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Secular Trends in Ischemic Stroke Subtypes

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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by

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Abstract

Background: With an aging population and an increasing prevalence of therapy for atherosclerosis, it might be expected that stroke subtypes would be changing over time. Limited information exists on the ischemic stroke subtypes in adults in Canada.

Methods: Patients referred to the Urgent TIA Clinic, in London, Ontario, between 2002-2012 were included. Secular trends were analyzed using Poisson regression with spline trend function. Ischemic stroke subtype classification was validated.

Results: 3,445 consecutive patients (mean age$\pm$SD 64.8$\pm$14.9) were included. Cardioembolic strokes/TIAs increased from 21% in 2002 to 56% in 2012, whereas all other ischemic stroke subtypes decreased ($p<0.05$). Separate analysis in men and women showed similar results.

Conclusions: The decrease in atherosclerotic risk factors resulted in fewer strokes/TIAs caused by large artery atherosclerosis. On the contrary, cardioembolic strokes/TIAs have increased. This has important implications for more intensive investigation and treatment to reduce the risk of recurrent embolic stroke/TIA.

Keywords

cerebrovascular disease (MeSH), transient ischemic attack (MeSH), cerebrovascular stroke, ischemic stroke subtype(s), cardioembolic stroke(s), large artery atherosclerosis stroke, small vessel disease stroke, lacunar infarction(s) (MeSH), classification (MeSH), ischemic stroke classification, secular trend(s), trends (MeSH).

Co-Authorship

The author of this thesis has designed and conducted two studies and will organize two manuscripts intended for publication. However, this work could not be completed without the contribution of the following scientists:

1. Dr. J. David Spence who supervised all steps of both studies and provided constructive guidance and feedback on a weekly basis,
2. Dr. A. Ian McLeod who supervised all the analysis of both studies and introduced us to the R statistics and the trend analysis,
3. Dr. Marnin Heisel who provided us with ideas for improving the validation strategy of SubtyPes of ischAemic stRoKe cLassification systEm (SPARKLE) and reviewed the final draft of the thesis,
4. Dr. Thapat Wannarong who was trained on using SPARKLE and volunteered in classifying 275 cases to assess the inter-rater reliability of SPARKLE,
5. Dr. Daniel G. Hackam who supervised and reviewed both studies.

The two manuscripts derived from this Master's dissertation will be authored by Chrysi Bogiatzi and will be edited by all co-authors.

Dedication

This work is dedicated to my sister Sofia Bogiatzi,
to my parents Ioannis Bogiatzis and Archontoula Thomidou-Bogiatzi
who have been a great influence to me and
who continue to provide me with their love and support.

In memory of Sofia and Dimos Bogiatzis, Chrysi and Georgios Thomidis.

Αφιερώνω εξαιρετικά την πτυχιακή μου

στην αδερφή μου, Σοφία Μπογιατζή
και στους γονείς μου, Ιωάννη Μπογιατζή και Αρχοντούλα Θωμίδου-Μπογιατζή
οι οποίοι συνέβαλλαν ουσιαστικά στην διαμόρφωση του χαρακτήρα μου
και συνεχίζουν να με στηρίζουν σε όλα τα βήματα μου.

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List of Abbreviations

AF	Atrial Fibrillation
ASA	Atrial Septal Aneurysm
B12	Vitamin B12
BMI	Body Mass Index
CAE / CA	CArdioEmbolic stroke/TIA
CCS	Causative Classification System
CT	Computed Tomography
DM	Diabetes Mellitus
HDL	High-Density Lipoprotein cholesterol
ICH	Intra-Cerebral Hemorrhage
INR	International Normalized Ratio
LAA / LA	Large Artery Atherosclerosis stroke/TIA
LDL	Low-Density Lipoprotein cholesterol
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
OGTT	Oral Glucose Tolerance Test
Other / OC	Other rare or unusual cause of stroke/TIA
PFO	Patent Foramen Ovale
PROGRESS	Perindopril Protection Against Recurrent Stroke
SAH	Sub-Arachnoid Hemorrhage
SDB	Stroke Data Bank
SPARC	Stroke Prevention and Atherosclerosis Research Center
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol levels
SPARKLE	SubtyPes of ischAemic stRoKe cLassification systEm
SVD / SA	Small Vessel Disease stroke/TIA
TCD	Trans-Cranial Doppler
TIA	Transient Ischemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TPA	Total Plaque Area
UND / UC	Undetermined cause of stroke/TIA
U.S.A.	United States of America
WHO	World Health Organization

Prevention is preferable to cure.

Hippocrates, 460-377 B.C., Father of Medicine

Κάλλιον τό προλαμβάνειν ἤ τό θεραπεύειν.

Ἱπποκράτης, 460-377 π.Χ., Πατήρ τῆς Ἰατρικῆς

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

1.1 Overview and Specific Aims of Proposed Research

The current literature suggests that there is a lack of research on the epidemiology of ischemic stroke subtypes in the Canadian adult population. The specific aims of the present study are to assess the secular trends of ischemic stroke subtypes and describe their risk factors using a validated classification system. We performed a retrospective case series study of patients diagnosed with minor stroke or transient ischemic attack (TIA) between the years 2002 and 2012 (inclusive). Our results provide evidence that may help prevent recurrent strokes or TIAs in this high-risk population. In this chapter, we will review the epidemiology of cerebrovascular disease and ischemic stroke subtypes, as well as their risk factors, followed by an overview of the development of previous classification systems of ischemic stroke subtypes.

1.2 Definition of Cerebrovascular Disease

Cerebrovascular disease is a heterogeneous group of medical conditions caused by disorders of the blood circulation in the brain and nervous system. These disorders result in either prolonged or transient loss of blood supply to the affected areas of the brain, leading to necrosis or ischemia of brain tissue, respectively. In the case of prolonged ischemia, permanent necrosis of brain tissue is commonly referred to as an infarction or ischemic stroke, whereas transient ischemia is referred to as a TIA. According to the World Health Organization (WHO), stroke is defined as a syndrome of "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin".[1] TIA was initially defined as a cerebrovascular event with symptoms lasting less than 24 hours,[2] whereas the new definition introduced in 2009 by the American Heart Association and American Stroke Association, refers to an "ischemic event in the brain, spinal cord or retina that leads to neurological symptoms without any acute and permanent tissue necrosis".[3]

Stroke and TIA have many subtypes. They can be broadly divided into two categories; hemorrhagic and ischemic. Hemorrhagic stroke can be caused by a rupture of the arteries in the brain (resulting in a hemorrhage into brain tissue – for example, Intra-Cerebral hemorrhage or ICH), or bleeding between the membranes surrounding the brain (resulting in Sub-Arachnoid Hemorrhage or SAH).[4] Ischemic stroke or TIA can be caused by a broad group of medical conditions, such as atherosclerosis, cardiac disease, small vessel disease or other unusual causes (for example, dissection, vasculitis).[4] Thus hemorrhagic stroke is the clinical outcome of excess blood in the brain tissue or the surrounding areas, whereas ischemic stroke or TIA is the result of limited blood circulation and nutritional supply to particular areas in the brain. Hemorrhagic strokes account for approximately 13% of all incidents of cerebrovascular events and ischemic strokes account for 87% of such events.[5] The focus of this thesis will be limited to the study of ischemic strokes or TIAs, as they represent a large majority of the cerebrovascular disease burden. For the purpose of this paper, ischemic stroke or TIA will be referred to as stroke/TIA.

1.3 Epidemiology of Cerebrovascular Disease

Cerebrovascular disease is a major health concern worldwide. In the year 2005, 16 million new strokes were reported in patients who had no previous history of stroke, with 5.7 million patients suffering a fatal stroke.[6] The WHO predicts that patients with first-ever stroke are expected to increase to 23 million, with 7.8 million expected to die from a stroke by the year 2030 worldwide.[7]

There is large regional variation in the incidence of stroke. The WHO MONICA cross-sectional study indicated that Finland, Lithuania and Russia have the highest incidence of stroke among 18 countries studied.[8] In this study, differences in risk factors were responsible for 42% of the variation in stroke rates in women.[8] Therefore, continual study of risk factors and subtypes of stroke/TIA is necessary over the course of many years, and ideally should be limited to a well-defined catchment area.

In previous years, stroke was the third most common cause of death and has only very recently fallen to fourth place overall.[9] Currently, in Canada, a stroke occurs every 10 minutes, and at present there are approximately 315,000 stroke survivors who live with some degree of permanent disability.[10, 11] Between the years 1953 and 1978, there was a decrease by 51% in deaths due to stroke, which has been attributed to better medical control of blood pressure.[12] A similar decrease was recorded in London, Ontario, between the years 1977 and 1984, when hospital admissions due to stroke decreased from 500 to 250 per year.[13] The decline was almost entirely due to reduction of ICH and lacunar infarction, with no change in strokes due to large artery atherosclerosis disease.[13] A survey conducted in Middlesex County in Ontario between the years 1981 and 1982 showed that 92% of hypertensive individuals were treated for hypertension and 72% had well-controlled blood pressure.[14]

More recently, between the years 1994 and 2001, there was a 27.6% decline in hospitalization due to stroke of all causes and a 28.2% decline in stroke-related mortality throughout the country.[15] In 2004, in Canada, 53,629 hospital admissions and 14,591 deaths occurred due to acute stroke.[15] However, an increase in obesity was observed in the Canadian population from 10% in 1970 to 24.1% in 2007-2009; as well, an increase in obesity-attributed strokes from 5% in the year 1970 to 11% in the year 2004 has been documented in other countries.[16, 17]

Currently, 20% of all cardiovascular deaths are caused by stroke.[18] Moreover, Ontario currently ranks third among the Provinces in the prevalence of cardiovascular risk factors; residents in Ontario ranked second in smoke-free habits and sixth in physical activity.[19] Ontario residents ranked fourth in terms of healthy body weight, as well as fruit and vegetable consumption.[19] Together these results suggest that there is an unfavorable alteration in risk factors such as body weight and physical activity. Consequently, the results of our study can be generalized only to Ontario residents and cannot be extrapolated to all Canadians. Secular trends in stroke/TIA subtypes and risk factors should ideally be studied together, to identify areas that require more intensive prevention strategies. Below we provide definitions and discuss the epidemiology of stroke/TIA subtypes.

1.4 Definition of Stroke/TIA Subtypes

In this section, we provide a brief overview of stroke/TIA subtypes. Based on the identified etiological mechanism that contributed to any given cerebrovascular event, stroke/TIA is divided into five subtypes: large artery atherosclerosis, cardioembolic origin, small vessel disease, stroke/TIA of other determined (unusual or rare) cause, and stroke/TIA of undetermined etiology.[20]

Large artery atherosclerosis is defined as the formation of atherosclerotic plaques in the large diameter vessels that supply the brain with blood. These plaques reduce the delivery of blood to the brain. The decreased blood flow results in ischemia or necrosis due to decreased oxygenation and nutritional supply to the brain tissue. The mechanism operates when platelet aggregates form on roughened plaques and parts of the aggregates or the plaques themselves detach from the arteries, and enter the distal blood circulation. These emboli can then block the blood circulation in the smaller diameter vessels. Therefore, large artery atherosclerosis stroke/TIA is the outcome of the sequence of plaque formation, plaque rupture, thrombus formation on ruptured plaque, and embolization of thrombus or plaque fragments into the arterial vascular system supplying oxygenated blood to brain tissue.

In **cardioembolic stroke/TIA,** a blood clot originates centrally in the heart or aorta and circulates to the brain tissue. In particular, the oxygenated blood from the heart carries these embolic particles that can potentially cause ischemia or necrosis in any type of tissue if they block arteries. Moreover, cardioembolic stroke/TIA is typically caused by cardiac conditions that involve the cardiac rhythm, cardiac valves or the ability of the heart muscle to contract and send blood to the brain and the rest of the body (such as post-myocardial infarction, chronic heart failure, or atrial fibrillation).

The third type of stroke/TIA is characterized as **small vessel disease** (also known as lacunar infarction) where a small area of brain tissue (less than 15mm in diameter on brain imaging) is necrotic or ischemic.[21] Distinct stroke syndromes arise from the formation of small vessel disease stroke/TIA at particular parts of the brain supplied by smaller-sized arteries. The five well validated clinical syndromes of small vessel disease include pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, sensorimotor stroke and dysarthria-clumsy hand syndrome.[22]

In stroke/TIA classified as **"other"** determined etiology, unusual or rare medical conditions are present, such as inflammation of the arteries (e.g. vasculitis), dissection of the arterial wall, disorders of blood cells, or genetic diseases.

Finally, there are strokes/TIAs for which the cause of the presenting event cannot be identified by investigations performed at the time of the event. These events are categorized as strokes/TIAs of "**undetermined**" or "**unknown**" etiology.

1.5 Epidemiology of Stroke/TIA Subtypes

In this section, we provide a brief overview of the epidemiology of stroke/TIA subtypes worldwide. The results of a literature review performed for this thesis show considerable variation in the epidemiology of stroke/TIA subtypes in different geographic areas (Appendix A).

In Europe and the United States of America (U.S.A.), there is inconsistency between epidemiological studies assessing the distribution of stroke/TIA subtypes. The largest study conducted to date, including 5,298 patients, was based in Switzerland during the years 1979-1987 and 1996-2003 and showed a decrease in large artery atherosclerosis from 45% to 26%, and an simultaneous increase in cardioembolic strokes from 18% to 28%.[23] Similar trends were evident in more recent reports from Spain.[24] Yet studies in other European nations observe that the most common stroke/TIA subtypes are due to large artery atherosclerosis[25-34] or small vessel disease.[35-41] One of the largest studies in the U.S.A., in the years 1982-1985, showed that 73% of patients with ischemic stroke had large artery atherosclerosis,[42] whereas a more recent population-based study showed that 20% had cardioembolic stroke, which was the most common subtype.[43] Other studies showed the predominance of either large artery atherosclerosis[44] or small vessel disease strokes [45-48] in different areas of the country with different racial population composition, access to health and management of stroke risk factors.

In contrast to studies performed in Europe and the U.S.A., early and more recent studies from South America and Asia show a consistently higher prevalence of small vessel disease. Rojas et al[49] from Argentina and Lee et al[50] from Taiwan found that

small vessel disease was prominent in their populations even after stratifying by age. Small vessel disease has consistently remained the most prevalent stroke/TIA subtype over many years in Asia, even if there is an overall decreasing trend in this subtype.[51] It would be expected that given the trend in decreasing small vessel disease, there will be a proportional increase in other stroke/TIA subtypes in this population. However, this has not yet been observed.[51] Genetic factors might be responsible for the high prevalence of small vessel disease in Asians,[52] whereas lifestyle and risk factors may account for this in South Americans.[53]

It is impressive that differences in the classification systems account for significant variations in stroke/TIA subtypes within the same country or population. In Patra, Greece, Polychronopoulos et al[33] showed that 37% of patients had large artery atherosclerosis as the most prominent subtype, whereas Vemmos et al[54] in Athens, Greece, observed a predominance of cardioembolic strokes/TIAs in 31% of patients for the same period of time. Similarly, Sempere et al[41] from Segovia in Spain demonstrated that 31% of patients had small vessel disease as the most prevalent subtype, whereas Arboix et al[24] showed that in Barcelona, Spain, 28% of patients had predominantly cardioembolic stroke/TIA. Regional differences in the distribution of risk factors and misclassification bias may account for the aforementioned differences. Consequently, it is not possible to provide summary statistics of previous literature for all stroke/TIA subtypes over the past decades.

There is a burgeoning literature showing that the prevalence and effectiveness of management of stroke risk factors play the most significant role in the distribution of stroke/TIA subtypes, even among different ethnoracial groups. Koch et al[47] and Uchino et al[55] from the U.S.A., Saposnik et al[53] from Argentina, Sharma et al[56] from Singapore and Feigin et al[57] from New Zealand demonstrate that patients from different ethnic groups in a defined geographical area have similar distributions of stroke/TIA subtypes. The latter might be related to the shared prevalence of risk factors for stroke/TIA within an area, rather than the genetic predisposition to specific subtypes of stroke/TIA related to ethnicity.

A recent study from Norway by Ihle-Hansen et al[58] showed that small vessel disease was more frequent than expected. In this study, 31% of patients had small vessel disease, and equally 31% of patients had cardioembolic strokes. Comparable results

were shown earlier from the Northern Manhattan Study, U.S.A., where White et al[59] showed that between the years 1993 and 1997, equal numbers of patients had cardioembolic stroke and small vessel disease, each accounting for 20%. This finding addresses the importance of continual study of risk factors and stroke/TIA subtypes to develop more intensive prevention strategies as well as considerations related to the management of acute stroke/TIA.

Currently, there are no studies in a Canadian population in a geographically defined area assessing stroke/TIA subtypes and their risk factors in all adults, which is what this present work hopes to address. A previous study showed that cardioembolic strokes are marginally more prominent in young patients only, but there has been no report on adults older than 45 years old.[60] Moreover, in 2009, 90% of Canadians had at least one risk factor for cerebrovascular or cardiovascular disease.[10] Therefore, a reference study is needed as a starting point, and more studies are required to demonstrate the distribution of stroke/TIA subtypes and their risk factors, for the development of primary and secondary prevention strategies. Below, we will discuss how risk factors for stroke are associated with stroke/TIA subtypes.

1.6 Ischemic Stroke Subtypes and Risk Factors

According to Fletcher, risk factors are conditions that may lead to a specific disease in exposed individuals more frequently than in those people who are not exposed.[61] Stroke risk factors are divided into non-modifiable (age, sex, genetic predisposition) and modifiable (e.g., hypertension, diabetes mellitus, obesity).[62] A meta-analysis by Hackam and Spence showed that the use of aspirin, statins, medications for hypertension, as well as smoking cessation, exercise and Mediterranean diet could reduce the risk of recurrent stroke by more than 80%, and the number of patients who would be needed to treat to prevent one stroke in ten years with more intensive medical treatment was only three.[63] Therefore, early identification and treatment of risk factors for stroke can dramatically reduce the burden of cerebrovascular disease.

1.6.1 Non-Modifiable Risk Factors for Stroke/TIA

Age, Sex and Stroke/TIA

Statistics Canada reports that life expectancy is increasing.[64] Indeed, life expectancy in the years 1970-1972 in Canada was 69 years for men and 76 years for women, whereas in the years 2007-2009, specifically in Ontario, life expectancy increased to 79 years for men and 84 years for women.[64] With this change, it is expected that in the future, there will be an increase in elderly individuals surviving in the general population[65], and this age related phenomenon is expected to contribute to an overall increased stroke prevalence.[66]

The risk of each stroke/TIA subtype differs across age groups. Young patients (age<50) are more likely to have minor cardiac sources of embolism (e.g., patent foramen ovale, atrial septal aneurysm, etc.),[67] whereas the elderly have a higher likelihood of developing atrial fibrillation (AF) causing cardioembolic strokes.[68] Middle-aged individuals are more likely to have large artery atherosclerosis and small vessel disease and a higher prevalence of hypertension, diabetes mellitus, obesity, smoking or hyperlipidemia.[67, 68] Moreover, individuals who have a high prevalence of atherosclerotic risk factors may die early; therefore, older survivors have a higher risk of developing AF and, consequently, cardioembolic strokes/TIAs.[68]

Overall, men tend to have more strokes than women.[69] This difference diminishes in older age groups, with older women having a higher incidence of clinically severe first-ever stroke/TIA as compared to men.[69] On the one hand, women have a longer life expectancy[65] and older women are more prone to AF, which increases with age and can lead to cardioembolic stroke/TIA.[68, 70] Also, young women have a greater incidence of low risk cardiac sources of embolism as compared to young men.[67] On the other hand, men have a higher prevalence of atherosclerotic risk factors earlier in life and tend to have a greater degree of large artery atherosclerosis, small vessel disease, or undetermined etiology of their stroke/TIA at a younger age than women.[68, 70] In summary, very young (age<50) and very old (age>85) women are expected to experience a first-ever cardioembolic stroke/TIA, in contrast to men, who will

experience a first large artery atherosclerosis or small vessel disease stroke/TIA in middle age.[67, 68]

Ethnicity and Stroke/TIA

Many studies show different results in stroke/TIA subtypes among different ethnic groups. It has consistently been shown that Asians and South Americans have a higher prevalence of small vessel disease, whereas Caucasians are more prone to cardioembolic and large artery atherosclerosis stroke/TIA.

Differences between ethnic groups within the same country have been reported. Black patients in the Johannesburg Registry, South Africa, were prone to small vessel disease more often than white patients, but with a higher rate of undetermined causes of stroke/TIA.[71] In this registry, black patients were approximately ten years younger, were less likely to smoke and have AF or high cholesterol, and were equally hypertensive and diabetic compared to whites.[71] Similarly, African Americans in the U.S.A. also tend to be younger at the time of their first stroke/TIA.[72] They are more hypertensive and diabetic compared to whites in the U.S.A., denoting the important effect of Western diet and lifestyle in the development of hypertension and diabetes in genetically susceptible races (people of African descent are more likely to carry a mutation that increases sodium reabsorption from their kidneys; consequently, they are prone to hypertension with an increase in dietary sodium, a condition known as Liddle's syndrome).[72] Similar results were shown in the South London Ethnicity and Stroke study, United Kingdom, where the increased prevalence of obesity, diabetes and hypertension led to a significant increase in small vessel disease, despite the decrease of smoking, AF and myocardial infarction, which explained the decrease in large artery atherosclerosis and cardioembolic strokes/TIAs in black patients (mainly from the Caribbean) compared to whites.[73]

Even if these regional differences in risk factors between ethnic groups seem to affect stroke/TIA subtypes, there is evidence demonstrating the complexity of developing specific stroke/TIA subtypes. Previous studies have shown that populations in a geographically defined area share a common distribution of stroke/TIA subtypes among different ethnic groups.[47, 53, 56, 57] Equal access to health care and appropriate

primary prevention strategies towards controlling risk factors related to specific race characteristics, can reduce the risk of particular stroke/TIA subtypes in more susceptible populations (for example, appropriate treatment of hypertension in Africans), eliminating the effect of race on the overall risk of stroke and in particular stroke/TIA subtypes.[74]

1.6.2 Modifiable Risk Factors for Stroke/TIA

Smoking and Stroke/TIA

Smoking is an unhealthy behavior that promotes cerebrovascular disease (among other maladies). One in three men and one in four women die prematurely because of various diseases caused by cigarette smoking.[75] Since the beginning of the Framingham study, exposure to smoke has been shown to increase the risk of stroke.[76] A more recent meta-analysis suggests that there is a probable causal relationship between smoking and stroke even after adjusting for other risk factors,[77] and other evidence shows that smoking triples the risk of a fatal stroke.[78] In Canada, there are 11,000 deaths per year related to heart disease and stroke attributable to smoking and it is estimated that one million Canadians will die in the next two decades because of tobacco use.[79] There is a dose-response relationship between cigarettes smoked and the risk of large artery atherosclerosis and small vessel disease, especially in men.[80]

Nutrition, Body Mass Index and Stroke/TIA

A balanced diet is an important component in stroke prevention. Based on data from Statistics Canada, fat comprises more than 35% of the daily nutritional intake of more than 25% of middle-aged Canadians.[81] The most appropriate diet to maintain a healthy lifestyle and reduce the overall risk of stroke is probably the Mediterranean Diet from Crete, Greece. Keys et al. in 1986 compared 15 groups from different countries and showed that residents from Crete had lower death rates compared to residents from different countries.[82] Risk factor distribution was equal between all

study groups except for diet, where inhabitants of Crete had consumed a low protein diet.[82] Analysis of this diet has shown that it is suitable for promotion of a healthy lifestyle because it is rich in olive oil, legumes, fruits and vegetables and low in meat and dairy products.[83] This diet helps to reduce coronary heart disease, known to be related to atherosclerosis.[83]

Increased body weight (obesity) has been related to carotid atherosclerosis, which significantly increases the risk of stroke/TIA.[84] A meta-analysis of more than 2 million participants showed that overweight people had a 22% relative increased risk of stroke and obese people had a 64% relative increased risk of stroke, even after adjusting for all other risk factors.[85] Evidence shows that there is a linear association between increasing body mass index (BMI) and increasing risk of stroke in women.[86] Moreover, increased BMI has been related to increased risk of all large artery atherosclerosis, small vessel disease and cardioembolic stroke/TIA subtypes, with a linear relationship between increasing BMI and increasing blood pressure and non-HDL cholesterol levels.[87]

Blood Pressure and Stroke/TIA

Increased blood pressure or uncontrolled hypertension is the most important modifiable risk factor for stroke. In Canada, a 2009 survey showed that 22% of the population had hypertension, among which 65% had adequate control of their blood pressure.[88] This was a significant improvement in the control of blood pressure since the year 1992, when another survey showed that 20% of the population was known to have hypertension and only 14% achieved a desirable level of blood pressure control.[88] The increase in the control of blood pressure was attributed to the increase in awareness of the importance of measuring blood pressure and identifying hypertension by 25.6% and to the increase in appropriate treatment by 44.4% between the years 1992 and 2009, when the aforementioned studies were conducted.[88] This was also demonstrated by the significantly increasing trend in visits to primary health care practitioners for control of increased blood pressure.[89]

Nonetheless, the almost half of individuals inadequately treated for hypertension have a higher risk of stroke/TIA.[90] A number of randomized controlled trials have shown

that this risk can be reduced by lowering blood pressure. The Perindopril Protection Against Recurrent Stroke (PROGRESS) Trial showed that reduction of either systolic or diastolic blood pressure or both, can reduce the risk of stroke.[91] Arboix et al showed that increased blood pressure is a significant risk factor for both small vessel disease and large artery atherosclerosis, which is consistent with other observational studies.[92]

Diabetes Mellitus and Stroke/TIA

Diabetes Mellitus (DM) is a significant risk factor for stroke. According to Statistics Canada, approximately 2 million residents in the year 2005 lived with diabetes, and by the year 2016, diabetics are expected to increase to 2.4 million.[93] A meta-analysis of 698,782 stroke patients showed that individuals with diabetes had 2.27 times higher risk of ischemic stroke.[94] Also, based on the 2011 report of the American Heart Association and American Stroke Association, observational studies show that diabetes increases the risk of stroke from 1.8 to 6 times.[95]

There is an association between diabetes and specific stroke/TIA subtypes. Increased blood glucose had been mostly related to small vessel disease strokes,[96-99] but there are also studies showing a significant role of diabetes in large artery atherosclerosis ischemic strokes.[96, 100, 101] Patients with abnormal Oral Glucose Tolerance Test (OGTT) and yet no diagnosis of diabetes had increased risk of large artery atherosclerosis, which indicates that high glucose levels might be involved at the initial stages of the atherosclerotic process.[102] Moreover, patients with diabetes are more likely to have atherosclerosis of the intracranial large arteries as compared to the carotid arteries of the neck, and are more likely to have detection of atheroembolic microemboli particles in ultrasound monitoring of the arteries inside the brain, a condition that increases their risk of large artery atherosclerosis stroke/TIA.[103] Some studies demonstrate that uncontrolled diabetes is related to increased risk of AF and, consequently, increased risk for cardioembolic stroke/TIA.[100, 104] Overall, there is evidence showing that diabetes increases the risk of small vessel disease, large artery atherosclerosis and cardioembolic stroke/TIA subtypes.[104, 105]

Dyslipidemia and Stroke/TIA

High levels of blood lipids involve in the pathophysiology of cerebrovascular disease. Increased Low-Density-Lipoprotein (LDL) cholesterol and triglycerides are independent risk factors for stroke,[106] whereas high levels of High-Density Lipoprotein (HDL) cholesterol can significantly reduce this risk.[107] Currently in Canada, almost 40% of residents have increased cholesterol, which translates to approximately one million Canadians with cholesterol levels above the normal range.[108]

Increased levels of LDL cholesterol are related to large artery atherosclerosis and small vessel disease after adjusting for age and sex, and the relation between LDL and stroke is significant only for large artery atherosclerosis after further adjusting for HDL cholesterol, triglycerides, systolic blood pressure, fasting blood glucose, BMI, current alcohol consumption and smoking, regular exercise and electrocardiogram abnormalities.[109] The Stroke Prevention by Aggressive Reduction in Cholesterol levels (SPARCL) randomized clinical trial showed that lowering LDL cholesterol could prevent strokes, and that this relationship was linear.[110] Additional results from this clinical trial showed that reducing LDL cholesterol was associated with a 33% decrease in all types of stroke in patients with carotid stenosis due to carotid atherosclerosis.[111]

Cardiac Disease and Stroke/TIA

The most common cardiac disease associated with increased risk of stroke is AF. Results from the Framingham Study showed that among 5,070 people followed for 34 years, those who developed AF had almost a 20% higher risk of stroke.[112] This risk was age-dependent; the attributable risk of stroke from AF increased from was 1.5% to 23.5% at age 50-59 and $\geq$80 years, respectively.[112] Similar results were demonstrated almost 10 years later in Scotland, where Stewart et al observed middle-aged individuals over a 20 year period of time and found similar results.[113] Krahn et al showed that in Manitoba, Canada, 7.5% of air-crew male participants developed AF over the 44-year study period and this risk again increased in relation to increasing age.[114] Elderly women with a first stroke had a higher prevalence of AF.[115] Based on

estimates from the Heart and Stroke Foundation, approximately 350,000 Canadians have AF, which causes approximately 15% of all strokes.[116]

Myocardial Infarction (MI) preceding a cerebrovascular event is another significant cardiac condition related to stroke. Patients with MI have a higher risk of stroke in the month following their heart attack and are more likely to have a fatal stroke; this risk is reduced and is not significantly different from controls after the first 12 months following the heart attack.[117] Moreover, Wienbergen et al found that 1.2% of 21,330 patients had a stroke following a MI. In this population, age, previous stroke and AF were significant factors that increased the risk of stroke after a MI.[118] This was also shown in a more recent study in Massachusetts, where 1.4% of patients with MI experienced a stroke and had an increased prevalence of AF.[119]

Additional cardiac conditions are related to increased risk of stroke. Paradoxical embolism is a well-defined cause of stroke.[120] This condition refers to the presence of an arterial and venous blood mixture through a hole in the heart at the level of right and left cardiac atria that represents a remnant from the embryonic period of life called a Patent Foramen Ovale (PFO).[120, 121] Similar mixture of the arterial and venous blood circulation can be found in the lungs allowing the transfer of emboli from venous to arterial circulation.[122] This condition results in the access of these emboli to the brain and all other organs, instead of being cleared by the lungs, which normally act as a major filter for emboli found in the venous circulation.[120] There is an increased risk of stroke in patients younger than 55 years having one of these two communication pathways, and even greater risk in patients who have both conditions present.[123] Almost 40% of patients with cryptogenic or unknown stroke have a PFO versus 10% of normal controls.[121] Moreover, a larger diameter of PFO with an increased level of communication between the two parts of the heart relates to an increased risk of additional strokes.[124]

Collectively, the aforementioned risk factors increase the risk of stroke and particular stroke/TIA subtypes. The knowledge of the distribution of these medical conditions will help primary care physicians to intensively treat these risk factors and achieve more adequate primary prevention of stroke. Moreover, in the aftermath of a stroke,

awareness of the most prevalent stroke/TIA subtypes and risk factors will aid in implementation of tailored treatment options to decrease the overall burden of cerebrovascular disease. Therefore, our study results will provide information for both primary and secondary prevention strategies, given that the collection of clinical measurements at the time when patients experience their first stroke/TIA represent the most prominent risk factors that remain untreated.

1.7 Classification of Stroke/TIA Subtypes

In this section, we will discuss in brief the development of past classification systems of stroke/TIA and a newly developed system for classifying the etiology of stroke/TIA. Our goal is to provide the background evidence demonstrating the need to modify previous classification systems with the use of more advanced diagnostic tests and with an improved understanding of mechanisms of the underlying diseases. Taken together, we will furnish an informative classification system, to study the distribution of stroke/TIA subtypes, and inform policy makers to intensify prevention strategies towards the most predominant ischemic stroke subtypes and related medical conditions.

The first systematic classification system came from the Harvard Cooperative Stroke Registry, published in the year 1978 from a single center in Massachusetts, U.S.A.[125] According to this classification in its seminal series, 34% of patients had large artery atherosclerosis, 19% of patients had small vessel disease and 31% of patients had cardioembolic or unknown cause of stroke/TIA.[125] The diagnosis of stroke/TIA subtypes was mainly based on clinical signs and symptoms, and large vessel atherosclerosis was a diagnosis of exclusion.[125] Patients with cardiac and atherosclerotic source of embolism, and patients with unknown cause of stroke/TIA were classified under a single category, named "embolic".[125] At that time, there were limited diagnostic tests offered for imaging of the brain and the cardiac sources of embolism.[126] Only 3% of patients had Computed Tomography (CT) and the vast majority had angiography.[126] Ultrasound of the heart (echocardiography) was not offered for diagnostic purposes.[126]

With the improvement of diagnostic investigations, the Stroke Data Bank (SDB) classification system was developed in the following decade, including a multi-ethnic population from different centers.[46] At that time, 97% of patients had CT and echocardiogram was regularly used,[126] but Magnetic Resonance Imaging (MRI) had just started to develop and was not provided regularly in clinical practice.[46] For the first time, it was noted that the presence of infarcts in different arterial territories and hemorrhagic transformation of the infarct favor the diagnosis of cardioembolic stroke.[46] Also, it was recognized for the first time that emboli could arise from atherosclerotic plaques and lead to embolic stroke from large artery atherosclerosis disease.[46] Based on SDB, 9% of patients had large artery atherosclerosis, 27% had small vessel disease, 19% had cardioembolic, and 45% had unknown cause of stroke.[46] The impressive differences between SDB and Harvard Cooperative Stroke Registry arise from the more frequent use of CT that classified more cases as small vessel disease that were previously classified as large artery atherosclerosis due to differences in definitions of large artery atherosclerosis (stenosis≥90% in angiography in SDB versus total occlusion or diagnosis of exclusion in Harvard Cooperative Stroke Registry). Nonetheless, with the absence of MRI, strokes arising from atherosclerotic basilar artery stenosis could not be differentiated from small vessel disease, resulting in a decrease in large artery atherosclerosis.[46] Also, cases that were previously classified as large artery atherosclerosis as a diagnosis of exclusion are now classified as unknown causes of stroke, inflating the number of cases where no cause of stroke could be identified.[46]

The use of MRI and the better understanding of mechanisms of cerebrovascular events led to the development in the year 1993 of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.[127] The initial goal of this classification was to better categorize stroke/TIA subtypes in patients participating in clinical trials assessing new therapies, and has been thereafter used in most epidemiological studies.[127] According to TOAST, patients who had more than one reason to have a stroke/TIA were classified as “undetermined or unknown etiology of stroke”, and patients who had the clinical diagnosis of large artery atherosclerosis but stenosis ≤50% were also classified as undetermined cause of stroke.[127] This first problem was resolved in the year 2005 when the Causative Classification System (CCS) of acute ischemic stroke was published, and patients with multiple causes for stroke were

classified according to the most probable cause of the presenting stroke event.[128] The second problem of TOAST led us to develop the SubtyPes of ischAemic stRoKe cLassification systEm (SPARKLE), which uses an ultrasound-based measurement of carotid atherosclerosis (total plaque area, TPA)[129] for more accurate classification of large artery atherosclerosis and is used for the classification of ischemic stroke subtypes in the present study.

In previous classification systems, before SPARKLE, peak velocity of the blood flow with a stenosis ≥50% has been used as a measure of carotid stenosis and large artery atherosclerosis disease. However, high measurements of blood flow velocity can be found in normal vessels with small anatomical diameter or in patients after endarterectomy.[130] Moreover, Iemolo et al showed that women have higher frequency of apparent stenosis compared to men, who have higher levels of TPA, and men more frequently have large artery atherosclerosis at a younger age compared to women.[130] This study also showed that TPA was a stronger predictor of stroke, death or myocardial infarction than carotid stenosis. Spence et al showed in the year 2002 that carotid atherosclerosis, measured by TPA, is a strong predictor of the combined outcome of stroke, heart attack and death.[129] After adjustment for age, sex, blood pressure, serum cholesterol, smoking, diabetes, homocysteine and treatment of blood pressure and cholesterol, patients with TPA in the highest quartile (above 1.19 cm^2) had a 3.4 times increased risk of these events as compared to patients in the lowest quartile (below 0.12 cm^2)[129]; furthermore patients with TPA≥1.19cm^2 have a 20% 5-year risk of stroke, death or myocardial infarction.[129] Thus TPA was a much stronger predictor of risk than a Framingham or other risk score based on risk factors and can be used reliably in all clinical settings (intraclass correlation 0.94).[129, 131] Moreover, the Tromsø study showed that TPA was a strong predictor of stroke,[132] and a meta-analysis by Inaba et al showed that TPA was a stronger predictor of MI than intima-media thickness.[133] More recently, results from the Northern Manhattan Study, U.S.A., showed again that TPA predicts vascular disease.[134] In that study, Kuo et al showed that traditional risk factors explain only a small portion of TPA and modification of traditional risk factors is warranted in healthy individuals to decrease the risk of a vascular event.[134] All these studies show that TPA measurements are widely available and, consequently, we considered it important to incorporate TPA measurement in the diagnosis of large artery atherosclerosis.

The last problem that remained unsolved in classification systems before SPARKLE was the inclusion of particular risk factors in the diagnosis of specific stroke/TIA subtypes. For instance, the presence of hypertension and diabetes supported the diagnosis of small vessel disease. However, a systematic review by Jackson et al showed that diabetes was no longer significant in propensity for small vessel disease, among classification systems that did not include risk factors in the definition of stroke/TIA subtypes.[135] Similarly, a meta-analysis by Schulz and Rothwell showed that only hypertension and not diabetes was significantly related to small vessel disease in population-based studies.[136] In this meta-analysis, hospitalized patients had a higher prevalence of cardioembolic strokes compared to outpatients (28.3% versus 17.8%, $p<0.0001$), but a much lower prevalence of small vessel disease (14.3% versus 27.5%, $p<0.0001$), respectively.[136] This was not a limitation in the present study, given that SPARKLE is a classification system free from *a priori* assumptions of the role of risk factors in the mechanisms of stroke/TIA subtypes. A detailed description of SPARKLE is provided in the next chapter.

1.8 Relevance of Proposed Research

To our knowledge, there are no studies analyzing the secular trends of stroke/TIA subtypes in a Canadian population for patients who have survived a minor stroke/TIA, other than a study in young patients only, which used the TOAST classification system. The study of patients with minor stroke/TIA in an ambulatory setting is of particular interest and should be studied separately from hospitalized stroke/TIA patients, given that these two populations share different clinical characteristics in terms of risk factors, stroke/TIA subtype and severity of stroke. Patients who have suffered only a minor stroke or have recovered completely will have also more to lose from recurrent stroke. Patients who have experienced a minor stroke/TIA are at much higher risk of developing an additional and potentially disabling or even fatal stroke, and they require intensive investigation and secondary prevention strategies, as compared to healthy individuals. Moreover, the distribution of the risk factors in this population is changing over time and the pattern of this change will inform primary health care practitioners as to how particular risk factors are changing to improve management in areas with suboptimal treatment success.

The results of this study will provide evidence on the most common stroke/TIA subtypes that warrant specialized medical therapy, improving patients' prognosis and reducing the cost of health care services. The changing distribution of stroke origins is of great importance, because patients with cardioembolic stroke/TIA require different treatments (for example, anticoagulant as opposed to antiplatelet agents) to prevent recurrent stroke, and require more specialized investigations to detect the cardiac source of brain embolism.[137] A study in Saskatchewan showed that 75% of stroke patients required hospitalization due to cardiovascular complications.[138] This increased annual health care costs by $24 million (Canadian) in that Province alone.[138] We believe that implementation of more intensive prevention strategies as well as increased identification of the most probable mechanism can help reduce this cost. By initiating appropriate treatment early, these funds can be redistributed to more intensive prevention strategies as well as more effective therapies.

At present, there is no up-to-date research in this rapidly changing field in a geographically-defined Canadian locale in adults with stroke/TIA other than a study exclusively focused on young patients (age<45).[60] Therefore, our retrospective case series study will provide evidence about the change in risk factors and the secular trends in stroke/TIA subtypes based on the risk factor-free classification system, with the ultimate goal of informing and improving the organization of more effective strategies for primary and secondary prevention. If we indeed find an important increase in cardioembolic stroke/TIA, the results of our study will assist health care practitioners to place appropriate weight on the need for specialized cardiac investigations, and alert them to the need for anticoagulants in a higher proportion of patients with stroke/TIA.

1.9 Objectives and Hypothesis of Proposed Research

1.9.1 Primary Objective

Has there been any change in the secular trends in stroke/TIA subtypes in patients with minor stroke/TIA in a Canadian geographically defined area in the past decade?

Hypothesis

We hypothesize that with more intensive management of atherosclerotic risk factors, there will have been a decrease in large artery atherosclerosis and small vessel disease and, as a consequence, an increase in cardioembolic strokes as a proportion of ischemic strokes. This hypothesis is driven by our anecdotal clinical experience and requires systematic, scientific confirmation.

1.9.2 Secondary Objective

What is the distribution of risk factors for stroke/TIA in patients with minor stroke/TIA and separately in each stroke/TIA subtype?

Hypothesis

We hypothesize that there will have been an increase in age of patients presenting with a first-ever stroke/TIA and an increase in cardioembolic stroke/TIA related to atrial fibrillation. Also, we hypothesize that there will be a decrease in atherosclerotic risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, etc.) and an increase in high and low risk cardiac sources of embolism.

1.9.3 Tertiary Objective

How valid and reliable is SPARKLE as compared to TOAST and CCS?

Hypothesis

We hypothesize that SPARKLE will provide a better diagnosis of stroke cases assigning fewer patients to the undetermined category compared to CCS and TOAST. As a result, we also expect to have better agreement with CCS as compared to TOAST.

CHAPTER TWO: PATIENTS AND METHODS

2.1 Overview of Study Methodology

We performed a retrospective case series study to assess the secular trends in stroke/TIA subtypes and their risk factors in the Thames Valley area of Ontario. Also, we used these data to assess the validity and the reliability of the SubtyPes of ischAemic stRoKe cLassification systEm (SPARKLE). In this chapter, we present the features of the population from which we retrieved our data and the measurements we collected. We provide a description of SPARKLE and the pilot study we conducted to assess the feasibility and the performance of both Causative Classifications System (CCS) of acute ischemic stroke and SPARKLE, and discuss our methodology of assessing the validity and the reliability of SPARKLE, and the statistical methods used for the analysis of our data.

2.2 Study Population

Canada is divided into 13 Provinces and Territories. Most of these regions have their own stroke network that connects the population to specific centers specialized in prevention, acute treatment and continued care of patients inflicted by stroke/TIA. In particular, the Ontario Stroke Strategy divides the Province into 11 geographically defined areas to cover all residents living in Ontario, accommodating 24 regional secondary prevention clinics.[139] Each of these areas offers health services to patients who have presented with a stroke/TIA to their nearest community hospital, walk-in clinic, emergency department or primary care practitioner. Thereafter, those patients who survive a stroke/TIA and are not directly transferred to rehabilitation services (patients who had a minor stroke/TIA), receive a referral to a secondary prevention clinic, where they are provided with expert management, diagnosis and follow-up of their stroke/TIA.

The Ontario Stroke Strategy was implemented in 2000 and contributed to a significant increase in stroke symptoms awareness.[139] At the same time, in 2000, the Urgent TIA Clinic in London, Ontario, began operating. The Urgent TIA Clinic is the secondary

prevention center that covers referrals from the Thames Valley area that includes the city of London, Oxford County, Elgin County, Middlesex County, and areas of Muncee-Delaware Nation and Chippewa of the Thames First Nation. However, the Ontario Stroke Strategy was established after the year 2002 and, consequently, we decided to exclude patients referred to the Urgent TIA Clinic during the first two years of the development of this clinical setting to limit selection bias in our retrieved patient cases.

Patients were recruited from the Urgent TIA Clinic, in London, Ontario, where they were referred either to Dr. David Spence or Dr. Vladimir Hachinski or another attending neurologist. Our data was collected from patients referred to Dr. Spence, because they were all included in the database of the Stroke Prevention & Atherosclerosis Research Centre (SPARC). Appointments were assigned to Dr. Spence or Dr. Hachinski by the Urgent TIA clinic receptionist on the basis of the next appointment available in a semi-random order and, consequently, there was no selection bias. As a result, our study population is a representative sample of stroke survivors who experience a minor stroke/TIA.

Approximately, 4,500 patients were seen in the Urgent TIA Clinic between the years 2000 and 2012. However, in 2000 and 2001 there were only 20 and 123 patients seen in our clinic, respectively. As mentioned above, we decided to exclude these cases and compile a database including patients who were diagnosed with stroke/TIA between the years 2002 and 2012, at the time when the clinic was better established. Moreover, we decided to proceed with data entry based on paper chart review, to ensure the minimum possible missing information bias and confirm these information with data from the SPARC database.

Patients with a first-ever stroke/TIA were included in the study and were classified based on their medical history, physical examination and laboratory and imaging investigations. Therefore, the sole **inclusion criterion** of our study population is:

1. Patients with a confirmed first-ever minor stroke/TIA between the years 2002-2012.

Medical history and investigations data were collected at the first clinical visit. Recurrent events were collected as follow-up strokes or follow-up TIAs.

Clinical information was not collected from patients who were referred to the clinic and the stroke expert (Dr. Spence) reported the final diagnosis of stroke mimics (for example, focal seizure, brain tumor, subdural hematoma, syncope, peripheral vertigo from inner ear diseases, meningioma, brain metastasis, etc.) as well as patients who did not attend their appointment. Consequently, our **exclusion criteria** are:

1. Patients with no diagnosis of stroke/TIA,

2. Patients who did not attend their clinic appointment,

3. Patients who were seen for a recurrent stroke/TIA and had their first stroke/TIA before the year 2002.

We believe that this is the most appropriate strategy to approach our population study, because eligible patients who access any kind of health care services in the Thames Valley area, (family physicians, emergency departments or urgent care centers) are referred to our facility, and hence, a representative sample of the population study has been created to collect data for our analysis.

2.3 Data Sources

Eligible patients who had a stroke/TIA between the years 2002 and 2012 were identified through the administrative office of the Urgent TIA Clinic that receives referrals from all patients with acute stroke/TIA in the Thames Valley area and confirmed by data from the SPARC database. A graduate physician (Dr. Bogiatzi) performed the data entry of all variables needed for the classification of stroke/TIA subtypes (medical diseases related to stroke/TIA). The diagnosis of stroke/TIA subtype was reported previously by the stroke expert (Dr. Spence) who examined the clinical cases at the time of their stroke/TIA. The final categorization of patients into one of the five stroke/TIA subtypes relied on the SPARKLE classification system, using all available collected information, and was decided in conjunction with the stroke expert.

Based on the literature review of risk factors and medical diseases related to stroke/TIA, the following information necessary for the complete assessment, diagnosis and classification of stroke/TIA was retrieved from the paper chart review and was entered into an SPSS spreadsheet:

1. self-reported stroke/TIA risk factors (age, sex, smoking, hypertension, DM, hyperlipidemia, AF),

2. laboratory tests and imaging at the time of the stroke/TIA (glucose, INR, lipids, B12, homocysteine, TPA, pack years, blood pressure, CT and/or MRI, Holter, transcranial Doppler, carotid Doppler ultrasound, echocardiography),

3. medications for hypertension, DM, hyperlipidemia, antiplatelet and anticoagulant agents,

4. self-reported past medical history of MI and vascular surgery,

5. family history of stroke and MI, and,

6. follow-up events of stroke, TIA, MI, and death.

Information about diet and physical activity was not collected given that it was based on a non-validated questionnaire. Moreover, race was not collected as it was not provided in the clinical notes.

2.4 Measurements of Collected Variables

Age and year of event: Age and year were entered as continuous variables corresponding to the patients' age at the time of their first cerebrovascular event. The date of this event was also recorded.

Sex: Men and women were recorded using a code of 0 and 1, respectively.

Smoking and pack-years: Self-reported smoking status (never smoked, quit smoking>1year ago, active smoker) as well as total exposure to smoke, measured as pack-years, were assessed in all patients with the same set of questions by the stroke expert and the technologists who performed the carotid ultrasound.

Medical history of hypertension, DM, hyperlipidemia and AF: A history of each of these risk factors was collected as a discrete variable, based on the self-reported or referral report of presence of newly diagnosed or earlier known hypertension, DM, hyperlipidemia and AF. This information was confirmed based on the use of medications to treat the aforementioned medical conditions.

Glucose and International Normalized Ratio (INR): Laboratory measurements of glucose and INR were collected from reports of the emergency department.

Total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, B12, total homocysteine: Laboratory measurements were ordered at the first clinical assessment of patients at the Urgent TIA clinic and the results were collected and entered as continuous variables.

Carotid ultrasound, TPA and blood pressure: Before the first clinical assessment at the Urgent TIA Clinic, all patients underwent ultrasound assessment of carotid stenosis and measurement of TPA, as well as measurement of systolic and diastolic blood pressure with a regularly calibrated automated blood pressure manometer.

Brain imaging (CT, MRI): Investigation of brain imaging was either collected from the emergency department reports or was ordered at the first visit at the Urgent TIA Clinic and was entered as a discrete variable, based on the presence of acute and/or chronic infarction or normal imaging.

Cardiac evaluation: Echocardiogram and holter monitoring was ordered at the Urgent TIA Clinic in patients whose medical history and physical examination suggested a cardiac source of embolism. Electrocardiograms were available in all patients presented to an emergency department.

Treatment of hypertension, DM, hyperlipidemia: Type of medications used before the first cerebrovascular event was collected on history or after a contact with their pharmacy. The use of medication for each medical condition was entered as a discrete variable as in "Yes/No".

Antiplatelet and anticoagulant agents: The use of antiplatelet or anticoagulant agents within a month before a stroke or TIA was collected from the medical history or their pharmacy, and was entered as a discrete variable.

Past medical history of MI and vascular surgery: Self-reported or referral report of past medical history of MI and past vascular surgery was collected at the first visit at the Urgent TIA Clinic and was entered as a discrete variable.

Family history of stroke and MI: Self-reported or referral report of family history of stroke and MI was collected at the first visit at the Urgent TIA Clinic and was entered as a discrete variable.

Follow-up events: Information about stroke, TIA, MI and death at the time following the first stroke/TIA was collected from paper chart review and was entered as a discrete variable.

Population coverage of Urgent TIA Clinic: Information about the number of residents living in the coverage areas of the Urgent TIA Clinic was collected from the Census reports of the years 2001, 2006 and 2011 from Statistics Canada and was entered as a continuous variable. Population estimates are presented in Appendix C.

2.5 Classification System

As mentioned in the introduction, SPARKLE was used for the classification of stroke/TIA in our study. This classification was adapted from the existing CCS classification system.[128] In SPARKLE, we included TPA measurements of large artery atherosclerosis, currently used in clinical practice,[129] and we revised the CCS criterion of parallel testing for imaging investigation for all patients with stroke/TIA. Based on CCS, imaging of the brain, cardiac imaging and evaluation of intracranial and extracranial arteries are all necessary to classify an "evident" cause of stroke/TIA. Alternatively, in the absence of one of the aforementioned investigations, CCS classified an otherwise "evident" cause of stroke as "possible" cause within the same stroke/TIA subtype. Likewise, when at least one of the investigations was missing, a "possible" cause is classified as "incomplete evaluation" in CCS, which falls under the "undetermined cause of stroke" category. However, in our practice, parallel testing using brain imaging (CT and/or MRI), ECG, carotid ultrasound and basic blood test was used to differentiate between stroke mimics and cerebrovascular events at baseline, and additional laboratory investigation as serial testing was guided by the

medical history and the physical examination. The inclusion of baseline carotid ultrasound in all patients helped reduce selection bias of patients who will be chosen to have additional investigation (based on a more thorough clinical assessment by the stroke expert) by providing evidence to differentiate between different stroke/TIA subtypes (for example, differentiate between large artery atherosclerosis and carotid dissection). Consequently, there were patients who had no indication for cardiac imaging, angiography or complete intracranial and extracranial vascular evaluation. These criteria provide a classification system that is highly sensitive in diagnosing a cerebrovascular event (based on baseline parallel testing) and highly specific and cost effective in differentiating between particular stroke/TIA subtypes (based on the additional serial testing). "Incomplete investigation" was assigned to patients who had indication for additional investigation of their cause of stroke and they did not attend their appointment or an appointment for further investigation was not scheduled.

In the presence of more than two "evident" causes of stroke/TIA, we classified the most "probable" stroke/TIA subtype, in contrast to CCS, where patients with more than two evident causes are classified as "undetermined etiology". Also, cases that had more than one "possible" cause of stroke/TIA were classified according to the "possible" stroke/TIA subtype that is more likely to be related to the presenting stroke/TIA, whereas in CCS, cases with more than one "possible" etiology are simply classified as being of "undetermined etiology". The assignment of cases in the most "probable" or most "possible" cause of stroke/TIA was based on information from the patients' history showing a close-in-time relationship between the onset of a stroke-related medical condition to the onset of stroke/TIA symptoms and a mechanism of disease explaining the presenting stroke/TIA (for example, new onset of AF and multiple territory stroke/TIA leads to the diagnosis of cardioembolic stroke/TIA, motor-vehicle accident and carotid or vertebral dissection leads to the diagnosis of stroke/TIA of other rare or unusual cause). All clinical cases that had an unclear final diagnosis of their stroke/TIA, with information from the medical history and findings from the physical examination that did not match together, were reviewed during regular meetings with the stroke expert (Dr. Spence). In these meetings, all elements from medical history, physical examination, laboratory investigation and test results were reviewed in order to assign the most relevant stroke/TIA subtype.

The final stroke/TIA subtype was assigned to our cases when the clinical assessment and basic laboratory tests were able to reach to a definitive diagnosis, by ruling out medical conditions that mimic vascular etiologies. We investigated this by testing the consistency of the diagnosis between baseline and one year follow-up. We believe that our classification system can become useful to enhance current clinical practice and be applied elsewhere, since it reflects "real world" clinical management.

SPARKLE consists of five categories of stroke/TIA subtypes:

1. large artery atherosclerosis,
2. cardioembolic,
3. small vessel disease,
4. other rare or unusual etiology, and
5. undetermined etiology.

We categorized cases into each stroke/TIA subtype based on information from the medical history and physical examination, as well as results of brain and vascular imaging, and subsequently we confirmed or altered our clinical suspicion based on the results of additional laboratory diagnostic tests (for example, confirm the presence of a cardioembolic stroke/TIA when results from the echocardiogram show a cardiac source of embolism). Below, we present the criteria for each ischemic stroke subtype.

Large Artery Atherosclerosis Stroke/TIA

Clinical aspects: These patients present with fluctuating symptoms that vary between normal and gradual worsening with varying periods of improvement. Symptoms involve disability related to cerebral or cortical dysfunction (asymmetric motor or sensory impairment, aphasia, etc.) or to brain stem or cerebellar dysfunction. At the physical examination, a carotid bruit may be present.[140] Clinical symptoms of

Subclavian Steal Syndrome can be present.[141] Cardiac sources of embolism must be excluded.

Laboratory properties: Brain imaging can indicate cortical, cerebral or cerebellar infarction ≥2cm in diameter on CT or MRI; in TIA normal brain imaging is expected. Additional investigations include carotid Doppler ultrasound and/or angiography to assess presence of atherosclerotic lesions and significant stenoses. Ultrasound evidence of clinically relevant Subclavian Steal Syndrome denotes "evident" diagnosis of large artery atherosclerosis.[141]

Evident etiology: The final etiology of these cases is significant, ipsilateral internal carotid or intracranial artery stenosis of ≥50%, or TPA≥1.19cm^2 with no evidence of acute infarction in vascular territories other than the symptomatic vascular territory.[128, 129] Amaurosis Fugax can be present. Clinically relevant imaging confirmation of Subclavian Steal Syndrome and ipsilateral Microemboli detection on TCD monitoring denote presence of symptomatic large artery atherosclerosis disease.[141-143]

Probable etiology: Medical history suggesting Amaurosis Fugax or previous undiagnosed TIA, all occurring in the same vascular territory, with evidence of hemodynamically significant and ipsilateral internal carotid or intracranial artery stenosis of ≥50%, or TPA≥1.19cm^2 within a month before symptom onset. Additional presence of "evident" causes of different stroke/TIA subtypes are present and are well controlled with a mechanism of disease unrelated to the presenting stroke/TIA.

Possible etiology: Presence of low-risk atherosclerotic plaque causing mild ipsilateral internal carotid or intracranial artery stenosis <50%, or 0.12cm^2≤TPA<1.19cm^2 without evidence of any other "possible" cause of stroke/TIA or in the presence of another "possible" cause of stroke/TIA that is well-controlled within a month before symptom onset and with a mechanism of disease unrelated with the presenting stroke/TIA.

Cardioembolic Stroke/TIA

Clinical aspects: These patients present with acutely developed cerebral or cortical symptoms of increased severity at the onset of the event with rapid clinical improvement.[144] Symptoms and signs can indicate involvement of multiple vascular territories (involvement of both anterior carotid circulations, or both anterior carotid and posterior vertebrobasilar circulations), based on information from the medical history and/or the physical examination, respectively.[128, 145]

Laboratory properties: Patients with stroke have brain imaging (CT and/or MRI) indicating cerebral or cortical infarction; brain imaging is normal in patients with TIA. Echocardiogram (TTE and/or TEE) investigates high and/or low risk cardiac source of embolism (Table 1).[128, 146] Holter monitoring of the heart rhythm is indicated where cardiac arrhythmia is suspected. Transcranial Doppler (TCD) bubble test confirms right-to-left cardiac shunt in the case of immediate presence of bubbles in the TCD of middle-cerebral artery (MCA) or pulmonary arterial-venous malformation (AVM) in the presence of delayed bubbles.[147-149] Carotid ultrasound excludes presence of large artery atherosclerosis.

Evident etiology: Patients present with multiple territory acute infarcts in CT or MRI, or normal brain imaging with symptoms related to multiple territory transient symptomatology, or evidence of systemic embolism in the presence of a high risk cardiac source of embolism (Table 1).[128, 146] These patients can also have clinical clues to paradoxical embolism, with evidence suggesting pulmonary embolism or deep vein thrombosis at the time of their stroke/TIA, and confirmation of cardiac sources of embolism on echocardiography, or TCD bubble study.[150]

Probable etiology: Patients present with acute multiple infarcts and involvement of different vascular territories or systemic embolism at the time of their stroke/TIA or within a month before symptom onset. Additional "evident" causes of different stroke/TIA subtypes are present, but are unrelated in time to the onset of the presenting stroke/TIA.

Possible etiology: Multiple territory symptomatology with evidence of clinical clues to paradoxical embolism and negative echocardiogram or transcranial bubble study Doppler. Presence of low risk cardiac sources of embolism (Table 1).[128, 146]

Investigation can reveal presence of additional "possible" causes of different stroke/TIA subtypes, unrelated in time and in terms of mechanism of disease with the presenting stroke/TIA.

Small Vessel Disease Stroke/TIA

Clinical aspects: These patients have acute onset of symptoms compatible with one of the five described "lacunar syndromes": pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, sensorimotor stroke, dysarthria-clumsy hand syndrome (Table 2).[22] Medical history and physical examination should exclude cardiac sources of embolism and ipsilateral high-risk large artery atherosclerosis.[151]

Laboratory properties: Brain imaging: deep brain infarction ≤2cm in diameter on CT or MRI without focal stenosis or other vascular pathology (e.g., dissection, vasculitis, etc.) in the main artery providing blood to the penetrating arteries, and without cortical or cerebral dysfunction.[128] Normal imaging can be present in patients with TIA. Carotid ultrasound excludes large artery atherosclerosis disease or high grade stenosis. Echocardiography excludes cardiac sources of embolism.

Evident etiology: Presence of one of the five described "lacunar syndromes" with imaging and clinical evidence of deep brain infarction. Normal or low risk carotid Doppler ultrasound ($0.12cm^2 \leq TPA < 1.19cm^2$), or low risk cardiac source of embolism can be present, but are unrelated in time with stroke/TIA symptoms onset.

Probable etiology: Presence of a "lacunar syndrome" with presence of at least one more "evident" cause of a different stroke/TIA subtype.

Possible etiology: Clinical evidence of a "lacunar syndrome" with normal brain imaging. Additional investigation can bring to light "possible" causes of different stroke/TIA subtypes, unrelated with presenting stroke/TIA in time and in terms of mechanism of disease.

Other Rare or Unusual Cause of Stroke/TIA

Clinical aspects: These patients may have evidence of event onset after traumatic overextension of the neck or forced movement (e.g. chiropractic neck manipulation), or after medical intervention involving the heart or other parts of the vascular circulation. Alternatively, there may be clinical evidence of rare genetic or hematological disorders, causing increased blood viscosity or any other rare or unusual medical condition (Table 3).[128]

Laboratory properties: Based on the medical history and the physical examination, the following diagnostic tests are used to confirm the diagnosis, where applicable: Carotid Doppler ultrasound and/or angiography to differentiate arterial dissection from large artery atherosclerosis disease, blood tests for genetic or hematological disorders, urine drug testing, etc. Investigations for cardiac sources of embolism are ordered (e.g. echocardiography) to rule out cardiac sources of embolism.

Evident etiology: Laboratory confirmation of a rare or unusual cause of stroke/TIA or mechanism of disease occurring immediately preceding symptom onset (e.g. dissection, etc.).

Probable etiology: Medical history suggesting mechanism of unusual or rare disease closely related in time with present stroke/TIA, in the presence of other "evident" etiologies of stroke/TIA (for example, evidence of vertebral dissection after traumatic neck injury in the presence of TPA$\geq$1.19cm^2 or atrial fibrillation, etc.).

Possible etiology: Medical history supporting a rare or unusual cause of stroke/TIA, with negative investigations (e.g., forced neck movement suggesting acute arterial dissection with negative ultrasound or angiography a few weeks after the event).

Undetermined Cause of Stroke/TIA

Clinical aspects: Patients with evidence of stroke/TIA on the physical examination and brain imaging or evidence of TIA on the medical history with normal laboratory investigation. These patients present with symptoms and clinical signs not explained by one of the aforementioned categories.

Laboratory properties: Brain imaging (CT and/or MRI) may indicate presence of stroke or is normal in patients with TIA. Further investigations including carotid and TCD ultrasound, echocardiogram and/or Holter, blood tests for rare or unusual genetic or hematologic disorders are within normal limits.

Unknown etiology: Patients present a medical history that cannot suggest any possible mechanism of disease. In the case of clinical characteristics suggestive a specific mechanism of disease, initial and additional investigations return normal results.

Incomplete Evaluation: Positive medical history for one of the four aforementioned categories, with lack of appropriate investigations (e.g., medical history and physical examination favouring a given stroke/TIA subtype with absence of supporting investigations).

2.6 Pilot Study and Results

We created a final database of approximately 4,350 cases using records from the Urgent TIA Clinic with all patients diagnosed with stroke/TIA between the years 2002-2012. To ensure feasibility of data collection and analysis within a year of the study period, we reviewed the first 476 clinical cases of our database using SPARKLE and CCS, and classified cases eligible to participate in the study including all aforementioned variables.

The main objectives of the pilot study were:

1. to determine the time needed for chart review and collection of all variables,

2. to determine the applicability of the two classification systems (CCS, SPARKLE) in our clinical practice, by comparing the assignment of cases into stroke/TIA subtypes with previous studies in different countries, and

3. to determine the agreement between CCS and SPARKLE.

Eligible cases were included based on the inclusion and exclusion criteria of the retrospective case series study. Among the first 476 reviewed cases, 76 were excluded because they did not have a diagnosis of stroke/TIA or did not attend their appointment or had a first-ever stroke/TIA before the year 2002. The remaining 400 classified cases were analyzed and a random sample of approximately 50 charts among the classified 400 cases was selected for review with the stroke expert (Dr. Spence) to confirm the assigned stroke/TIA subtype and to ensure quality of data entry. Cases with unclear stroke/TIA diagnosis were also assessed with the stroke expert to decide the most relevant stroke/TIA subtype.

Case review for the pilot study began in May, 2012. We received the approval of the study from the Western University Research Ethics Board in January, 2012. A graduate physician (Dr. Bogiatzi) was trained between January and April 2012 in chart review and application of both classification systems of approximately 100 cases diagnosed with stroke/TIA between the years 2000 and 2001. Information about stroke/TIA subtype from the cases presented in 2000 and 2001 that were used during the training period (January-April 2012) were not entered in the final analysis, as patients referred to the Urgent TIA clinic between 2000 and 2001 were excluded from our study, as mentioned previously.

Time interval between review of the first and the last clinical chart until completion of the 476 charts was recorded. Simple descriptive statistics and the exact McNemar's test were used to compare stroke/TIA subtypes in dependent cases classified twice based on CCS and SPARKLE. Cohen's Kappa statistics was used to assess the agreement between CCS and SPARKLE.

The duration of the pilot study was three weeks in total, denoting that double time is probably needed to complete data entry using both classification systems. The categorization of stroke/TIA patients using SPARKLE and CCS showed significant differences between the two classification systems, in all stroke/TIA subtypes (Table 4). We recorded fair agreement between SPARKLE and CCS (Cohen's Kappa 0.39).

The results of our pilot study show that CCS has poor applicability in our clinical practice. Patients who had cardioembolic stroke/TIA rarely had intracranial vascular assessment and patients who had large artery atherosclerosis frequently didn't undergo

cardiac assessment, unless there was a specific indication (for example, multiple territory stroke) for the aforementioned tests to be ordered. Using CCS and in the absence of complete investigation, 76% of the cases were registered under the "Undetermined" stroke/TIA subtype, and of these, 68% cases had "Incomplete Evaluation" that could not be realistic in the case of our clinical practice. Similar high scores in assignment of cases under the "undetermined etiology" of stroke/TIA have been reported previously by Sagui et al[152] in Dakar, Africa, where there was a great shortage in medical imaging and laboratory equipment, which is totally different from the current clinical practice in Canada. However, using SPARKLE, only 23.8% of the cases were classified as "Undetermined", which is in line with results from previous studies in other countries that used classification systems developed before SPARKLE.[29, 31, 32, 35, 48, 56, 58, 153-155] For the same reason, the majority of cases in CCS were regarded as "possible" causes of stroke/TIA, whereas there was a broad distribution across all the three subgroups within each subtype by using SPARKLE (Appendix B). Consequently, we performed data entry using SPARKLE as the most germane classification system with accurate application to our practice.

2.7 Methodology of Validation and Reliability Study

To validate SPARKLE with antecedent classification systems (CCS and TOAST), we performed a best-case scenario comparison of cases. We decided to include only cases that could be fully classified with CCS, in order to accurately compare the results with SPARKLE. It is worth noting that one-fourth of our classified clinical cases (880 cases from the cohort of 3,445 patients) fulfilled complete diagnostic investigation of the vascular system based on CCS, and our random sample was retrieved within the cases that satisfied CCS criteria.

A random sample of 25 cases per year was selected from this subgroup of our cases that had intracranial and extracranial vascular evaluation and cardiac testing. The final retrieved sample of 275 cases was entered in a new dataset, in which all investigations and measurements of risk factors were retained. The initial categorization into stroke/TIA subtypes was removed to ensure unbiased testing of validity and reliability.

Cases were independently assessed by a graduate physician (Dr. Bogiatzi) and a medical graduate research fellow physician (Dr. Wannarong), who both classified the 275 cases according to SPARKLE to measure intra-rater and inter-rater reliability, respectively. The selected cases were classified again by the graduate physician (Dr. Bogiatzi) according to CCS and TOAST classification system, to measure the agreement with SPARKLE and follow-up events were classified based on SPARKLE and CCS. Finally, SPARKLE was determined again at one year follow-up after the first stroke/TIA, to measure the consistency of the initial classification within a year after the first stroke/TIA.

2.8 Sample Size Calculation for Validation Study

Based on the results of our pilot study, we calculated the sample size needed to validate SPARKLE against CCS and TOAST and to achieve 80% power at the level of significance α=0.05. Given that cardioembolic stroke/TIA was the most common subtype, we calculated the sample size with a proportion of cardioembolic stroke/TIA of 11.3% (according to CCS) and an expected proportion of 45.8% (according to SPARKLE) based on the results of our pilot study, and we found that we would need 52 individuals to have 80% power to detect significant differences between CCS and SPARKLE at α=0.05. We repeated again the calculations for CCS and TOAST using information from patients with cardioembolic stroke in TOAST Trial (21%) and 45.9% in CCS study (45.9%).[127, 156] Based on these proportions, we would need 112 individuals to have 80% power to identify differences at the level of significance α=0.05. Also, given the availability of all the data, we retrieved a random sample of 25 cases per study year. As a result, with the final 275 individuals, we will have more than 80% power to detect differences between the three classification systems (SPARKLE, CCS, TOAST). To confirm the adequacy of our sample size, we repeated the calculation using as a reference the population-based study by Palm et al,[157] which showed that the predominance of cardioembolic strokes was 35%, as well as the study by Ay et al[156] that proposed CCS as a classification system and showed that 45.9% of strokes were cardioembolic. Therefore, to be within 10% of the true proportion of cardioembolic strokes and to maximize the proportion at p=0.50, we would need 96 individuals to produce a 95% confidence interval estimate for the

proportion of patients with cardioembolic stroke with a margin of error of 10%, and this would be an adequate sample size for all other stroke/TIA subtypes.[158]

2.9 Statistical Analysis

Quality of entered data was assessed using scatter plots for the continuous variables. All cases of unexplained outliers were re-evaluated comparing the information with paper chart documents, and erroneous data entry was corrected. Descriptive statistics were used to explore the distribution of risk factors in each stroke/TIA subtype in both sexes and in each year of the study. Continuous data were analyzed with analysis of variance (ANOVA) and discrete data were analyzed with Chi-Square statistics.

Secular trends in stroke/TIA subtypes using SPARKLE for all cases in the cohort were analyzed using a Poisson regression model, which is a form of "count regression analysis" appropriate for positive counts of the number of patients presenting with stroke/TIA during every clinic day. We plotted for each stroke/TIA subtype a lattice plot[159] counting all patients presenting with each stroke/TIA subtype per clinic day (y_t=counts of patients presenting with each stroke/TIA subtype). We calculated the number of days from January 2002 until December 2012 and called this variable "clinic day number" (t="clinic day number" or "Julian day number"), which serves as the response variable in our Poisson regression model [$y_t \sim Po(\mu_t)$].[160] Secular trends were assessed using a fitted cubic spline function of the "clinic day number"[log (μ_t) – fitted cubic spline function of t], which is a smoothing function that divides the plotting of our data into separate periods with similar trends of increasing or decreasing counts of observations and provides the overall trend of all plotting data.[161] For each of the five different subtypes of stroke/TIA, we computed the total counts of females, of males and of both sexes and implemented a Poisson regression model with spline trend function that is testing the null hypothesis that there is no trend in the data. This model was tested for serial correlation in the deviance residuals. In the case of autocorrelation, the p-values of the Poisson regression model with the spline function were compared to the Mann-Kendall trend test with blocked boodstrap,[162, 163] which is a widely used test for monotonic simple linear trend model testing the null hypothesis that the data are independent and identically distributed. The Mann-Kendall trend test

with blocked bootstrap tests the null hypothesis of stationary time series versus the alternative hypothesis that there is a monotonic trend with random autocorrelated errors. Negative serial correlation implies that p-values in regression are conservative.[164] This means that the p-values in Mann-Kendall trend test are more significant as compared to Poisson regression analysis with spline trend function in the presence of negative autocorrelation (the opposite applies in the presence of positive autocorrelation). All p-values were two sided and were considered significant if $p<0.05$. Bonferroni correction was used to control for multiple testing.

A logistic regression model with stepwise procedure was used to assess the relation of risk factors with each stroke/TIA subtype.[158] Risk factors were initially assessed for collinearity. Based on literature review, age, sex and BMI were analyzed as confounders; therefore, we stratified our population in age groups (<40, 40-50, 50-60, 60-70, 70-80, >80), in obese and normal weight individuals (BMI≥25, BMI<25, respectively) and in men and women. Only main effects were investigated in this thesis. It is likely that there could be some interesting interactions but their study and elucidation is beyond the scope of this thesis.

To assess construct validity, results from the comparison of the three classification systems (SPARKLE, CCS, TOAST) were analyzed using McNemar's test for the comparison of discordant cases in the dependent cases classified multiple times to compare SPARKLE and CCS, as well as SPARKLE and TOAST.[165] Moreover, Cohen's kappa statistic was used to assess the agreement of SPARKLE with CCS and TOAST. Cohen's kappa was also used to measure the agreement between the two raters and derive the intra-rater and the inter-rater reliability of SPARKLE.[166]

According to the kappa statistics, the strength of agreement was interpreted based on Landis and Koch criteria[167] as:

- Poor agreement (κ-value < 0.00)
- Slight agreement (κ-value = 0.00 – 0.20)
- Fair agreement (κ-value = 0.21 – 0.40)
- Moderate agreement (κ-value = 0.41 – 0.60)

- Substantial agreement (κ-value = 0.61 – 0.80)
- Almost Perfect Agreement (κ-value > 0.80)

Simple descriptive statistics were analyzed with IBM SPSS Statistics version 20.[168] Trend analysis, McNemar's test and regression analysis was performed using R for Windows, Version 2.15.2.[169]

2.10 Additional Analysis

We measured agreement between the initial classification and the assignment of cases one year after the first stroke/TIA using the same SPARKLE criteria to assess consistency and predictive validity in light of additional results from more laboratory investigation at one year follow-up. Moreover, recurrent stroke/TIA (irrespective of the time of the events) was also classified based on SPARKLE and CCS and agreement between first and recurrent events was calculated. Differences between cases that had recurrent events and those who did not, was assessed using Chi-square.

2.11 Ethics Approval

This study commenced soon after the approval of our application from the Office of Research Ethics of Western University. All data were already in existence. There was no contact with patients, nor any additional testing. All variables had been collected as part of routine clinical care. There was no potential for physical, psychological, emotional, social or economic harm to patients in these analyses of existing data, and participants will remain anonymous in subsequent reports and publications.

Table 1. Cardiac Sources of Cerebrovascular Embolism[128, 146]

High Risk Cardiac Sources of Embolism	Left Atrial Thrombus
	Left Ventricular Thrombus
	Atrial Fibrillation (AF)
	Paroxysmal Atrial Fibrillation
	Sustained Atrial Flutter
	Recent Myocardial Infarction (within 1 month)
	Chronic Myocardial Infarction with ejection fraction <28%
	Symptomatic Congestive Heart Failure with ejection fraction <30%
	Ventricular Dyskinesia or Hypokinesia in Echocardiogram
	Rheumatoid Mitral or Aortic Valve Disease
	Bioprosthetic or Mechanical Heart Valve
	Nonbacterial Thrombotic or Infective Endocarditis
	Papillary Fibroelastoma
	Left Atrial Myxoma
	Left Ventricular Aneurysm or PFO with clinical clues to paradoxical embolism*
Low Risk Cardiac Sources of Embolism	Mitral Annular Calcification and/or Aortic Valve Calcification
	Atrial Septal Aneurysm without Shunt
	Left Ventricular Aneurysm without Thrombus or PE or DVT
	Isolated Left Atrial Smoke, without Mitral Stenosis or AF

	Mitral Valve Prolapse
	Complex Atheroma in the Ascending Aorta or Proximal Arch
	Clinical clues to paradoxical embolism with negative imaging for shunt*

PFO: Patent Foramen Ovale

DVT: Deep Venous Thrombosis

PE: Pulmonary Embolism

*Clinical clues to paradoxical embolism: young patient with no other defined cause of stroke, with a history of DVT or PE, Valsalva maneuver at the onset of the cerebrovascular event, recent prolonged travel or sitting or immobilization, waking up with stroke symptoms, sleep apnea, shortness of breath during the cerebrovascular event, loud pulmonary regurgitation murmur (P2), varicose veins, asymmetric swollen legs, DVT or PE in the past.[150]

Table 2. Clinical Signs and Symptoms of Small Vessel Disease Stroke/TIA[22]

Lacunar syndrome	**Clinical signs and symptoms**
Pure Motor	Unilateral paresis/paralysis of face, arm and leg
Pure Sensory	Unilateral numbness of face, arm and leg
Ataxic Hemiparesis	Unilateral motor paresis/paralysis and limb ataxia
Sensorimotor	Ipsilateral motor and sensory impairment of face, arm and leg
Dysarthria-clumsy hand syndrome	Unilateral motor impairment of face and hand with hand clumsiness and with dysarthria and dysphagia

Table 3. Other Defined Rare or Unusual Causes of Stroke/TIA[128]

Acute or Chronic Arterial Dissection
Acute Disseminated Intravascular Coagulation
Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
Cerebral Venous Thrombosis/Cerebral Sinus Thrombosis/Retinal Vein Occlusion
Arteritis (Giant Cell, Necrotizing or Granulomatous), Vasculitis[144]
Clinically Relevant Aneurysm
Drug-Induced Stroke
Fibromuscular Dysplasia
Meningitis

Migraine-Induced Stroke
Segmental Vasoconstriction or Vasospasm
Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-Like Episodes
Moyamoya Disease
Fabry Disease
Primary Antiphospholipid Antibody Syndrome or Sneddon Syndrome
Primary Infection of the Arterial Wall
Sickle Cell Disease, Polycythemia Vera, Essential Thrombocytosis, Acute or Chronic Leukemia
Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome
Connective Tissue Disorders (e.g., Scleroderma)
Beauty Parlor Stroke Syndrome, Chiropractic stroke or Hangman's Fracture
Hypoperfusion Syndromes (e.g., sepsis, medications, etc.)
Iatrogenic Causes (e.g., stroke after coronary artery bypass graft surgery, other vascular intervention, etc.)

Table 4. Pilot Study Results Comparing Stroke/TIA Subtypes Between SPARKLE and CCS.

	SPARKLE		CCS		p-value
	n	%	n	%	
Large Artery Atherosclerosis	75	19	34	9	<0.001
Cardioembolic	183	46	45	11	<0.001
Small Vessel Disease	37	9	13	3	<0.001
Other Causes	10	3	3	1	0.008
Undetermined Causes	95	24	305	76	<0.001
Total	400		400		

CHAPTER THREE: RESULTS

3.1 Baseline Population Characteristics and Ischemic Stroke Subtypes

Among the 4,350 cases in our database, approximately 500 cases were excluded based on our exclusion criteria. In addition, 400 paper charts equally distributed in all study years were probably shredded or misallocated and could not be found; consequently, these 400 cases were removed from our database.

A total of 3,445 consecutive patients with first-ever stroke/TIA between the years 2002-2012 were studied with mean age±SD of 65±15. There were 1,693 men (49.1%) and 1,753 women (50.9%) with mean age±SD of 65±14 and of 65±16, respectively (p=0.442). Baseline population characteristics are provided in Table 5.

At the time of referral, 77% of patients with a new or old diagnosis of hypertension were treated with blood pressure lowering medications, and similarly, 74% of patients with new onset and known DM were on oral or injectable medications for controlling hyperglycemia. Also, 50% of patients with newly diagnosed or known high levels of cholesterol and triglycerides were treated with lipid lowering medications. Finally, 50% of patients with known or newly diagnosed AF were treated with anticoagulant agents. In total, among the 307 patients with AF, 153 patients were treated with anticoagulant agents and 25 patients were on antiarrhythmic medications. Among those who had AF and for whom we were able to obtain INR measurements (186 patients), 121 patients were treated with anticoagulant agents and 76 of them (63%) were in the therapeutic range, with INR≥2.

Concerning the distribution of stroke/TIA subtypes, 1,132 (33%) patients had large artery atherosclerosis, 1,298 (38%) patients had cardioembolic, 354 (10%) patients had small vessel disease, 221 (6%) patients had other rare or unusual causes, and 440 (13%) patients had an unknown cause of stroke/TIA.

In patients with cardioembolic stroke/TIA, 454 patients had PFO and clinical clues of paradoxical embolism such as evidence of deep venous thrombosis or pulmonary embolism, 108 patients had echocardiographic evidence of cardiac wall abnormalities

related to MI, 253 patients had AF and 118 of them (47%) were treated with anticoagulant agents. For patients with cardioembolic stroke/TIA and AF for whom we had INR measurements (150 cases), only 51 of them achieved INR≥2 (Table 6). The remaining cases had low risk cardiac sources of embolism.

In patients with cardioembolic stroke/TIA, there was a steady presentation of patients with AF (23 patients in the year 2002 vs. 21 patients in the year 2012), but there was a significant increase in Holter monitoring, from 73 tests ordered in the year 2002, as compared to 147 Holter tests in the year 2012 ($p<0.05$). Also, more patients with cardioembolic stroke/TIA and AF were treated with anticoagulant agents in more recent years, but not all of these patients achieved adequate treatment with INR≥2 (Table 6). There was no significant difference in homocysteine levels in patients with cardioembolic stroke/TIA and AF ($p=0.2$) between the years 2002-2012. However, there was a significant increase in high or low risk cardiac sources of embolism on the echocardiogram from 43 cases in the year 2002 to 73 cases in the year 2012, and also a significant increase in echocardiograms from 73 in the year 2002 to 147 in the year 2012. Finally, there was an increase in patients presenting with PFO and clinical clues or evidence of paradoxical embolism, from 25 in the year 2002 to 58 in the year 2012.

In all patients with cardioembolic stroke/TIA, 47% of patients had an "evident" cause of stroke/TIA, 20% of patients had multiple and, therefore, a "probable" cause of stroke/TIA and 33% of cases had a "possible" cause of stroke/TIA. Among patients with large artery atherosclerosis, 72% of patients had an "evident", 12% of patients had a "probable", and 16% of patients had a "possible" cause of stroke/TIA. In patients with small vessel disease, 26% of patients had an "evident", 31% of patients had a "probable", and 42% of patients had a "possible" cause of stroke/TIA. In patients with other rare or unusual causes of stroke, 29% of patients had an "evident", 15% of patients had a "probable", and 56% of patients had a "possible" cause of stroke/TIA. Finally, among patients with undetermined causes of stroke/TIA, 81% of patients had an unknown cause of stroke/TIA and 18% of patients had "incomplete evaluations".

We further investigated the counts per year of patients presenting with large artery atherosclerosis (Figure 1) and cardioembolic stroke/TIA (Figure 2) in each subgroup ("evident", "probable", "possible"). We found a decrease in the counts of patients

having large artery atherosclerosis stroke/TIA (Figure 1) and an increase in the counts of patients presenting with a cardioembolic stroke/TIA (Figure 2).

Figure 1. Graphical Illustration of the Counts of "Evident", "Probable", "Possible" and "Total" Large Artery Atherosclerosis Stroke/TIA.

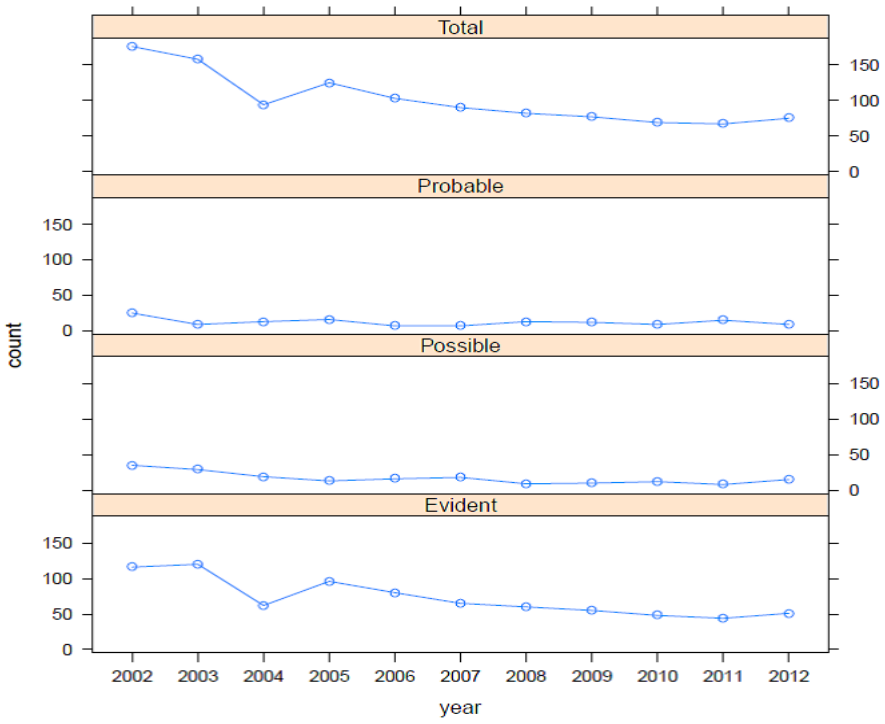


Figure 1 shows the same pattern of changing counts between "evident" and "total" causes of large artery atherosclerosis stroke or TIA.

Figure 2. Graphical Illustration of the Counts of "Evident", "Probable", "Possible" and "Total" Cardioembolic Stroke/TIA.

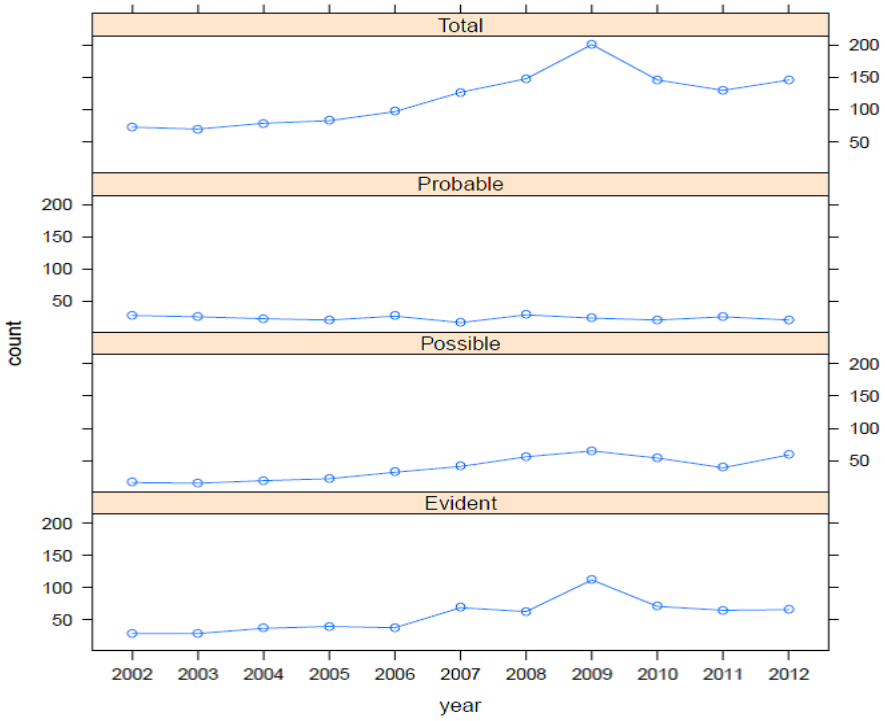


Figure 2 shows the same pattern of changing counts between "evident" and "total" causes of cardioembolic stroke or TIA.

In large artery atherosclerosis stroke/TIA, there was a significant decrease in "evident" causes from 116 cases in the year 2002 to 50 cases in the year 2012, in "probable" causes from 25 cases in the year 2002 to 9 cases in the year 2012 and in "possible" causes from 35 in the year 2002 to 15 in the year 2012. Also, there was a significant increase in "evident" cardioembolic stroke/TIA from 29 patients in the year 2002 (40%) to 66 patients in the year 2012 (45%). Similarly, there was a significant increase in "possible" cardioembolic stroke/TIA from 16 cases in the year 2002 (22%) to 59 cases in the year 2012 (40%).

In addition to the baseline characteristics of our population, we investigated the number of imaging tests patients received for the diagnosis of their stroke or TIA. The results showed that 3,387 patients had carotid duplex ultrasound (98% of the total population) and 3,361 patients had TPA measurements. This difference arose because

26 patients with symptomatic carotid stenosis and large artery atherosclerosis stroke or TIA had angiography and urgent endarterectomy before they received a measurement of their TPA. Also, 1,221 patients had transcranial Doppler ultrasound (35%). In terms of cardiology investigations, 1,502 patients received an echocardiogram (44%), and 807 patients had a 24 hour or 48 hour Holter monitoring of their cardiac rhythm (23%). Also, all patients had resting electrocardiograms at the time of their event in the emergency department. In terms of brain imaging, 2,346 patients had CT (68%), 1,320 patients had MRI (38%), 2,980 patients had either CT or MRI (87%), and 686 patients had both CT and MRI (20%). Patients with cardioembolic stroke/TIA had significantly more diagnostic imaging tests compared to all other ischemic stroke subtypes ($p<0.05$).

3.2 Secular Trends in Ischemic Stroke Subtypes

Based on our primary objective, we wanted to assess whether there is any change in the secular trends in stroke/TIA subtypes in the Thames Valley area between the years 2002 and 2012.

Poisson regression analysis with spline trend function was used to test the hypothesis:

H_o: There is no trend in the counts of stroke/TIA

H_A: A significant trend in the data exists

The results of our analysis showed no significant trend in the counts of all strokes/TIAs and in men and women separately of the total cohort of patients with stroke/TIA (Figure 3). The Delta (Δ) shown on the plots represent the percentage change from the trend line between the first clinic in 2002 and the last clinic in 2012.

Figure 3. Trend Analysis of All Patients with Stroke/TIA

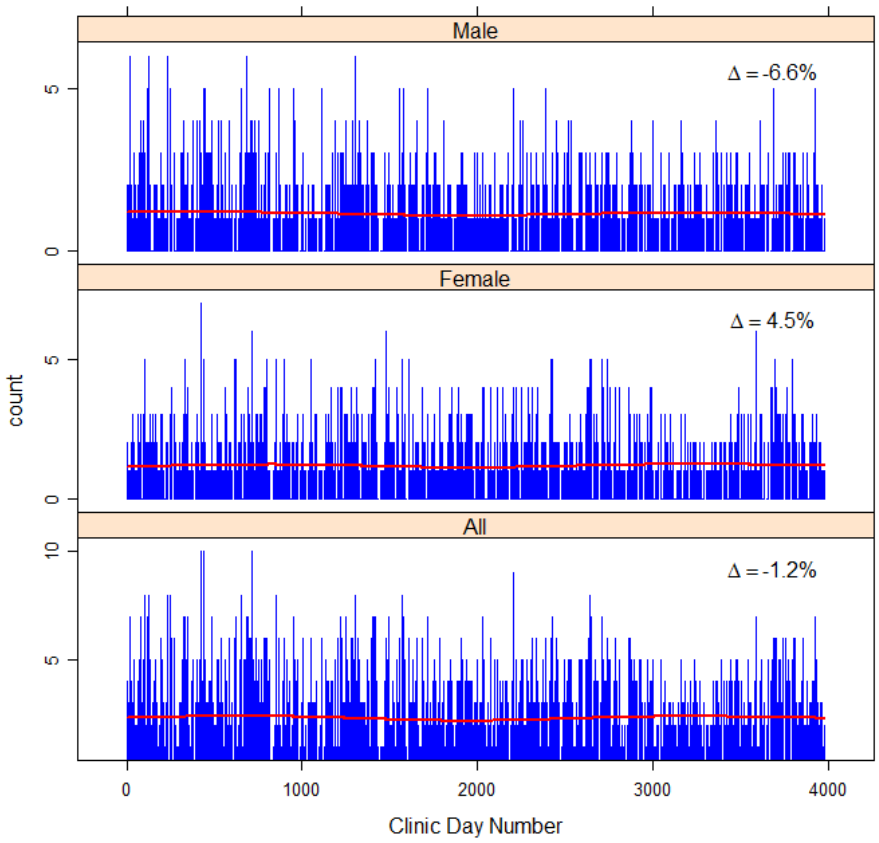


Figure 3 shows no change in the counts of all patients presenting between 2002-2012 ($p>0.05$). Similarly, no trend is shown in separate analyses of men and women ($p>0.05$).

However, separate analyses for each stroke/TIA subtype show a significant increase in the counts of cardioembolic strokes/TIAs and a significant decrease in the counts of all other stroke/TIA subtypes (Figure 4). The number and the percentage of each stroke/TIA subtype per year are presented in Table 7.

Figure 4. Poisson Regression with Fitted Spline Function of the Counts of Stroke/TIA Subtypes.

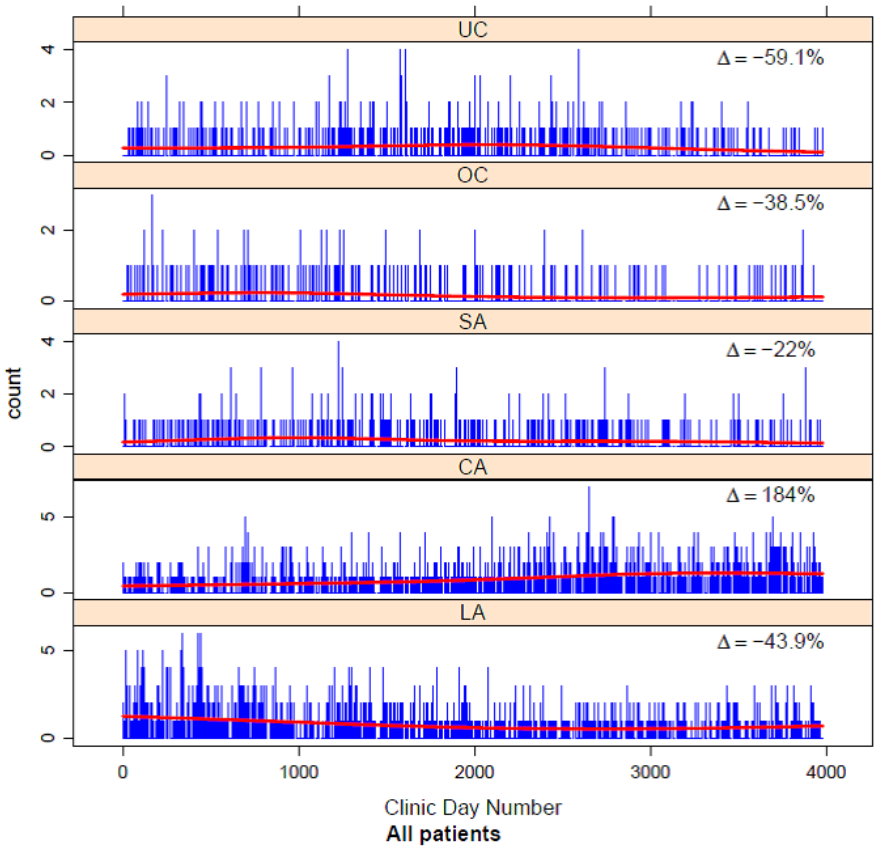


Figure 4 shows a significant increase in cardioembolic stroke/TIA (CA) and a significant decrease in large artery atherosclerosis (LA), small vessel disease (SA), other rare or unusual cause (OC) and undetermined etiology of stroke/TIA (UC) ($p<0.05$).

There is no evidence of serial correlation in the deviance residuals for the Poisson spline regressions for small vessel disease, other rare or unusual causes and undetermined causes of stroke/TIA, so the p-values are correct. In the case of large artery atherosclerosis and cardioembolic stroke/TIA the serial correlation is slightly negative (large artery atherosclerosis p-value=0.016, cardioembolic p-value=0.0001). This means the test is conservative, that is, the true p-values are even slightly smaller in magnitude. Indeed, the Mann-Kendall trend test with blocked bootstrap showed that the p-values for large artery atherosclerosis and cardioembolic stroke/TIA are more significant as compared to the Poisson regression with spline function. The hypothesis tested using the Mann-Kendall test was the following:

H_o: There is a stationary time series

H_A: A monotonic trend with random autocorrelation errors exists

To further determine the possible extent of the change in counts of presenting stroke/TIA subtypes, we investigated the change in the population covered by the Urgent TIA Clinic, based on information from Statistics Canada. There was a 7.5% increase of the coverage population (Appendix C). A repeat analysis, using as an outcome the rate in the change of number of patients presenting with stroke/TIA based on the change of the population (rate=count/population), showed the same results (Figure 5). There was again a significant increase in the rate of cardioembolic stroke/TIA and a significant decrease in all other stroke/TIA subtypes.

Figure 5. Poisson Regression with Fitted Spline Function Adjusting for the Change at the Population Level of Stroke/TIA Subtypes.

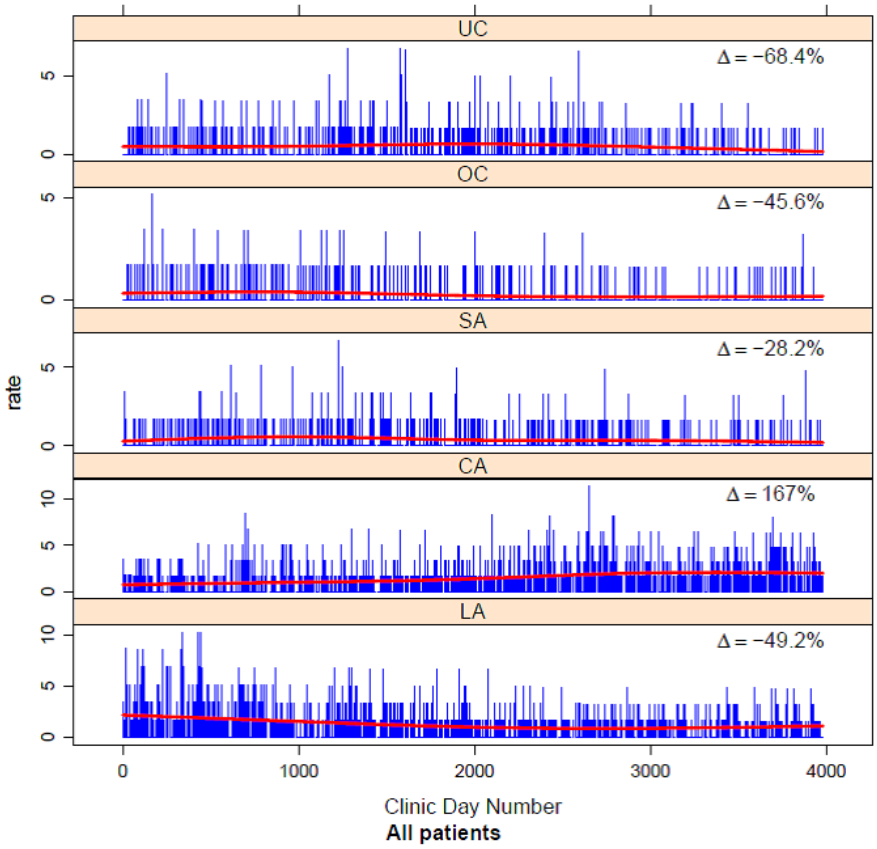


Figure 5 shows a significant increase in cardioembolic stroke/TIA (CA) and a significant decrease in large artery atherosclerosis (LA), small vessel disease (SA), other rare or unusual cause (OC) and undetermined etiology of stroke/TIA (UC) ($p<0.05$).

The change in the population was highly correlated with the variable representing the number of clinic days when patients presented with stroke/TIA. Since there was no change in the trends adjusting for the change at the population level, we removed the variable representing the change at the population level from our statistical model.

Age did not have a role in the trends found in stroke/TIA subtypes. We used the average age of patients presenting with stroke/TIA at the clinic on a given date as a response variable and we did not find sufficient evidence for any trend in stroke/TIA subtypes (Figure 6). As a result, the significant trends that we observed earlier are not a result of a change in the patients' age.

Figure 6. Secular Trends of the Average Age of Stroke/TIA Patients in each Stroke/TIA Subtype.

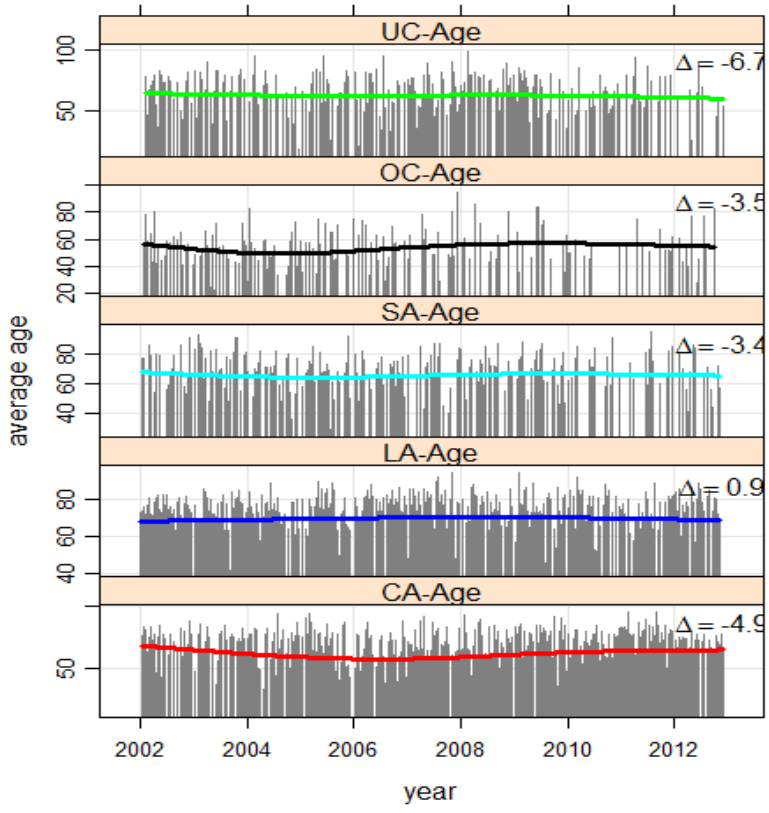


Figure 6 shows that there is no change in the average age of patients presenting with stroke/TIA on a given clinic day.

A further analysis that separated men from women shows the same trends in both sexes. There was a significant increase in cardioembolic stroke/TIA in women from 21% in the year 2002 to 62% in the year 2012 (Table 8). Figure 7 shows that Poisson regression with a fitted spline function demonstrates the increase in cardioembolic stroke/TIA and the decrease in all other stroke/TIA subtypes ($p<0.05$) in women. Trends remained significant even after adjusting for population change (Figure 8).

Figure 7. Poisson Regression with Fitted Spline Function in the Counts of Women with Stroke/TIA.

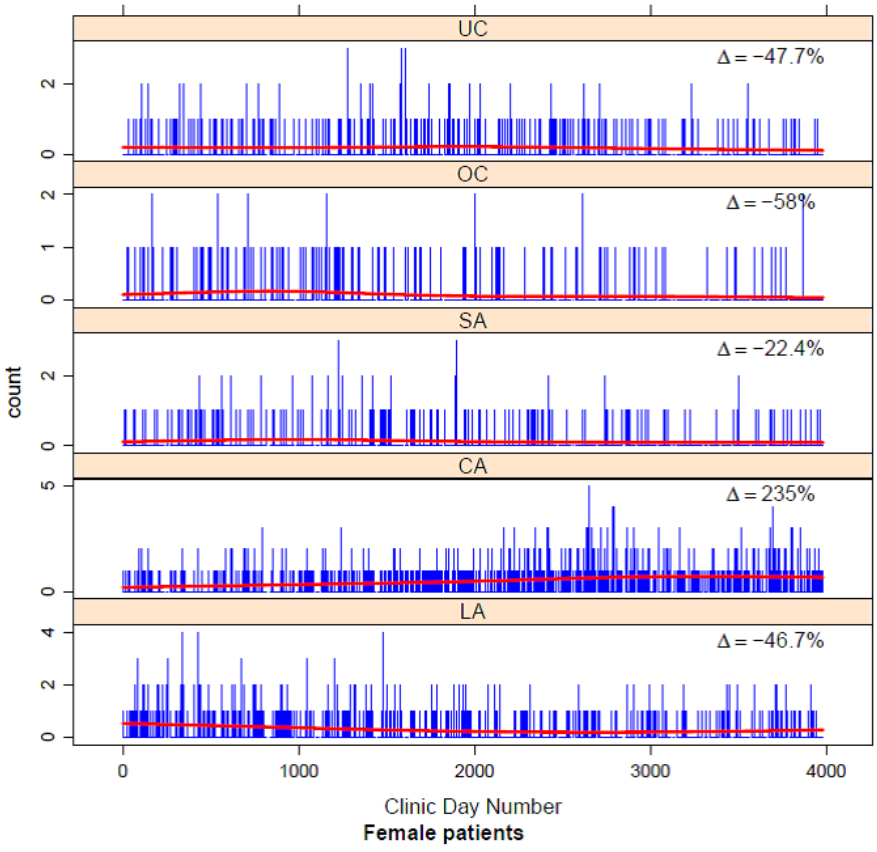


Figure 7 shows a significant increase in cardioembolic stroke/TIA (CA) and a significant decrease in large artery atherosclerosis (LA), small vessel disease (SA), other rare or unusual cause (OC) and undetermined etiology of stroke/TIA (UC) ($p<0.05$) in women.

Figure 8. Poisson Regression with Fitted Spline Function Adjusting for the Change at the Population Level in Women with Stroke/TIA

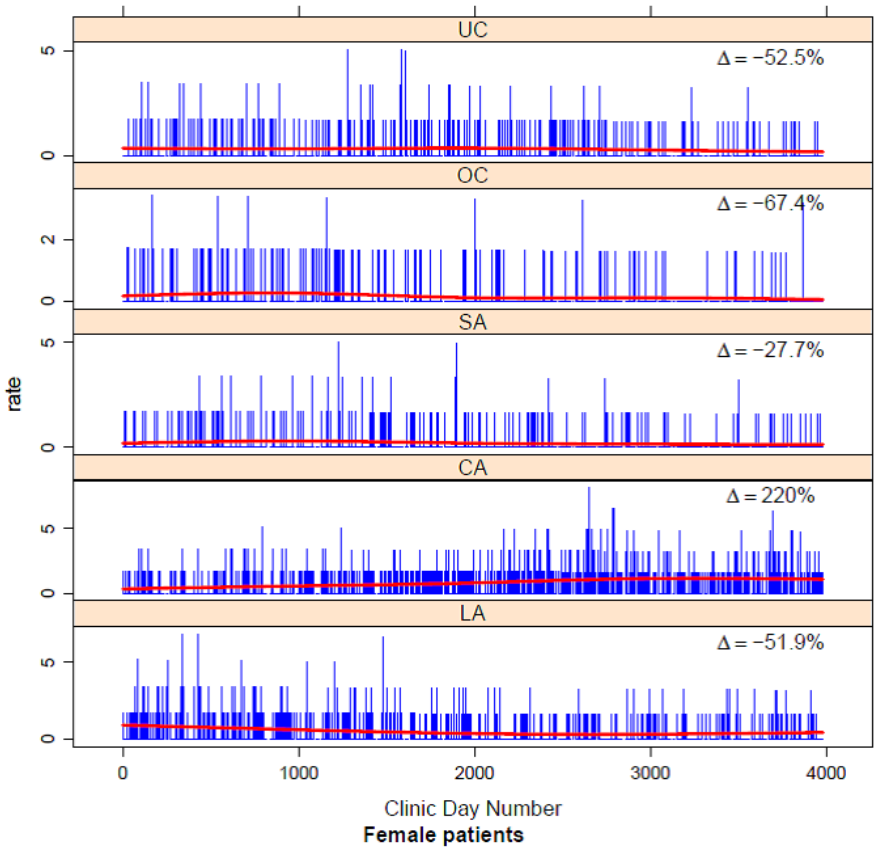


Figure 8 shows a significant increase in cardioembolic stroke/TIA (CA) and a significant decrease in large artery atherosclerosis (LA), small vessel disease (SA), other rare or unusual cause (OC) and undetermined etiology of stroke/TIA (UC) ($p<0.05$) in women.

Similarly, there was a significant increase in cardioembolic stroke/TIA in men ($p<0.05$) from 21% in the year 2002 to 50% in the year 2012 (Table 9). Poisson regression analysis (Figure 9) and adjustment for population change (Figure 10) show the same results.

Figure 9. Poisson Regression with Fitted Spline Function in Men with Stroke/TIA.

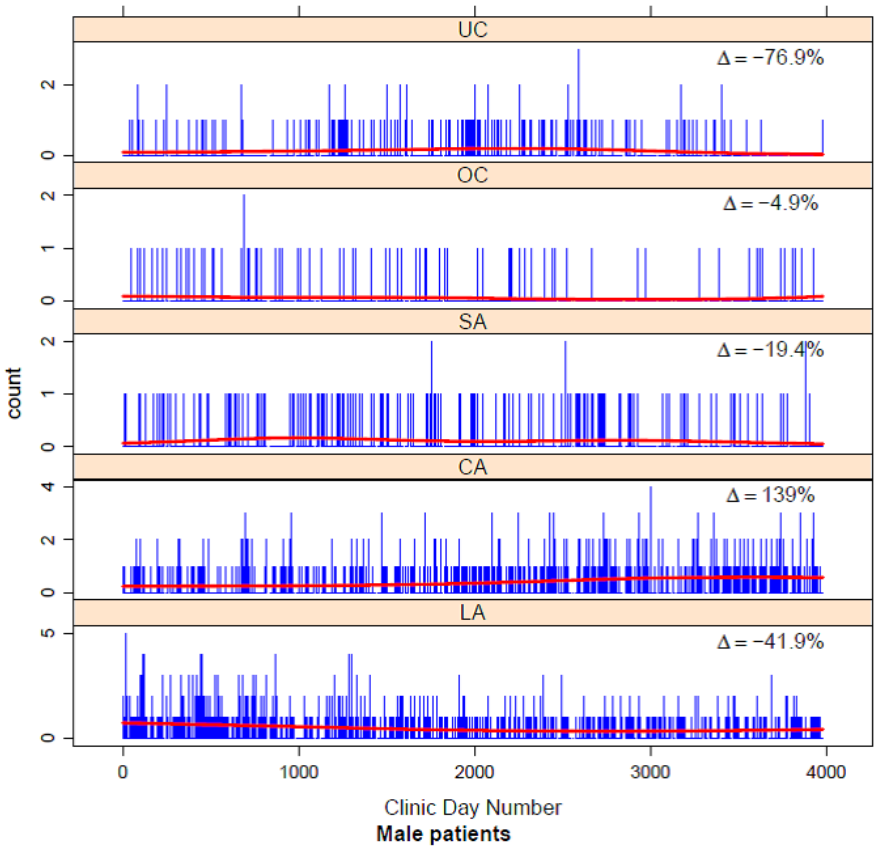


Figure 9 shows a significant increase in cardioembolic stroke/TIA (CA) and a significant decrease in large artery atherosclerosis (LA), small vessel disease (SA), other rare or unusual cause (OC) and undetermined etiology of stroke/TIA (UC) ($p<0.05$) in men.

Figure 10. Poisson Regression with Fitted Spline Function, Adjusting for the Change at the Population Level in Men with Stroke/TIA.

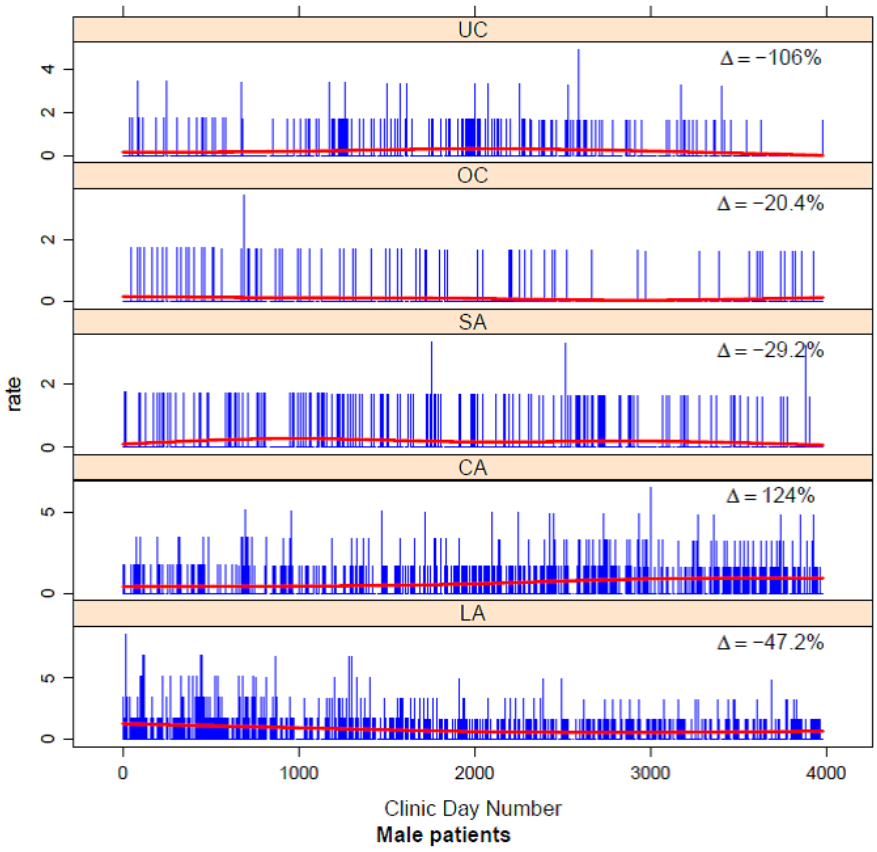


Figure 10 shows a significant increase in cardioembolic stroke/TIA (CA) and a significant decrease in large artery atherosclerosis (LA), small vessel disease (SA), other rare or unusual cause (OC) and undetermined etiology of stroke/TIA (UC) ($p<0.05$) in men.

3.3 Baseline Population Characteristics and Stroke/TIA Risk Factors

According to our secondary objective, we were interested in investigating the distribution of risk factors for stroke/TIA in all of our cases and separately in each stroke/TIA subtype.

As expected, systolic blood pressure significantly decreased during the study period ($p<0.05$), reflecting the effectiveness of hypertension treatment in clinical practice (Figure 11).

Figure 11. Mean Blood Pressure of Patients with Minor Stroke/TIA Between 2002-2012.

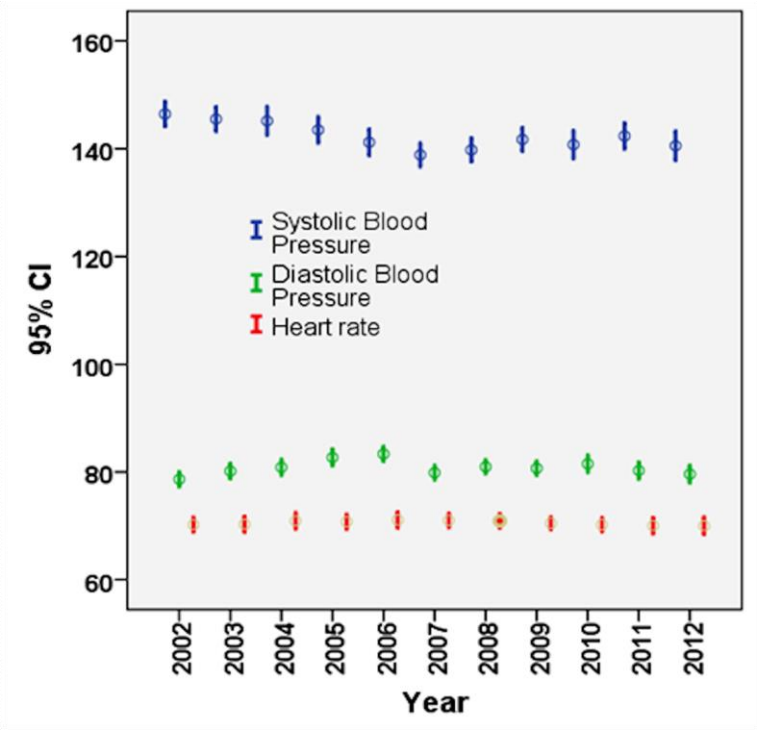


Figure 11 shows a significant decrease in systolic blood pressure and a significant increase in diastolic blood pressure ($p<0.05$) with no change in heart rate at the time patients presented with a first cerebrovascular event.

Moreover, our patients exhibited a significant decrease in total cholesterol and LDL cholesterol, as well as demonstrating the increasing use of statins in treatment of hypercholesterolemia (Figure 12). Also, there was a significant decrease in triglyceride levels ($p<0.05$).

Figure 12. Mean Total Cholesterol, Triglycerides, HDL Cholesterol and LDL Cholesterol of Patients with Minor Stroke/TIA Between 2002-2012.

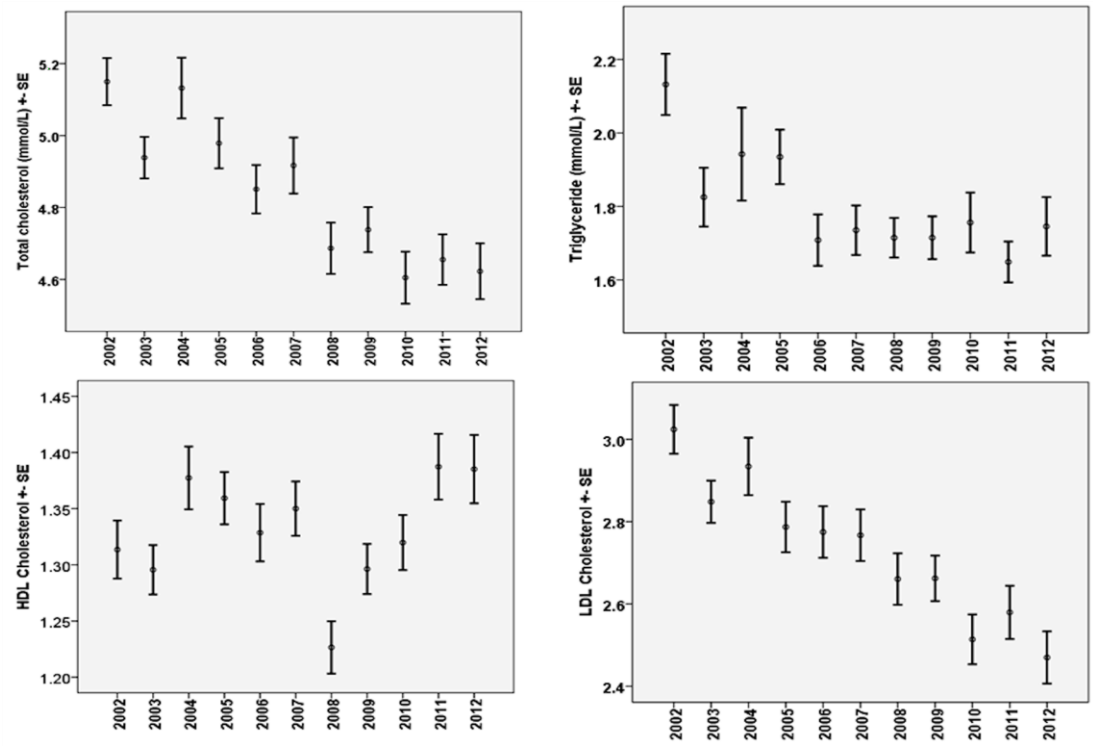


Figure 12 shows a significant decrease in total cholesterol, LDL cholesterol and triglyceride levels with a significant increase in HDL cholesterol ($p<0.05$).

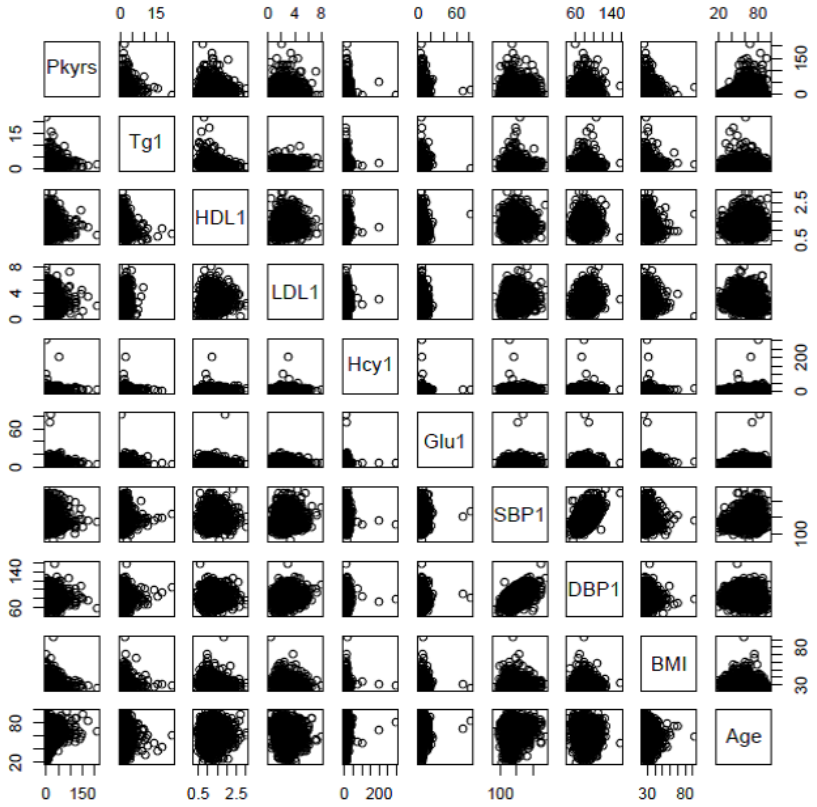
Our study demonstrates significant differences between men and women who had large artery atherosclerosis (41% vs. 25%, $p<0.001$), cardioembolic (34% vs. 41%, $p<0.001$), other rare or unusual causes (5% vs. 8%, $p<0.001$) and undetermined causes of stroke/TIA (11% vs. 15%, $p<0.001$), but there were no differences between men and women who suffered from small vessel disease stroke/TIA (10% vs. 10.4%, $p=0.353$) over the 10-year study period (Table 11).

To further explore the risk factor characteristics of our population, we compared stroke risk factors in men and women. The results showed that risk factors for stroke/TIA (smoking, BMI, systolic and diastolic blood pressure, total cholesterol, triglyceride, LDL, HDL, vitamin B12, homocysteine) are significantly different ($p<0.05$), except for age. However, a closer investigation of each stroke/TIA subtype comparing risk factors in men and women revealed different results (Table 10).

Women with large artery atherosclerosis were not different from men in BMI, homocysteine, triglyceride or glucose levels. Also, there were no significant differences between sexes with cardioembolic stroke/TIA in age, systolic blood pressure, vitamin B12, and triglycerides levels. In patients with small vessel disease, no differences in BMI, total homocysteine, triglyceride and LDL cholesterol levels were observed between men and women. Patients with other rare or unusual causes of stroke/TIA had no significant differences between two sexes in almost all risk factors (age, BMI, systolic blood pressure, total homocysteine, total cholesterol, triglyceride, LDL cholesterol, glucose). Finally, no significant differences were found in age, BMI, systolic blood pressure, total homocysteine, LDL cholesterol or glucose levels in men and women with undetermined cause of stroke/TIA ($p>0.05$).

We performed a stepwise logistic regression analysis to explore the role of risk factors in each stroke/TIA subtype. Collinearity between predictors was assessed by measuring the correlation of each variable with all other predictors (Figure 13). The results show high correlation between systolic and diastolic blood pressure; therefore, we included only systolic blood pressure in our regression model.

Figure 13. Correlation Between Predictors to Assess Collinearity.



Stepwise logistic regression shows that large artery atherosclerosis stroke/TIA is related to male sex, pack-years of smoking and systolic blood pressure in all age groups. The further analysis that separated men from women demonstrates that presence of large artery atherosclerosis stroke/TIA was related to high pack-years in all age groups in both sexes. Cardioembolic stroke/TIA was related with high levels of systolic blood pressure, pack-years and blood glucose in our cases. In particular, men with cardioembolic stroke/TIA had high systolic blood pressure and increased pack-years as compared to women who had high levels of systolic blood pressure, pack-years and glucose. Increased systolic blood pressure was the only risk factor related to small vessel disease in all patients of our cohort and separately in men and women. Moreover, low levels of total homocysteine are related to stroke/TIA of other rare or unusual etiology in all patients and in women, whereas men with this subtype of stroke/TIA had high levels of LDL cholesterol. In this subtype, any age over 60

years was related to having a stroke/TIA of other rare or unusual causes, something that was not shown in the separate analysis between men and women. Finally, low levels of total homocysteine were related to undetermined cause of stroke in all patients and in men, and high levels of HDL cholesterol were related with strokes or TIAs of undetermined etiology in both sexes.

Of note, the analysis of risk factors was conducted as an effort to describe the characteristics of our population, without providing evidence of a particular role of the aforementioned risk factors to the occurrence of each stroke/TIA subtype.

3.4 Validation of SPARKLE

Our tertiary objective was to assess the validity and the reliability of SPARKLE.

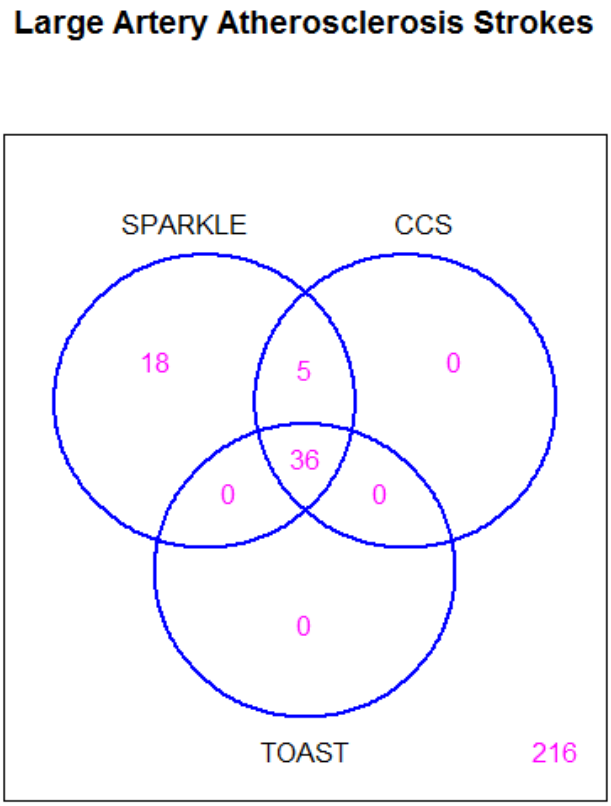
A random sample of 25 cases per year from the initial 880 cases (25.5% of the cohort), was chosen to compare SPARKLE with CCS based on the best scenario of cases that fulfilled the ideal criteria of classification under CCS. Cases were also classified based on the TOAST classification, which is the most widely used classification system in previous studies. Cases were selected based on the availability of brain imaging examination (all cases had at least one brain imaging; 75% had CT, 68% had MRI, 43% had both CT and MRI), and any combination of diagnostic tests that evaluated both intracranial and extracranial vascular systems (52% had CTA or MRA or both, 72% had transcranial Doppler ultrasound, 99.6% had carotid Doppler ultrasound). The final random sample consisted of 122 men (44%) and 153 women (56%). Mean age ± SD 57 ± 16 (mean age ± SD of men 59 ± 15, mean age ± SD of women 55 ± 17, p=0.064).

The comparison of the three classification systems indicated substantial agreement between SPARKLE and CCS (κ-value=0.75), but fair agreement between SPARKLE and TOAST (κ-value=0.38).

There were 18 more cases classified as large artery atherosclerosis under SPARKLE compared to different subtype assignment in CCS. There were 15 cases classified as

undetermined in CCS because of a lack of the TPA criterion, one case had been misclassified as cardioembolic due to the omission of ipsilateral symptomatic stenosis, and two patients, who had an echocardiogram showing cardiac wall akinesia and clinical presentation compatible to large artery atherosclerosis and high TPA, were classified as cardioembolic in CCS and as large artery atherosclerosis in SPARKLE based on the TPA criterion in addition to the medical history and the physical examination. Also, 23 more cases had large artery atherosclerosis in SPARKLE compared to TOAST; 21 cases had multiple cases or high TPA without stenosis were classified as undetermined in TOAST, and two cases were classified as cardioembolic, in the absence of TPA criterion. Results are illustrated in the Venn diagram in Figure 14.

Figure 14. Venn Diagram of the Number of Concordant Cases with Large Artery Atherosclerosis Stroke/TIA Between SPARKLE, CCS and TOAST.



Concerning cardioembolic stroke/TIA, there were differences between the three classification systems (Figure 15), even though cardioembolic stroke/TIA is the prominent ischemic stroke/TIA subtype in SPARKLE and CCS (58.2% vs. 49.8%, $p<0.05$). To illustrate, 20 cases with medical history and clinical examination strongly suggesting cardiac sources of embolism with negative imaging confirmation or identification of low-risk cardiac source of embolism (e.g. aortic valve calcification, etc.) were classified as "possible" cardioembolic stroke/TIA under SPARKLE and as "undetermined causes" of stroke/TIA under CCS and TOAST. Also, 87 cases with multiple etiologies of stroke and most "probable" cause cardioembolic stroke/TIA were classified as cardioembolic with SPARKLE and CCS and as undetermined cause of stroke with TOAST. In addition, three cases with multiple territory infarcts and missed cardiac sources of embolism were classified as other rare or unusual causes of stroke/TIA in CCS and TOAST, and as cardioembolic stroke/TIA in SPARKLE (Figure 15, Figure 16). One other case with diagnosis of multiple territory infarcts was classified as cardioembolic under SPARKLE and TOAST and misclassified under other rare or unusual causes of stroke/TIA, given a medical history suggesting dissection, but with normal MRA that was missed during the review of additional diagnostic investigations (Figure 15, Figure 16). Finally, one case with atrial septal defect and presence of the Factor V Leiden was classified as cardioembolic under SPARKLE, as other rare or unusual cause under CCS, and as undetermined cause of stroke/TIA subtype under TOAST (Figure 16).

Figure 15. Venn Diagram of the Number of Concordant Cases with Cardioembolic Stroke/TIA Between SPARKLE, CCS and TOAST.

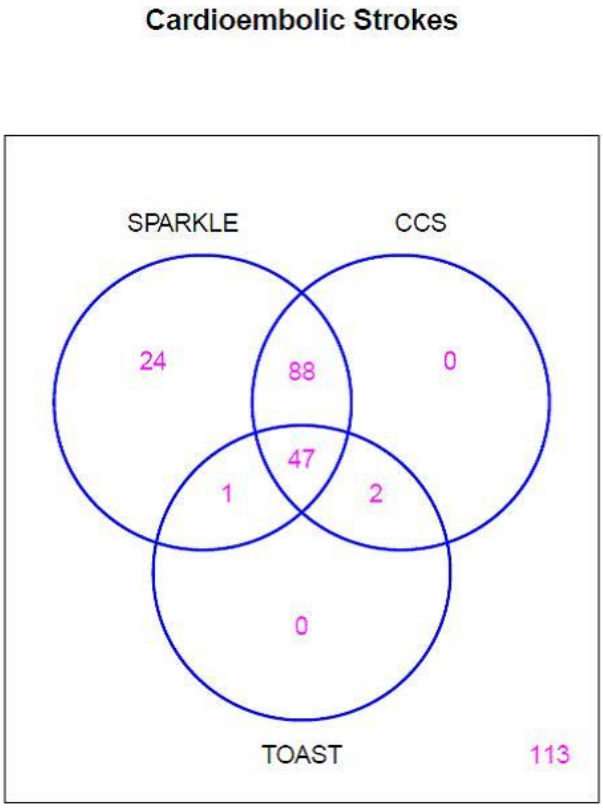
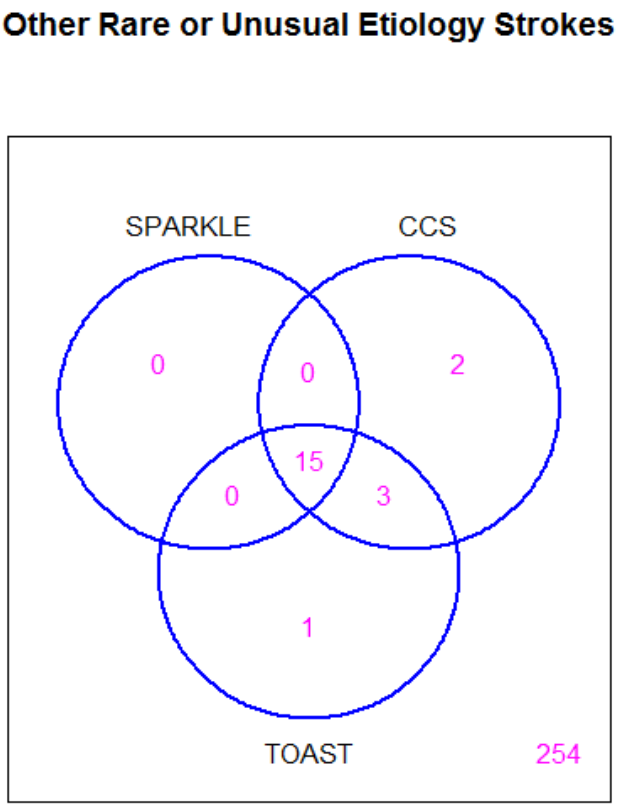


Figure 16. Venn Diagram of the Number of Concordant Cases with Other Rare or Unusual Causes of Stroke/TIA Between SPARKLE, CCS and TOAST.



The three classification systems exhibited non-significant differences concerning small vessel disease stroke/TIA (Figure 17). One case with high TPA and MRI showing an acute infarct of unspecified small size was classified as large artery atherosclerosis in SPARKLE and as small vessel disease in CCS and TOAST. Moreover, three cases with medical history and clinical presentation and imaging compatible with small vessel disease stroke/TIA were classified as such in SPARKLE and CCS, but fell under the undetermined cause of stroke/TIA category in TOAST with the presence of additional causes of stroke/TIA. There was a significant difference in the undetermined cause of stroke/TIA subtype between the three classification systems (Figure 18). There were 15 patients classified as large artery atherosclerosis and 20 cases classified as cardioembolic stroke in SPARKLE who fell under the undetermined category in CCS in the absence of TPA criterion and other

low risk of cardiac sources of embolism not included in the CCS criteria ($p<0.05$). Similarly, 131 cases with either multiple causes of embolism (111 cases) or high TPA, without carotid stenosis, and otherwise large artery atherosclerosis stroke in SPARKLE were classified as undetermined causes of stroke/TIA in TOAST ($p<0.05$).

Figure 17. Venn Diagram of the Number of Concordant Cases with Small Vessel Disease Stroke/TIA Between SPARKLE, CCS and TOAST.

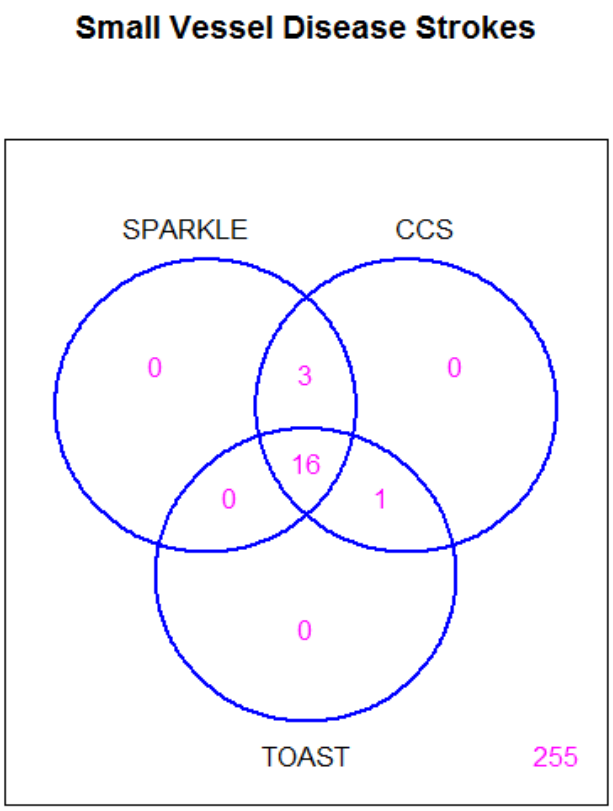
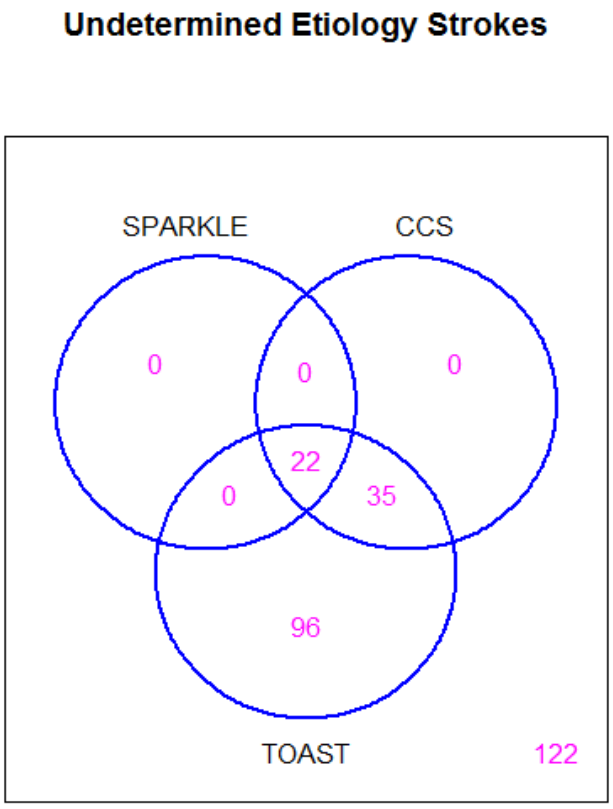


Figure 18. Venn Diagram of the Number of Concordant Cases with Undetermined causes of Stroke/TIA Between SPARKLE, CCS and TOAST.



Cardioembolic stroke/TIA was the predominant stroke/TIA subtype in SPARKLE and CCS, whereas undetermined cause of stroke/TIA was the predominant subtype in TOAST, as expected. The comparison of the three classification systems shows a significant difference in large artery atherosclerosis, cardioembolic and undetermined cause of stroke/TIA ($p<0.001$), but no difference was found in small vessel disease and in other rare or unusual cause of stroke/TIA (Table 12).

3.5 Additional Analysis in the Validation Study

We repeated the classification with the same 275 cases at one year after the stroke/TIA using SPARKLE, as well as for the follow-up events (recurrent stroke/TIA events at the follow-up period) using both SPARKLE and CCS. The results showed an almost excellent agreement in SPARKLE between the baseline classifications and at the one year follow-up period (κ-value 0.95), and substantial agreement between first-ever stroke/TIA and recurrent events (κ-value 0.71). Similarly, substantial agreement was shown between first-ever stroke/TIA and recurrent events based on CCS (κ-value 0.68).

No significant differences in stroke/TIA subtypes were found in patients who had recurrent events as compared to those who had no such events (Table 13), except for cardioembolic stroke/TIA in SPARKLE. From those patients having had a cardioembolic stroke/TIA, there were 133 cases with no recurrent events as compared to 27 cases who had a stroke/TIA at the follow-up period ($p=0.038$).

In patients who had follow-up events, no significant difference was found between SPARKLE and CCS for all stroke/TIA subtypes ($p<0.05$), except for undetermined causes of stroke/TIA, where there was a significant difference in the categorization of the undetermined causes of first-ever stroke/TIA ($p=0.02$) as well as at the events during the follow-up period ($p=0.01$). In particular, four cases in SPARKLE and nine cases in CCS were categorized as undetermined at the time of the first event and their cause of stroke/TIA remained undetermined during the follow-up period. Also, 13 cases in SPARKLE and 9 cases in CCS were categorized as large artery atherosclerosis at the first-ever stroke and at the recurrent stroke/TIA. In addition, 26 cases in SPARKLE and 22 cases in CCS were classified as cardioembolic at the time of their first and recurrent stroke/TIA. In SPARKLE, there was only one case initially categorized as other rare or unusual cause of stroke/TIA that had an undetermined cause of stroke/TIA at the follow-up period of time. However, three patients in CCS, who were initially classified as large artery atherosclerosis, small vessel disease and other rare or unusual causes of stroke/TIA, were classified as undetermined during the time of their recurrent stroke/TIA.

3.6 Reliability of SPARKLE

We found an almost excellent intra-rater agreement (κ-value 0.91) and substantial inter-rater agreement (κ-value 0.76). Moreover, the intra-class correlation coefficient was 0.94 for the intra-rater reliability and 0.81 for the inter-rater reliability.

No significant differences in large artery atherosclerosis, cardioembolic and small vessel disease strokes between the raters ($p<0.05$) were identified, but there were significant differences in undetermined causes of stroke or TIA ($p=0.003$) and in other rare or unusual causes of stroke ($p=0.031$). Firstly, six cases with cardioembolic stroke were classified as undetermined from one rater, and another eight cases with cardioembolic stroke were classified as undetermined by the other rater due to omission of clinical information suggesting cardiac sources of brain embolism with normal imaging investigations (e.g., multiple territory stroke or TIA with dyspnea or Valsalva maneuver at the onset of the event, prolonged sitting, etc.). Secondly, one case with a stroke due to hypercoagulable state was classified as undetermined from one rater, and another five cases with rare or unusual causes of stroke or TIA (e.g., CADASIL, vertebral dissection, connective tissue disorders) were categorized as undetermined by the other rater due to omission of clinical and laboratory information.

Table 5. Baseline Characteristics of Patients Presenting with Stroke/TIA

Age (mean±SD)	64.8±14.9
Sex(males) [n(%)]	1693(50%)
Body Mass Index>25 [n(%)]	2079(65%)
Systolic Blood Pressure (mean±SD)	142±22
Low-Density Lipoprotein (mean±SD)	3±1
Glucose (mean±SD)	6±3
Never Smoked n(%)	1318(38%)
Active Smoker n(%)	682 (20%)
Quit Smoking n(%)	1446 (42%)
Antiplatelet medications used at baseline [n(%)]	1579(46%)
Anticoagulant agents used at baseline n(%)	258 (8%)
Medications used to treat hypertension [n(%)]	2137 (62%)
Medications used to treat hyperlipidemia [n(%)]	1488(43%)
Medications used to treat Diabetes Mellitus [n(%)]	470 (14%)
Myocardial Infarction [n(%)]	418 (12%)
Vascular Surgery [n(%)]	432 (13%)
Atrial Fibrillation [n(%)]	307 (9%)
Patent Foramen Ovale [n(%)]	489 (14%)
Large Artery Atherosclerosis stroke/TIA subtype [n(%)]	1132(33%)
Cardioembolic stroke/TIA subtype [n(%)]	1300(38%)

Small Vessel Disease stroke/TIA subtype [n(%)]	353 (10%)
Other rare or unusual cause of stroke/TIA subtype [n(%)]	221 (6%)
Undetermined cause of stroke/TIA subtype [n(%)]	439 (13%)
Computed Tomography [n(%)]	2346(68%)
Magnetic Resonance Imaging [n(%)]	1320(38%)
Holter monitoring [n(%)]	807 (23%)
Echocardiography [n(%)]	1502(44%)

Table 6. Patients with Cardioembolic Stroke/TIA and Atrial Fibrillation

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
AF	23	22	15	19	23	20	25	37	21	27	21	253
Anticoag + INR≥2	2	4	2	4	8	3	5	12	4	4	3	51

Anticoag+ INR≥2: Patients who succeeded on treatment with anticoagulant agents for atrial fibrillation and had INR≥2

Table 7. Distribution of Stroke/TIA Subtypes per year. Percentages are presented in parentheses. n(%)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
LAA	176(51)	158(46)	107 (39)	125 (37)	103 (33)	90 (28)	82 (24)	82 (22)	69 (30)	66 (26)	74 (28)	1132 (33)
CAE	73 (21)	70 (20)	78 (28)	84 (25)	98 (31)	127 (39)	154 (46)	184 (50)	146 (53)	139 (54)	147 (56)	1300 (38)
SVD	29 (8)	44 (13)	37 (14)	46 (14)	42 (13)	29 (9)	32 (10)	36 (10)	24 (9)	16 (6)	18 (7)	353 (10)
Other	29 (8)	34 (10)	26 (10)	30 (9)	19 (6)	20 (6)	17(5)	13 (4)	10 (4)	11 (4)	12 (5)	221 (6)
UND	41 (12)	39 (11)	27 (10)	53 (16)	51 (16)	60 (18)	52 (15)	52 (14)	28 (10)	26 (10)	10(4)	439 (13)
Total	348	345	275	338	313	326	337	367	277	258	261	3445

Table 8. Distribution of Stroke/TIA Subtypes per year in Women. Percentages are presented in parentheses. n(%)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
LAA	78 (44)	58 (35)	48 (32)	45 (27)	37 (24)	38 (23)	26 (15)	29 (15)	26 (19)	29 (22)	28 (20)	442(25)
CAE	37 (21)	32 (20)	47 (31)	49 (29)	56 (36)	67 (41)	95 (55)	111(57)	73 (55)	71 (55)	87 (62)	725(41)
SVD	15 (9)	27 (17)	20 (13)	22 (13)	21 (14)	16 (10)	19 (11)	14 (7)	11 (8)	7 (5)	11 (8)	183(10)
Other	17 (10)	22 (13)	17 (11)	24 (14)	10 (6)	14 (9)	6 (3)	12 (6)	7 (5)	6 (5)	6(4)	141 (8)
UND	29 (17)	25 (15)	20 (13)	27 (16)	32 (21)	30 (18)	28 (16)	28 (14)	17 (13)	17 (13)	9(6)	262(15)
Total	176	164	152	167	156	165	174	194	134	130	141	1753

Table 9. Distribution of Stroke/TIA Subtypes per year in Men. Percentages are presented in parentheses. n(%)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
LAA	98(57)	100(55)	59 (48)	80 (47)	66 (42)	52 (32)	56 (34)	53 (31)	43 (30)	37 (29)	46 (38)	690(41)
CAE	36 (21)	38 (21)	31 (25)	35 (21)	42 (27)	60 (37)	59 (36)	73 (42)	73 (51)	68 (53)	60 (50)	575(34)
SVD	14 (8)	17 (9)	17 (14)	24 (14)	21 (13)	13 (8)	13 (8)	22 (13)	13 (9)	9 (7)	7(6)	170(10)
Other	12(7)	12 (7)	9 (3)	6 (4)	9 (6)	6 (4)	11 (7)	1 (1)	3(2)	5 (4)	6(5)	80 (5)
UND	12(7)	14 (8)	7 (6)	26 (15)	19 (12)	30 (19)	24 (15)	24 (14)	11 (8)	9 (7)	1(1)	177(11)
Total	172	181	123	171	157	161	163	173	143	128	120	1692

Table 10. Comparison of Risk Factors for Stroke/TIA in Men and Women in all Stroke/TIA Subtypes.

	LAA		CAE		SVD		Other Etiology		Unknown Cause	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
Age	69±11	72±1	63±15	62±17	63±13	68±14	55±14	53±15	62±15	64±16
	p<0.001*		p=0.134		p=0.001*		p=0.278		p=0.439	
Pack Years	27±27	18±23	17±21	8±15	18±23	11±18	19±25	6±10	16±20	10±15
	p<0.001*		p<0.001*		p=0.003*		p<0.001*		p<0.001*	
BMI	27±5	27±6	28±5	27±6	29±5	28±6	28±5	28±7	28±5	27±5
	p=0.549		p=0.016		p=0.049		p=0.872		p=0.060	
SBP	143±20	151±24	135±18	136±19	156±21	162±27	139±17	138±19	140±19	142±19
	p<0.001*		p=0.211		p=0.011		p=0.532		p=0.294	

Table 10. Comparison of Risk Factors for Stroke/TIA in Men and Women in all Stroke/TIA Subtypes (continue from page 77).

	LAA		CAE		SVD		Other Etiology		Unknown Cause	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
DBP	80±12	78±14	81±11	78±12	91±14	88±15	86±13	81±13	83±11	79±11
	p=0.006		p<0.001*		p=0.025		p=0.004		p<0.001*	
HR	68±12	71±12	70±13	71±12	72±13	73±13	74±13	74±13	70±12	72±11
	p<0.001*		p=0.076		p=0.407		p=0.921		p=0.151	
Homo-cysteine	13±15	12±6	12±7	11±10	11±5	11±5	11±4	8±4	10±3	10±5
	p=0.455		p=0.031		p=0.149		p<0.001*		p=0.377	
Vitamin B12	307±173	360±261	318±196	335±203	302±149	367±254	300±182	321±160	295±161	354±276
	p<0.001*		p=0.132		p=0.006		p=0.382		p=0.014	

Table 10. Comparison of Risk Factors for Stroke/TIA in Men and Women in all Stroke/TIA Subtypes (continue from page 78).

	LAA		CAE		SVD		Other		UND	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
Total Chol.	5±1	5±1	5±1	5±1	5±1	5±1	5±1	5±1	5±1	5±1
	p<0.001*		p<0.001*		p<0.001*		p=0.292		p=0.002*	
Trigly-cerides	2±1	2±1	2±1	2±1	2±2	2±1	2±2	2±1	2±2	2±1
	p=0.293		p=0.047		p=0.268		p=0.136		p=0.008	
HDL	1±0	1±0	1±0	2±0	1±0	2±0	1±0	2±0	1±0	2±1
	p<0.001*		p<0.001*		p<0.001*		p<0.001*		p<0.001*	
LDL	3±1	3±1	3±1	3±1	3±1	3±1	3±1	3±1	3±1	3±1
	p=0.001*		p<0.001*		p=0.072		p=0.869		p=0.216	

Table 10. Comparison of Risk Factors for Stroke/TIA in Men and Women in all Stroke/TIA Subtypes (continue from page 79).

	LAA		CAE		SVD		Other		UND	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
Glucose	7±4	6±2	6±4	6±2	7±3	7±2	6±1	6±2	6±2	6±2
	p=0.217		p=0.010		p=0.024		p=0.298		p=0.801	

*Using Bonferroni correction to control for multiple testing in the 13 tests applied in each stroke/TIA subtype and have significant test at the level of significance 5%, we calculate that p=0.05/13=0.004.

Table 11. Comparison of Stroke/TIA Subtypes in Men and Women.

	MEN		WOMEN		p-value
	n	%	n	%	
LAA	690	41	442	25	<0.001
CAE	575	34	725	41	<0.001
SVD	170	10	183	10	0.35
Other	80	5	141	8	<0.001
UND	177	11	262	15	<0.001
Total	1692	49	1753	51	

Table 12. Comparison of SPARKLE, CCS and TOAST

	SPARKLE		CCS		TOAST		SPARKLE vs CCS p-value	SPARKLE vs TOAST p-value
	n	%	n	%	n	%		
LAA	59	22	40	15	36	13	7.629e-06	2.384e-07
CAE	160	58	138	50	50	18	1.049e-05	<2.2e-16
SVD	19	7	20	7	17	6	1	0.625
Other	15	6	20	7	19	7	0.125	0.0625
UND	22	8	57	21	153	56	5.821e-11	<2.2e-16

Table 13. Comparison of Patients Who Had Recurrent Stroke/TIA During the Follow-Up Period (FU Events) with Patients Who Remained Symptom-Free During the Follow-Up Period (NO FU).

	SPARKLE					CCS				
	NO FU		FU Events		p-value	NO FU		FU Events		p-value
	n	%	n	%		n	%	n	%	
LAA	44	20	15	27	0.07	30	14	11	20	0.07
CAE	133	61	27	49	0.04	114	52	24	44	0.07
SVD	15	7	4	7	0.23	16	7	4	7	0.23
Other	11	5	4	7	0.19	14	6	5	9	0.18
UND	17	8	5	9	0.20	46	21	11	20	0.15
Total	220		55			220		55		

CHAPTER FOUR: DISCUSSION

4.1 Summary of Findings in Stroke/TIA Subtypes and Risk Factors

To our knowledge, this is the first retrospective case series study in a Canadian geographically defined area assessing secular trends in ischemic stroke subtypes in patients with minor stroke/TIA. We performed a paper chart review of approximately 3,950 cases and created a dataset of 3,445 newly diagnosed patients who experienced a first-ever stroke or TIA between the years 2002 and 2012 in the Thames Valley area in Ontario. Our findings confirm a trend of increasing cardioembolic stroke/TIA subtype in patients with minor stroke/TIA and a decrease in all other stroke/TIA subtypes ($p<0.05$), which is in agreement with studies in other countries.[23, 24]

Approximately 50% of all patients with AF and almost one third of patients with cardioembolic stroke/TIA and AF were treated for their arrhythmia, which is different than an earlier study by Gladstone et al. who showed that, in the years 2003-2007, 40% of patients with AF were receiving treatment.[170] One possible explanation of this difference is that hospitalized patients are expected to have a more severe stroke and be less adequately treated compared to patients with minor stroke/TIA. This knowledge will assist primary care physicians in investigating and treating cardiac sources of brain embolism more intensively in patients with minor stroke/TIA to prevent additional major strokes that will need hospital care or even lead to death.

With better management of baseline stroke risk factors,[171] we would expect that the number of new patients with stroke would decrease over time. However, we could not find any significant change in the counts of patients presenting with confirmed stroke/TIA (Figure 3). We considered that part of the problem might be the increase in the population as “baby-boomers” are now reaching older age, which might explain the higher incidence of stroke. Nonetheless, there is no significant change at the population level, and the 7.5% increase had no effect on the trends for stroke/TIA subtypes in all patients in our cohort, as well as in men and women separately. Trends remained the same in both sexes in direction and significance, even after adjusting for population change. We believe that there is a decrease in older patients who were

admitted to hospital or who died from a stroke as compared to a constant number of younger patients who experienced a minor stroke/TIA. Indeed, a population-based study in Canada showed a 28.2% decrease in deaths and a 27.6% decrease in hospitalization due to stroke, but there was not any report of patients with minor stroke/TIA.[15] Further research is required to investigate the reasons for the remaining constant number of new patients presenting with minor stroke/TIA to prevent an increase in cerebrovascular events in this group of patients.

In our study, cardioembolic stroke/TIA was the predominant subtype after the year 2007 in all patients and in men, as well as in women after the year 2005. On the contrary, large artery atherosclerosis stroke/TIA was the most frequent subtype before 2007 in all patients and in men, as well as in women before the year 2005, and decreased thereafter. One explanation is that the Canadian Hypertension Education Program (CHEP) was put in place in 1999, and offers training for physicians on better management of hypertension, which also resulted in decreasing systolic blood pressure in our cohort.[172] Moreover, large artery atherosclerosis stroke/TIA was expected to decrease given that statins are among the most widely prescribed medications for cholesterol control, and this was confirmed by a decrease in LDL cholesterol levels in our patients.[173] Similar results were illustrated previously when Spence et al showed in 2000-2007 that stroke risk factors of patients who experience a minor stroke/TIA at the time of their first event are better controlled over time.[171] Similar results were also shown by Abbott et al in Australia, where better treatment of baseline risk factors was observed,[174] which probably influenced the decrease in large artery atherosclerosis and small vessel disease and resulted in a proportional increase in cardioembolic strokes.[57, 155] Additional evidence of decreasing prevalence of atherosclerosis has been shown in studies using autopsy reports of U.S.A. military service members. In these studies, the prevalence of coronary atherosclerosis was 77% in 1953 in the Korean War and decreased to 45% in 1975 during the Vietnam War.[175, 176] More recently, autopsy results showed that the prevalence of coronary atherosclerosis further decreased to 8.5% in soldiers who died in Iraq.[177]

We further investigated the potential causes for a significant increase in patients presenting with cardioembolic stroke/TIA. There was no change in patients presenting with MI or AF. Moreover, in recent years, more patients with AF were

treated with anticoagulant agents even though there are still cases where the level of dosage failed to mitigate the effects of emboli formation in the heart. Considering that our cohort had patients of younger ages compared to inpatients, we expected to find no change in patients with cardioembolic stroke/TIA due to AF.[138] Young patients are more likely to have low-risk cardiac sources of embolism[67] compared to older patients who are more likely to have AF[68] and the risk of developing AF increases with advancing age.[112-115] However, this finding is prone to change in light of more evidence if, in the future, it is proven that longer monitoring of cardiac rhythm is required to capture an event of AF or paroxysmal AF, which may be missed with the current standard practice of 24 hour or 48 hour Holter monitoring.

Furthermore, we investigated the number of diagnostic tests ordered through the total study period. Between the years 2002 and 2012, we found a marginal decrease in CT (70% in 2002 vs. 65% in 2012, $p=0.04$), but no significant difference in MRI (33% in 2002 vs. 35% in 2012, $p=0.06$), which denotes the almost constant availability of brain imaging in patients of our cohort during the past ten years. Nonetheless, there was a significant increase in Holter monitoring (14% in the year 2002 vs. 47% in the year 2012, $p<0.05$) and echocardiograms (37% in the year 2002 vs. 61% in the year 2012, $p<0.05$) ordered. One explanation of this increase can be the increased suspicion of the high prevalence of cardioembolic stroke/TIA in patients with minor stroke/TIA. However, all patients were assessed by the same stroke expert (Dr. Spence) with the same clinical criteria and without *a priori* assumptions of the most "probable" or "possible" stroke/TIA subtype. Also, additional tests (e.g., Holter, echocardiogram, etc.) were ordered after the first clinical assessment and in presence of symptoms and signs suggesting cardiac sources of embolism (e.g., infarcts in multiple vascular territories in the brain). Consequently, if a misclassification bias exists, this will be non-differential and minimal.

Life expectancy is increasing[65] and stroke risk increases in older individuals.[66] With better management of baseline stroke risk factors,[171] we would expect to see an increase in age of patients presenting with stroke in more recent years compared to earlier years. Surprisingly, patients in the year 2012 were almost one year younger than patients in 2002 ($p=0.035$). However, this decrease in age was not significant in each sex separately, even though women and men in the year 2012 were still one year

younger compared to patients presenting in the year 2002. There was a significant difference in the age of patients in different stroke/TIA subtypes. Older patients were more likely to have large artery atherosclerosis stroke and younger patients were more likely to have other rare or unusual causes followed by cardioembolic stroke/TIA (Table 10). Continuous campaigns from the Heart and Stroke Foundation have potentially contributed to an increasing awareness of stroke symptoms in younger patients who reach health care services earlier in the presence of minor warning symptoms. More patients are knowledgeable about the warning symptoms of stroke and manage to be further referred to stroke clinics for thorough investigation and treatment of their minor stroke/TIA with an ultimate goal of preventing a massive stroke that could lead to great disability or death. However, we had no measure of stroke symptom awareness in our patients, which is a potential limitation of our study. Also, because of the retrospective nature of our study design, our investigation for cardiac sources of embolism was not as thorough or complete as it could have been. Further prospective research is required to reveal all possible causes and mechanisms of cardiac sources of embolism.

We developed SPARKLE, which was based on the previously validated CCS classification system, for the classification of stroke/TIA subtypes. A comparison with previous studies using CCS[156, 157, 178] showed a predominance of cardioembolic as compared to other stroke/TIA subtypes (Appendix D) and fewer cases classified as undetermined cause of stroke/TIA, as would be expected compared to previous classification systems.[44, 57, 58]

Ay et al[156] and Michael et al[178] used data from hospitalized patients and found higher frequency in cardioembolic strokes, which is in line with results from a meta-analysis by Schulz and Rothwell.[136] In this meta-analysis, there were significant differences in all stroke/TIA subtypes between hospitalized patients with major disabilities from a massive stroke and non-hospitalized patients with minor stroke/TIA, with hospitalized patients having higher frequency of cardioembolic strokes mainly due to AF and non-hospitalized patients having higher frequency of small vessel disease strokes.[49, 58] Therefore, the results of our study cannot be directly compared with studies using data from hospitalized patients only.

Palm et al used a modification of CCS and showed again that cardioembolic stroke was the predominant ischemic stroke subtype in more recent years.[157] Previous population-based studies show inconsistent results. In Asian countries, small vessel disease is the most frequent stroke/TIA subtype.[51, 104, 179-181] While Kubo et al showed a decreasing frequency in small vessel disease stroke and an increasing frequency of large artery atherosclerosis and cardioembolic strokes, small vessel disease remained the most predominant ischemic stroke subtype in Asia.[51] The same group identified a gene (PRKCH), specifically found in Asians, to be related to higher risk of developing small vessel disease.[182] Similarly, in population-based studies in South America, small vessel disease is the most frequent ischemic stroke subtype and is probably related to lifestyle and management of risk factors.[153, 183] On the other hand, in Australia, in the year 1986, 13.6% of patients suffered from a cardioembolic stroke and 32.6% had small vessel disease stroke,[155] whereas, in the years 2002-2003, 29.4% had cardioembolic strokes and 11.2% had small vessel disease,[57] showing the predominance of cardiac sources of brain embolism in more recent years. Similar changes are shown in the U.S.A. and in European countries, but the distribution of stroke/TIA subtypes is highly affected by the distribution and management of risk factors and, consequently, it is not possible to extract a single summary statistic. This denotes the importance of studying a geographically defined population with follow-up studies investigating the change in the distribution of risk factors and the stroke/TIA subtypes over time.

In our study, mean age was approximately the same as in previous studies.[30, 56, 153, 156, 184] However, other studies with hospitalized stroke patients show higher mean age, probably related to the increased clinical severity of stroke in older ages requiring hospital care.[178, 185] Different studies show a lower mean age in stroke patients, which is related to a higher prevalence of stroke risk factors in younger ages in parts of the world, such as African, Arabian Gulf or Asian countries.[154, 186] In Canada, patients more than 65 years old are more likely to have a major stroke and be hospitalized with a mean age of 71, which is at least five years older than our cohort.[138] A national study by Tu et al showed that patients who were admitted to hospital with stroke had a mean age of 75 years.[15] This denotes that younger patients are more likely to have a minor stroke/TIA, and as a result, they require more intensive treatment to prevent

additional strokes that can lead to hospital admission or death as these high-risk patients grow older.

Significant differences exist between men and women in the distribution of risk factors and in stroke/TIA subtypes. As expected, men had significantly more large artery atherosclerosis stroke/TIA compared to women who had significantly more cardioembolic stroke/TIA. Also, men with large artery atherosclerosis had higher pack-years compared to women with large artery atherosclerosis. Nonetheless, in both sexes, the trends in increasing cardioembolic stroke/TIA and decreasing counts in all other stroke/TIA subtypes were similarly significant. This finding indicates that, in both sexes, atherosclerotic risk factors are better controlled and cardiac risk factors for stroke/TIA are increasing.

Stroke risk factors other than age were significantly different in men and women. On the one hand, men had higher levels of pack-years, total plaque area, BMI, triglyceride, homocysteine and glucose, which might explain the higher proportion of large artery atherosclerosis stroke/TIA. On the other hand, women had higher blood pressure, LDL and HDL cholesterol and B12 measurements. Unmeasured genetic factors and differences relating to sex hormones may have prevented women from having the excess atherosclerosis observed in men. Moreover, the regression analysis showed that systolic blood pressure was significantly related with large artery atherosclerosis, small vessel disease and cardioembolic stroke/TIA subtypes, as shown in previous studies.[29, 31, 183, 187] Small vessel disease was not associated with diabetes mellitus, similar to previous studies that used a risk factor-free classification system.[188-191] Nonetheless, the results of our regression analysis are inconclusive given the stepwise analysis and the inability to determine the level of significance needed for multiple hypothesis testing, as well as due to the absence of a control group of individuals without cerebrovascular disease.

4.2 Ischemic Stroke Classification System

In clinical practice, we need a simple and informative classification system for grouping patients into separate categories without omitting complicated cases.[192] An ideal and useful classification system should include the minimal diagnostic tests necessary to reach an accurate diagnosis, reflecting real clinical practice, and to accommodate the latest diagnostic tools available to be used in different clinical settings.[192] SPARKLE is a classification system that incorporates all the elements of an easy and thorough classification system. In SPARKLE, all clinically relevant information is considered (medical history, physical examination and basic laboratory investigation) to achieve the most "probable" diagnosis. It is flexible enough to allow additional testing to confirm or reject the initial diagnostic plan in a systematic way by using specific rules to prevent physicians from performing individual diagnosis. Moreover, it is a risk factor-free classification system that allows investigation of the role of risk factors in the subtypes of ischemic stroke[135] as a useful tool in epidemiological studies.

SPARKLE is based on information from medical history and physical examination, and is useful to guide medical management of patients with stroke/TIA. It uses basic diagnostic testing applied in clinical practice (for example, brain imaging, echocardiography, Holter monitoring, carotid and transcranial ultrasound, etc.). It introduces a diagnostic tool for atherosclerosis (TPA), which is easy to measure with a regular ultrasound machine,[134] without any specific software requirements.[193] In their recently published population-based study, Palm et al used CCS for categorizing their ischemic stroke patients, adding a criterion for "probable atherosclerosis" in cases with carotid stenosis <50%, brain lesions >1.5 cm and no cardiac source of embolism.[157] In SPARKLE, we used an actual measurable quantity of atherosclerosis based on classified stroke risk to distinguish high risk large artery atherosclerosis ($TPA \geq 1.19 cm^2$) from low risk ($TPA < 0.12 cm^2$).[129]

SPARKLE provides a more comprehensive view of each stroke/TIA subtype than CCS without omitting cases under the "undetermined" category if there are more than two "possible" causes of stroke, a criterion not included in CCS. This approach might suppress the "undetermined" category of stroke/TIA subtypes and inflate all other determined causes of stroke/TIA. However, it creates more homogenous groups of

patients sharing similar clinical characteristics and prognosis. In our study, the 10-year prognosis shows that 12.2% of patients had a recurrent stroke/TIA, with other rare or unusual causes of stroke/TIA having the highest recurrent rates, followed by strokes/TIAs of "undetermined" etiology (Appendix E). The 10-year risk of stroke/TIA in our cohort was lower than seen in previous studies,[194, 195] suggesting that cases were treated according to the most precise cause of stroke/TIA with SPARKLE and, consequently, more strokes/TIAs were prevented. This evidence is supported by the different prognosis of patients with large artery atherosclerosis, as compared to patients with undetermined cause of stroke/TIA. This is in contrast with the TOAST trial, where patients in these two subtypes of stroke had a common prognosis, suggesting misclassification of large artery atherosclerosis cases under the undetermined category.[127]

Adams et al discuss in the TOAST trial that small vessel disease strokes share similar risk factors with large artery atherosclerosis strokes.[127] Indeed, it is not easy to differentiate the nature of small subcortical infarcts in the brain and declare with certainty that they are not caused by small emboli of atherosclerotic lesions formed in large vessels that perfuse the area of infarct or from embolic particles of cardiac origin. A genetic analysis showed that in patients with stroke of "undetermined" etiology and small deep infarcts on brain imaging, 34% had a genetic profile similar to cardioembolic stroke, 13% had a genetic profile compatible with large artery atherosclerosis and 47% were predicted to have small vessel disease.[196] However, based on the current knowledge, we decided to retain the description of the classical clinical lacunar syndromes referred to as small vessel disease as previously described. We acknowledge that in light of emerging evidence about the nature of small vessel disease, this subtype of stroke/TIA might change in the future, as all stroke classifications are dynamic systems with a tendency toward evolution with incorporation of new discoveries.

In our study, 13% of all patients, 8% of patients included in the random sample of the 275 cases and 24% of consecutive patients included in the pilot study had "undetermined" cause of stroke/TIA. Even though special effort was made to classify all patients into defined stroke etiologies, there is still a high portion of patients who receive conventional treatment to modify all identifiable risk factors, without

elucidating a specific mechanism causing the presenting stroke/TIA event. Genetic analysis in these patients might be able to show a genetic profile similar to a defined subtype of stroke/TIA; however, based on the current evidenced-based management, this genetic profile would not be able to alter the received treatment, in the case where a specific mechanism of disease is not possible to be identified and treated.

Validity of SPARKLE

An inherent limitation of all stroke classification systems is the absence of a comparison with a gold standard. The ideal gold standard is still the pathology examination to accurately prove the cause of a stroke or TIA, something that is unrealistic and impossible to obtain from survivors of cerebrovascular disease, and this explains why we cannot assess the criterion validity of SPARKLE.[197] Instead, Ay et al proposed the most accurate classification system to date (CCS), based on evidence from the annual threshold of 2% stroke risk, to differentiate an "evident" from a "possible" cause of stroke.[128] However, the ideal application of CCS required a full set of diagnostic investigation, currently not available in all stroke cases in all clinical settings. Based on evidence suggesting the use of TPA in the diagnosis of large artery atherosclerosis strokes, we developed SPARKLE as a more applicable diagnostic tool in clinical practice to include all dimensions in each subtype of stroke/TIA to ensure content validity. The results of the comparison with CCS, as a surrogate of a gold standard, using ideal cases best classified under CCS, show substantial agreement between the two systems (κ-value=0.749) indicating construct validity, but the results from the pilot study show that in real practice, the agreement is fair (κ-value=0.382). Therefore, we decided to classify our cohort based on SPARKLE criteria, which are more applicable to our clinical practice.

There were no significant differences between SPARKLE and CCS and TOAST in assignment of cases in small vessel disease and other rare or unusual causes of stroke/TIA subtypes. While SPARKLE did not provide a better description of these two subtypes, it introduced more information for the classification of cases as large artery atherosclerosis and cardioembolic stroke/TIA subtypes, which were not provided by previous classification systems. Indeed, in SPARKLE, with the inclusion

of TPA criterion, there were 18 more cases of large artery atherosclerosis compared to CCS and 23 more cases compared to TOAST. As expected, no cases with large artery atherosclerosis were assigned in CCS and TOAST that were not classified under SPARKLE, denoting the accuracy of the classification of patients with this subtype. Similarly, SPARKLE was able to classify 20 more cases with "possible" cardioembolic stroke/TIA, not described previously in CCS. However, 8 cases were misclassified due to omission of information either from the medical history or the additional diagnostic investigations, something that highlights the importance of a comprehensive medical history in the final management of cases. Based on Figure 2 that illustrates the changing counts between all subgroups in cardioembolic stroke, we see that the pattern of increasing counts was similar between "evident" and "total" counts in cardioembolic stroke/TIA; therefore, we believe that the aforementioned differences in additional "possible" cardioembolic cases, assigned in SPARKLE that were not previously described in CCS, will not affect the overall increasing trend in cardioembolic stroke/TIA.

Reliability of SPARKLE

The inter-rater reliability of SPARKLE (κ-value=0.763) was not significantly different from CCS (κ-value=0.8).[198] Nonetheless, the greatest disagreement between the raters occurred in cases when information from the medical history was overlooked. Reliable assignment of cases in each stroke/TIA subtype requires a thorough investigation of the agreement between declared symptoms from the medical history to signs identified during the physical examination, in relation to additional laboratory investigations. Consideration of laboratory investigations with less weight placed on the clinical examination can lead to erroneous classification of cases and missed opportunities for accurate diagnosis and treatment options.

Consistency of Classifying Ischemic Stroke/TIA using SPARKLE

There was a great consistency in classification of cases with SPARKLE at the time of their first stroke/TIA and in one year after this first event (κ-value=0.947). This shows that with the current knowledge about stroke syndromes and with the available diagnostic tests, SPARKLE can be used to accurately diagnose patients with particular stroke/TIA subtypes and guide appropriate treatment with good predictive validity. Recurrent stroke/TIA occur shortly after the first event; therefore, the consistency between baseline and one year follow-up in SPARKLE shows that clinical cases are classified accurately and few cases are missed with conditions not treated at the time of the first stroke (e.g., paroxysmal atrial fibrillation missed in Holter monitoring, etc.). Moreover, there was no significant difference in follow-up events between SPARKLE and CCS, other than CCS classifying more cases under the "undetermined" causes of stroke/TIA category. This analysis may be underpowered with only 55 individuals from the initial sample having a stroke/TIA at the follow-up period of time, and is greatly affected by the fact that all cases were treated prospectively based on the SPARKLE categorization. However, based on SPARKLE, more cases are classified into defined stroke/TIA subtypes, which offers the opportunity to patients to receive intensive treatment to reduce their risk of recurrent stroke/TIA. Nonetheless, the results are not conclusive, and a randomized clinical trial would be more appropriate to show the success of treatment by classifying and treating cases based on CCS as compared to SPARKLE, to measure the type and the frequency of additional cerebrovascular events occurring during the follow-up period.

4.3 Strengths

A considerable strength of our study is the large number of patients we were able to collect and the availability of all clinically relevant information in paper charts to classify patients in each stroke/TIA subtype. Despite the large size of this study, data entry and cleaning lasted approximately only seven months and the final dataset was quickly ready for analysis, which is the reason for choosing a retrospective study design. Clinical charts of patients with minor stroke/TIA were located in one clinical setting, which facilitated the collection of our data.

A major problem in previous studies was the lack of carotid Doppler ultrasound in the investigation of stroke cases.[57, 183] This was not an issue in our study, given that almost all patients had carotid ultrasound. This helped differentiate large artery atherosclerosis from strokes/TIAs caused by dissection or other vascular diseases and avoid misclassification bias due to incomplete diagnostic assessment. Moreover, the availability of services from a tertiary teaching hospital allowed additional diagnostic testing for cardiac evaluation or other imaging and laboratory technologies, which might not be available in rural areas. This might have contributed to the lower rate of cases with "undetermined" cause of stroke/TIA, compared to previous studies.[156, 178]

Furthermore, the majority of previous studies used TOAST for classifying ischemic stroke subtypes with an increased number of "undetermined" cases. The use of CCS managed to considerably eliminate that restriction, without being able to completely differentiate large artery atherosclerosis from "undetermined" causes of stroke, a limitation mentioned in another study that used CCS.[157] The introduction of SPARKLE resolved this problem and enriched our study with criteria to classify stroke/TIA subtypes, which can be used elsewhere and reflect real clinical practice. Moreover, SPARKLE, as CCS, was able to classify patients with more than one cause of stroke into the most "probable" or most "possible" stroke/TIA subtype. This reduced the number of "undetermined" causes of stroke/TIA and is probably responsible for inconsistent results in studies in the U.S.A. and Europe, where different classification systems have been used over time.

Another significant strength of classifying our cases based on SPARKLE is the lack of *a priori* assumptions concerning stroke risk factors in each stroke/TIA subtype. A meta-analysis by Jackson et al showed that risk-factor free classification systems were not able to show a role of diabetes mellitus in the pathogenesis of small vessel disease stroke, which was the case in our study, even if our regression results were inconclusive.[135] Consequently, SPARKLE can be used in prospective studies investigating in more depth the role of risk factors in the pathophysiology of small vessel disease strokes and other stroke/TIA subtypes.

Also, a considerable strength in our study is that all cases were examined by the same stroke expert, who collected all information, diagnosed and treated patients in the same manner throughout the study period. Therefore, we believe that any information bias will be non-differential.

4.4 Limitations

Spectrum and selection bias is a significant limitation in our study. We were able to capture a representative sample of patients experiencing a minor stroke/TIA, but our conclusions cannot be generalized to all patients who die or experience a major stroke. Moreover, it is likely to have missed patients with minor stroke/TIA who did not seek medical attention or have not been referred to the clinic. However, a study by Webster et al showed that in Ontario, patients who are not seen in a secondary stroke prevention center are more likely to have atrial fibrillation, myocardial infarction, conestive heart failure, diabetes, dementia and history of stroke as compared to patients who are seen in these clinical settings and are more likely to have history of hyperlipidemia.[199] As a result, the incidence of cardioembolic stroke/TIA might be higher in the total population. Nonetheless, this study can only serve as a starting point to provide evidence of stroke/TIA subtypes and risk factors in patients with minor stroke/TIA and motivate additional population-based studies in the same geographic area including all patients who die or experience a major or minor stroke/TIA.

The retrospective nature of our study was a significant restriction to obtaining more information to characterize thoroughly our population. Information such as race and socioeconomic status was not available in clinical charts. Future research can probably obtain this information by matching the postal codes of the residencies of patients to geographic census areas to speculate neighborhood average income quintiles. Also, information about physical activity and diet was collected through non-validated questionnaires, which prevented us from obtaining valid measurements of these variables. Moreover, environmental risk factors were not available to be collected, even if this is not a significant limitation, given that our population comes

from the same geographically defined area and all patients share the same environmental risk factors.

Diagnostic tests ordered in the earliest years might have been missed if they were not entered in the clinical chart, something that we believe is highly unlikely, given that all clinical, imaging and laboratory information was collected in the same manner throughout the study. All cases were assessed with standardized clinical criteria without *a priori* assumption about the most "probable" stroke/TIA subtype, and the investigation and clinical decision-making were based on thorough information from the medical history and the physical examination. Therefore, we believe that if there is any bias, this would be minimal. On the contrary, the introduction of TPA in the definition of large artery atherosclerosis would have been expected to inflate this category and would have biased our classification towards large artery atherosclerosis. However, we actually saw a significant decrease in this subtype of stroke/TIA, suggesting that if such misclassification bias exists, it would be minimal.

The lack of a control group to compare risk factors and stroke/TIA subtypes was an important limitation for obtaining information about the significance of risk factors in the occurrence of particular stroke/TIA subtypes. In addition, the lack of differentiation between patients with minor stroke and patients with TIA restricted us from further investigating the change in risk factors before and after the cerebrovascular event. Cholesterol[41, 200] and blood pressure[201] are transiently decreasing after a stroke event, and this is not observed in TIA. Consequently, we cannot infer any conclusions about the role of risk factors in each stroke/TIA subtype. Moreover, the lack of a pathology examination restricted us from measuring accurately the sensitivity and the specificity of SPARKLE, compared to the gold-standard.

A physician (Dr. Bogiatzi) performed the data entry and categorization of patients into stroke/TIA subtypes based on SPARKLE criteria and on the final diagnosis of the stroke expert (Dr. Spence) who examined all patients. This is in contrast to previous studies, where neurologists categorized the cases. However, controversial cases that required a more expert clinical decision were assessed with the stroke expert to ensure the accuracy of data entry. Ideally, prospective studies should use all clinical and laboratory criteria from different physicians trained to use the classification system to

examine patients with stroke/TIA and assign the most appropriate stroke/TIA subtype at the time of clinical evaluation of individual stroke/TIA cases.

Finally, it has been acknowledged that specific genetic markers are related to specific stroke/TIA subtypes.[182] Cardioembolic stroke/TIA can be differentiated from large artery atherosclerosis stroke/TIA based on screening 40 genes.[202] Also, 41 genes have been identified as different between patients with small vessel disease compared to all other stroke/TIA subtypes.[203] Therefore, this study is limited by the lack of genetic profiles in enrolled patients. Nonetheless, a study by Jickling et al showed that in patients with unknown cause of stroke/TIA based on previous classification systems, 58% had a genetic profile compatible with cardioembolic stroke and 18% of patients were predicted to have large artery atherosclerosis stroke, even if they had no significant differences in hypertension, diabetes, hyperlipidemia and smoking status.[196] We believe that based on SPARKLE we were able to identify more stroke causes in patients that would otherwise remain undiagnosed, but a genetic profile is needed to confirm our findings.

4.5 Implications

Even if patients who die from a major stroke decrease over time,[15] the number of patients presenting with minor stroke/TIA has remained approximately the same. This information is important to motivate future research toward identifying prevailing medical risk factors for patients with minor stroke/TIA. These can then be ameliorated to decrease the incidence and burden of stroke/TIA.

In this study, we saw a significant increase in cardioembolic stroke/TIA in a high proportion of patients with low risk cardiac sources of embolism, at a relatively younger age than expected. This evidence is important for health care services. Previous studies have shown that cardioembolic strokes have a high recurrence rate compared to other stroke subtypes. Moreover, as life expectancy increases,[65] these younger patients with an initial cardioembolic stroke/TIA are at high risk of surviving for a longer time with disabilities due to additional strokes that will require expensive rehabilitation services. Consequently, additional studies are required to thoroughly investigate low and high risk cardiac sources of embolism that predominate in patients

with minor stroke/TIA and provide the opportunity for intensive prevention strategies to decrease incidence and recurrence in this stroke subpopulation.

Additional research in our patients with cardioembolic stroke/TIA and AF showed that therapeutic goals are suboptimal. From 23 patients with AF and cardioembolic stroke/TIA in the year 2002, only two were treated with anticoagulant agents. Similarly, among 21 patients with AF and cardioembolic stroke/TIA in the year 2012, only four were treated, from whom only three achieved INR≥2. This evidence should alarm primary care practitioners who follow patients with AF closely and motivate them to implement more stringent control of their anticoagulation to prevent unnecessary cardioembolic strokes/TIAs.

A final contribution of our study is the introduction of a classification system of ischemic strokes that reflects current clinical practice and can be used in all clinical settings. Using SPARKLE, we saw that the prognosis of patients varies in different stroke/TIA subtypes, denoting the improved categorization of patients based on the most probable etiology of their stroke/TIA. This system can be used in clinical practice and in further epidemiological studies. However, confirmation of the reliability of SPARKLE is required.

4.6 Perspectives – Future Considerations

This study illustrates for the first time in a Canadian population that cardioembolic strokes/TIAs have been increasing in the past ten years in patients with minor stroke/TIA. This finding can motivate the design of a prospective population-based study to include investigation of all possible cardiac sources and mechanisms of brain embolism. Such a study should ideally include information on genetic markers and race to more accurately classify stroke/TIA subtypes and investigate differences in subtypes and risk factors in different racial groups. In addition, enrollment of individuals with no cerebrovascular disease and of the same age and sex is needed to serve as a control group to compare with stroke/TIA patients and to provide evidence of the role of risk factors on each stroke/TIA subtype.

An important limitation in this study is the inability to differentiate patients with minor stroke from patients with TIA. In the latest update of the American Heart and Stroke Association, TIA was defined as a cerebrovascular event in the presence of transient neurological symptoms with no evidence of permanent necrosis on brain imaging.[3] Nonetheless, in our cohort, patients that satisfied this definition of TIA had signs in the clinical examination of brain ischemia not shown on brain imaging, indicating presence of a stroke. Further studies are required to revisit the criteria for differentiating between stroke and TIA. This has considerable value in assessing the role of risk factors in each stroke/TIA subtype. Serum cholesterol decreases transiently after a stroke[41, 200] , probably because of hemodilution,[204, 205] and also systolic blood pressure decreases steeply in hospitalized patients with large artery atherosclerosis and small vessel disease stroke as opposed to other ischemic stroke subtypes.[201] These changes in cholesterol and blood pressure are not observed in patients with TIA. Therefore, further research is required to refine current definitions of stroke and TIA, both in anterior and posterior brain circulations.

SPARKLE has been validated in one centre by researchers who developed the criteria for categorizing patients into five stroke/TIA subtypes. Further validation is required in multiple centers to assess the reliability of this classification system with different raters, not involved in the development of this system. In SPARKLE, we included TPA measurements in the definition of large artery atherosclerosis and also measured prognosis in different stroke/TIA subtypes. However, a cluster randomized clinical trial would provide the best possible evidence on the performance of SPARKLE compared to CCS. In this clinical trial, clinical settings could be randomized to clinical care without measurement of TPA versus clinical care with measurement of TPA and, consequently, patients in the two types of settings will be categorized based on CCS versus SPARKLE, respectively.

This could also be accompanied by examination of the genetic profile of all patients to identify which classification system can better identify patients of a particular stroke/TIA subtype confirmed by genetic markers significantly related to each stroke/TIA subtype. A clinical trial of this design would assess the prognostic value of each classification system. If it is proven that SPARKLE with TPA measurements contributes to better categorization of patients with large artery atherosclerosis or that

SPARKLE helps reduce the rate of recurrent strokes or TIAs, then ultrasound assessment of all patients should incorporate TPA measurements to guide treatment success. This has been shown to be clinically effective,[206] but it has not yet been tested in a clinical trial.

4.7 Conclusions

With more intensive medical therapy, a significant decrease in atherosclerotic risk factors was observed, with a significant decreasing trend in strokes/TIAs caused by large artery atherosclerosis or small vessel disease. However, there was a significantly increasing trend in cardioembolic stroke/TIA in patients presenting with minor stroke/TIA between 2002-2012 in the Thames Valley area in Ontario. Patients in 2012 were by one year younger compared to patients in 2002. Also, many patients with cardioembolic stroke/TIA and AF did not receive anticoagulant agents and the few of them who were on anticoagulant treatment did not achieve INR≥2.0. Our findings suggest that more intensive investigation of high and low-risk cardiac sources of embolism is required, and greater use of anticoagulant agents may be warranted. Also, further studies are required to investigate in more depth the risk factors leading to a minor stroke/TIA.

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APPENDIX A: Stroke/TIA Subtypes in Different Geographic Areas

NORTH AMERICA

Table 1.1 Stroke/TIA Subtypes in North America Using Classification Systems Other Than TOAST

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Gross et al[207]	1980	U.S.A. (Alabama) White and Black	135	Yes	No	7%	31%	15%	-	47%
LaRue et al[42]	1982-1985	U.S.A.	2141	Yes	No	73%	19%	8%	-	-
Foulkes et al[46]	1983-1986	U.S.A.	1273	Yes	Yes	9%	19%	27%	-	45%
Sacco et al[48]	1983-1986	U.S.A.-ALL	394	Yes	No	19%	14%	32%	-	35%
		U.S.A.-Whites	135			30%	18%	24%	-	27%
		U.S.A.-Blacks	177			14%	15%	29%	-	43%
		U.S.A.-Hispanic	82			13%	5%	52%	-	35%
Petty et al[208]	1985-1989	U.S.A. (Minnesota) - Mixed	454	Yes	Yes	16%	29%	16%	3%	36%
Jones et al[209]	1987-2008	U.S.A. (ARIC study)	861	Yes	Yes	56%	23%	21%	-	-

Table 1.1 Stroke/TIA Subtypes in North America Using Classification Systems Other Than TOAST (continue from page 92)

Woo et al[210]	1993	U.S.A. - Black	245	Yes	No	7%	23%	21%	7%	42%
Schneider et al[43]	1993-1994	U.S.A. – White and Black	1956	Yes	Yes	12%	20%	16%	3%	50%
White et al[59]	1993-1997	U.S.A. – White/Black/ Hispanics	427	Yes	Yes	15%	20%	20%	1%	45%

Table 1.2 Stroke/TIA Subtypes in North America Using TOAST Classification System.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
TOAST Trial[45]	1990-1997	U.S.A.	1268	Yes	No	18%	21%	24%	2%	34%
Saposnik et al[53]	1997-1999	Boston – Caucasian	479	Yes	No	21%	29%	23%	13%	-
		Argentina - Natives	361			9%	15%	29%	16%	-
Koch et al[47]	1998-2002	U.S.A. Miami	126	Yes	No	16%	17%	44%	3%	21%
Uchino et al[55]	2000-2002	U.S.A. Texas	402	Yes	Yes	14%	21%	19%	1%	44%
Rodriguez et al[44]	2005	U.S.A.	175	Yes	No	23%	19%	21%	6%	31%

SOUTH AMERICA

Table 2.1 Stroke/TIA Subtypes in South America Using Classification Systems Other Than TOAST

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Del Brutto et al[153]	1992	Ecuador-Hispanics	313	Yes	Yes	7%	14%	43%	6%	29%

Table 2.2 Stroke/TIA Subtypes in South America Using TOAST Classification System

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Saposnik et al[53]	1997-1999	Boston – Caucasian	479	Yes	No	21%	29%	23%	13%	-
		Argentina - Natives	361			9%	15%	29%	16%	-
Lavados et al[183]	2000-2002	Chile - Mixed	184	Yes	Yes	4%	27%	31%	-	38%
Rojas et al[49]	2003-2006	Argentina	535	Yes	No	10%	16%	41%	1%	32%
Vallejos et al[211]	2007-2009	Chile	380	Yes	No	29%	24%	15%	12%	20%

EUROPE

Table 3.1 Stroke/TIA Subtypes in Europe Using Classification Systems Other Than TOAST

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Carrera et al[23]	1979-2003	Switzerland (Lausanne)	5298	Yes	No	33%	25%	17%	9%	17%
Eriksson et al[28]	1986	Sweden	309	Yes	No	62%	23%	15%	-	-
Arboix et al[24]	1986-2004	Spain	2028	Yes	No	27%	28%	27%	5%	13%
Moulin et al[32]	1987-1994	France (Besancon)	1996	Yes	No	35%	31%	6%	6%	23%
Aszalós et al[25]	1990-1996	Hungary (Budapest)	500	Yes	No	55%	12%	30%	4%	-
Sempere et al[41]	1992-1994	Spain (Segovia)	235	Yes	Yes	11%	26%	31%	6%	26%
Modrego et al[31]	1994	Spain (Teruel)	1855	Yes	Yes	39%	16%	35%	-	11%
	2001					27%	24%	25%	-	24%
Markus et al[30]	1998	UK (London) -White	361			14%		13%		
Elbaz et al[27]	2000	France - Caucasian	460	Yes	No	23%	16%	21%	4%	36%
Polychronopoulos et al[33]	2001	Greece (Patra) - Caucasian	351	Yes	No	37%	20%	27%	-	16%

Table 3.1 Stroke/TIA Subtypes in Europe Using Classification Systems Other Than TOAST (continue from page 95)

Díaz-Guzmán et al[212]	2006	Spain	1779	Yes	Yes	35%	20%	18%	3%	24%

Table 3.2 Stroke/TIA Subtypes in Europe Using TOAST Classification System

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Kolominsky-Rabas et al[213]	1994-1998	Germany	583	Yes	No	13%	27%	23%	2%	35%
Henrotin et al[214]	1994-2004	France	1487	Yes	Yes	33%	36%	27%	-	5%
Roquer et al[215]	1995-2002	Spain	1339	Yes	No	19%	21%	11%	2%	46%
Poppert et al[38]	1995-2004	Germany	653			16%	22%	23%	5%	35%
Paciaroni et al[37]	1998	Italy	1284	Yes	No	21%	20%	37%	6%	16%
Grau et al[184]	1998-1998	Germany	5017	Yes	No	21%	26%	21%	4%	33%
Vemmos et al[54]	1998-2001	Greece - Caucasian	278	Yes	No	21%	31%	27%	-	21%
Sciolla et al[34]	1999	Italy	443	Yes	No	33%	17%	30%	3%	17%

Table 3.2 Stroke/TIA Subtypes in Europe Using TOAST Classification System (continue from page 96)

Jood et al[36]	1999-2003	Sweden - Caucasian	566	Yes		12%	16%	21%	9%	42%
Hajat et al[187]	1999-2005	UK - Mixed	1181	Yes	Yes	9%	28%	27%	3%	32%
Nencini et al[216]	2001-2002	Italy	93	Yes	No	28%	33%	23%	-	16%
Jerrard-Dunne et al[29]	2002	UK	1000	Yes	Yes	26%	12%	23%	9%	30%
Schulz et al[40]	2002-2003	UK	596	Yes	Yes	15%	22%	22%	6%	36%
Alzamora et al[35]	2003	Spain - Caucasian	196	Yes	Yes	19%	27%	29%	-	26%
Bejot et al[26]	2005-2006	France	332	Yes	Yes	36%	24%	27%	13%	
Sartori et al[39]	2006	Italy	71	Yes	No	21%	32%	34%	-	13%
Naess et al[185]	2006-2009	Norway	1098	Yes	No	11%	28%	15%	3%	41%
Ihle-Hansen et al[58]	2007-2008	Norway	210	Yes	No	11%	31%	31%	-	26%

AFRICA

Table 4. Stroke/TIA Subtypes in Africa Using TOAST Classification System

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Hoffmann et al[217]	1992-1998	South Africa - Mixed	972	Yes		27%	13%	27%	23%	10%
Sagui et al[152]	2003-2004	Dakar	75	Yes	No	1%	13%	20%	-	65%

ARAB COUNTRIES

Table 5.1 Stroke/TIA Subtypes in Arab Countries Using Classification Systems Other Than TOAST.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Awada et al[218]	1982-1991	Saudi Arabia	756	Yes	No	67%	-	33%	-	-
Rajeh et al[219]	1982-1992	Saudi Arabia	545	Yes	No	48%	21%	22%	5%	4%

Table 5.2 Stroke/TIA Subtypes in Arab Countries Using TOAST Classification System.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Al-Shammri et al[220]	1995-1999	Kuwait	62	Yes	No	31%	10%	60%	-	-
Deleu et al[186]	2006-2007	Arabian Gulf	760	Yes	No	39%	14%	36%	7%	4%

ASIA

Table 6.1 Stroke/TIA Subtypes in Asia Using Classification Systems Other Than TOAST.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Yokota et al[221]	1978-1997	Japan (Osaka)	1382	Yes	No	21%	27%	40%	12%	
Turin et al[181]	1988-2004	Japan - Asian	1389	Yes	Yes	21%	23%	54%	-	2%
Kitamura et al[222]	1992, 1997, 2002	Japan (Yao)	357	Yes	No	26%	16%	54%	-	5%
Adachi et al[223]	1994-1997	Japan (Tokyo)	171	Yes	No	31%	22%	43%	-	4%
Yip et al[224]	1995	China	676	Yes	No	17%	20%	29%	6%	29%
Kimura et al[225]	1999-2000	Japan	16922	Yes	No	33%	22%	39%	-	-
Ghandehari et al[226]	2001-2005	Iran (Khorasan)	1392	Yes	No	54%	12%	-	3%	20%
Kate et al[154]	2008-2009	India	118	Yes	Yes	31%	6%	30%	4%	28%

Table 6.2 Stroke/TIA Subtypes in Asia Using TOAST Classification System.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Tanizaki et al[104]	1961-1993	Japan	298	Yes	Yes	20%	19%	56%	-	4%
Kubo et al[51]	1961-1973	Japan	383	Yes	Yes	21%	11%	64%	-	4%
	1974-1986		383			21%	23%	54%	-	2%
	1988-2000		383			27%	24%	49%	-	0%
Sumer et al[227]	1996-2000	Turkey	266	Yes	No	9%	33%	25%	-	33%
Hong et al[179]	1999-2000	Korea	131	Yes	Yes	30%	14%	34%	23%	
Tan N.C. et al[180]	1999-2001	Singapore - Asian	109	Yes	Yes	28%	12%	44%	17%	
Liou et al[228]	2001-2002	Taiwan	587	Yes	No	41%	10%	44%	6%	
Liu et al[229]	2002	China	619	Yes	No	19%	26%	20%	-	35%
Jung et al[230]	2002-2010	Korea	36,191	Yes	No	36%	17%	25%	2%	20%
Sharma et al[56]	2003-2004	Singapore -Asians	481	Yes	No	14%	8%	48%	3%	27%
Lee et al[231]	2004-2006	Taiwan	533	Yes	No	26%	18%	33%	1%	22%
Wu et al[232]	2007-2008	Taiwan	1161	Yes	No	15%	12%	39%	2%	33%

OCEANIA

Table 7.1 Stroke/TIA Subtypes in Oceania Using Classification Systems Other Than TOAST.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Ward et al[155]	1986	Australia (Perth)	154	Yes	Yes	25%	14%	33%	-	29%

Table 7.2 Stroke/TIA Subtypes in Oceania Using TOAST Classification System.

Author	Year	Country-Ethnicity	# of Cases	Inpatients	Outpatients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Feigin et al[57]	2002-2003	New Zealand - Mixed	1032	Yes	Yes	6%	29%	11%	3%	51%
Leyden et al[233]	2009-2010	Australia (Adelaide)	238	Yes	Yes	16%	42%	11%	6%	25%

Table 8. Stroke/TIA Subtypes Using CCS Classification System

Author	Year	Country-Ethnicity	# of Cases	In-patients	Out-patients	LAA	CAE	SVD	Other Cause	Unknown Etiology
Ay et al[156]	2000-2006	U.S.A. (Massachusetts)	61	Yes	No	30%	46%	0%	10%	15%
Michel et al[178]	2003-2008	Switzerland (Lausanne)	1742	Yes	No	27%	32%	15%	9%	17%
Palm et al[157]	2006-2007	Germany	626	Yes	Yes	29%	35%	26%	1%	9%

APPENDIX B: Pilot Study Results

	SPARKLE Large Artery Atherosclerosis		**CCS Large Artery Atherosclerosis**	
	n	%	n	%
Evident	58	14.5	1	0.3
Probable	9	2.3	0	0
Possible	8	2	33	8.3
	SPARKLE Cardioembolic		**CCS Cardioembolic**	
	n	%	n	%
Evident	100	25%	0	0
Probable	17	4.3%	0	0
Possible	66	16.5%	45	11.3
	SPARKLE Small Vessel Disease		**CCS Small Vessel Disease**	
	n	%	n	%
Evident	9	2.3%	0	0
Probable	8	2%	0	0
Possible	20	5%	13	3.3
	SPARKLE Other rare or unusual causes		**CCS Other rare or unusual causes**	
	n	%	n	%
Evident	3	0.8	0	0
Probable	2	0.5	0	0
Possible	5	1.3	3	0.8
	SPARKLE Undetermined Causes		**CCS Undetermined Causes**	
	n	%	n	%
Cryptogenic	-		7	1.8
Incomplete Evaluation	70	17.5	272	68
Unclassified	25	6.3	26	6.5

APPENDIX C: Thames Valley Area Population[234, 235]

		2001	2006	2011
Oxford Country:	Blansford-Blenheim	7422	7149	7359
	East Zorra-Tavistock	7238	7350	6836
	South-west Oxford	7782	7589	7544
	Ingersoll	10977	11760	12146
	Tillsonburg	14052	14822	15301
	Woodstock	33269	35480	37754
	Zorra	8052	8125	8058
Elgin Country:	Aylmer	7158	7069	7151
	Bayham	6375	6727	6989
	Central Elgin	12293	12723	12743
	Dutton/Dunwich	3696	3821	3876
	Malahide	8777	8828	9146
	Southwold	4487	4724	4494
	St. Thomas	33303	36110	37905
	West Elgin	5464	5349	5157
Middlesex Country:	Strathroy-Caradoc	19154	19977	20978
	Southwest Middlesex	6144	5890	5860
	Adelaide-Metcalfe	3109	3135	3028
	Lucan-Biddulph	4201	4187	4338
	Middlesex Centre	14242	15589	16487
	North Middlesex	6901	6740	6658
	Thames Centre	12473	13085	13000
City of London			336539	352395
Muncee-Delaware Nation			0	167
Chippewa of the Thames First Nation			0	747
Total		573108	599538	619881

APPENDIX D. Comparison of Stroke/TIA Subtypes with Studies Using CCS.

	Country	Year	# of cases	LAA*	CAE*	SVD*	Other*	UND*
Ay et al.[156]	U.S.A.	2000 2006	61	30%	46%	0%	10%	15%
Michael et al.[178]	Switzerland	2003 2008	1742	27%	32%	15%	9%	17%
Palm et al.[157]	Germany	2006 2007	626	29%	35%	26%	1%	9%
Bogiatzi et al.	Canada	2002 2012	3445	33%	38%	10%	6%	13%

*LAA=Large-Artery Atherosclerosis, CAE=CArdioEmbolic, SVD=Small Vessel Disease, Other=Other rare or unusual causes, UND=Undetermined causes of stroke/TIA

APPENDIX E. 10-year Prognosis of Patients With Minor Stroke/TIA

	Stroke/TIA		All patients
	n	%	N
LAA*	127	11.2	1132
CAE*	153	11.8	1298
SVD*	38	10.7	354
Other*	46	20.8	221
UND*	56	12.7	440
Total	420	12.2	3445

*LAA=Large-Artery Atherosclerosis, CAE=CArdioEmbolic, SVD=Small Vessel Disease, Other=Other rare or unusual causes, UND=Undetermined causes of stroke/TIA

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Publications:

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