment of TIA and determine the optimal strategies to address these barriers. An increased awareness among health care providers of existing gaps between guideline recommendations and current practices for the utilization of imaging procedures may help promote increased utilization of these procedures and improve strategies for identifying individuals at high risk of stroke, to optimize preventive management in the TIA population.

3.5. Strengths and Limitations

The main strengths of this study were the use of data from longitudinal, population-based administrative databases to define the TIA cohort and identify the study variables, and the use of a case definition that enabled the examination of imaging utilization in a population-based cohort of individuals with TIA prior to stroke. The use of population-based administrative data eliminated several potential sources of selection bias that prior studies of imaging utilization may have been subject to, ensuring greater generalizability of these findings. In addition, these longitudinal data enabled the before and after comparison of imaging utilization in relation to the implementation of the 1997 AHA clinical practice guideline, allowing the evaluation of changes in practice over time not previously captured in cross-sectional studies of imaging utilization. The identification of a population-based study cohort also enabled the evaluation of differential practice changes by imaging modalities and within the different care settings where individuals with TIA may be diagnosed and managed, providing novel information about potential sources of variability in imaging utilization in this population.

This study also had several limitations. Despite the use of a methodology that employed the criterion of post-TIA stroke to identify TIA cases and minimize the potential for bias due to
the misclassification of TIA diagnoses (42), the potential that misclassified cases were included in the study cohort remains. However, as prior work has shown, recurrent cerebrovascular events are absent in individuals with TIA mimic, and the likelihood of this potential bias was minimal. The potential impact of the inclusion of misclassified cases on the study findings would be the underestimation of the proportion of TIA cases that underwent imaging prior to stroke after TIA. However, given the before and after design of the present study, this potential bias would only have impacted the primary analyses if there was differential misclassification in the periods before and after guideline implementation.

Another limitation of the present study is that the data used to define the TIA cohort and study variables did not include measures of TIA severity or etiology. As previous evidence has shown that TIAs with motor features and those with large-artery atherosclerotic etiology are considered more severe and are at higher risk of stroke (34, 36), individuals with these clinical features may be more likely to undergo imaging investigations during the diagnostic assessment. As these factors may influence both the indication for imaging and the type of procedure performed, findings of the present study may be subject to confounding due to TIA severity and etiology. To minimize the potential impact of bias due to differences in severity among cases, the cohort evaluated in the present study involved a subset of TIA cases that all had subsequent recurrent stroke. As a result, this cohort represents a higher risk TIA cohort, with presumably less heterogeneity in severity across cases. In addition, all multivariable analyses in the present study were adjusted for comorbid risk factors, including diabetes, heart disease, hypertension and atrial fibrillation that may be indicators of the etiology of the presenting symptoms. Despite these methods, differences may remain between guideline periods in the severity of the TIA population. Future studies examining imaging utilization would benefit from prospective evaluation where clinical features, including the severity and etiology of the presenting TIA may be identified and incorporated into the analytic plan.
Further, although year was used as an indicator of potential increases in temporal trends for imaging use over the study period and bivariate analyses showed no significant effect of year on study outcomes, it is possible that potential confounding due to temporal changes in care was not sufficiently addressed using this methodology. Future studies employing interrupted time-series or segmented regression analytic methodologies may be more sensitive to this potential source of bias.

3.6. Conclusions

Findings of this study showed that practice guidelines for neuroimaging in individuals with TIA were associated with a significant increase in overall utilization, demonstrating an observable change in practice for the use of these procedures across care settings where individuals presenting with TIA were evaluated. However, despite this increase in utilization, the overall use of imaging procedures in this population-based cohort remained low and observed practice changes were limited to the use of CT procedures and varied across diagnostic settings. Findings of this study suggest that the implementation of clinical practice guidelines had an impact on population-based practices for the use of imaging in the diagnostic evaluation of TIA, but also highlight gaps that remain between guideline recommendations and current practice for the utilization of neuroimaging in individuals with TIA. Specific gaps include an overall underutilization of imaging after TIA; a lack of increase in the use of carotid ultrasound imaging procedures; and, the differential uptake of guideline recommendations in primary care and hospital diagnostic settings. Further population-based studies are required to characterize imaging times in the Canadian TIA population and determine whether practice changes for the timing of these procedures have occurred in the diagnostic evaluation of individuals with TIA.
4 Temporal Trends in the Timing of Imaging Procedures in Individuals with Transient Ischemic Attack

4.1. Introduction

Previous population-based studies have estimated that up to 20% of individuals with TIA experience a recurrent stroke within 90 days (21-26, 34). It was previously thought that the risk of stroke in the early period after TIA was quite low, with commonly quoted estimates in the range of 1%-2% at 7 days and 4% at 30 days (264). However, many of these studies enrolled individuals several weeks after their event excluding those with early recurrent stroke, and as a result, underestimated the early risk of stroke in this population (23). In recent years, there has been an increasing recognition that much of the risk of stroke after TIA accrues very early, with almost half of recurrent strokes occurring within 48 hours of the index TIA (22, 23, 27, 170). Prospective studies incorporating time at risk for individuals within early time windows have shown that early stroke risk is higher than previously thought, with recent reports estimating risk closer to 5% at 7 days (22, 265).

Recently, a number of other studies have also shown that the early risk of stroke after TIA can be reduced with rapid diagnostic assessment and initiation of preventive treatments (59, 78, 171). Two prospective observational studies comparing assessment and treatment in rapid access clinics with standard clinic-based assessment and primary-care-initiated treatment reported significant reductions in stroke risk associated with a rapid assessment protocol (within 48 hours) (78, 171). Another Canadian study compared 90-day stroke rates associated with the evaluation of emergency department patients with TIA in urgent access outpatient stroke prevention clinics and also showed a significant decrease in the rate of stroke compared to the predicted rate(172). Further, results from a recent randomized controlled pilot trial assessing the impact of the initiation of antiplatelet or statin therapy within 24 hours after TIA or minor stroke
on recurrent stroke risk showed a potential role for urgent treatment in reducing recurrent events and underscored the need for continued investigation of the potential benefits of intervention in the hyper acute phase of TIA (59). Further, although available structural imaging techniques, such as MRI, are sensitive to detect ischemic changes early after the onset of the ischemia (101), prior work has demonstrated that this sensitivity is limited to the acute phase post-event, with few individuals showing abnormalities on MRI subacutely after TIA (200). Given this evidence, there is an evolving consensus that early neuroimaging provides critical information to help identify individuals at high risk of stroke who may benefit from urgent evaluation and treatment (266). Thus, effective treatment strategies for the prevention of stroke after TIA may rely not only on the use of imaging investigations to help accurately establish an ischemic origin for transient symptoms and identify the underlying mechanisms of the event, but also on the timing of these investigations.

Despite evidence for the benefits of early evaluation after TIA, previous Canadian hospital-based studies have indicated that delays are present in the timing of imaging procedures performed in individuals presenting to emergency departments or admitted to hospital after TIA, with the majority of individuals receiving no imaging investigations prior to discharge (134, 135) or undergoing delayed imaging upon admission (5). Findings from these studies suggest that gaps may remain between current evidence for the benefit of early assessment and practice for the timing of imaging procedures performed after TIA in Canada. However, as a significant proportion of individuals with TIA present to primary care and may also be managed on an outpatient basis by their primary care provider, data on the timing of imaging after TIA from hospital-based cohorts may not reflect population-based practices for the timing of procedures.

There are currently no available population-based studies characterizing temporal trends of imaging procedures performed after TIA in Canada or examining whether the timing of imaging investigations used in individuals with TIA has improved with the increase in evidence
for early evaluation. The purpose of this study was to evaluate population-based trends in the timing of imaging procedures performed among those individuals that underwent neuroimaging within 90 days of TIA from 1998 to 2007 in Canada. The primary objectives of this study were to characterize the timing of procedures performed after TIA and evaluate potential changes in temporal trends for time to imaging after TIA in Canada. The secondary objective was to determine whether temporal trends in the timing of imaging procedures differed based on the setting of TIA diagnosis.

4.2. Methods

4.2.1. Study Design

This was a retrospective cohort study, designed to characterize trends in the timing of neuroimaging procedures performed in a cohort of individuals with TIA from 1998 to 2007.

4.2.2. Data sources

All administrative databases used in the present study were previously described in Chapter 2 (Section 1.2.1.).

4.2.2. Target Population and Cohort Definition

The target population for the present study was individuals with TIA. A subset of TIA cases diagnosed during the calendar period from 1998 to 2007 were retrospectively identified for inclusion in the study cohort, using the same cohort definition as described in Chapter 3 (section 3.2.2). Cohort entry was defined as the date of presentation to medical care where the initial diagnosis of TIA was recorded (i.e. date of physician encounter or date of admission) and the study cohort was followed for a period of 90 days.

4.2.3. Primary Outcome

The primary outcome was time to first imaging procedure performed after TIA among those within the study cohort that underwent neuroimaging within 90 days of TIA. Imaging
procedures for this study period were identified using fee-for-service procedural codes from the MSP physicians billing database and CCP/CCI procedures and intervention codes from the discharge abstract database (see Chapter 3, Table 8) and included all CT, MRI, US, echocardiography and angiography procedures performed on individuals in the study cohort. Although echocardiography was included in the outcome definition, these procedures represented <1% of all captured procedures and, as a result, the primary outcome represents primarily neurovascular imaging procedures.

4.2.4. Censoring Events

Censoring events were imaging, stroke or death, which ever occurred first within 90 days post TIA. Criteria for the identification of these events have previously been described (Chapter 3, Section 3.2.4). For the present study, all observations were censored where the first recorded imaging procedure occurred subsequent to the date of TIA diagnosis and prior to the date of stroke or death were uncensored within 90 days post TIA. To ensure that the imaging procedure was related to the TIA and not the stroke event, observations were censored at the date of stroke if and only if the first recorded imaging procedure occurred subsequent to the date of TIA diagnosis and either on or after the date of stroke. Observations were censored at the date of death if death occurred within the follow-up period (90 days) but no imaging was performed between TIA and death. Remaining observations were administratively censored at the end of study follow-up (90 days).

4.2.5. Demographic and Clinical Characteristics

Demographic and clinical variables identified as potential confounding variables for adjustment in models investigating the effect of the clinical guideline on the timing of imaging procedures included the following: age; sex; income decile; health service delivery area (HSDA); comorbid clinical conditions of diabetes, hypertension, heart disease, and atrial fibrillation; and prescription drug class (Table 10), using the same criteria for variable
identification as previously described (Chapter 3, Section 3.2.3.4.). For the present study, age was categorized into three categories from age 20 to 65, with the final category including individuals aged 65 and older.

4.2.6. Statistical Analyses

Frequency statistics were generated to characterize the study cohort with respect to all study variables from 1998 to 2007. Chi-square testing was used to compare characteristics of individuals with TIA across study years. Summary statistics were generated to characterize time to the first imaging procedure performed after TIA across all years during the study period (1998-2007).

To examine changes in the temporal trends of imaging procedures among those that underwent imaging within 90 days of TIA, the Kaplan-Meier method was used to estimate time from the date of the physician encounter or hospital admission to the date of the first imaging procedure performed prior to stroke or death across years (249). Differences in the cumulative probability of imaging prior to stroke or death between 1998 and 2007 were assessed with the log rank test. To examine trends in early versus late timing of neuroimaging procedures, procedures were categorized as early (≤ 7 days) and late (8-90 days), according to previously established risk windows for the occurrence of early recurrent stroke after TIA (36). Multivariate logistic regression was then used to determine whether the likelihood of early imaging after TIA among those that underwent imaging increased from 1998 to 2007.

Secondary analyses were also performed to determine whether imaging times and temporal trends differed by diagnostic setting, using separate Kaplan-Meier probability estimates and multivariate logistic regression models for individuals diagnosed in the primary care versus hospital setting, respectively. All multivariate analyses were adjusted for relevant demographic and clinical variables.
4.3. Results

Demographic data characterizing the study cohort are presented in Table 15. Among the 1018 individuals with TIA from 1998 to 2007, the majority of individuals with TIA were aged 65 or older (83.2%) with no significant differences in the distribution of age groups by year. There were also no significant differences in the study population by gender or income decile across study years. Overall, the proportion of individuals with TIA presenting to care within an urban health region was slightly higher than those presenting in a rural region (56.4%) with significant differences in the rural/urban distribution across years. The majority of individuals in the study cohort were diagnosed in the primary care setting (80.1%) and the proportion of individuals diagnosed in a primary care versus hospital setting also differed across fiscal years. Among individuals aged 65 and older, higher proportions were prescribed medications from the cardiovascular (58.2%) and central nervous system (52.2%) medication classes at the time of TIA diagnosis and differences in the proportions of individuals prescribed blood coagulation and formation and central nervous system classes of medications were significant across fiscal years. Hypertension was the most commonly identified co-morbid clinical condition (43.5%), although only the proportion of individuals with TIA diagnosed with atrial fibrillation differed significantly across study years.
Table 15. Characteristics of 1018 individuals diagnosed with transient ischemic attack within 90 days and prior to stroke by year from 1998 to 2007

<table>
<thead>
<tr>
<th>Factor</th>
<th>1998 (%)</th>
<th>1999 (%)</th>
<th>2000 (%)</th>
<th>2001 (%)</th>
<th>2002 (%)</th>
<th>2003 (%)</th>
<th>2004 (%)</th>
<th>2005 (%)</th>
<th>2006 (%)</th>
<th>2007 (%)</th>
<th>Total N (%)</th>
<th>Chi-Square (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-54</td>
<td>8.3</td>
<td>5.0</td>
<td>2.0</td>
<td>6.0</td>
<td>7.9</td>
<td>7.8</td>
<td>6.1</td>
<td>4.4</td>
<td>5.3</td>
<td>1.6</td>
<td>58 (5.7)</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>12.8</td>
<td>11.0</td>
<td>11.5</td>
<td>5.2</td>
<td>9.9</td>
<td>8.4</td>
<td>15.5</td>
<td>9.5</td>
<td>14.9</td>
<td>14.5</td>
<td>113 (11.1)</td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>78.9</td>
<td>84.0</td>
<td>86.5</td>
<td>88.8</td>
<td>82.2</td>
<td>83.8</td>
<td>78.4</td>
<td>85.3</td>
<td>79.8</td>
<td>83.9</td>
<td>847 (83.2)</td>
<td>18.1 (0.45)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>54.1</td>
<td>47.0</td>
<td>45.2</td>
<td>49.1</td>
<td>40.6</td>
<td>40.6</td>
<td>46.5</td>
<td>47.4</td>
<td>51.7</td>
<td>58.8</td>
<td>505 (49.6)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>45.9</td>
<td>53.0</td>
<td>54.8</td>
<td>50.9</td>
<td>59.4</td>
<td>59.4</td>
<td>53.5</td>
<td>52.6</td>
<td>48.3</td>
<td>41.2</td>
<td>513 (50.4)</td>
<td>11.0 (0.27)</td>
</tr>
<tr>
<td>HSDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>56.9</td>
<td>40.0</td>
<td>43.3</td>
<td>32.8</td>
<td>43.6</td>
<td>47.5</td>
<td>43.3</td>
<td>36.2</td>
<td>43.0</td>
<td>56.5</td>
<td>444 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>43.1</td>
<td>60.0</td>
<td>56.7</td>
<td>67.2</td>
<td>56.4</td>
<td>52.5</td>
<td>56.7</td>
<td>63.8</td>
<td>57.0</td>
<td>43.5</td>
<td>574 (56.4)</td>
<td>21.3 (.01)</td>
</tr>
<tr>
<td>Income Decile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.3</td>
<td>22.0</td>
<td>16.3</td>
<td>12.9</td>
<td>14.9</td>
<td>9.1</td>
<td>11.3</td>
<td>12.7</td>
<td>8.8</td>
<td>14.5</td>
<td>131 (12.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18.4</td>
<td>10.0</td>
<td>12.5</td>
<td>12.9</td>
<td>13.9</td>
<td>16.2</td>
<td>18.6</td>
<td>10.3</td>
<td>13.2</td>
<td>9.7</td>
<td>139 (13.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10.1</td>
<td>7.0</td>
<td>8.7</td>
<td>11.2</td>
<td>8.9</td>
<td>8.0</td>
<td>15.5</td>
<td>12.1</td>
<td>10.5</td>
<td>12.9</td>
<td>106 (10.4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8.3</td>
<td>11.0</td>
<td>10.6</td>
<td>12.1</td>
<td>5.9</td>
<td>10.1</td>
<td>13.4</td>
<td>6.9</td>
<td>7.9</td>
<td>11.3</td>
<td>98 (9.6)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8.3</td>
<td>7.0</td>
<td>10.6</td>
<td>10.3</td>
<td>11.8</td>
<td>11.1</td>
<td>9.3</td>
<td>8.6</td>
<td>9.7</td>
<td>8.5</td>
<td>96 (9.4)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6.4</td>
<td>12.0</td>
<td>6.7</td>
<td>12.1</td>
<td>11.9</td>
<td>7.1</td>
<td>4.1</td>
<td>6.0</td>
<td>13.2</td>
<td>9.7</td>
<td>91 (8.9)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>11.0</td>
<td>10.0</td>
<td>8.7</td>
<td>6.0</td>
<td>9.9</td>
<td>7.1</td>
<td>5.2</td>
<td>11.2</td>
<td>8.8</td>
<td>14.5</td>
<td>92 (9.0)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>11.9</td>
<td>9.0</td>
<td>5.8</td>
<td>8.6</td>
<td>6.9</td>
<td>10.1</td>
<td>7.2</td>
<td>9.5</td>
<td>10.5</td>
<td>8.1</td>
<td>90 (8.8)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>6.4</td>
<td>7.0</td>
<td>10.6</td>
<td>6.9</td>
<td>7.9</td>
<td>6.0</td>
<td>9.3</td>
<td>8.6</td>
<td>12.3</td>
<td>4.8</td>
<td>83 (8.2)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>11.0</td>
<td>5.0</td>
<td>9.6</td>
<td>6.9</td>
<td>7.9</td>
<td>15.2</td>
<td>6.2</td>
<td>14.7</td>
<td>5.3</td>
<td>8.1</td>
<td>92 (9.0)</td>
<td>73.2 (0.72)</td>
</tr>
<tr>
<td>Diagnostic Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>73.4</td>
<td>90.0</td>
<td>85.6</td>
<td>79.3</td>
<td>76.2</td>
<td>78.8</td>
<td>77.3</td>
<td>85.3</td>
<td>77.2</td>
<td>85.5</td>
<td>821 (80.7)</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>26.6</td>
<td>10.0</td>
<td>14.4</td>
<td>20.7</td>
<td>23.8</td>
<td>21.2</td>
<td>22.7</td>
<td>14.7</td>
<td>22.8</td>
<td>14.5</td>
<td>197 (19.4)</td>
<td>16.6 (.05)</td>
</tr>
<tr>
<td>Factor</td>
<td>1998 (%)</td>
<td>1999 (%)</td>
<td>2000 (%)</td>
<td>2001 (%)</td>
<td>2002 (%)</td>
<td>2003 (%)</td>
<td>2004 (%)</td>
<td>2005 (%)</td>
<td>2006 (%)</td>
<td>2007 (%)</td>
<td>Total N (%)</td>
<td>Chi-Square (p)</td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Y</td>
<td>22.9</td>
<td>18.0</td>
<td>12.5</td>
<td>12.9</td>
<td>10.1</td>
<td>5.2</td>
<td>4.3</td>
<td>3.5</td>
<td>4.8</td>
<td>111 (10.9)</td>
<td>39.9 (&lt;.001)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>77.1</td>
<td>82.0</td>
<td>87.5</td>
<td>87.1</td>
<td>89.9</td>
<td>94.6</td>
<td>95.7</td>
<td>96.5</td>
<td>95.2</td>
<td>907 (89.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>62.4</td>
<td>66.0</td>
<td>67.3</td>
<td>61.2</td>
<td>53.5</td>
<td>59.64</td>
<td>55.7</td>
<td>51.7</td>
<td>49.1</td>
<td>54.8</td>
<td>592 (58.2)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>37.6</td>
<td>34.0</td>
<td>32.7</td>
<td>38.8</td>
<td>46.5</td>
<td>0.4</td>
<td>44.3</td>
<td>48.3</td>
<td>50.9</td>
<td>45.2</td>
<td>426 (41.8)</td>
<td>14.7 (.10)</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>59.6</td>
<td>59.0</td>
<td>66.4</td>
<td>50.0</td>
<td>59.4</td>
<td>46.5</td>
<td>42.3</td>
<td>49.1</td>
<td>38.6</td>
<td>51.6</td>
<td>531 (52.2)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>40.4</td>
<td>41.0</td>
<td>33.7</td>
<td>50.0</td>
<td>40.6</td>
<td>53.5</td>
<td>57.7</td>
<td>50.9</td>
<td>61.4</td>
<td>48.4</td>
<td>487 (47.8)</td>
<td>28.9 (.007)</td>
</tr>
<tr>
<td>ECWB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>33.0</td>
<td>38.0</td>
<td>47.1</td>
<td>44.0</td>
<td>32.7</td>
<td>40.4</td>
<td>35.1</td>
<td>46.6</td>
<td>36.8</td>
<td>46.8</td>
<td>406 (39.9)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>67.0</td>
<td>62.0</td>
<td>52.9</td>
<td>56.0</td>
<td>67.3</td>
<td>59.6</td>
<td>64.9</td>
<td>53.4</td>
<td>63.2</td>
<td>53.2</td>
<td>612 (60.1)</td>
<td>12.3 (.20)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14.7</td>
<td>27.0</td>
<td>24.0</td>
<td>17.2</td>
<td>11.9</td>
<td>18.2</td>
<td>21.7</td>
<td>17.2</td>
<td>21.9</td>
<td>25.8</td>
<td>200 (19.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>85.3</td>
<td>73.0</td>
<td>76.0</td>
<td>82.8</td>
<td>88.1</td>
<td>81.8</td>
<td>78.4</td>
<td>82.8</td>
<td>78.1</td>
<td>74.2</td>
<td>818 (80.4)</td>
<td>13.4 (.14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33.0</td>
<td>39.0</td>
<td>45.2</td>
<td>45.7</td>
<td>40.6</td>
<td>38.4</td>
<td>53.6</td>
<td>45.7</td>
<td>44.7</td>
<td>53.2</td>
<td>443 (43.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67.0</td>
<td>61.0</td>
<td>54.8</td>
<td>54.3</td>
<td>59.4</td>
<td>61.6</td>
<td>46.4</td>
<td>54.3</td>
<td>55.3</td>
<td>46.8</td>
<td>575 (56.5)</td>
<td>14.2 (.11)</td>
</tr>
<tr>
<td>Heart Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20.2</td>
<td>22.0</td>
<td>23.1</td>
<td>25.0</td>
<td>15.8</td>
<td>14.1</td>
<td>23.7</td>
<td>25.0</td>
<td>18.4</td>
<td>21.0</td>
<td>213 (20.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79.8</td>
<td>78.0</td>
<td>76.9</td>
<td>75.0</td>
<td>84.2</td>
<td>85.9</td>
<td>76.3</td>
<td>75.0</td>
<td>81.6</td>
<td>79.0</td>
<td>805 (79.1)</td>
<td>7.9 (.54)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.3</td>
<td>2.0</td>
<td>1.1</td>
<td>3.4</td>
<td>6.9</td>
<td>11.1</td>
<td>7.2</td>
<td>5.2</td>
<td>4.4</td>
<td>3.2</td>
<td>42 (4.1)</td>
<td>(.003)‡</td>
</tr>
<tr>
<td>No</td>
<td>98.7</td>
<td>98.0</td>
<td>98.9</td>
<td>96.6</td>
<td>93.1</td>
<td>88.9</td>
<td>92.8</td>
<td>94.8</td>
<td>95.6</td>
<td>96.8</td>
<td>976 (95.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BFC=blood formation and coagulation, CV=cardiovascular, CNS=central nervous system, ECWB=electrolytic, caloric, water balance ‡Fisher’s Exact Test
Distributions characterizing time to imaging for the first recorded imaging procedure performed after TIA among those that underwent an imaging procedure within the study period (90 days) are presented in Table 16. Descriptive data indicated that the mean and median times to the first imaging procedure performed after TIA across years were 9 and 4 days respectively, with 25% of cases undergoing their first imaging procedure at 7 days or longer. No apparent decreases in mean and median time to imaging post-TIA by year were observed over this time period. Yearly trends over time in early (<7 days) versus late imaging times (8-90 days) among those TIA patients that underwent an imaging procedure within the 90-day follow-up period are presented in Figure 5. These descriptive data showed that, overall, a higher percentage of patients with TIA underwent early compared to late imaging across years, but that there was little variation in the percent of individuals with TIA that underwent early versus late imaging from year to year across the study period.

Table 16. Characteristics of time to procedure for the first recorded imaging procedure among those that underwent neuroimaging within 90 days after TIA across years from 1998 to 2007

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Cases</th>
<th>No. that underwent imaging procedure</th>
<th>Mean (days to procedure)</th>
<th>Median (days to procedure)</th>
<th>10</th>
<th>25</th>
<th>75</th>
<th>90</th>
<th>Max Time (censor at 90 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>109</td>
<td>32</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>1999</td>
<td>100</td>
<td>33</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>16</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>2000</td>
<td>104</td>
<td>25</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>25</td>
<td>63</td>
</tr>
<tr>
<td>2001</td>
<td>116</td>
<td>23</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>2002</td>
<td>101</td>
<td>28</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>2003</td>
<td>99</td>
<td>32</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>14</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>2004</td>
<td>97</td>
<td>27</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td>2005</td>
<td>116</td>
<td>41</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>34</td>
<td>81</td>
</tr>
<tr>
<td>2006</td>
<td>114</td>
<td>44</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>19</td>
<td>36</td>
<td>87</td>
</tr>
<tr>
<td>2007</td>
<td>62</td>
<td>21</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>17</td>
<td>21</td>
<td>33</td>
</tr>
</tbody>
</table>
Figure 5. Percent of individuals with TIA that underwent early (≤ 7 days) and late (8-90 days) imaging among those that underwent an imaging procedure within 90 days of TIA from 1998 to 2007 (n=306)

Results of the Kaplan-Meier probability estimation examining changes in temporal trends of imaging after TIA across the study period indicated that there was no significant difference in the cumulative probability of undergoing an imaging procedure prior to stroke or death in individuals with TIA from 1998 to 2007 (test statistic=0.15, df=1, \( p=0.70 \)). Results of the adjusted multivariable logistic regression revealed that, although there was a 30% increase in the likelihood of undergoing early imaging (within 7 days) after TIA from 1998 to 2007, this difference was not statistically significant (OR=1.3, 95%CI=0.7-2.5, \( p=0.46 \)).

Secondary analyses characterizing yearly trends over time in early versus late imaging times for individuals diagnosed in the primary care setting compared to those diagnosed in the hospital setting, among those that underwent imaging within 90 days post-TIA (Figure 6). These descriptive data indicated that a higher percentage of individuals diagnosed in the hospital
setting underwent early compared to late imaging than those diagnosed by their primary care provider and also showed greater variability between years in the percentage of individuals with TIA undergoing early versus late imaging for hospital based diagnoses, across the study period.

a.

![Graph showing the percent of individuals with TIA diagnosed in the primary care setting that underwent early (≤ 7 days) and late (8-90 days) imaging for hospital based diagnoses, across the study period from 1998 to 2007.]

b.

![Graph showing the percent of individuals with TIA diagnosed in the hospital setting that underwent early (≤ 7 days) and late (8-90 days) imaging for hospital based diagnoses, across the study period from 1998 to 2007.]

Figure 6. Percent of individuals with TIA diagnosed in the a) primary care setting and b) hospital setting that underwent early (≤ 7 days) and late (8-90 days) imaging among those that underwent imaging within 90 days after TIA from 1998 to 2007.
Secondary analyses examining differences in the time to first imaging procedure prior to stroke or death for individuals diagnosed in the primary care setting revealed no significant differences in imaging times in 1998 compared to 2007 (test statistic=0.53, df=1, \( p=.47 \)). Similarly no significant differences in the time to first imaging procedure prior to stroke or death among those that underwent imaging within 90 days after TIA were apparent for individuals diagnosed in the hospital setting (test statistic=0.15, df=1, \( p=.70 \)). Results of the adjusted multivariable logistic regression indicated that there was a 20% increase in the likelihood of undergoing early imaging after TIA among those that underwent imaging within 90 days of TIA and who were diagnosed in the primary care setting from 1998 to 2007, but that this difference was not statistically significant (OR=1.2, 95%CI=0.6-2.7, \( p=0.61 \)). Among those diagnosed in the hospital setting that underwent imaging within 90 days of TIA, there was a 30% increase in the likelihood of undergoing early imaging after TIA from 1998 to 2007, but this difference was also not statistically significant (OR=1.3, 95%CI=0.3-5.7, \( p=0.74 \)).

4.4. Discussion

The primary purposes of this study were to characterize the timing of imaging procedures performed among those that underwent imaging prior to stroke in a population-based cohort of individuals with TIA and evaluate temporal trends in the timing of these procedures across years from 1998 to 2007. A secondary objective was to determine whether the timing of imaging varied across diagnostic settings (i.e. primary care versus hospital). Results of this study showed that the median time to imaging across years in this study period was 4 days, with 25% of the study cohort undergoing imaging at 7 days or longer. These findings indicated that the timing of the first imaging procedure exceeded the previously established window of highest risk for stroke after TIA (i.e., 48 hours) (27) and that 25% of individuals in this population-based cohort also did not undergo imaging within the acute phase after TIA, when available structural
imaging techniques show the highest sensitivity to detect post-ischemic changes (199). In addition, no significant differences in the timing of imaging procedures performed after TIA or the likelihood of undergoing early (≤ 7 days) compared to late (8-90 days) imaging were observed across this period, indicating that no improvements in time to imaging after TIA occurred from 1998 to 2007. Although, descriptively, the percentage of individuals with TIA diagnosed in the primary care setting that underwent early compared to late imaging across years was very similar, a higher percentage of those diagnosed in hospital underwent early imaging over time, suggesting that longer imaging times were associated primarily with the primary care assessment of individuals with TIA. As no significant differences in time to imaging from 1998 to 2007 were present for those diagnosed in either the primary care or hospital setting, this pattern appeared to be consistent over the study period. These findings suggest that gaps remain between current evidence for the benefits of early assessment and population-based practices for the timing of imaging investigations performed in the diagnostic evaluation of individuals with TIA.

Previous cross-sectional studies have shown that, among individuals with TIA presenting to emergency departments in Ontario and Alberta that underwent brain or vascular imaging, the majority of procedures were delayed and performed on an outpatient basis post-discharge (134, 135). Further, a recent Canada-wide audit of hospital-based practices for individuals admitted to hospital with TIA, with imaging as one of several performance indicators, demonstrated that initial imaging investigations were delayed in 30% of admitted patients (5). Results of the present study were consistent with these findings, demonstrating that the timing of imaging investigations performed after TIA in this population-based cohort were delayed beyond the window of highest stroke risk after TIA and also did not improve over time from 1998 to 2007. These findings offer new evidence to characterize population-based practices for the timing of imaging after TIA and indicate that delays in imaging times extend across all settings where
individuals with TIA are diagnosed, including primary care. Further, they demonstrate that this practice pattern has remained unchanged over a recent 10-year period. Given increasing evidence for the potential benefits of early assessment and intervention for stroke prevention after TIA during this same period (59, 78, 171), these data highlight the need for an increased understanding of the barriers to accessing urgent imaging after TIA.

Secondary analyses also revealed that the lack of improvement in imaging times among individuals who underwent an imaging procedure post-TIA across the study period was consistent across diagnostic settings, with no significant changes in time to imaging after TIA observed for those diagnosed either by a primary care provider or in hospital. The majority of individuals included in this study cohort were diagnosed in the primary care setting (81%), thus, although results did not demonstrate an improvement in imaging times among individuals admitted to hospital with a diagnosis of TIA, it is possible that these analyses were underpowered to detect differences in hospital-based imaging times across the study period. Descriptive data on temporal trends for early (<7 days) versus late (8-90 days) imaging from the present study suggested that the hospital-based assessment of individuals with TIA may be associated with shorter imaging times. These data indicated that a higher percentage of individuals diagnosed in hospital underwent early compared to late imaging than those diagnosed in primary care, suggesting an overall trend towards earlier procedure times in this setting. This trend was consistent across the study period and did not appear to decrease over time. However, as the majority of individuals in the study cohort were diagnosed by a primary care provider, these findings suggest that the lack of improvement in imaging times observed in the present study was primarily associated with the primary care assessment of TIA.

Previous studies have shown that primary care providers demonstrate low preferences for the use of urgent neuroimaging in the evaluation of individuals with TIA (133, 259, 260), suggesting that practitioners’ perceptions of the urgency of TIA may have contributed to the
lack of improvement in imaging times over time observed in the present study. However, there is also considerable evidence that many individuals with TIA delay seeking medical care, particularly for those presenting to primary care (32, 136, 198). It is thus also possible that delays in the timing between the onset of TIA symptoms and presentation to medical care influenced the subsequent timing of imaging investigations performed in individuals with TIA in this population-based cohort. Although guidelines for the outpatient management of individuals with TIA who present to their family physician from the Canadian Best Practices Recommendations for Stroke Care recommended urgent evaluation (within 24 hours) for those presenting within 48 hours and up to 2 weeks from symptom onset, these guidelines also stated that individuals presenting more than 2 weeks after the onset of symptoms should be considered less urgent, with recommendations for evaluation by a stroke specialist within one month of presentation (267). Thus, a potentially important factor for observed trends in the timing of imaging from the present study relates to the trends in the timing between the TIA symptoms and patient’s presentation to care diagnosis of TIA. The retrospective design of the present study limited the ability to adjust for potential differences in time of symptom onset to presentation, and prospective studies are required to explicitly evaluate the contribution of delays in presentation to longitudinal trends in imaging times in the assessment of individuals with TIA.

Delays in the timing of imaging investigations in the diagnostic evaluation of TIA may have important implications for the prevention of stroke in the TIA population. In a previous population-based study of the timing of carotid ultrasound imaging procedures and surgical intervention after TIA, delayed assessment and intervention were associated with a high risk of preventable early recurrent stroke, with results showing a 21% risk of stroke prior to surgery at 2 weeks and a 32% risk at 12 weeks, in which half of the strokes occurring subsequent to TIA were disabling or fatal events (252). The lack of improvement in imaging times observed in the present study suggests that a potential area for improvement in stroke prevention after TIA may
relate to the timing of imaging investigation used to inform the clinical evaluation of individuals presenting with TIA. However, it is important to note that the benefits of improved imaging times cannot easily be linked to improved patient outcomes (268). The lack of available information on TIA severity and etiology and limited information on interventions used in individuals identified in the study cohort rendered the present analyses highly susceptible to potential treatment selection biases and restricted the ability to investigate patient outcomes in this population-based cohort. Future population-based studies would benefit from the prospective follow-up of TIA cases, including measures of severity and etiology, to minimize selection biases and enable the investigation of associations between imaging times, acute interventions, and clinical outcomes after TIA.

Recent increases in the development and implementation of strategies to facilitate the rapid assessment of individuals with TIA provide evidence for a potential shift in practice for the timing of TIA evaluation that may have an impact on stroke outcomes after TIA. Several different approaches are currently being used to expedite the assessment and treatment of individuals with TIA, including rapid access TIA clinics (269), fast track imaging services (270) and TIA hotlines for rapid assessment (271, 272). Previous observational studies have demonstrated that rapid access specialty clinics are associated with reduced stroke risk after TIA (78, 172) and a meta-analysis of observational research comparing urgent specialist services to other service models showing pooled early stroke risks of 0.6% (2 days) and 0.9% (7 days) in individuals treated urgently by specialists, compared with 3.6% (2 days) and 6.0% (7 days) for other service models (25). However, other prospective studies have reported equivalent risk factor diagnosis between TIA clinics and in-hospital assessment (273), or limited benefits for prevention for this approach, at high costs (114). Fast track carotid duplex screening services have been shown to significantly decrease delays between imaging referral and surgery in individuals with recent TIA (270) and, recently, regions in both Canada and Europe have
implemented models involving hotlines for rapid specialty assessment of patients with TIA (271, 272). This hotline model has been associated with shorter delays in specialist assessment, greater immediate prescribing practices for preventive therapies, and earlier surgery for carotid endarterectomy (272). Given these data, it is possible that population-based practices for the timing of imaging are evolving and that changes in the temporal trends of imaging procedures performed in individuals with TIA will become apparent in future studies assessing the timing of imaging after TIA. The findings of the present study support the need for continued evaluation of the impact of rapid access to specialty assessment, including the urgent delivery of imaging services, on preventive interventions and clinical outcomes in individuals with TIA.

4.5. Strengths and Limitations

Strengths of the present study included the use of data from longitudinal, population-based databases to examine temporal trends in the timing of imaging in individuals with TIA. While cross-sectional studies have previously reported delays in imaging times for individuals with TIA assessed in the emergency department or in hospital, the present study was able to characterize longitudinal population-based practice patterns for the timing of imaging procedures performed after TIA. With access to these data, the present study addressed knowledge gaps regarding the timing of imaging procedures performed after TIA and provided new information to characterize recent practice for the timing of imaging in a population-based cohort of individuals with TIA.

This study also had a number of limitations. Given the inability to adjust for the severity and etiology of TIA using the available data, the present study was unable to explore potential associations between the timing of imaging and clinical outcomes after TIA. In addition, the retrospective design of the present study limited our ability to adjust for potential differences in the time between symptom onset and time of presentation to medical care. As a result,
descriptive findings indicating that the median time to imaging across years in the present study exceeded the window of highest stroke risk after TIA may have been influenced by delays in the time of presentation to medical care. Finally, as the majority of individuals in the study cohort were diagnosed in an outpatient setting, secondary analyses examining temporal trends by diagnostic setting were potentially subject to increased variability and underpowered to detect differences in imaging times across years for those diagnosed in hospital.

4.6. Conclusions

The present study sought to determine whether population-based trends in the timing of neuroimaging procedures performed among those that underwent imaging after TIA have changed over time. Findings of this study indicated that, despite increasing evidence that urgent assessment and intervention reduce the high early risk of stroke in this population, no significant changes in the timing of imaging were observed over the study period. These findings suggest that gaps remain between current evidence for the benefit of early diagnostic assessment after TIA and highlight the need for studies to identify potential barriers for the delivery of urgent imaging after TIA. Given the evidence of the potential role that the timing of presentation may play in diagnostic assessment of TIA, further studies are also required to evaluate alternative techniques that may provide information about the impact of transient ischemia on the brain beyond the acute phase post-TIA. The present study underscored the need for continued efforts to implement strategies for rapid access to specialty assessment after TIA and optimize the urgent evaluation and initiation of interventions for the prevention of stroke in individuals with TIA.
5 Intracortical Inhibition and Facilitation are altered after Transient Ischemic Attack and are Associated with ABCD² Score

5.1. Introduction

A transient ischemic attack (TIA) is an episode of transient focal neurological deficit with an ischemic vascular cause (17). Although TIA symptoms rapidly resolve, the risk of stroke after TIA is very high (25), particularly in the early period after the index event (170). Despite previous evidence indicating that brain and vascular imaging can help identify individuals at high risk of stroke after TIA (274) and that the urgent assessment and initiation of appropriate preventive management reduces stroke risk (78, 171, 172), many individuals with TIA delay seeking medical care after experiencing TIA symptoms (31, 198) and are not evaluated by a physician within the window of highest risk for recurrent stroke. Further, although available brain imaging techniques, such as diffusion-weighted MRI (DWI), show high sensitivity to detect acute ischemic changes, these abnormalities are only present in approximately 30% of individuals (99, 101), and prior studies have shown that this sensitivity is limited to the acute phase after TIA (199) and that DWI negativity does not necessarily rule out a diagnosis of TIA (109). It is thus important to evaluate alternative health technologies that may provide information about the effects of transient ischemia beyond the acute phase post-event.

Paired-pulse transcranial magnetic stimulation (TMS) at different interstimulus intervals (208) enables the non-invasive measurement of excitability in inhibitory and facilitatory interneurons (275). Previous studies have shown that persisting changes in cortical excitability occur in the ipsilesional and contralesional cerebral hemispheres, both immediately following and during recovery from acute ischemic stroke. Specifically, these studies reported reduced intracortical inhibition (ICI) in the affected and unaffected primary motor cortices after stroke (203, 204, 210-214) and showed that these effects are robust in the early phases of stroke.
recovery (276), but decrease in the unaffected hemisphere with time (277) and vary depending on degree of clinical recovery (210), disease duration and lesion location (278). Although this technique has been used extensively to map neuroplastic changes after stroke (203, 204, 210-214); however, very little is known about whether changes in cortical excitability also occur after transient episodes of cerebral ischemia.

Two previous investigations have used TMS to evaluate motor cortex excitability in individuals with TIA (224, 225) but only one examined intracortical circuits (225). Similar to stroke populations, Koerner & Meinck (2004) showed disinhibition in the affected compared to unaffected hemisphere in individuals with TIA; a trend for enhanced intracortical facilitation (ICF) in the affected hemisphere was also noted (225). However, this study did not include a healthy comparison group to distinguish TIA-induced changes in intracortical excitability from potential differences associated with normal aging. In addition, the method of measuring ICI and ICF used in previous work has been shown to have a high degree of variability both within participants and across sessions (226). Recently, a threshold based method for the measurement of intracortical excitability that yields a precise threshold for ICI and ICF across a range of conditioning stimulus intensities has been reported to increase sensitivity for the detection of post-ischemic intracortical changes (226). Although studies in other clinical populations have adopted iterations of this approach (279-281), no previous study has yet determined the thresholds for ICI and ICF in individuals with TIA or investigated the potential clinical relevance of intracortical changes after TIA.

The purposes of this study were to investigate if changes in the threshold for ICI and ICF are present after TIA and if intracortical effects are associated with clinical predictors of stroke risk. The present study employed a threshold-based paired-pulse TMS protocol (226) in both a group of individuals with a recent TIA and an age-matched healthy control group. It was hypothesized that changes in the thresholds for ICI and ICF would be present in the affected
compared to unaffected hemispheres after TIA and that these thresholds would also differ in comparison to healthy control participants. It was also predicted that a relationship would be present between the degree of asymmetry in thresholds for ICI and ICF between the hemispheres and clinical predictors of stroke risk, including the ABCD² score and TIA etiology.

5.2. Methods

5.2.1. Participants

Thirteen participants with acute TIA affecting unilateral motor or sensorimotor systems and thirteen community-dwelling age-matched healthy control participants were recruited for this study (see Table 19). Individuals with TIA were recruited from the Stroke Prevention Clinic at Vancouver General Hospital within 30 days of their most recent event (mean 14.5 days, SD 4.6 days). Inclusion criteria were a diagnosis of TIA with unilateral motor or sensorimotor features and symptom resolution within 24 hours and exclusion criteria were prior stroke, individual or family history of epilepsy, and/or history of seizures. All participants underwent one session of paired-pulse TMS and all provided institutionally approved informed consent prior to participation.

Table 17. Demographic characteristics of individuals with TIA and healthy control participants

<table>
<thead>
<tr>
<th>Participant</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Affected Hemisphere</th>
<th>Time from Event to Stimulation (days)</th>
<th>ABCD² Score (0-7)</th>
<th>TIA Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>79</td>
<td>RH</td>
<td>10</td>
<td>5</td>
<td>SV</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>39</td>
<td>RH</td>
<td>23</td>
<td>4</td>
<td>UN</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>79</td>
<td>RH</td>
<td>17</td>
<td>4</td>
<td>SV</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>53</td>
<td>RH</td>
<td>15</td>
<td>4</td>
<td>LV</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>71</td>
<td>RH</td>
<td>19</td>
<td>5</td>
<td>SV</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>60</td>
<td>LH</td>
<td>11</td>
<td>5</td>
<td>SV</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>69</td>
<td>RH</td>
<td>9</td>
<td>4</td>
<td>CE</td>
</tr>
<tr>
<td>Participant</td>
<td>Gender</td>
<td>Age (years)</td>
<td>Affected Hemisphere</td>
<td>Time from Event to Stimulation (days)</td>
<td>ABCD² Score (0-7)</td>
<td>TIA Etiology</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-------------</td>
<td>---------------------</td>
<td>--------------------------------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>89</td>
<td>LH</td>
<td>7</td>
<td>6</td>
<td>CE</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>43</td>
<td>LH</td>
<td>15</td>
<td>3</td>
<td>Un</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>78</td>
<td>LH</td>
<td>20</td>
<td>4</td>
<td>CE</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>82</td>
<td>LH</td>
<td>14</td>
<td>4</td>
<td>LV</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>66</td>
<td>LH</td>
<td>14</td>
<td>5</td>
<td>CE</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>58</td>
<td>LH</td>
<td>15</td>
<td>4</td>
<td>CE</td>
</tr>
</tbody>
</table>

Healthy Control Group

<table>
<thead>
<tr>
<th></th>
<th>Gender</th>
<th>Age</th>
<th>Affected Hemisphere</th>
<th>Time from Event to Stimulation (days)</th>
<th>ABCD² Score (0-7)</th>
<th>TIA Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>62</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>79</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>46</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>58</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>54</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>61</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>78</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: RH = right hemisphere, LH = left hemisphere, LV=large vessel, SV=small vessel, Un=unknown, CE=cardioembolic

5.2.2. Clinical Evaluations

A stroke neurologist evaluated all patients in the Stroke Prevention Clinic at Vancouver General Hospital. For all participants, an evaluating physician confirmed diagnoses of TIA with unilateral motor or sensorimotor symptoms. Structural brain imaging was used to identify event-related infarcts and, at the time of this study, all patients were clinically resolved and none demonstrated event-related structural lesions on CT or MR imaging. ABCD² scores for each participant were derived using chart information regarding patients’ age, blood pressure, clinical features, symptom duration, and the presence of co-morbid diabetes. A stroke neurologist confirmed the ABCD² scores. Clinical and imaging information were also used to determine TIA etiology. For the purposes of this study, the patient group was divided into the following
etiologic categories: large vessel, small vessel, cardioembolic, and unknown.

5.2.3. Measurement of Intracortical Excitability

Single and paired-pulse TMS were used to measure intracortical excitability in the primary motor cortices (M1) of both cerebral hemispheres. In the paired-pulse TMS paradigm, a suprathreshold non-conditioned stimulus is preceded by a sub-threshold conditioning stimulus. If the conditioning stimulus precedes the non-conditioned stimulus by 1-6 ms, the net effect is an inhibition of the response elicited by the non-conditioned stimulus alone. A conditioning stimulus that precedes the test stimulus by 6-15 ms results in facilitation. The magnitude of these effects is modulated by the relative intensities of the conditioning and non-conditioned stimuli (282).

TMS was delivered via a figure-of-eight shaped coil, which delivers focal stimulation, with a current spread small enough (10 x 10 x 20mm) to stimulate M1 and two Magstim 200 stimulators, connected via a Bistim2 Module (Magstim Co., UK). Motor evoked potentials (MEPs) were recorded using surface electromyography placed over the flexor carpi radialis muscles. EMG data were collected for each trial using LabChart software, in conjunction with the Powerlab amplification and EMG systems (AD Instruments, Colorado Springs, CO). The stimulating coil was positioned over the scalp at the optimal site for evoking an MEP in FCR, with the handle pointing posterior-laterally laterally at an angle of 45° to the mid-sagittal plane. Motor threshold was determined in steps of 1% absolute stimulator output intensity. Resting motor threshold (RMT) was defined as the lowest intensity to elicit MEPs of at least 50µV in 5 of 10 trials in the relaxed FCR. Active motor threshold (AMT) was the lowest intensity to elicit MEPs of at least 200µV in 5 out of 10 trials, during activation of FCR to 20% of the maximum voluntary contraction.

Baseline corticomotor excitability was measured by delivering 10 single-pulse stimuli to each motor cortex with an absolute stimulator output intensity of 115% resting motor threshold.
Unlike traditional paired-pulse TMS methods, in the present study, conditioning stimuli were based on active motor threshold instead of resting motor threshold and intracortical inhibition and facilitation were measured by varying the intensity of the conditioning stimulus, while maintaining a fixed interstimulus interval (226) (279). Active motor threshold was used to derive the following range of conditioning stimuli intensities: 0%, 15%, 35%, 55%, 75%, 95%, 105% and 125% of the active threshold (279). For each individual participant, the test stimulus for each hemisphere was identified as the absolute stimulator intensity to elicit a muscle response as close to 1mV as possible in the contralateral muscle group. For each hemisphere, two series of 64 paired-pulse stimuli were delivered using interstimulus intervals of either 2 ms for intracortical inhibition or 12 ms for intracortical facilitation, to avoid potential facilitatory effects associated with indirect wave interactions in motor cortices (283). Each series contained 8 randomized stimuli delivered for each conditioning stimulus intensity value. Pulses with a conditioning stimulus intensity of 0% active motor threshold served as the unconditioned baseline and were randomly interspersed within the 64 pulse series. Thresholds for intracortical inhibition and facilitation were assessed in both the right and left hemispheres. Order of testing of each hemisphere and the order of interstimulus interval presentation within each hemisphere were counterbalanced.

5.2.4. Data Analyses and Statistical Evaluations

The percent of intracortical inhibition (%ICI) or facilitation (%ICF) produced at each conditioning stimulus intensity was determined by calculating the peak-to-peak amplitude of the conditioned MEP for each trial and expressing this as a percentage of the mean non-conditioned MEP amplitude. Trials exceeding two standard deviations of the mean peak-to-peak amplitude at each conditioning stimulus intensity were identified and excluded (<5% for each conditioning stimulus at each ISI).

Recruitment curves for %ICI and %ICF, as a function of %AMT, were generated for each
participant for both cerebral hemispheres. Linear and quadratic regression functions were then fit to these curves and the line of best fit was identified using adjusted $R^2$ values. For all participants, adjusted $R^2$ values indicated that quadratic regression functions best represented the distributions for both %ICI and %ICF. Using these quadratic functions, we then calculated the precise threshold (%AMT) at which the amplitude of %ICI and %ICF exceeded baseline variability in each hemisphere (226).

To determine if the thresholds for ICI and ICF differed between individuals with TIA and healthy age-matched participants, threshold values were subjected to a 3-way Hemisphere (affected, unaffected) X Stimulation Interval (inhibition, facilitation) X Group (TIA, healthy) repeated measures analysis of variance (ANOVA), with Group entered as a between-subjects factor. For the purposes of this analysis, thresholds in the affected hemisphere of the patient group were compared to thresholds in the non-dominant hemisphere of the healthy control group. Follow-up 2-way ANOVAs and paired t-tests were conducted within each group to identify significant contrasts.

Thresholds for ICI and ICF were then used to calculate *interhemispheric asymmetry indices*, designed to provide a measure of the degree of asymmetry in inhibitory and facilitatory thresholds between the hemispheres, in each individual. Separate asymmetry indices were calculated for the data collected at inhibitory and facilitatory ISIs for each group (see Figure 10). To determine if changes in the thresholds for ICI and ICF have potential clinical relevance, we conducted correlation analyses, assessing the relationship between asymmetry indices in the patient group and clinical variables, including ABCD² score, TIA etiology, and time from event (days). All analyses were conducted with SPSS for Windows (version 13.0)(SPSS Inc., Chicago IL).

\[
\text{Interhemispheric Asymmetry Index} = \frac{(\text{Ipsilesional} - \text{Contralesional})}{(\text{Ipsilesional} + \text{Contralesional})}
\]
5.3. Results

Results of the 3-way repeated measures ANOVA revealed a significant Hemisphere (affected, unaffected) X Stimulation Interval (inhibition, facilitation) X Group (TIA, healthy) interaction ($F(1,24)=5.90$, $MSE=7196.79$, $p<.05$), indicating that a significant difference in thresholds for intracortical excitability between the hemispheres was present for the patient group compared to the healthy control group. Indeed, follow-up 2-way repeated measures ANOVAs showed a significant interaction of Hemisphere X Stimulation Interval within the TIA group ($F(1,12)=7.76$, $MSE=9158.70$, $p<.05$), but no significant interaction for healthy age-matched participants ($F(1,12)=0.47$, $MSE=589.14$, $p=.51$)(Figure 7).

Figure 7. Mean threshold for ICI and ICF in a) the affected and unaffected hemispheres after TIA and b) the dominant and nondominant hemispheres in healthy participants
Paired t-tests revealed that, in individuals with TIA, the thresholds for ICI were significantly greater in the affected compared to unaffected hemisphere ($t(12)=2.21$, $SE=9.27$, $p<.05$), indicating a reduction in intracortical inhibition in the affected hemisphere after TIA. By contrast, thresholds for ICF were significantly greater in the unaffected compared to affected hemisphere after TIA ($t(12)=-2.74$, $SE=11.88$, $p<.05$), suggesting that facilitation is enhanced in the affected hemisphere after TIA.

Correlation analyses indicated that asymmetry in the thresholds for ICI and ICF were highly correlated ($r=-0.68$, $p=.005$). In addition, ABCD$^2$ score was significantly associated with asymmetry indices both for thresholds of ICI ($r=-0.47$, $p=.05$) and thresholds of ICF ($r=0.67$, $p<.05$) (Figure 8). However, asymmetry indices were not significantly correlated with TIA etiology or time from event (days).
5.4. Discussion

The present study examined changes in cortical excitability in individuals with TIA compared to healthy age-matched participants. By identifying specific thresholds for ICI and ICF after TIA, and correlating threshold asymmetries between the hemispheres with clinical variables, we report two novel findings. First, results indicated that, despite the clinical resolution of symptoms and the absence of acute structural lesions, thresholds for ICI and ICF were altered in the affected hemisphere in the TIA patient group compared to age-matched healthy participants. Specifically, mean threshold for ICI was increased in the TIA-affected hemisphere compared to the unaffected hemisphere, indicating a decrease of ICI on the side of the brain affected by the transient ischemia. By contrast, mean threshold for ICF was decreased in the affected hemisphere, indicating an increase in facilitation on the TIA-affected side. Second, results showed that, in individuals with TIA, the degree of asymmetry in the thresholds
for both ICI and ICF were significantly correlated with ABCD² scores.

The disinhibition observed in the TIA-affected hemisphere in the present study is consistent with previous findings of reduced ICI in the affected hemisphere in individuals with short episodes of transient ischemia (225). In addition, although Koerner & Meinck (2004) (225) showed a trend for enhanced facilitation, results of the present study showed significant increases in ICF in the affected hemisphere after TIA, suggesting that hyperexcitability in the affected hemisphere after TIA involves both inhibitory and facilitatory systems (225). Unlike previous work, the present study also involved a healthy age-matched comparison group. Importantly, no differences in thresholds for ICI or ICF were present in healthy participants, confirming that the presence of TIA-related changes in the patient group. These results indicated that changes in intracortical excitability may be induced, even after transient episodes of ischemic insult, potentially via similar mechanisms that alter function in inhibitory and facilitatory systems after ischemic stroke.

Converging evidence from studies of animal and human neurophysiology has demonstrated that, after stroke, post-ischemic changes in cortical excitability are mediated primarily by the interplay between inhibitory gamma-aminobutyric acid (GABA)ergic activity and excitatory activity in the N-methyl-D-aspartate (NMDA) receptors of the glutamatergic system (284). ICI is modulated by GABAergic neurotransmission and glutamate antagonists modulate intracortical facilitation (ICF) (285). Following a lesion to the motor cortex, reductions in GABA_A activity have been reported in regions surrounding the infarct and have also been observed remotely, via changes in transcallosal neurotransmission (203). Motor cortex disinhibition may also be accompanied by the upregulation of glutamatergic function, contributing to perilesional hyperexcitability after stroke (286, 287). Results from the present study suggest that, like stroke, TIA may also impact GABA and glutamatergic function and that both local reductions in inhibition and increased facilitation contribute to hyperexcitability in the
affected hemisphere after TIA.

The regulation of inhibitory and facilitatory systems is thought to play an important role in post-stroke functional recovery. This relationship is supported by findings that GABAergic drugs impair motor recovery after stroke and inhibit motor learning in healthy individuals (288). Similarly, individuals with better recovery after stroke demonstrate greater disinhibition of the affected motor cortex (204, 289, 290). However, the functional significance of changes in intracortical excitability after TIA remains unclear. It is possible that, like stroke, changes in the excitability of intracortical circuits are a direct consequence of TIA. Alternately, they may reflect a compensatory or protective mechanism in response to ischemia insult, even if brief. Some studies have suggested that there may be an endogenous neuroprotective mechanism of prodromal transient ischemic episodes on subsequent ischemia (291, 292). This hypothesis was derived from rodent models of ischemia (293), clinical studies showing that prior TIA was independently associated with lower stroke severity at admission (294), and findings from brain imaging demonstrating smaller final infarct volume for individuals with prior TIA (295). To date, there is no clear evidence for the existence of a positive effect of cortical ischemic preconditioning in humans. A crucial issue that appears to mediate the long-term impact of transient ischemia is its duration. In rodent models showing neuroprotective effects, ischemia is induced for very brief episodes, typically lasting only minutes (296, 297); in patient trials, the relationship between ischemia and neuroprotection is only valid for TIA with durations of less than 20 minutes (291, 292). Although Koerner & Mernick (2004) (225) showed changes in ICI after TIA of very short duration (<1hr), there is still limited evidence to indicate that the net effect of clinically significant TIAs, which tend to last longer, is neuroprotective in nature.

Several factors may account for this study’s ability to detect changes in ICF not previously shown after TIA. Individuals in the present study were evaluated later post-TIA than those in the Koerner & Meinck study (225) (on average 14 days post-TIA vs. less than 7 days
It is possible that the changes in the threshold for ICF observed in the present study emerged with time after the ischemic event. Data from individuals with stroke support this possibility (210), showing that changes in both ICI and ICF evolve with time since ischemia. Further, changes in glutamate transmission are dynamic the peri-infarct area following ischemia. In a rodent model, Centonze et al. (2007) (298) found that selective facilitation of non-NMDA receptor transmission upregulated glutamate in the later phases of recovery. In the present study, increases in ICF in the affected cortex persisted on average two weeks after TIA (mean = 14.5 days), potentially reflecting similar changes in the latter phases of recovery from even transient episodes of ischemia. It remains unclear whether changes in intracortical circuits are permanently altered after TIA. Further longitudinal investigations are necessary to determine the length of these effects.

It is also possible that the methodological differences in the paired-pulse stimulation employed in the current study may account for the facilitatory effects observed in these individuals. The paired-pulse TMS paradigm used in the present study has several strengths compared to paradigms employed in previous studies assessing intracortical excitability in individuals with stroke and TIA. Primarily, in this approach, the dependent measure was fixed to a physiological criterion (i.e., a threshold), which unlike measurements of excitability magnitude derived from a fixed CS intensity at a chosen ISI (299), indexes an individualized threshold for the onset of excitability. As a result, this approach has previously demonstrated reduced variability in the measurement of SICI and ICF across participants (226). The use of AMT to determine CS intensity in the present study also likely enhanced within and between participant reliability (226). An extensive range of CS intensities (from 15%-125% AMT) were employed in the present study to allow the generation of individual curves depicting recruitment of intracortical activity and account for the possibility of differences between participants in the onset of SICI and ICF along these curves (226, 299). It is thus possible that our ability to detect
differences in the onset of both SICI and ICF that have not previously been reported after TIA (225) may in part be attributed to these differences.

Like the Koerner & Mernick (2004) study, intracortical changes in the present study occurred in the absence of clinically relevant abnormalities on structural imaging (225). Although the clinical symptoms of TIA rapidly resolve, several studies have shown that individuals with TIA demonstrate structural abnormalities on CT (300, 301) and MR imaging (100). Diffusion MR imaging (DWI) is sensitive to early cerebral infarction (101) and the presence of DWI lesions in individuals with TIA is associated with ABCD² scores (274) and is predictive of increased stroke risk (125). However, there is substantial variability in the proportion of individuals with TIA that show abnormalities on MR and diffusion MR imaging, with reports ranging from 21% to 67% (302). Further, the intracortical effects shown in the present study also were also observed at a later time point post-TIA (mean 14.5 days, SD 4.6 days) than previous findings for abnormalities on DWI after TIA (101). As many individuals delay seeking medical attention for TIA (198), the TMS assessment of changes in the excitability intracortical circuits may provide an alternative measure of the impact of TIA on the underlying neurophysiology, for individuals with negative findings on DWI or for those that present at the subacute phase after the index event. The findings of this study provide the basis for future work evaluating the sensitivity and specificity of TMS as a diagnostic tool in the evaluation of individuals with TIA and for a health technology assessment of paired-pulse TMS, examining the clinical and economic implications of the more widespread application of this technique across the different care settings where individuals with symptoms of TIA present for assessment.

Similar to diffusion MR, results of this study indicated that asymmetries in the thresholds for ICI and ICF are significantly correlated with ABCD² scores in individuals with TIA. Specifically, increases in ABCD² score were associated with both the degree of
disinhibition and the degree of enhanced facilitation in the affected motor cortex (see Figure 8). Clinical profile is of considerable importance in assessing stroke risk after TIA and the ABCD² score is a validated predictor of early stroke risk after TIA (36). We extended this finding to individuals with TIA and showed that individuals with higher stroke risk (i.e.: higher ABCD² scores) demonstrated greater disinhibition, even following transient ischemia. The presence of a relationship between changes in ICI and ICF after TIA and ABCD² score has not previously been described. These data offer preliminary evidence that there may be a relationship between intracortical excitability and stroke risk, although future work would benefit from the explicit investigation of the predictive value of ICI and ICF in stratifying stroke risk after TIA.

5.5. Limitations

This study has a number of limitations. As individuals with TIA in the present study were selected from an outpatient stroke prevention clinic, there is a possibility of misclassification in the diagnosis of TIA for those included in the study sample. However, as all participants were carefully screened for vascular risk factors and all TIA diagnoses confirmed by a stroke neurologist, the potential for misclassification in this study was minimal. Further investigation is required to determine if intracortical changes are present in patients with neurological episodes of non-vascular origin (i.e. TIA mimic) and how these effects might compare to observed differences in the thresholds for ICI and ICF after TIA. Individuals with TIA in this study also varied in terms of etiologic subtype, with more participants having TIA of large vessel etiology than other subtypes. This variability in the number of participants from each etiologic category may have limited the ability to detect correlations between altered thresholds for intracortical excitability and TIA etiology. In addition, given the short time window within which to acquire stimulation data after the clinical event in TIA patients, the paired pulse stimulation protocol in the present study did not employ the use of neuronavigation,
increasing the potential for bias in the measurement of these effects. In addition, the outcome assessors were not blinded to case control status. Future studies may benefit from the explicit investigation of ICI and ICF thresholds in a sample of individuals with TIA, stratified by etiologic subtype and incorporating the use of neuronavigation and blinding into the study design.

5.6. Conclusions

The present study sought to determine whether changes in intracortical excitability were observed after TIA and related to clinical features associated with increased stroke risk in individuals with TIA. Findings of this study showed significant alterations in the thresholds for ICI and ICF in individuals with TIA compared to healthy age-matched adults and a significant association between these changes and increasing ABCD² scores. These findings provide new evidence to suggest that both inhibitory and facilitatory intracortical circuits are affected after TIA and that these effects persist into the subacute phase post-event and occur in the absence of changes on structural imaging (CT or MRI). Associations between these neurophysiological changes and ABCD² scores also represent preliminary evidence for the potential clinical relevance of alterations in intracortical excitability after TIA. Findings of this study provide the basis for further investigations into the potential of the utility of paired-pulse TMS techniques in the evaluation of individuals with TIA.
6 Conclusions

6.1. Summary

The purposes of this PhD dissertation were to address gaps in the knowledge of population-based practices for the use of neuroimaging investigations after transient ischemic attack (TIA) and contribute new evidence to inform the diagnostic evaluation of individuals with TIA. To address these knowledge gaps, specific research questions evaluated in this dissertation were: 1) can a valid algorithm for the ascertainment of TIA cases from physicians billing administrative health data be identified?, 2) did the population-based utilization of neuroimaging procedures in individuals presenting with TIA increase after the implementation of practice guidelines?, 3) have population-based trends for the timing of neuroimaging procedures performed among those that underwent imaging after TIA changed over time?, and 4) are changes in intracortical excitability observed after TIA and do they relate to clinical features associated with increased stroke risk in individuals with TIA?

Using classification algorithms based on potential pathways of care for individuals with TIA presenting initially to their primary care provider, the findings of Chapter 2 demonstrated that it was not possible to validate an algorithm for the ascertainment of TIA cases from physician billing data. Using linked population-based datasets to define the reference and validation cohorts and comparison of multiple different cohort definitions, findings of this study represented a comprehensive, population-based assessment of the validity of physicians billing records for the identification of TIA.

Chapter 3 showed a significant increase in overall neuroimaging utilization among individuals with TIA, suggesting that an uptake of guideline recommendations and resulting change in practice for the use of imaging procedures after TIA occurred after the implementation of clinical guidelines. This study also demonstrated that, despite the increase in
imaging use, there was an overall underutilization of imaging after TIA; a lack of increase in the use of carotid ultrasound imaging procedures; and differential uptake of guideline recommendations for those diagnosed in primary care and hospital settings. Thus, although findings of this study provided evidence of an impact of clinical guidelines on population-based practices for imaging in this cohort, they also indicated that recommended imaging procedures were underutilized in individuals with TIA. The results suggest that the evaluation of imaging utilization may have potential as a quality indicator of secondary stroke prevention in individuals presenting with TIA.

The findings of Chapter 4 indicated that no changes in the timing of imaging procedures performed prior to stroke in a population-based cohort of individuals with TIA were observed over time from 1998 to 2007. Findings of this study suggested that, despite increasing evidence that urgent assessment and intervention can reduce the high early risk of stroke after TIA, the majority of individuals in this population-based cohort did not undergo imaging until after the period of highest stroke risk and beyond the acute phase when available imaging techniques show the highest sensitivity to detect acute ischemic changes post-TIA. Further, the likelihood that individuals with TIA underwent acute imaging within 7 days after TIA did not change over the study period, regardless of diagnostic setting. Results of this study highlight the need for further research to identify potential barriers for the delivery of urgent imaging after TIA and for the evaluation of alternative techniques that may provide information about the impact of transient ischemia on the brain beyond the acute phase post-TIA.

The findings of Chapter 5 indicated that significant alterations in the thresholds for intracortical inhibition and facilitation, measured using paired-pulse transcranial magnetic stimulation (TMS), were present in individuals with TIA compared to healthy age-matched adults and that these changes were associated with increases in ABCD² scores after TIA. The findings of this study provided new evidence that transient ischemia has an impact on the
inhibitory and facilitatory intracortical neurophysiology and demonstrated that these effects were present in the subacute phase post-TIA and occurred in the absence of changes on structural imaging (CT or MRI). This study also provided preliminary evidence that changes in intracortical excitability may have clinical relevance and that there is a potential role for the use of paired-pulse TMS techniques in the subacute evaluation of individuals with TIA.

Taken together, the studies conducted for this dissertation provided new knowledge regarding: 1) the use of administrative data for population-based studies of individuals with TIA, 2) population-based practices for the use and timing of neuroimaging in individuals with TIA, and 3) the potential contribution of neurophysiological techniques to the evaluation of individuals with TIA. This work represents a significant contribution to the fields of health services research, clinical epidemiology and neurology, and neuroscience. The key contributions of this work to epidemiological research methodology, guideline dissemination, and clinical practice are described below.

6.2. Methodological Contributions

The primary methodological contribution of this work relates to the findings for the validity of using physicians billing data for the ascertainment of TIA cases described in Chapter 2. Although prior studies have shown that the inclusion of outpatient data reduces the sensitivity of algorithms for the identification of TIA (184), to our knowledge, the study described in this chapter was the first to explicitly evaluate the validity of multiple different algorithms for the ascertainment of TIA using data consisting of outpatient diagnoses from an entire population. Findings of this study contributed to evidence that physicians billing data alone are not valid for the ascertainment of TIA and that diagnostic records from a physicians billing administrative database had insufficient sensitivity for the valid ascertainment of TIA diagnoses. These findings offer an important methodological contribution to epidemiological researchers seeking
to conduct studies on individuals with TIA using administrative health data and suggest that such studies should either; 1) involve case definitions limited to hospitalization or emergency department encounters, which have previously shown high sensitivity for the identification of TIA (184); or, 2) employ alternative case definitions for TIA, such as the one employed in the present work, which utilized the clinical criterion of a hospital admission for stroke within 90 days of TIA to minimize potential biases due to inaccurate clinical diagnoses (171), thus enabling the identification of a population-based cohort of individuals with TIA that included cases diagnosed from both hospital and outpatient encounters.

A secondary methodological contribution of this work relates to the methodology employed to define the population-based TIA cohort in the studies described in Chapter 3 and 4. The case definition used to identify TIA cases for this cohort involved first sampling cases with stroke, using a previously validated algorithm for the ascertainment of stroke from hospital discharge data, and then limiting this cohort to those with a prior TIA from either inpatient or outpatient records. The use of this clinical criterion has previously been employed to decrease misclassification in the identification of individuals with TIA in the context of a large prospective population-based study (171). The present work demonstrates that this methodology can also be employed for the retrospective ascertainment of TIA cases using data from linked administrative health databases and used to conduct robust investigations of population-based practices for the use and timing of neuroimaging procedures after TIA.

6.3. Contributions to Clinical Guideline Development and Dissemination

The present work also offers important contributions to the development and implementation of future clinical guidelines for the use of imaging in the assessment of individuals with TIA. The findings of the study described in Chapter 3 demonstrated that clinical guidelines were associated with a significant increase in the utilization of imaging
procedures after TIA and thus had an observable effect on practice for the use of imaging in the evaluation of individuals with TIA. These findings add to previous literature indicating that clinical guidelines can improve access to services and quality of care (147-149) and suggest that professional associations involved in the development of clinical guidelines for TIA should continue efforts to update and implement recommendations to promote practice change for imaging utilization in this population. However, the overall low utilization of imaging procedures also observed in this study indicated that, despite increases in imaging use, barriers remained for the uptake of guideline recommendations for the use of imaging after TIA. Previous studies have shown that factors potentially contributing to the reduced adherence to guideline recommendations may include physician perceptions and experience, guideline dissemination and complexity, limited integration of recommendations into organizational structures and processes, and time and resource constraints (303). The putative contributions of these potential barriers to the access and delivery of imaging procedures for patients with TIA should be explored prior to the development and implementation of future guidelines.

This study also indicated that increases in utilization were driven by the increased use of CT procedures, with limited uptake for the recommended use of carotid ultrasound imaging procedures. These findings contribute new knowledge about the differential uptake of guideline recommendations for different imaging modalities and suggest that the implementation of future guidelines may benefit from dissemination strategies with an increased focus on recommendations for less utilized procedures, such as carotid ultrasound imaging. In addition, depending on the factors shown to be involved in reduced adherence, policies at the institutional level may be required to ensure resource needs are met for all guideline-recommended imaging technologies. As the awareness of modifications to institutional policies as a result of guideline implementation has previously been shown to influence health professionals’ perceptions of organizational support for guideline implementation (304), dissemination strategies highlighting
both guideline recommendations and resulting institutional policy changes may be required to improve guideline adherence.

As the majority of individuals in this population-based cohort had outpatient diagnoses of TIA, the overall underutilization of imaging procedures observed in this study indicated that the uptake of imaging guideline recommendations for TIA was particularly low in the primary care setting. This finding contributed to previous evidence for the low adherence to some clinical guidelines recommendations in the primary care management of patients with stroke and TIA (162) and suggested that clinical guidelines had a minimal overall impact on practice for the use of imaging procedures after TIA in this setting. These findings support the need for dissemination strategies associated with the implementation of future clinical guidelines that involve educational interventions for imaging use targeted at primary care providers, to promote increased adherence to guideline recommendations within all care settings where individuals with TIA may present for evaluation.

6.4. Clinical Contributions

The present work also provides important contributions to the knowledge of clinical practices for the evaluation of individuals with TIA and to clinical knowledge of the effects of transient ischemia on the brain. The finding that the utilization of imaging procedures in the TIA population remained low after the implementation of clinical guidelines observed in Chapter 3 provided evidence to indicate that population-based practices for the diagnosis of TIA in this cohort were based primarily on information from the clinical assessment. Given prior evidence that neuroimaging investigations can provide important information regarding acute ischemic changes and vascular mechanisms to complement the clinical assessment of TIA (101, 112, 115), the underuse of available imaging procedures may have contributed to misclassification in the identification of the mechanisms underlying clinical symptoms in these individuals. As
information regarding vascular mechanisms influences management for the prevention of stroke after TIA (53-55), the finding that the majority of individuals in this cohort did not undergo an imaging procedure prior to experiencing a stroke secondary to TIA provided evidence for the potential role of imaging underuse in the failure to prevent stroke in individuals with TIA. These findings also suggest that the evaluation of imaging practices may be an important quality indicator for secondary stroke prevention after TIA.

The finding that utilization was particularly low for carotid ultrasound imaging procedures also provided new knowledge regarding population-based practices specific to the use of this imaging modality in the diagnostic assessment of TIA. Given previous evidence for the high risk of stroke among individuals with TIA due to large artery mechanisms (52) and data from prior population-based studies demonstrating that delays to carotid ultrasound imaging and surgical intervention after TIA were associated with a high risk of preventable stroke (252), these findings provided further support for the potential impact of imaging underutilization on secondary stroke prevention and suggest that increased use of carotid ultrasound imaging procedures in clinical practice may improve management for the prevention of stroke in individuals with TIA.

Findings of Chapter 4 indicated that no changes in the timing of imaging procedures performed after TIA occurred over a recent 10-year calendar period. These findings contributed new evidence characterizing population-based practices for the timing of imaging procedures in individuals presenting with TIA. Descriptive findings indicated that the majority of individuals in this cohort did not undergo imaging within the window of highest risk for stroke after TIA (169) or during the acute phase after TIA when structural imaging techniques are most sensitive to detect ischemic changes (199). These findings suggest that delays in imaging assessment are present across all diagnostic settings and may have important implications for the prevention of stroke in this population.
The results of Chapter 5 contributed new evidence for the potential clinical relevance of measuring intracortical excitability using paired-pulse transcranial magnetic stimulation (TMS) in the evaluation of individuals with TIA. The finding that alterations in the thresholds for intracortical inhibition and facilitation were present in affected hemisphere in individuals with TIA provided new knowledge to the clinical literature characterizing the specific neurophysiological mechanisms affected by transient ischemia and demonstrated that both GABA- and glutamatergic intracortical pathways are impacted after TIA. In addition, the observation that these mechanisms were affected in the absence of clinical symptoms or observed changes on structural imaging (CT and MRI) and at a mean of 14 days post-TIA provided new evidence to indicate that ischemia-induced cortical changes are independent of abnormalities captured by conventional neuroimaging modalities and can be detected in individuals presenting to care beyond the acute phase post-TIA. The additional finding that alterations in intracortical excitability correlated with increases in the ABCD² scale score also provided preliminary evidence showing the potential clinical relevance of these effects for the identification of individuals at high risk of stroke after TIA. Overall, findings of this study provided an important theoretical contribution to clinical knowledge regarding the effects of transient ischemia on the brain and the potential clinical utility of paired-pulse TMS in the evaluation of individuals with TIA.

6.5. Strengths and Limitations

One of the main strengths of the research conducted in this dissertation involved the use of data from longitudinal, population-based administrative health databases to define the study cohorts and outcomes in the studies described in Chapters 2 to 4 of this work. The use of population-based data to define the TIA cohorts used in each of these studies eliminated several potential sources of selection bias that may have been present in prior research examining
imaging utilization and timing after TIA and ensured greater generalizability of these findings to the TIA population. For Chapter 2, access to these databases also enabled us to conduct a population-based evaluation of the validity of physicians billing data for identifying TIA cases via the comparison with linked information from hospital discharge records. In addition, for the studies described in Chapters 3 and 4, these longitudinal data made it possible to conduct analyses of population-based practices for the use and timing of imaging procedures over several years, also enabling comparisons of imaging practices across different calendar periods to index changes in the use and timing of imaging procedures not previously captured in cross-sectional studies of imaging utilization in individuals with TIA.

Another strength of the present work related to the use of a case definition employing the criterion of stroke secondary to TIA for the retrospective ascertainment of TIA cases from inpatient and outpatient diagnostic records. The use of this methodology minimized the potential for misclassification in TIA cases identified from outpatient encounters, enabled the identification of population-based cohorts of individuals with TIA prior to stroke, and made it possible to investigate differential practices for the use and timing of imaging procedures associated with the different care settings where individuals with TIA were diagnosed. As a result, this work provided new insights into practice differences for the utilization and timing of imaging in individuals presenting with TIA across both primary care and hospital diagnostic settings.

The main limitations of the studies conducted in the present work involved the potential for bias due to misclassification, the inability to adjust for potential confounders, the inability to examine clinical outcomes after TIA, insufficient data on imaging procedures for certain modalities, and the potential for measurement bias in the acquisition of paired-pulse TMS data. Despite the use of a case definition for TIA previously shown to minimize potential biases due to clinical misclassification of diagnoses (42) the potential for misclassification in the
identification of individuals with TIA for these studies remains. However, as prior work has shown, recurrent cerebrovascular events are absent in individuals with TIA mimic, and the potential for this bias in the retrospective ascertainment of TIA cases for the study cohorts in Chapters 2 to 4 was minimal. Careful screening for vascular risk factors and the confirmation of TIA diagnoses from stroke subspecialists in Chapter 5 also reduced the potential for this bias in this study.

Another limitation of the studies in this work was that the available administrative data did not include measures of TIA severity or etiology. As these factors may influence both the indication for imaging and the type of procedure performed, the studies in Chapters 3 and 4 may be subject to confounding due to TIA severity and etiology. To minimize the potential impact of this severity bias, these studies involved a subset of high-risk TIA cases that all had stroke subsequent to TIA, reducing the heterogeneity in severity across cases. In addition, all multivariable analyses in these studies were adjusted for comorbid risk factors, including diabetes, heart disease, hypertension and atrial fibrillation that may be indicators of the etiology of the presenting symptoms.

Given the retrospective design of the studies in this dissertation and the inability to adjust for the severity and etiology of TIA using the available data, we were unable to examine potential associations between the use and timing of imaging procedures after TIA and clinical outcomes in individuals with TIA. The available data were also limited in information regarding advanced imaging procedures such as CTA, MRI, and diffusion-weighted imaging performed in individuals in this TIA cohort. As a result, the studies in Chapters 3 and 4 were unable to assess practices for the utilization and timing of these imaging modalities.

Given the short time window within which to acquire stimulation data after the clinical event in TIA patients, participants in the study in Chapter 5 did not undergo structural MR imaging prior to paired pulse stimulation. As a result, we were unable to account for potential
differences in white matter disease burden in TIA participants in this study and were also unable to employ the use of neuronavigation during the acquisition of stimulation data, increasing the potential for bias in the measurement of intracortical excitability in TIA participants.

6.6. Future Research

The studies in this dissertation represent an initial evaluation of population-based practices for the utilization and timing of neuroimaging procedures after TIA. Several important questions remain regarding the impact of imaging investigations on the management and outcomes of individuals with TIA. The consistent finding of imaging underutilization in both previous studies and the present work suggests that future studies are required to identify barriers to the use of imaging after TIA and reduce gaps between guideline recommendations and practice for the use of imaging in the assessment of TIA. Future studies examining imaging use and timing after TIA would also benefit from the prospective evaluation of TIA cases. Prospective follow-up of individuals with TIA would allow for the measurement of potential confounders including the severity and etiology of TIA symptoms. The ability to incorporate this information into the study design would allow future studies to examine the impact of imaging use on management strategies and clinical outcomes after TIA. Further, the ability to prospectively measure this information in the study population would also enable stratified analyses to explore potential associations between the use and timing of imaging and TIA severity and etiologic subtype. Studies involving more comprehensive information on advanced structural and vascular imaging modalities are also required to adequately characterize current practices for imaging utilization in individuals presenting with TIA and evaluate the putative contributions of information from each of these modalities on decision-making for the management of individuals with TIA.

Findings from the study in Chapter 5 provided initial evidence to establish that alterations in the thresholds for intracortical excitability are present after TIA, but many
questions remain regarding the potential utility of paired-pulse TMS for the evaluation of TIA. Although this study indicated that changes in intracortical excitability are present on average two weeks post-TIA, the duration of these changes is not known. Future longitudinal studies are required to determine if changes in intracortical excitability persist after TIA or normalize within a certain time period post-event. It is also unclear whether measuring intracortical excitability after TIA has diagnostic utility to distinguish between patients presenting with transient neurological symptoms of vascular and non-vascular origin. Future studies evaluating the sensitivity and specificity of paired-pulse TMS are required to determine the potential diagnostic utility of this technique. In addition, the present work did not examine the potential role of periventricular white matter disease in the changes in intracortical excitability observed after TIA. Future studies pairing MRI with TMS are also required to quantify the extent of periventricular white lesion burden in individuals with TIA and determine the putative contributions of white matter disease to alterations in the cortical neurophysiology. Further, although findings of this work showed a correlation between changes in intracortical excitability and ABCD² scores, the predictive value of these changes is not known. To determine whether altered intracortical excitability is predictive of increased stroke risk in individuals with TIA, future work would require a large, prospective study to examine potential associations between intracortical effects and the risk of stroke in individuals with TIA. If this technique was shown to have diagnostic and predictive utility for the evaluation of TIA, a health technology assessment examining the potential clinical and economic implications of the widespread implementation of paired-pulse TMS in different clinical settings would also be warranted.
References

4. Canada PHAo. Tracking Heart Disease and Stroke in Canada. 2009.


86. Sheehan OC, Merwick A, Kelly LA, Hannon N, Marnane M, Kyne L, et al. Diagnostic usefulness of the ABCD2 score to distinguish transient ischemic attack and minor ischemic
137. Lasserson DS, Chandratheva A, Giles MF, Mant D, Rothwell PM. Influence of general practice opening hours on delay in seeking medical attention after transient ischaemic attack
(TIA) and minor stroke: prospective population based study. BMJ (Clinical research ed. 2008;337:a1569.


176. BC PD. Available from: www.popdata.bc.ca.
232. Williams JI, Young W. Inventory of studies on the accuracy of Canadian health administrative databases.: ICES1996 Contract No.: 96-03-TR.
239. Information CIH. Average Payment per Physician Report, Fee-for-Service Physicians in Canada 2004-20052006.