Survival, Stroke Recurrence and Functional Outcome after Lacunar Stroke

by

Cheryl S. Jaigobin

A thesis submitted in conformity with the requirements

for the degree of Master's of Science

Graduate Department of Institute of Medical Sciences

University of Toronto

Survival, Stroke Recurrence and Functional Outcome after Lacunar Stroke

Master's of Science, Institute of Medical Science, University of Toronto, 2001

Cheryl S. Jaigobin

Abstract

Objectives: 1.To assess stroke recurrence, survival and functional outcome in patients with lacunar stroke. 2. To determine if there are differences between patients with first and recurrent stroke and between patients with and without an embolic source.

Methods: A cohort of 147 patients with lacunar infarction admitted between January 1, 1993 and December 31, 1996 was followed until March 2000. Linkage with the Canadian Institute for Health Information (CIHI) discharge abstract identified recurrent stroke. Linkage with the Vital Statistics database identified deaths. Functional outcome was assessed using the Barthel Index.

Results: Survival at 5.5 years was 72 +/- 8 %. Stroke-free survival at 5.3 years was 75 +/-14%. Functional independence (Barthel=100) was identified in 63% of patients contacted. Patients with an embolic source had shorter survival times ($p<0.05$). Patients with recurrent stroke had worse functional outcome ($p<0.001$).

Conclusions: While patients with lacunar infarction have a high chance of independence and a low risk of stroke recurrence, survival was worse in patients with an embolic source and functional outcome was worse in patients with recurrent stroke.

Acknowledgments

This research would not have been possible without the support and guidance of my thesis committee supervisor, Dr. Paul O'Connor. In addition to serving as a committee member, Dr. Frank Silver, has provided mentorship, encouragement and constant support. The second committee member, Dr. Jack Tu, provided invaluable advice and assistance. Dr. Peter Austin provided statistical assistance.

Information about stroke recurrence was provided by the Institute of Clinical and Evaluative Sciences. Mr. Paul Inkila from the Vital Statistics Information System, Office of the Registrar General, Ministry of Consumer and Commercial Relations, provided access to death certificates.

I dedicate this thesis to my family for their unwavering support and encouragement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Chapter 1: Introduction

Stroke is defined by the World Health Organization as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin"[1]. This disease is the third leading cause of death in Canada[2]. The incidence is 50 000 per year and the prevalence is 300 000[3]. Twenty per cent of stroke survivors require placement in long-term care institutions and fifteen per cent require assistance with activities of daily living[2]. In one year, the direct and indirect costs of stroke in Ontario is estimated at $857 million[4] and $2.7 billion in Canada[5].

Stroke can be classified on the basis of location (cortical, subcortical, or brainstem) or pathology (ischemic or hemorrhagic). Ischemic stroke is further divided into subgroups according to mechanism (thrombotic, embolic, hemodynamic), clinical categories (atherothrombotic, cardioembolic, lacunar, other) and vascular territory[6]. One diagnostic system, the TOAST classification, incorporates both clinical features and the results of standard investigations to divide ischemic stroke in the following five etiological categories: large artery atherosclerosis, cardioembolic, small-artery occlusion (lacune), stroke of other determined etiology and stroke of undetermined etiology[7].

One subtype, lacunar stroke, refers to a subcortical or brainstem infarction secondary to small vessel disease. This comprises 19% of all strokes and 21%-25% of all cerebral infarctions[8,10,11]. Lacune is a French term traced to the writings of Durand-Fardel in his 1843 treatise on the softening of the brain[12]. He referred to a lacune as a small fluid-filled cavity that marked the healed stage of small regions of infarcted brain tissue. A lacunar stroke refers to a type of stroke with a distinct presentation, pathology, and pathophysiology.

The assumption is that these small infarcts result from occlusion of deep penetrating arterioles that arise from larger cerebral arteries. These vascular abnormalities have long been recognized in association with hypertension and diabetes. Associations with other vascular risk factors including tobacco use and hyperlipidemia have also been reported[13,14]. The small perforating branches of cerebral arteries supply the subcortical white matter of the brain, internal capsule, basal ganglia, thalamus and the brainstem. Lesions in these areas are associated with a number of clinical syndromes. While early writings described four syndromes, this number has grown to exceed seventy[15]. The five classical syndromes consist of pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, clumsy hand dysarthria and sensorimotor stroke[15]. A pure motor deficit refers to weakness of the face, arm and leg on one side of the body. A pure sensory deficit consists of numbness involving the same distribution. Ataxic hemiparesis refers to weakness and inco-ordination on the same side of the body. Clumsy hand dysarthria describes slurring of speech associated with clumsiness of one hand. A sensorimotor stroke consists the combination of sensory impairment and weakness of the same side. The remaining syndromes, collectively identified as miscellaneous syndromes, include the presence of additional neurological impairment such as eye movement abnormalities and movement disorders[16].

The evolution of our knowledge about the nature of lacunar stroke can be divided into three stages. The first stage consists of pathological investigations in the mid-nineteenth century. Following the initial description by Durand-Fardel, the nature of the lesion was the subject of interest. Proust postulated that these lesions were the result of a vascular lesion. It was suggested that they might be the result of infarction, hemorrhage or disorganization[17]. Marie and Ferrand offered the first clinico-pathological correlation. The neurological deficits

in patients with lacunar stroke identified at autopsy included weakness, clumsiness, sensory loss, dysarthria and dementia[18]. The next stage in the development of our knowledge about this stroke subtype occurred in the 1960's largely due to the work of one individual, C. Miller Fisher. His work included detailed descriptions of location, size, appearance (macroscopic and microscopic) of lacunes, correlation with clinical syndromes, description of the vascular anatomy and etiologic mechanisms. In a series of 1042 consecutive adults whose brains were examined at autopsy, Fisher identified lacunes in 114 (11%)[19]. Lesions were identified in the following regions of the brain: basal ganglia, pons, thalamus, caudate nucleus, internal capsule and subcortical white matter. Evidence of hypertension was reported in 97% of patients. Subsequent to this, the vascular supply to areas with lacunar infarction was studied. The basal ganglia and pons from four patients with a diagnosis of stroke prior to death was examined[20]. Fifty lacunes were identified and the arterial supply to these regions was studied microscopically in over 18 000 sections. Segmental disorganization resulting in occlusion was reported in walls of forty arterioles studied. This abnormality was later labelled *lipohyalinosis* and attributed to hypertension. The net result of Fisher's autopsy studies was the identificaton of a specific stroke subtype presenting as identifiable clinical syndromes due to well-defined lesions in specific anatomical locations caused by intrinsic disease of small perforating arterioles. This initiated the concept of the lacunar hypothesis. According to this hypothesis, "among patients with cerebral infarction of diverse causes, there are a number of distinct syndromes associated with small deep infarcts" which "result from the occlusion of single perforating arteries"[21]. In the third stage in the development of our understanding of lacunar stroke, the validity of this hypothesis was challenged. Improved neuro-imaging enabled detection of small lesions in the brain detected previously only by pathological

studies at autopsy. The radiological criteria for lacunar stroke were based on infarct size and location. Although the cerebral vasculature could not be visualized, small deep lesions were inferred to be the result of the type of small vessel disease described by Fisher. This assumption was subsequently challenged. It was argued that emboli, originating in the heart or from large proximal arteries, although generally responsible for causing large cerebral infarcts, could occlude small arteries and produce lacunar-like infarctions[22]. Small lesions identified previously as lacunar strokes were shown to also occur also on the basis of emboli in animal models[22,23]. The possibility of embolism was also raised in Fisher's prior studies. Serial sections of the arteries implicated in eleven internal capsule infarcts revealed patent and intact vessels in two cases[24]. An embolic source was postulated but this was not investigated. Clinical studies also reported both potential large artery and cardiac sources of emboli in patients with lacunar stroke[25,26]. While the term lacunar stroke has been applied to any small deep cerebral infarct, the arguments put forth imply that the pathophysiology cannot be assumed to be always related to intrinsic disease of small blood vessels. The possibility that emboli from the heart or large proximal arteries are responsible has to be considered. The mechanism of the infarct may also depend on the specific arterial supply to the affected area. The subcortical structures are supplied by perforating arteries from the middle cerebral artery, anterior cerebral artery, anterior choroidal artery, posterior cerebral artery and by the white matter medullary arteries. These arteries are not uniform in size. The white matter medullary arteries are larger arteries. It has been proposed that while infarcts which are less than 1.5 cm in diameter may be due to small-artery disease, infarcts which encompass the territory of several perforators or in those in the territory of the white matter medullary arteries are usually caused by emboli from larger arteries or the heart[27]. In the

classification of stroke, lacunar stroke represents a distinct stroke subtype with a distinct natural history. The true natural history is unknown because the subset with "pseudo-lacunar strokes", small deep infarcts on an embolic basis, may have contaminated previously published studies.

In this study, a cohort of patients with lacunar stroke was identified from all patients discharged from Toronto Western Hospital between 1993-1996 with a diagnosis of stroke. Patients with first and recurrent strokes were identified. For each patient, potential sources of emboli were determined. The specific study questions are "What is the natural history of lacunar stroke and are there differences between patients who have a potential source of embolus to the brain and those without.

The overall objective of this study was to assess the outcome of patients with lacunar stroke. There were six specific objectives: (a) to determine the number and proportion of patients who have a recurrent stroke, (b) to determine the stroke-free survival and the type of recurrent stroke (ischemic or hemorrhagic), (c) to determine the survival of patients with this stroke type, (d) to identify vascular risk factors (hypertension, diabetes, hyperlipidemia and tobacco use) and comorbid conditions, (e) to identify measures of secondary stroke prevention such as antiplatelet therapy (aspirin or ticlopidine) or anticoagulation(warfarin), (f) to assess functional outcome using the Barthel Index.

Chapter 2: Background

2.1 The natural history of stroke

The natural history of stroke has been investigated in two large population based studies. In the Framingham study, a cohort of 5184 individuals was followed prospectively for 26 years beginning in 1949[28]. Over this period, there were 394 initial strokes. The outcome events consisted of 30-day case fatality, survival at five and ten years, and stroke recurrence. Among initial strokes, 57% were atherothrombotic brain infarction and 16% were attributed to cerebral embolism. The other strokes included intracerebral hemorrhage (4%), subarachnoid hemorrhage (16%), transient ischemic attacks (10%) and strokes attributed to other causes (3%). The 30-day case fatality was 22% for all strokes. The cumulative survival rate at five years was 56% for men and 64% for women and 35% for all patients at ten years. The five-year cumulative recurrence rate for second stroke was 42% in men and 24% in women. Survival and stroke recurrence in residents of Rochester, Minnesota between 1955 and 1969 was assessed by a retrospective review of all hospital records in this area[29]. The population was estimated as 32,600 in 1955 and 52 629 in 1970. During this interval, there were 993 first strokes. Seventy-nine per cent of strokes were infarction (cerebral thrombosis and embolism), sixteen per cent were hemorrhages (intracerebral hemorrhage and primary subarachnoid hemorrhage) and five per cent were due to unknown causes. The one-month survival was 82% for patients with cerebral thrombosis and 67% for patients with cerebral embolism. The five-year stroke recurrence rate was twenty per cent. Both studies divided all strokes into ischemic and hemorrhagic subgroups and the mechanism of ischemic strokes was divided into the broad categories of atherothrombosis and embolic. While lacunar

strokes likely belong to the category of atherothrombosis, one must exercise caution in extrapolating the above information to this stroke subtype. A third community–based study, the Oxfordshire Community Stroke Project, addressed stroke recurrence in 675 patients after a first stroke[30]. First strokes were classified as infarction (81%), hemorrhage (15%) and unknown pathological type (5%). The cumulative risk of a first recurrent stroke was 19.9% at two years, 24.9% at three years, 28.2% at four years and 29.5% at five years. These values are comparable to both the Framingham and Rochester, Minnesota studies. However, only 7% of patients in this cohort were treated with antiplatelet therapy (6%) or anticoagulation (1%). These values may reflect stroke recurrence in untreated patients.

2.2 Lacunar and non-lacunar stroke

Subsequent studies have compared the natural history of lacunar stroke with nonlacunar stroke. In a retrospective case-control study of patients with a first stroke, survival and stroke recurrence was compared in 159 patients with lacunar stroke and 1223 patients with nonlacunar stroke[26]. In patients with lacunar stroke, the survival was 97% and 75% at one year and five year respectively using a Kaplan-Meier life table analysis. The survival was 72% at one year and 45% at five years in patients with nonlacunar stroke. There was no difference in stroke recurrence between the two groups. In a prospective case-control study, 88 patients with lacunar stroke and 103 patients with nonlacunar stroke were followed for a mean period of 28.1 months after presentation to hospital with a first stroke[31]. Patients with lacunar stroke had a significantly lower risk of stroke recurrence and lower mortality. Both of the above studies suggest better survival and a lower risk of recurrent stroke. However,

lacunar strokes were compared with a heterogeneous group including identifiable cardiac and large artery disease. The risk of recurrent stroke has been shown to depend on the type of cardiac abnormality and in the case of large artery atherosclerosis, the degree of stenosis[32,33]. In a more recent prospective study, 323 patients with infarction were followed for a mean period of 3.3 years[34]. Patients were classified into one of the following etiological subtypes: atherosclerotic, cardioembolic, lacunar and cryptogenic. The following cumulative risk of mortality for each subtype at five years was reported: atherosclerotic 61.9%, cardioembolic 68.4%, lacunar 15.4% and cryptogenic 52.8%. The following cumulative stroke recurrence risk at five years was reported: atherosclerotic 36.0%, cardioembolic 35.5%. lacunar 17.3% and cryptogenic 30.0%. When compared with other subtypes of ischemic stroke, patients with lacunar strokes had both a lower risk of mortality and stroke recurrence.

2.3 The natural history of lacunar stroke

Since the initial description of this stroke type in the nineteenth century. there has been some speculation regarding its outcome. Although there was little description of the spectrum of disease, a malignant form known as l'etat lacunaire was described initially by Pierre Marie[35]. This manifested clinically as chronic progressive deterioration often without clear stroke-like episodes and culminated in a variable combination of dementia. incontinence and gait abnormality. This state was attributed to the cumulative effect of multiple strokes. This form of disease is rarely encountered today. Possible reasons suggested by contemporary investigators include alternate diagnoses such as normal pressure hydrocephalus[36]. It has also been suggested that with the treatment of underlying risk factors such as hypertension, the more severe form of the disease is averted.

Since the mid-1980's, there have been six studies which have assessed the outcome of lacunar stroke. In these studies, mortality and survival, stroke recurrence and disability have been examined. The results are summarized in Table 1. A critical appraisal of these studies using current guidelines[37] is summarized in Table 2.

In summary, Gandolfo et al. concluded that survival after a lacunar stroke was less than the general Italian population[38]. Bamford et al. assessed survival (30 day and 1 year) and stroke recurrence after a first lacune. At one year, the authors reported 9.8% mortality and functional dependence in 34%[9]. In a subsequent report, Bamford et al. compared the natural history of lacunar stroke, over a one-year period, with other subgroups of cerebral infarction classified by vascular territory and extent of vascular territory[10]. Compared with partial and complete infarction of the anterior or posterior circulation, the authors reported better survival in patients with lacunar stroke. However, 28% of patients with lacunar stroke were functionally dependent at one year. Clavier et al. followed patients with a lacunar stroke over a four-year period[39]. The four-year survival and survival without recurrent stroke rates was greater than eighty per cent. Seventy-four per cent had a Barthel score of 100 indicating independence. The authors concluded that this stroke subtype is associated with a favourable prognosis. Salgado et al. reported a higher rate of recurrent stroke in their study[40]. However, the presence of both large artery and cardioembolic sources for stroke in this cohort may underlie this difference. Thirty-seven per cent of recurrent strokes were nonlacunar. Samuelsson et al. assessed functional outcome using measures of disability and handicap. Functional dependence increased over time and was attributed to recurrent strokes[41].

As illustrated in Table 1, comparing the results of these studies, the mortality ranged from 1-2% at one month and 10-11% one year after a first-time stroke. Other studies reported survival rates of greater than 80% four years after stroke. There was variability in the rates of recurrent strokes. Bamford et al. reported a recurrence rate of 11.8% during the first year after stroke. The survival rate free of stroke at two years was reported by Clavier et al as 94% and 81% by Salgado et al. Functional outcome was assessed in four out the six studies. The outcome criteria were not defined in one study[9]. Different scales were used in the remaining three studies and comparison is therefore limited. Samuellson et al. reported agreement between measures of disability and handicap[41]. Collectively these studies suggested functional impairment in a substantial proportion of patients after lacunar stroke.

One must exercise some degree of caution in interpreting the above studies. A number of concerns were raised in the critical appraisal summarized in Table 2. The most striking criticism is the method by which lacunar stroke was identified in each study. The cohort in each study was defined on the basis of the presentation with one of the four or five classical lacunar syndromes. CT or MRI was used to rule out other stroke types such as hemorrhage or stroke in the territory of large vessels. In four of the five studies, the presentation was presumed to be on the basis of small vessel changes without other investigations to identify other potential mechanisms. Salgado et al. used EKG, echocardiography and carotid duplex scanning to investigate for potential sources of emboli in their cohort. Potential cardiac sources were identified in 10% of subjects and a potential large artery lesion was identified in 37% of subjects. Another criticism is the inclusion of patients in two studies at an unspecified stage of disease. In the studies by Gandolfo et al. and Clavier et al., patients were enrolled after presentation with a stroke. The authors provided no detail about their

previous stroke history. In the remaining four studies, patients were enrolled after their first stroke. The measures of outcome were not clearly defined in four of the studies. In the two studies of the Oxfordshire Community Stroke Project conducted by Bamford et al.[9,10], a questionnaire was used to assess functional outcome. The contents of the questionnaire and the results of any validation studies were not provided. Based on the results of the questionnaire, a Rankin score was assigned. Based on this score, patients were dichotomized to functionally independent (0-2) or independent (3-5)[10]. It was also unclear as to what method was used to administer the questionnaire. Self-administration may be difficult in stroke patients. Research nurses were involved in this study. Reliability studies for the questionnaire were also not described. In the studies by Gandolfo et al. and Clavier et al., information regarding recurrent stroke was obtained at follow-up. Recall bias can affect the validity of the results of these studies. A final concern about the two studies by Bamford et al is the length of follow-up. A follow-up of one year is too short to accurately assess recurrent strokes.

The current study was designed to provide information about the natural history of patients with lacunar stroke. While patients with embolic sources have been recognized, to date, there has not been a systematic analysis of patients with lacunar stroke with and without potential embolic sources. The current study identified patients with a first or recurrent lacunar stroke. The presence of a potential embolic source was identified and classified as cardiac or large artery. The outcome criteria consisted of death, recurrent stroke and functional outcome. The Barthel Index was used in the assessment of functional outcome. Lastly, the period of follow-up represents one of the longest to date in the study of lacunar stroke.

Chapter 3: Methods

3.1 Research Design

This is a retrospective cohort study carried out in four stages. A detailed discussion of each stage will follow in the outline below. Patients with a discharge diagnosis of stroke at the Toronto Western Hospital between January 1, 1993 and December 31, 1996 were identified. Patients admitted between 1993 and 1995 were identified by the Clinical Modification of the ICD-9 (ICD-9-CM) code assigned at discharge. The Toronto Western Hospital Stroke Registry, a prospective clinical database of all patients admitted with stroke, started in January 1996, was used to identify patients admitted in 1996. A cohort of patients with lacunar stroke was assembled from the above group after review of the hospital record of each patient. The patient selection process is summarized in Figure 1. Deterministic linkage with the Canadian Institute for Health Information (CIHI) database was carried out to identify hospital admissions in Ontario for recurrent stroke and other forms of vascular disease, coronary artery disease and peripheral vascular disease. A second deterministic linkage with the Vital Statistics database was carried to identify any deaths in the cohort and to determine the date and cause of death. Patients were contacted by telephone for a functional outcome assessment using the Barthel Index.

3.1.1 Identification of patients with stroke: 1993-1995

Patients discharged from the Toronto Western Hospital with the most responsible diagnosis of ischemic stroke between January 1, 1993 and December 31, 1995 were identified. These patients were identified by the three and four digit ICD-9-CM codes

encoding cerebrovascular disease in a primary or secondary position. These codes are listed in Table 3.

3.1.2 Identification of patients with stroke: 1996

A list of patients was generated for patients admitted to the Acute Stroke Investigations Unit in 1996 with a diagnosis of cerebral infarction from the Toronto Western Hospital Stroke Registry.

3.1.3 Identification of patients with lacunar stroke

The medical record of each identified patient was reviewed by the investigator and a diagnosis of infarction, hemorrhage (intracerebral, subarachnoid, or subdural), other diagnosis or unknown diagnosis was made. Patients with infarction were classified as lacunar or nonlacunar stroke. The diagnosis of lacunar stroke was based on clinical and radiological criteria. The clinical criteria included presentation with one of the five classical syndromes. These consist of a pure motor deficit, pure sensory deficit, sensorimotor deficit, ataxic hemiparesis and clumsy hand dysarthria. Other less common lacunar syndromes were included if this diagnosis was made by a neurologist and if there was corresponding radiological evidence. Patients with deficits such as visual loss, language impairment and neglect, features suggesting a cortical lesion, were excluded. The radiological criteria consisted of a CT scan or MRI study of the head that was reported as normal or demonstrated a hypodense lesion with a diameter of less than 1.5 cm in the basal ganglia, subcortical white matter, or ventral pons. The results of investigations to identify a potential embolic source were reviewed for all patients. All patients admitted with stroke at this hospital are usually

investigated with an electrocardiogram, a transthoracic echocardiogram and carotid doppler studies. Potential cardiac and large artery sources of emboli were defined by the TOAST study[7]. High risk sources of cardiac emboli consisted of the following: mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation, left atrial or atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction (<4 weeks), dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis. A large artery embolic source was defined by the presence of greater than 50% stenosis or occlusion of the cerebral artery supplying the area of infarct. Patients who did not meet the criteria for lacunar stroke were designated nonlacunar strokes and were further subdivided by the vascular territory involved. This consisted of the following territories: middle cerebral artery, anterior cerebral artery, posterior cerebral artery, vertebrobasilar system, multiple and watershed. This was based on the clinical presentation and results of neuro-imaging studies. The designation of unknown territory was assigned to patients with cortical features but without supporting imaging studies.

For all patients with lacunar stroke, identifiers and details about their vascular history were collected by chart abstraction. This consisted of demographic information (health insurance number, medical record number, date of birth, gender), admission and discharge dates. This information is routinely recorded in the face sheet of all charts at Toronto Western Hospital. The address of patients, telephone numbers and the name of their family physician were recorded to enable contact for the functional assessment. Patients were excluded if they were not Ontario residents. The race of the patient was recorded if it was present in the hospital record. The type of lacunar syndrome was abstracted from the physicians' notes or determined based on the presenting complaint and deficits on physical

examination. The admission note, discharge summary and consultation notes were reviewed to establish the stroke history, and to identify comorbid illnesses and vascular risk factors such as hypertension, diabetes, hyperlipidemia and tobacco use. A comorbidity score was calculated using the Charlson Index[42]. This assigned weights of 1, 2, 3 or 6 to a series of predefined medical conditions listed in Table 4 to derive a total score. The results of CT, MRI and doppler ultrasound were abstracted from the typed radiology report. The results of echocardiography were abstracted from the chart. Treatment at the time of discharge was obtained from the typed discharge summary, the Dear Doctor letter and carbon copies of prescriptions completed for each patient at the time of discharge.

3.1.4 Linkage

Linkage between the cohort and the CIHI database were carried out to identify all subsequent admissions in any acute care hospital in Ontario during the follow-up period (between hospital discharge and March 31,1999). Demographic information is considered high-quality and can be used in deterministic linkage[43,44]. The variables for linkage consisted of date of birth, sex and the Health Card Number. By using this strategy, candidate pairs were generated between the cohort and CIHI data based on agreement of these variables. This linkage approach identified separations from acute care hospitals with IC9-9-CM codes matching discharge diagnoses of cerebral infarction (433, 434, 436), cerebral hemorrhage (430, 431), coronary artery disease (410. 411, 413) and peripheral vascular disease (440, 441, 442, 443). A second deterministic linkage between the cohort and Vital Statistics Information System was carried out to identify patients who died after discharge. A copy of the death certificate was provided for all patients who were deceased. This identified the

date and cause of death. The linkage strategies with the two administrative databases are summarized in Figure 2.

3.1.5 Functional Assessment

Surviving patients were notified by letter approximately two weeks before telephone contact was attempted. The letter provided a brief summary of the study (Appendix 1). After verbal consent was obtained from the patient or their designate, a functional assessment was conducted by telephone interview. This was assessed using the Barthel Index[45]. This measure assigns a score for each of ten activities of daily living based on how the subject performs each task daily. The activities and scores are listed in Table 5.

Each item in the Barthel Index is rated on whether the subject can perform the task independently, with some assistance or is dependent. Extensive guidelines in the scoring of the Barthel Index have been published[45]. The design of the Barthel Index allows it to be administered by a health professional or self-administered. This test can be administered by a telephone or face-to-face interview. For patients who were disabled or non-English speaking and could not provide answers, this information was provided by a caregiver or nurse. A score out of 100 was tabulated based on the above responses. A higher score signified better functioning.

3.2 Database

In this study, data was obtained from the hospital discharge summary, Toronto Western Hospital Stroke Registry, CIHI database, Vital Statistics Information System and a telephone assessment. Each database is described in detail in the following sections.

3.2.1 Hospital Discharge Summary

At the time of admission to the Toronto Western Hospital, a chart is initiated for each patient. During this process, a face sheet containing identifiers is created and placed at the front of each chart. This information consists of the following: name, address, health care number, medical record number, date of admission, age, sex and religion. At discharge, the second page of the face sheet is completed. The diagnoses and definitions contained on this page are listed in Table 6. This information is completed by physicians. Additional information is added by abstracters after review of the hospital record. Diagnoses, complications and procedures are subsequently translated into ICD-9-CM codes. After coding is completed, a computerized abstract is submitted to CIHI.

The accuracy of hospital discharge coding for stroke was assessed in two recent studies. Phillips et al. assessed the accuracy of discharge diagnoses at Camp Hill Medical Center in Nova Scotia[46]. Patients with a primary or secondary discharge diagnosis of stroke over a one-year period were identified by the ICD-9 codes 430-438. Of 381 patients identified, the records of 301 were reviewed. The authors reported that 35% (105/301) of patients in this study had a diagnosis of acute stroke. This number is admittedly low. However, patients with both primary and secondary diagnoses of stroke were identified. A secondary diagnosis of stroke refers to a previous stroke or a complication of a procedure. While the authors reported the number of acute strokes, they did not list the number of patients with a previous strokes. It is likely that the accuracy would be greater if the ICD-9 code was limited to the primary position. This study did not provide information on the type of acute stroke (infarction or hemorrhage) or the accuracy of each ICD-9 code. The accuracy of hospital discharge coding for stroke was also assessed by Mayo et al. [47]. Of patients discharged from

five acute care hospitals in Montreal with a primary diagnosis of acute stroke, a random sample of 96 hospital records were reviewed. Charts were reviewed independently by one of two neurologists. A number of charts were reviewed by both neurologists to test for inter-rater reliability. There was general agreement with the discharge diagnosis of stroke for 70-80% of all discharges. However, in the testing of inter-rater reliability, the two neurologists were in complete agreement for 56% of charts. Mayo's study indicated a higher accuracy in the discharge coding for stroke. A number of factors may account for the discrepancy between the two studies. Mayo et al. excluded the code 435 (transient cerebral ischemia). This is a transient event and there may have been uncertainty regarding the diagnosis of these episodes. As well, while Mayo et al. identified patients with a primary diagnosis of stroke. Phillips et al. included patients with a primary and secondary diagnosis of stroke. It is possible that few patients with acute stroke would have this code as the secondary diagnosis. Phillips et al. may have identified more patients with these criteria but without identifying more patients with acute stroke. Unlike the first study, Mayo et al. did not provide information on the ICD-9 codes. In the present study, patients with stroke codes in either a primary or secondary position were selected to ensure identification of all patients with lacunar stroke.

3.2.2 Toronto Western Hospital Stroke Registry

The Toronto Western Hospital Stroke Registry is a clinical database which contains a record of consecutive patients admitted with cerebral infarction since January 1, 1996. It is estimated that more than 90% of patients with cerebral infarction are admitted to the Acute Stroke Investigations Unit for investigations, observation and rehabilitation. The remaining

patients are admitted to the Neurology service. A Stroke Team composed of a physiotherapist, occupational therapist, speech pathologist, research nurse, social worker, neurologist, and physiatrist follows all patients. The Toronto Western Hospital Stroke Registry captures all patients followed by the Stroke Team. Data are entered into a Microsoft Access ® database by specially trained research nurses. This database contains demographic information (name, hospital record number, date of birth, gender). Additional information includes admission history, investigations, and in-hospital interventions. Discharge information includes date, disposition and secondary stroke prevention therapy. Each patient with ischemic stroke is classified into one of the following four subtypes as defined by the Oxfordshire Community Stroke Project (OCSP): lacunar infarct (LACI), total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI) and posterior circulation infarct (POCI)[10]. The completeness and accuracy of this database have not been studied.

3.2.3 Canadian Institute for Health Information (CIHI)

Information on admissions to acute care hospitals in Ontario for recurrent stroke was obtained by linkage with the CIHI database. CIHI is a non-profit, non-government federally chartered company established to provide health information for research. Abstracts containing demographic material, diagnoses and procedures from all acute care hospitals in Ontario are submitted to CIHI. At the time of discharge, trained hospital coders abstract this information. This information is then translated into ICD-9, ICD-9-CM, and the Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) codes before submission.

The CIHI database is complete in its coverage of the population of Ontario[48]. The completeness of demographic data (age, sex and place of residence) is 99%[48]. There are measures in place to maintain complete records. Abstracts with missing data are returned to hospitals for editing. The quality of the data in the CIHI database has been assessed by reabstraction studies. The matching of demographic information, diagnoses and procedures in the CIHI database compared with reabstracted material was assessed by two studies in Ontario. The first study conducted by the Ontario Hospital Association (OHA) compared 3000 records from 43 hospitals[49]. The second study compared 300 records from the Doctors Hospital, a community hospital[50]. Matching of demographic information was determined to be between 93-100% in the OHA study and 100% in the Doctors Hospital study. Discrepancies were reported in the coding of clinical diagnoses. In the OHA study, there was matching of the primary diagnosis in 81% of cases. Comorbid conditions and complications matched in 37% of records in this study. In the Doctors Hospital study, the matching of records for primary and secondary diagnoses was 95% and 96% respectively. In a third study, the CIHI database was compared with the entire hospitalization record in a sample of patients undergoing knee replacement surgery[51]. The reported results were in keeping with the above findings. Agreement between the two records in the coding of demographic information was greater than 99%. However, there was undercoding of both comorbid conditions and complications in the CIHI database.

Linkage with the CIHI database identified subsequent hospital admissions for recurrent stroke, coronary artery disease and peripheral vascular disease. The admissions were identified by ICD-9-CM codes. The accuracy of the ICD-9 codes for cerebrovascular disease in an administrative database, the Academic Medical Center Consortium, was recently

examined[52]. In this study, all patients with the following primary or secondary discharge codes from five academic medical centers were identified: 433 (occlusion and stenosis of precerebral arteries), 434 (occlusion of cerebral arteries), 435(transient cerebral ischemia), 436 (acute but ill-defined cerebrovascular disease). In a sample of 649 patients, the diagnosis of stroke, TIA or asymptomatic disease was made by chart review and telephone interview. The accuracy of ICD-9 coding for stroke was expressed as the percentage of patients with codes 433, 434 and 436 with a diagnosis of stroke after review of the hospital record. The accuracy of coding for TIA was expressed as the percentage of patients with code 435 with this diagnosis after review. The authors reported that 85% of patients with the code 434 and 77% of patients with the code 436 had an acute stroke. Similar findings were reported in the group with the code 435. In this group, 77% of patients had a TIA. The lowest accuracy was reported for the group with the code 433. In this group, only 6.1% of patients had a diagnosis of stroke. The authors concluded that although the ICD-9 coding scheme allowed identification of patients with specific diagnosis within administrative databases, there are limitations. Because of these results, ICD-9-CM codes 433, 434 and 436 were chosen to identify admissions for recurrent stroke in the CIHI database in the present study.

3.2.4. Vital Statistics Database

The Vital Statistics Information System is a division of the Office of the Registrar General in the Ministry of Consumer and Commercial Relations (MCCR). The MCCR collects and maintains information of births, adoptions, marriages, deaths and name changes in Ontario. At the time of death, a certificate of death is completed by the attending physician and a statement of death is completed by the funeral home. Both documents accompany the body

until the time of burial. After burial, the forms are directed to the municipality and then forwarded to the Office of the Registrar General for registration with the province of Ontario. The underlying cause of death is coded using the ICD-9 classification for deaths before January 1, 2000. The ICD-10 classification is used for deaths after January 1, 2000. The coverage and accuracy of this database has not been studied to date. Quality control is monitored internally and by Statistics Canada (Office of Registrar General, personal communications).

3.2.5. Barthel Index

For the functional assessment, a Barthel score was obtained by telephone interview. The ten items in the Barthel Index assessed the patients's present personal care and mobility. For subjects who were unable to provide this information, a caregiver (nurse or family member) was contacted. The Barthel Index is a measure of disability widely used in stroke studies. It is highly correlated with post-stroke status as measured by the Mathew, Toronto and Hemispheric Stroke scales[53]. There is also reported strong correlation with other stroke outcome measures including a neurologic status scale, a stroke severity scale, the Fugl-Meyer Scale which measures motor outcome, and with the activities of daily living and cognition subscales of the Level of Rehabilitation Scale[54]. Studies demonstrated both high reliability and validity in the use of the Barthel Index in patients with stroke. Colin et al. administered the scale to 25 patients in the following four ways: self-report, report by a nurse based on clinical impression, testing by a nurse, and testing by an occupational therapist. The measure of concordance, Kendall's coefficient of concordance, was 0.93[55]. Agreement was lower for transfers, feeding, dressing, grooming and toileting. In another reliability study, Roy et al.

reported an inter-rater correlation of 0.99[56]. The predictive validity of the Barthel Index has also been assessed. The admission score predicted the length of stay of stroke patients[57]. The score was also reported to be predictive of stroke mortality at six months[58]. The validity of this scale administered by telephone interview has been studied. The Barthel Index was assessed by both telephone and face-to-face interviews in 366 patients with a primary diagnosis of stroke or orthopedic condition discharged from a rehabilitation facility[60]. The per cent agreement between scores was greater than 90%. However, there was a trend for reporting of less disability in patients with moderate to severe impairment. Proxy-respondents were reported to be as good as self-respondents.

3.3 Linkage Strategies

A deterministic linkage strategy was used to link the cohort of patients with lacunar stroke with the CIHI database and with the Vital Statistics Information System. This approach generates linked records in two files if there is agreement on all or almost all of the variables. Candidate pairs of records are selected based on this agreement between identifier variables. There have been no studies evaluating deterministic matching with either of these databases. Probabilistic linkage, which assigns a numerical weight for each variable to estimate the probability that records are linked, was recently assessed to link a cohort of cardiac arrest patients identified in the Metro Toronto Ambulance database with either CIHI or the Vital Statistics Information System[61]. The identifying variables used included the following: first and last names, New York State Identification and Intelligence System code, date of event, date of death, city, admitting hospital number, mode of admission to hospital, age and sex. Using these variables, 91% of the cohort linked to one of the two databases.

3.4.Variables

The independent variables in this study consist of the following: date of birth, OHIP number, sex, most responsible diagnosis, hypertension, lacunar syndrome, diabetes, cardiac disease. The dependent variables consist of recurrent stroke, survival and functional outcome. The definitions of these variables are provided in Table 7 and 8.

3.5 Statistical Methods

3.5.1. Descriptive statistics

Descriptive statistics was used to describe the baseline clinical characteristics. Comparisons were made between patients with first time stroke and recurrent stroke and between patients with potential sources of emboli and those without. Comparisons of categorical variables were made using a Chi-square test. Comparisons were made for the presence or absence of risk factors. For patients with incomplete recording of risk factors, the risk factor was assumed to be absent for this analysis. Comparisons of continuous variables (age, Charlson comorbidity index scores) between these groups were made using a t-test.

3.5.2 Survival Analysis

The second part of data analysis was a survival analysis. Survival time was expressed in person-months. Life table analysis was carried out using a Kaplan-Meier survival curve for all patients with lacunar stroke. Survival curves were compared between patients with first and recurrent strokes and between patients with and without known potential sources of emboli using the log rank test. An association between baseline characteristics and survival

was evaluated by bivariate analysis using the log rank test. The baseline characteristics consisted of the following: age, sex, stroke subtype, race, comorbid disease, hypertension, diabetes, hyperlipidemia, tobacco use and secondary stroke prevention therapy. Age was dichotomized into the following two groups: ≤70 years and >70 years. Race was divided into the following three groups: Caucasian, Asian, other. Stroke prevention therapy was divided into groups of aspirin, ticlopidine and warfarin. Potential significant predictors of death were evaluated with a Cox proportional hazards regression analysis

3.5.3 Stroke Recurrence

The third part of analysis assessed stroke recurrence. A Kaplan-Meier curve was constructed for stroke-free survival with 95% confidence intervals. The data was also summarized in person-days.

3.5.4 Functional Outcome

The fourth part of the analysis examined functional outcome. Barthel scores were summarized in a histogram. Functional outcome scores were compared between patients with first and recurrent strokes and between patients with and without potential embolic sources using a t-test. A linear regression model was constructed which assessed the influence of the following predictor variables on functional outcome: age, sex, race, stroke subtype, hypertension, diabetes, hyperlipidemia, tobacco use, and secondary stroke prevention therapy. For patients with incomplete chart recording of vascular risk factors, this was regarded as absence of the risk factor for this analysis.

Statistical analyses were performed using SPSS version 10 software.

The study was submitted to and approved by the University Health Network Research Ethics Board.

Chapter 4: Results

4.1 All identified stroke patients

4.1.1 All stroke patients: 1993-1995

Between January 1, 1993 and December 30, 1995, there were 1716 discharges from Toronto Western Hospital with an ICD-9-CM code for stroke. One stroke code was present in 1443 discharges and two codes were present in the remaining 273 discharges. Stroke was identified as the most responsible diagnosis in 1367 discharges. The number of discharges identified for each stroke code is summarized in Table 9. A primary diagnosis refers to the most responsible diagnosis. A secondary diagnosis refers to the presence of a stroke code in any other position including comorbidity and complication. For discharges with a stroke code listed in the primary position, patients were assigned one of the following diagnoses after review of the hospital record: acute infarction, transient ischemic attack (TIA), intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, other diagnosis, and unknown diagnosis. This information is summarized for each ICD-9-CM code in Table 10.

After review of the hospital record, 656 discharges were identified as acute cerebral infarction. This was coded as the primary diagnosis in 563 discharges and as a secondary diagnosis in 93 discharges. In the patients with arterial territory infarction, 124(19%) were lacunar stroke. In 5% of patients, the information in the chart was insufficient to localize the arterial territory of the lesion. The distribution of arterial territory infarction is listed in Table 11.

In approximately one-quarter of the discharges, a diagnosis other than stroke was identified. These included both neurological and nonneurological disorders. A large

proportion of these were elective admissions for carotid endarterectomy (44%). A summary of the non-stroke diagnoses is provided in Table 12.

4.1.2 All stroke patients: 1996

A search of the Toronto Western Hospital Registry identified 242 admissions in 1996 for cerebral infarction. After review of the medical records of these patients, 166 admissions were for arterial territory infarction. This was more accurate than ICD-9-CM codes in identifying patients with cerebral infarction. As well, there were fewer patients with other non-stroke diagnoses. A summary of the broad diagnostic groups is provided in Table 13. The vascular distribution of arterial territory stroke is listed in Table 14. Most infarctions involved the middle cerebral artery territory. Sixteen per cent of infarctions were lacunar. This value is comparable to the results from 1993-1995.

4.2 Lacunar stroke

4.2.1 Baseline

After chart review, 149 patients were identified with admission to Toronto Western Hospital for lacunar stroke between 1993 and 1996. Two were non-residents (Australia and Vietnam) and were excluded from analysis. Follow-up data was obtained for a period averaging 54 +/- 19 months (ranging from 10 days to 86 months) for the 147 patients in the cohort. This represents 7896 person-months of follow-up. Patients were divided into groups of first time or recurrent stroke and by the presence or absence of a potential source of embolus to the brain. There were twenty-three patients with incomplete investigations. The subgroups are outlined in Table 15.

The hospital records were complete in their recording of patient demographic information (name, gender, date of birth, health card number). Information regarding discharge medication for secondary stroke prevention was also available for all patients in the cohort. Information regarding race was available for 98% of patients in this group. The recording of the presence or absence of vascular risk factors was less complete. Recording was highest for hypertension (96%) and diabetes (91%) and lowest for tobacco use (71%) and hyperlipidemia (49%).

The baseline characteristics of all patients with lacunar stroke are presented in Table 16. The mean age was 69 years. Approximately two-thirds of patients were male. The majority of patients were Caucasians. The second largest racial subgroup consisted of patients of Asian background. Remaining racial subgroups comprised ten per cent of the cohort. Most patients presented with a pure motor deficit. A sensorimotor presentation was second most frequent. Eighty-six per cent of patients had at least one vascular risk factor. Hypertension was the most commonly identified vascular risk factor. At the time of discharge from hospital, most patients were prescribed antiplatelet therapy for secondary stroke prevention. A comparison of baseline variables between patients with first and recurrent stroke and between patients with and without a potential source of embolus is summarized in Table 17. An association between the presence of hyperlipidemia and patients admitted with a recurrent stroke was identified ($p<0.02$). Because of incomplete recording of risk factors, a second analysis was conducted which excluded the missing values. The significance level in the comparison of the presence of hyperlipidemia between patients with a first and recurrent stroke was 0.374 and the association was not maintained.

All patients were investigated with a CT scan of the brain. Twenty-four patients were also investigated with MRI studies of the brain and one patient had a cerebral angiogram. The neuroimaging studies of 38 patients were normal or showed non-specific changes. In the remaining patients with radiographic evidence of lacunar infarction, 87 had one lesion, 17 had two lesions, 4 had three lesions and one patient had four lesions. Lesions were present in the basal ganglia (47), corona radiata or centrum semiovale (29), internal capsule (28), thalamus (15), pons (14), and external capsule (4). Four patients had additional cortical lesions which represented prior strokes.

4.2.2 Survival

There were 39 deaths at the end of the follow-up period. Death certificates were provided by the Vital Statistics database for 36 patients. Two deaths occurred outside of the country. A third death occurred one month prior to telephone contact and this information was not registered with the province of Ontario at the time of linkage. For these three patients, the date of death was provided by a family member or the family physician's office. The cause of death of these three patients and an additional death of unexplained cause are recorded as unknown. The remaining causes of death were divided into recurrent stroke, stroke related, other vascular and other. Seven deaths were attributed to recurrent stroke and two deaths were attributed to intracranial hemorrhage. Two deaths occurred within two weeks of the initial stroke. The causes were recurrent stroke and pulmonary embolus. Twenty-one deaths (54%) were attributed to other causes including pneumonia. Although possible, there was insufficient information to determine if these were aspiration pneumonias due to impairment related to the initial stroke. The cause of death is summarized in Table 18. Based on the

information provided by the death certificates, 27 deaths occurred in acute care hospitals and nine occurred at home (4), at a chronic care facility (2), at a nursing home (2) and at a retirement home (1).

The Kaplan-Meier survival curve for all patients with lacunar stroke is illustrated in Figure 3. The cumulative survival at 66 months was 71.39 +/- 8.38%. Survival between patients with first and recurrent stroke and between patients with and without a potential embolic source was compared using the log rank test. There was no difference in survival between patients with a first stroke and patients with a recurrent stroke. However, patients with a potential source of embolus had shorter survival times ($p<0.02$). This is illustrated in Figures 4 and 5. The results are summarized in Table 19. Possible associations between baseline characteristics and survival were evaluated by bivariate analyses using the log rank test. The potential significant predictors of survival were the presence of comorbid disease, age>70 years, diabetes and tobacco use. The results of the log rank test are summarized in Table 20. Because there was incomplete chart recording of vascular risk factors, this analysis was repeated for hypertension, diabetes, hyperlipidemia and tobacco use in which missing data was excluded. The results were similar to the initial analysis in Table 20. However, tobacco use was not a significant predictor in the second analysis. A Cox regression analysis was used to determine if the potential predictor variables retained their importance in the simultaneous context of each other. The presence of a potential source of embolus was included as a fifth covariate in this analysis. These results are summarized in Table 21. Comorbid disease, tobacco use and the presence of a potential embolic source were identified as significant covariates.

4.2.3 Recurrent Stroke

During the follow-up period (admission and March 31, 1999), there were 21 admissions to an acute care hospital for recurrent cerebral infarction. Fifty per cent of these occurred in patients followed after a first stroke with no potential embolic sources. There was one admission for intracranial hemorrhage, nine admissions for coronary artery disease and one admission for peripheral vascular disease. A Kaplan-Meier curve of stroke-free survival corrected for mortality is presented in Figure 6. The stroke-free survival at 1945 days (5.3 years) was 75 +/-14%.

4.2.4 Functional Outcome

Based on information obtained from the Vital Statistics Information System and from family members and family physician offices, 108 patients were alive at the completion of the follow-up period. Of these, 98 (91% of survivors) were contacted. Two declined to participate in the functional assessment. A Barthel score was obtained for 96 patients (89% of survivors). Among the ten who could not be reached, three had established residency outside of Ontario in Alberta, France and Vietnam. The Barthel scores are summarized in the histogram in Figure 7.

Of patients contacted, 19 (20%) were functionally dependent (Barthel <80), 17 (18%) had minimal disability (Barthel 80-95) and 60 (63%) were functionally independent (Barthel 100). Comparisons in the Barthel score were made with a t-test. These results are outlined in Table 22. A difference was present in the Barthel scores between patients who were followed after a first stroke and after a recurrent stroke with a $p<0.001$. Functional outcome was worse in patients followed after a recurrent stroke.

The influence of baseline variables on functional outcome was assessed using a linear regression model. The predictor variables consisted of age, sex, stroke subtype, race, comorbid disease, hypertension, diabetes, hyperlipidemia, tobacco use and secondary stroke prevention therapy. Because, initial analysis identified a worse outcome in patients with recurrent stroke, this was included as an additional predictor variable. Among these variables, diabetes and recurrent lacunar stroke were significant with a $p<0.05$. Both were associated with a worse functional outcome. The coefficient of determination (R^2) for this model was 0.700 and the adjusted R^2 was 0.490. This indicated the proportion of variance of the dependent variable that is explained by this model. The results of this analysis are summarized in Table 23.

Chapter 5: Discussion

5.1 Outcome after lacunar stroke

In this study of a cohort of patients followed after a lacunar stroke, the survival at 66 months was 71 +/-8%. Patients with a potential source of embolus to the brain had shorter survival times compared with patients without an identifiable embolic source. Among baseline variables, comorbid disease was identified as a predictor of death. Thirty-nine patients died by the completion of the follow-up period. One-third of deaths were attributed to recurrent stroke or the direct complications of a stroke. An additional 15% of deaths were caused by cardiac disease. During the follow-up period, there were 21 admissions to acute care hospitals for recurrent stroke. The stroke-free survival at 63 months was 75 +/-14%. Functional assessment was obtained for 89% of surviving patients. In this group, 63% were functionally independent, 18% had minimal disability and 20% were functionally dependent. Functional outcome was worse in patients followed after a recurrent stroke compared with patients followed after a first stroke. Both the presence of diabetes and recurrent stroke were associated with poorer functional outcome.

The outcome of patients in this study is in keeping with results from prior investigations. In the Framingham study, the five-year survival rate for all stroke subtypes was 56% in men and 64% in women[28]. Survival after lacunar stroke has been reported to be better than other stroke subtypes. In a case-control study, the five-year survival after lacunar stroke was 75% compared with 45% in nonlacunar stroke[26]. The results of the present study also compare favourably with a prior study assessing the natural history of lacunar stroke. Clavier et al. reported a four-year survival of 80%[39]. However, the five-year survival of 86% reported by Salgado et al. is higher than the current study. A possible explanation for this relates to the

difference in survival between patients with and without a potential source of embolus to brain. In this study, the five-year survival was 58% for patients with a potential source of embolus and 74% for patients without an identifiable embolic source. While this is the first study to report this difference, opponents of the lacunar hypothesis have suggested in the past that the two underlying mechanisms, intrinsic disease of small vessels and emboli, may be associated with different outcomes[22]. An alternate explanation for the lower survival in the current study is the presence of comorbid disease. This was associated with an increased risk of death. Thirty-five per cent of patients had a Charlson score of zero and the remaining 65% of patients had a Charlson score between one and four. This information was not provided in the prior outcome studies. Because a history of prior tobacco use was recorded in 71% of the medical records, any association between this risk factor and survival must be interpreted with caution.

The stroke recurrence reported in the current study also compares favourably with prior results. The five-year recurrence following any type of stroke was assessed in three prior studies. In the Framingham study, this was reported as 42% in women and 24% in men[28]. A comparable value of 30% was reported by the Oxfordshire Community Project[30]. A lower recurrence of 20% was reported in a population-based study from Rochester, Minnesota[29]. Two studies assessed stroke recurrence after lacunar stroke. Clavier et al. reported a stroke-free survival of 85% at three years[39]. Salgado et al. reported a higher recurrence rate of 63% at five years[40]. One possible explanation for the reported differences in stroke recurrence between these two studies and the current study is the method of identification of recurrent stroke. Linkage with the CIHI database identified the time to the first recurrent stroke. Subsequent strokes in the same patients were not identified. Also, recurrence rates may

differ because of differences in stroke care. The patients followed in present study were treated in a setting that provided organized stroke care including the treatment of underlying vascular risk factors and initiating secondary stroke prevention therapy. Over ninety per cent of patients were prescribed antiplatelet therapy or anticoagulation at discharge.

Functional assessment was obtained for 89% of survivors. The functional outcome was favourable. Eighty per cent of patients were functionally independent or had minimal disability at the completion of the follow-up period. Functional outcome assessed in prior studies of lacunar stroke are limited to follow-up periods of one and three years. Bamford et al. reported functional dependence in 28% of patients at one year[10]. Clavier et al. reported minimal or no disability in 82% of patients at one year[39]. In a third study, Samuellson et al. reported dependence in activities of daily living in 12% of patients evaluated at one year and in 24% of patients at three years post stroke[41]. The authors attributed increasing disability over time to recurrent strokes[41]. In the current study, patients followed after a recurrent stroke had poorer functional outcome at the completion of the follow-up period when compared with patients followed after a first stroke. While one must exercise caution in drawing conclusions, these results suggest increasing disability with additional neurological impairment. One must also recognize that comorbid disease can also contribute to functional impairment. In the current study, patients with diabetes identified at presentation with lacunar stroke, was a predictor of poor functional outcome. A possible explanation is disability secondary to the complications of diabetes. While differences were identified in survival, the present study did not identify differences in functional outcome between patients with and without a potential embolic source. There was a higher mortality in patients with an embolic source. This may have introduced a selection bias in functional

outcome assessment. It is possible that functional outcome was obtained in healthy survivors with minimal impairment. This should be addressed in further studies.

5.2 Limitations

Potential limitations have been identified at each stage of this study. The first is related to the available data in the chart abstraction process. Because this is a retrospective cohort study using a medical record review, there was no control over the clinical information recorded and the investigations for stroke. While most records contained the required baseline information, there was incomplete recording of vascular risk factors. This study also assessed for differences between the presence and absence of potential sources of emboli to the brain. The minimal baseline investigations to identify sources of emboli consist of an electrocardiogram, an echocardiogram and carotid dopplers (for patients with anterior circulation infarction). These studies were incomplete in 23% of patients. A second potential source of limitation is in the identification of a recurrent stroke. The CIHI database contains information about discharges from acute care hospitals in Ontario. There are situations in which recurrent strokes will not be captured by this database. Some patients with minor deficits may not seek medical attention. Others may consult their family physicians in their offices. Of those who present to an acute care hospital, some may be discharged from the emergency department. Patients in chronic care institutions may not be transferred to an acute care hospital for treatment. This group includes the elderly who are at increased risk of stroke because of age alone. Another potential limitation in this group is the accuracy of coding in this database. Two prior studies have reported an accuracy of 81% and 95% in the coding of clinical diagnosis[46,47].

A third area of concern is the presence of intervening factors which may have impacted on the functional assessment apart from the patient's lacunar stroke. A list of comorbid conditions was abstracted from the admission record and a comorbidity score was assigned to each patient. However, illnesses subsequent to the index stroke causing a functional impairment could not be identified in this study.

5.3 Future directions

This study assessed the survival, stroke recurrence and functional outcome of lacunar stroke. The follow-up period was one of the longest studied to date. This was the first study to conduct comparisons in outcome between patients followed after a first and recurrent lacunar stroke and between patients with and without a potential source of embolus. Patients with an embolic source had shorter survival times. However, only 17% of patients had an identifiable embolic source. This should be investigated with a larger sample size. It is recommended that with a larger cohort, large arterial and cardiac sources of emboli should be assessed separately.

One area that was not addressed in this study but should be mentioned is the appropriate treatment for the prevention of this stroke type. The results clearly demonstrate that this is not a benign type of stroke. Two deaths occurred within two weeks of presentation due to a direct complication and because of recurrent stroke. Patients followed after a recurrent stroke also had poorer functional outcome at the end of the follow-up period. Most patients in this study received antiplatelet therapy at discharge. This is based on the overwhelming evidence from clinical trials of the value of these agents in non-cardioembolic ischemic stroke. However these trials have not adequately determined the efficacy of antiplatelet

agents in specific stroke subtypes. Which antithrombotic agent is best and what the impact of risk factor modifications (for hypertension, diabetes, hyperlipidemia) as strategies for the secondary prevention of lacunar stroke are questions that remain unanswered. Future secondary stroke prevention studies must determine stroke subtypes, including lacunar infarction to answer these questions.

Of the baseline characteristics studied, diabetes was a predictor of poor functional outcome. One possible explanation is that diabetic patients tend to have more severe strokes. Alternatively, poor functional outcome could result from the non-stroke related complications of diabetes. Future studies are suggested to investigate the relationship between diabetes and stroke recurrence and the impact of glycemic control on both stroke recurrence and functional outcome.

Conclusions

This study is the first to provide evidence which suggests that among patients who present with a lacunar syndrome, survival is poorer in patients in patients with a potential source of embolus.

REFERENCES

1. WHO MONICA Project, Principal Investigators. The World Health Organization MONICA Project (monitoring trends and determinants of cardiovascular disease): a major international collaboration. Journal of Clinical Epidemiology 1988; 41: 105-114.

2. Statistics Canada. Causes of death 1993. Cat. 84-208 (annual).

3. Hodgson C. Prevalence and disabilities of community-living seniors who report the effects of stroke. CMAJ 1998; 159 (6Suppl): S9-S14.

4. Chan B, Hayes B. Cost of stroke in Ontario, 1994/95. CMAJ 1998; 159 (6Supp):S2-S8.

5. Moore R, Nao Y, Zhang J et al. Economic burden of illness in Canada 1993. Ottawa: Health Canada, Laboratory for Disease Control website (http:/www.hwc.ca/hpb/lcdc) 1997.

6. Whisnant JP, Basford JR, Bernstein EF, Cooper ES, Dyken ML, Easton JD, Little JR, Marler JR, Millikan CH, Petito CK, Price TR, Raichle ME, Robertson JT, Thiele B, Walker MD, Zimmerman RA. Classification of cerebrovascular diseases III. Stroke 1990:21:637-676.

7. Adams HP, Bendixen BH, Kappelle J et al. Classification of subtype of acute ischemic stroke. Stroke 1993; 24: 35-41.

8. Foulkes MA, Wolf PA, Price TR , Mohr JP, Hier DB. The stroke data bank: design, methods, and baseline characteristics. Stroke 1988;19:547-554.

9. Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, Pessin MS, Bleich HL. The Harvard Cooperative Stroke Registry: A prospective registry. Neurology 1978; 28:754-762.

10. Bamford J , Sandercock P, Jones L et al. The natural history of lacunar infarction: the Oxfordshire Community Stroke Project. Stroke 1987; 18: 545-551.

11. Bamford J, Sandercock P, Dennis M et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991; 337: 1521-1526.

12. Durand-Fardel M. Memoire sur une alteration particuliere de la substance cerebrale. Gaz Med Paris 1842; 10: 23-38.

13. Gandolfo C, Caponnetto C, Del Sette Mm Santoloci D, Loeb C. Risk factors in lacunar syndromes: a case-control study. Acta Neurol Scand 1988:77; 22-26.

14. You R. McNeil JJ, O'Malley HM, Davis SM, Donnan GA. Risk factors for lacunar infarction syndromes. Neurology 1995; 45:1483-1487.

15. Besson G, Hommel M. Lacunar syndromes. Advances in Neurology 1993; 62: 141-160.

16. Hommel M, Besson G. Clinical features of lacunar and small deep infarcts at specific anatomical sites. Advances in Neurology 1993; 62: 161-171.

17. Proust A. Des differentes formes de ramollissement du cerveal. These d'aggregation-medicine. Paris: 1866.

18. Ferrand J: Essai sur l'hemiplegie des viellards, Les lacunes de destintegration cerebrale. Paris Thesis, 1900, 1902.

19. Fisher CM. Lacunes: Small, deep cerebral infarcts. Neurology 1965; 15: 774-784.

20. Fisher CM. The arterial lesions underlying lacunes. Acta Neuropath (Berlin)1969; 12:1-15.

21. Bamford JM, Warlow CP. Evolution of the lacunar hypothesis. Stroke 1988; 19:1074-1082.

22. Millikan C, Futrell N. The fallacy of the lacune hypothesis. Stroke 1990; 20:1251-1257.

23. Swank RL, Hain RF. The effect of different sized emboli on the vascular system and parenchyma of the brain. Neuropathol EXP Neurol 1952;11: 280-299.

24. Fisher CM. Capsular infarcts-the underlying vascular lesions. Arch Neurol 1979;36:65-73.

25. Horowitz D, Tubrim S, Weinberger J et al. Mechanisms in lacunar infarction. Stroke 1992; 23: 325-327.

26. Sacco S, Whisnant J, Broderick J et al. Epidemiological characteristics of lacunar infarcts in a population. Stroke 1991; 22: 1236-1241.

27. Bogousslavsky J. The plurality of subcortical infarction. Stroke 1992; 23: 629-631.

28. Sacco RL, Wolf PA, Kannel WB, McNamara. Survival and recurrence following stroke-The Framingham study. Stroke 1982;13:290-295.

29. Matsumoto N, Whisnant JP, Kurland LT, Okazaki H. Natural history of stroke in Rochester, Minnesota, 1955 through 1969: an extension of a previous study, 1945 through 1954. Stroke 1973;4: 20-29.

30. J, Burn Dennis M, Bamford J, Sandercock P, Wade Derick, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. Stroke 1994;25:333-337.

31. Landi G, Cella E, Boccardi E, Musicco. Lacunar versus non-lacunar infarcts:pathogenetic and prognostic differences. Journal of Neurology, Neurosurgery and Psychiatry 1992:55:441-445.

32. Cerebral Embolism Task Force. Cardiogenic brain embolism: the second report of the Cerebral Embolism Task Force. Arch Neurol 1989; 46:727-743.

33. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. N Eng J Med 1991; 325:445-453.

34. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: The Northern Manhattan Stroke Study. Neurology 1994;44:626-634.

35. Marie P. Des foyers lacunaires de desintegration et de differents autres etats cavitaires du cerveau. Rev Med (paris)21:281, 1901.

36. Miller VT. Lacunar stroke: A reassessment. Arch Neurol 1983; 40: 129-134.

37. Laupacis A, Wells G, Richardson WS, Tugwell P for the Evidence-Based Medicine Working Group. Users' Guide to the Medical Literature V. How to use an article about prognosis. JAMA 1994;272:234-237.

38. Gandolfo C, Moretti D, Dall;Agata D et al. Long-term prognosis of patients with lacunar syndromes. Acta Neurologica Scandinavia 1986; 74: 224-229.

39. Clavier I, Hommel M, Besson G et al. Long-term prognosis of symptomatic lacunar infarcts. Stroke 1994; 25: 2005-2009.

40. Salgado A, Ferro J, Gouveia-Oliveira A. Long-term prognosis of first-ever lacunar strokes. Stroke 1996; 27: 661-666.

41. Samuellsson M, Soderfeldt B, Olsson GB. Functional outcome of patients with lacunar infarction. Stroke 1996; 27: 842-846.

42. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40: 373-383.

43. Roos LL, Wajda A. Record Linkage Strategies. Methods of Information in Medicine 1991;30:117-23.

44. Roos LL and Roos NP. Large databases and research on surgery. In: Ira M. Rutkow. editor,"Socioeconomics of Surgery." CV Mosby, St. Louis 1989, pp258-275.
45. McDowell I, Newell C. Measuring Health: A Guide to Ratings Scales and Questionnaires. Oxford University Press 1996.

46. Phillips SJ, Cameron K, Chung C. Stroke surveillance revisited. Canadian Journal of Cardiology 1993; 9 suppl D: 124D-125D.

47. Mayo N, Danys I Carlton J et al. Accuracy of hospital discharge coding for stroke. Canadian Journal of Cardiology 1993; 9: suppl D: 121D-124D.

48. ICES Practice Atlas. Patterns of Health Care in Ontario. 2nd edition.

49. Ontario Hospital Association, Ontario Ministry of Health, Hospital Medical Records Institute. Report of the Ontario data quality reabstracting study. Toronto; Ontario Hospital Association: 1991.

50. The Doctor's Hospital. Data Quality and Utilization Study. Toronto: Doctor's Hospital; 1992.

51. Hawker G, Coyte P, Wright J et al. Accuracy of administrative database for assessing outcomes after knee replacement surgery. Journal of Clinical Epidemiology 1997; 50: 265-273.

52. Benesch C, Witter DM, Willer AL et al. Inacurracy of the International Classification of Diseases (ICD-9-CM) in identifying the diagnosis of ischemic cerebrovascular disease. Neurology 1997; 49: 660-664.

53. Brown EB, Tiejten GE, Deveshar RK, Ramadan RM, Levine SR. Dietrich KL, Nazareno DF, Welch KMA. Clinical stroke scales: an intra- and inter-scale evaluation. Neurology 1990; 40 (S1): 352. Abstract.

54. Wood-Dauphinee SL, Williams JI, Shapiro SH. Examining Outcome measures in a clinical study of stroke. Stroke 1990; 21: 731-739.

55. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Studies 1988; 10: 61-63.

56. Roy CW, Jogneri J, Hay E et al. An inter-rater reliability study of the Barthel Index. Int J Rehabil Res 1987; 10: 356-367.

57. Granger CV, Dewis LS, Peters NC, Sherwood CC, Barrett JE. Stroke rehabilitation analysis of repeated Barthel measures. Arch Phys Med Rehabil 1979; 60: 14-17.

58. Wylie CM, White BK. A measure of disability. Arch Environ Health 1964; 8: 834-839.

59. Wylie CM. Gauging the response of stroke patients for rehababilitation. J Am Geriatric Soc 1967; 15: 797-805.
60. Korner-Bitensky N, Wood-Dauphinee S. Barthel Index information elicited over the telephone, is it reliable. Am J Phys Med Rehab 1995; 74: 9-18.

61. Waien SA. Linking large administrative databases: a method for conducting emergency medical services cohort studies using existing data. Academic Emergency Medicine 1997; 11: 1087-1095.

62. National Population Health Survey.

63. Concato J, Feinstein AR, Holford TR. The risk of determining risk of multivariable models. Annals of Internal Medicine 1993; 118: 201-210.

64. Kahn HA, Sempis CA. Statistical Methods in Epidemiology. Oxford University Press1989.

65. Hulley SB, Cummings SR. Designing Clinical Research. Williams & Wilkins 1988.

66. Fisher CM. Lacunar infarcts-a review. Cerebrovascular disease 1991; 1: 311-320.

67. Ostrow P, Miller L. Pathology of small artery disease. Advances in Neurology 1993;62: 93-123.

68. Inzitari D, Eliasziw M, Sharpe BL, Fox AJ, Barnett HJM for the North American Symptomatic Carotid Endarterectomy Trial Group. Risk factors and outcome of patients with carotid endarterectomy presenting with lacunar stroke. Neurology 2000;54:660-666.

69. Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982;32:871-876

Table 1: Summary of Studies Assessing Natural History of Lacunar Stroke

Author	Number of patients	Mortality/Survival	Stroke Recurrence	Functional Outcome
Gandolfo et al., 1986[38]	109	Survival rate lower than general Italian population	Average yearly recurrence rate: 4.74/100 patient years	
Bamford et al., 1987[10]	108	Case fatality: 1 month-1% 1 year-9.8%	11.8% during the first year	1 year: 66% functionally independent
Bamford et al., 1991[11]	133	Mortality: 30 days-2% 6 months-7% 1 year-11%	9% stroke recurrence at 1 year	Dependent: 30 days-36% 6 months-26% 1 year-28% Independent: 30 days-62% 6 months-66% 1 year-60%
Clavier et al.. 1994[39]	178	Survival rate: 2 year- 90+/-2.5% 4 year-80+/-4%	Survival rate free of stroke: 2 year-94+/-2% 4 year-85+/-3%	1 year: Barthel 100: 74% Barthel 80-95: 8% Barthel <79: 18%
Salgado et al., 1996[40]	145	Survival rate: 1 year-95% 2 year-92% 3 year-88% 4 year-86% 5 year-86%	Survival rate free of stroke: 1 year-90% 2 year-81% 3 year-71% 4 year-66% 5 year-63%	
Samuellson et al., 1995[41]	100			1 year 12% dependent in ADL 3 year 24% dependent in ADL

Table 2: Critical Appraisal of Outcome Studies

Appraisal Guidelines	**Gandolfo et al.,1986[38]**	**Bamford et al., 1987[10]**	**Bamford et al., 1991[11]**
Sampling strategy	Consecutive patients	Consecutive patients	Consecutive patients
Sample criteria for selection	Lacunar strokes defined by clinical syndrome and CT. Not investigated for embolic source.	Lacunar strokes defined by clinical criteria and CT. Not investigated for embolic source.	Lacunar strokes defined by clinical criteria and CT. No investigations for embolic source.
Stage of disease of patients in sample	Recruited after an ischemic stroke. Stage not given.	Followed after first Stroke.	Followed after first stroke.
Follow-up duration and completeness	Seven year follow-up. 107/109 patients	1 year (short)	1 year (short) Complete follow-up
Outcome criteria	1. Death (certificates) 2. Recurrent stroke (did not specify how this was determined)	1. Death (certificates) 2. Recurrent stroke assessed by neurologist if suspected 3.Functional outcome assessed by questionnaire (no details).	1.Death 2. Recurrent stroke diagnosed by neurologist if suspicion raised by questionnaire. 3.Disability: Rankin scale
Adjustment for prognostic factors and treatment	No Therapy not specified	No	No
Results- Likelihood of Outcome events	Expressed as survival rate and recurrence rate curves (Merrell and Shulman) over 7 years	1.Survival-case fatality rate 2. Recurrent stroke: 1 year recurrence rate 3..Functional outcome: % of patients independent at 1 month and 1 year	1.Survival:case fatality rate (30 days, 1year). 2.Recurrent stroke: rate at one year 3.Functional status: depend or independ at 1 mth, 6 mths, 1yr
Results- Precision of estimates	No confidence Intervals	95% confidence intervals	95% confidence intervals

Table 2 continued: Critical Appraisal of Outcome Studies

Appraisal Guidelines	**Clavier et al., 1994[39]**	**Salgado et al., 1995[40]**	**Samuellson et al., 1995[41]**
Sampling strategy	Consecutive patients	Consecutive patients	Consecutive patients
Sample criteria for selection	Lacunar strokes Defined by clinical Syndrome and CT. Not investigated For embolic source	Lacunar strokes defined by clinical syndrome and CT. Investigated for embolic sources but not analysed separately	Lacunar strokes defined by clinical syndrome and MRI. Not investigated for embolic sources.
Stage of disease of patients in sample	Stage of disease not Given	Enrolled after first Stroke	Enrolled after first Stroke
Follow-up duration and completeness	Follow-up period of 35+/-22 months. Followed 172/178 patients	Median follow-up of 39 months (range of 1-60 months). Followed 133/134	Followed for 3 years . Followed 76/81 Patients
Outcome criteria	1. Death: physician records, town hall 2. Recurrent stroke: Based on patient recall at follow-up. 3. Functional assessment Based on Barthel Index.	1. Death: observation, chart review, information from family or physician 2. Recurrent stroke based on patient recall.	1.Recurrent stroke (did not specify how this was determined). 2.Functional outcome: Rankin Scale. Katz's Index of ADL, Oxford Handicap Scale. 3. Cognitive: Mini-mental state exam
Adjustment for prognostic factors and treatment	No	No	No
Results- Likelihood of outcome events	Expressed as survival and stroke-free survival curves.	Expressed as survival and stroke-free survival curves	Correlation (Goodman-Kruskal)
Results- Precision of estimates	Confidence intervals Provided	Confidence intervals provided	

Table3: ICD-9-CM codes for cerebrovascular disease

ICD-9-CM code	Definition
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
433	Occlusion and stenosis of precerebral arteries
434	Occlusion of cerebral arteries
435	Transient cerebral ischaemia
436	Acute but ill-defined cerebrovascular disease
437.0	Cerebral atherosclerosis
437.1	Other generalized ischemic cerebrovascular disease

Table 4: Charlson Comorbidity Index

Assigned weights for disease	Condition
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver failure Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

Table 5: Activities of daily living and scoring guidelines of the Barthel Index

Activity	**With help**	**Without help**
Feeding	5	10
Transfer from wheelchair to bed and return	5-10	15
Personal toilet (grooming)	0	5
Getting on and off toilet	5	10
Bathing self	0	5
Walking on level surface	10	15
Ascend and descend stairs	5	10
Dressing	5	10
Controlling bowels	5	10
Controlling bladder	5	10

Table 6: Definitions of Diagnoses Recorded on Toronto Western Hospital Discharge Summary

Diagnosis	**Definition**
Most responsible diagnosis	The one diagnosis which describes the most significant condition of a patient which causes the stay in hospital. In a case where multiple diagnoses may be classified as most responsible, the diagnosis responsible for the greatest length of stay is recorded
Co-morbidities	The diagnoses describing other important conditions of the patient which usually have a significant influence on the patient's length of stay.
Complication	The diagnosis describing a condition arising after the beginning of hospital observation and/or treatment.
Secondary diagnosis	The diagnosis describing a condition for which a patient may (or may not) have received treatment but did not significantly contribute to the patient's length of stay.
Operations and other special procedures	Operations and procedures considered to be the most significant during the patient's hospital stay.

Table 7: Definitions of Independent Variables

Variable	Definition
Date of birth	Six digit code representing date, month and year on hospital face sheet
OHIP number	Hospital insurance number coded on face sheet
Sex	Male or female, coded on face sheet
Most responsible diagnosis	ICD-9-CMcodes:430,431,432,433,434,436,437.0, 437.1
Race	One of the following: Aboriginal, African, Asian, Caucasian, East Indian, Hispanic, Pacific Islander, Other. Determined from in-patient chart[56].
Lacunar syndrome	One of the following: pure motor deficit, pure sensory deficit, ataxic hemiparesis, clumsy hand dysarthria, sensorimotor deficit. Determined by clinical deficit at presentation.
Diabetes	Recorded as present, absent or unknown. Present if charted, or if the use of oral hypoglycemic agent or insulin is documented in hospital chart. Absent if reported as negative. Unknown if no information.
Hypertension	Recorded as present, absent or unknown. Present if diagnosis is charted or if use of antihypertensive agent is documented in hospital chart.
Hyperlipidemia	Recorded as present, absent or unknown. Present if diagnosis is charted of if any of the following parameters in fasting lipids: total cholesterol >5.2, LDL >3.4, TG >2.3.
Tobacco use	Recurrent as present (current, or remote) or absent.
Comorbid conditions	Any concurrent medical illness. A Charlson comorbidity index score was calculated for each patient based on comorbid conditions present[42].
Antiplatelet	Use of aspirin or ticlopidine at discharge
Anticoagulation	Use of warfarin at discharge

Table 8: Definitions of Outcome Variables

Variable	**Definition**
Cerebral infarction	ICD-9-CM codes 433, 434, 436
Cerebral hemorrhage	ICD-9-CM codes 430, 431
Coronary artery disease	ICD-9-CM codes 410, 411, 413
Peripheral vascular disease	ICD-9-CM codes 440-443
Mortality	Death identified by chart review, recorded by Vital Statistics Information System, or by contact with family or family physician
Functional Outcome	Barthel Index score 100: independent 80-95: minimal disability <80: significant disability

Table 9: Number of discharges identified for each stroke code between 1993-1995

ICD-9-CM stroke code	Diagnostic code in primary position	Diagnostic code in secondary position
430	66	9
431	213	83
432	8	2
433	258	42
434	344	112
435	105	81
436	356	293
437	17	0

Table 10: Diagnosis assigned after review of medical records identified with an ICD-9-CM stroke code in primary position between 1993-1995

ICD-9-CM Code	Diagnosis	Number
430	Subarachnoid hemorrhage	56 (85%)
(n=66)	Intracerebral hemorrhage	4 (6%)
	Other diagnosis	3 (5%)
	Chart unavailable	3 (5%)
431	Intracerebral hemorrhage	177 (83%)
(n=213)	Other diagnosis	22 (10%)
	Chart unavailable	8 (4%)
	Infarct	4 (2%)
	Diagnosis unknown	2 (1%)
432	Subdural hematoma	6 (75%)
(n=8)	Intracerebral hemorrhage	2 (25%)
433	Other diagnosis	208 (80%)
(n=258)	Infarct	34 (13%)
	Diagnosis unknown	7 (3%)
	TIA	6 (2%)
	Chart unavailable	3 (1%)

ICD-9-CM Code	Diagnosis	Number
434	Infarct	293 (85%)
(n=344)	Other diagnosis	19 (6%)
	Diagnosis unknown	14 (4%)
	Intracerebral hemorrhage	12 (4%)
	Chart unavailable	4 (1%)
	TIA	2 (1%)
435	Infarct	47 (45%)
(n=105)	Diagnosis unknown	27 (26%)
	TIA	21 (20%)
	Other diagnosis	8 (8%)
	Chart unavailable	1 (1%)
	Subarachnoid hemorrhage	1 (1%)
436	Infarct	185 (52%)
(n=356)	Other	57 (16%)
	Diagnosis unknown	45 (13%)
	Intracerebral hemorrhage	29 (8%)
	Chart unavailable	29 (8%)
	TIA	4 (1%)
	Subdural hematoma	4 (1%)
	Subarachnoid hemorrhage	1

ICD-9-CM Code	Diagnosis	Number
437.1, 437.2	Other diagnosis	6
(n=17)	Infarct	2
	Subarachnoid hemorrhage	1
	Chart unavailable	1

[a]191 (74%) discharges with code 433 in the primary position were for endarterectomy

Table 11: Subtypes of arterial stroke identified after hospital record review

Stroke Subtype	**Number**
Lacunar stroke	124 (19%)
Anterior cerebral artery territory	10 (2%)
Middle cerebral artery territory	295 (46%)
Posterior cerebral artery territory	31 (5%)
Vertebrobasilar territory	102 (16%)
Multiple territories	49 (8%)
Watershed	4 (1%)
Unknown	31 (5%)

Note. Subtypes are expressed as a percentage of the total number of acute ischemic strokes identified after hospital record review

Table 12: Non-stroke diagnoses with ICD-9-CM stroke codes (1993-1995)

Neurological disorders or procedures	**Number**
Carotid endarterectomy	207 (44%)
Cerebral angiography	17 (4%)
Aneurysm-surgical clipping	10 (2%)
Brain tumor	46 (10%)
Seizure	32 (7%)
Myelopathy	18 (4%)
Spinal stenosis	16 (3%)
Myopathy or neuropathy	7 (1%)
Head injury	7 (1%)
Migraine	5 (1%)
Blocked lumboperitoneal shunt	4 (1%)
Dementia	3 (1%)
Carotid cavernous fistula	2 (0%)
Vestibulopathy	2 (0%)
Parkinson's disease	2 (0%)
Demyelination	1 (0%)
Nonneurological disorders	
Cardiac disease	17 (4%)
Limb fracture	16 (3%)
Pneumonia	15 (3%)
Infection	9 (2%)
GI (abdominal pain, peptic ulcer disease)	8 (2%)
Metabolic abnormality	7 (1%)
Psychiatriac	6 (1%)
Ophthalmological surgery (cataract, corneal transplant)	6 (1%)
Failure to thrive	1 (0%)

Table 13: Diagnoses of patients identified with cerebral infarction in Toronto Western Hospital Stroke Registry (1996) after medical record review

Diagnosis after medical record review	**Number**
Arterial Infarction	165 (68%)
Venous Infarction	1
Intracerebral hemorrhage	16 (7%)
TIA	17 (7%)
Diagnosis indeterminate	21 (9%)
Other diagnosis	16 (7%)
Medical record incomplete or unavailable	6 (2%)

Table 14: Vascular territory of arterial stroke of patients hospitalized in 1996

Stroke subtype	**Number of patients**
Lacunar	25 (15%)
Middle cerebral artery territory	88 (53%)
Anterior cerebral artery territory	3 (2%)
Posterior cerebral artery territory	12 (7%)
Vertebrobasilar territory	23 (14%)
Multiple territories	12 (7%)
Unknown	2 (1%)

Note. Subtypes are expressed as a percentage of the total number of acute ischemic strokes identified after hospital record review

Table 15: Cohort of patients with lacunar stroke

Potential source of embolus	**First stroke**	**Recurrent stroke**
No embolic source		
Investigations complete	83 (56%)	15 (10%)
Investigations incomplete	16 (11%)	7 (5%)
Embolic source		
Cardiac	13 (9%)	6 (4%)
Large artery	6 (4%)	0
Cardiac and large artery	1(1%)	0

Table 16: Baseline characteristics of patients with lacunar stroke

Variable	Results
Age	Mean: 69 years (range 37-92)
Sex	Male: 93 (63%) Female: 54 (37%)
Race	Caucasian: 96 (65%) Asian: 31 (21%) African: 6 (4%) East Indian: 3 (2%) Other: 4 (3%) Pacific Islander: 1 (1%) Unknown: 6 (4%)
Stroke subtype	Pure motor: 92 (63%) Sensorimotor: 21 (14%) Sensory: 11 (8%) Ataxic hemiparesis: 15 (10%) Clumsy hand dysarthria: 3 (2%) Other:5 (3%)
Hypertension	Present: 86 (59%) Absent: 55 (37.4%) Unknown: 6 (4.1%)
Diabetes	Present: 51(35%) Absent: 83 (56%) Unknown: 13 (9%)
Hyperlipidemia	Present: 47 (32%) Absent: 25 (17%) Unknown: (51%)

Variable	Result
Tobacco use	Present: 61 (41%) Absent: 43 (29%) Unknown: 43 (29%)
Discharge medications	Aspirin: 94 (64%) Ticlopidine: 29 (20%) Warfarin: 14 (10%) None: 10 (7%)

Table 17: Comparison of baseline variables between patients with first and recurrent stroke and between patients with and without a potential source of embolus

Variable	Comparison groups	Significance level
Age	First and recurrent stroke	0.624
	Potential embolic source present and absent	0.059
Comorbidity	First and recurrent stroke	0.154
	Potential embolic source present and absent	0.065
Hypertension	First and recurrent stroke	0.677
	Potential embolic source present and absent	0.665
Diabetes	First and recurrent stroke	0.240
	Potential embolic source present and absent	0.643
Hyperlipidemia	First and recurrent stroke	0.025
	Potential embolic source present and absent	0.712
Tobacco use	First and recurrent stroke	0.601
	Potential embolic source present and absent	0.153

Table 18: Cause of death in cohort of patients followed after lacunar stroke

Cause of death	**All patients (n=39)**	**Patients without an embolic source (n=26)**	**Patients with an embolic source (n=12)**
Recurrent stroke	7(18%)	3	4
Intracranial hemorrhage	2 (5%)	2	0
Direct sequelae of stroke[a]	3 (8%)	3	1
Cardiac	6 (15%)	6	0
Other-pneumonia	5 (13%)	3	2
Other-sepsis	3 (8%)	2	1
Other-COPD	2 (5%)	2	0
Other-cancer	2 (5%)	1	1
Other-metabolic acidosis	1 (3%)	1	0
Other-pancreatitis	1 (3%)	1	0
Other-cirrhosis	1 (3%)	0	1
Other-aortic aneurysm	1 (3%)	0	1
Other-general debility	1 (3%)	1	0
Other-unknown	4 (10%)	3	1

[a] Includes 2 deaths due to aspiration pneumonia and pulmonary embolus

Table 19: Comparison of survival in patients with first and recurrent stroke and with and without a potential source of embolus

Comparison groups	**Log rank statistic**	**Significance**
First and recurrent stroke	1.88	0.17
Embolic source present and absent	5.60	0.02

Table 20: Bivariate analysis of relationship between baseline variables and survival

Baseline Variable	**Log rank statistic**	**Significance**
Age	3.94	0.0472*
Sex	0.84	0.3581
Stroke subtype	0.45	0.5023
Race	0.69	0.4071
Comorbid disease	16.22	0.0001*
Hypertension	2.36	0.1242
Diabetes	6.50	0.0108*
Hyperlipidemia	0.15	0.6962
Tobacco use	4.54	0.0300*
Stroke prevention therapy	0.83	0.3616

Table 21: Cox regression analysis of potential predictors of survival

Variable	B (estimated coefficient)	Wald statistic	Significance Level
Age	0.578	2.769	0.096
Comorbid disease	1.634	6.594	0.010*
Diabetes	0.556	2.308	0.129
Tobacco use	-0.911	6.455	0.011*
Presence of potential embolic source	0.718	3.866	0.049*

Table 22: Comparison of functional outcome between patients with first and recurrent stroke and between patients with and without a potential source of embolus

Comparison Groups	**T statistic**	**Significance Level**
First and recurrent stroke	3.773	0.001
Embolic source present and absent	2.012	0.134

Table 23: Multiple regression analysis of baseline variables and functional outcome

Predictor variable	Standardized Beta	Level of significance
Age	-0.171	0.435
Sex	-0.236	0.100
Race	0.223	0.130
Stroke subtype	0.037	0.767
Comorbid disease	0.128	0.553
Diabetes	-.0.313	0.044
Hypertension	-0.273	0.088
Hyperlipidemia	0.277	0.071
Tobacco use	0.051	0.728
Secondary prevention therapy	-0.090	0.505
Stage of disease (first or recurrent stroke)	-0.339	0.021

Figure 1: Summary of Patient Selection Process

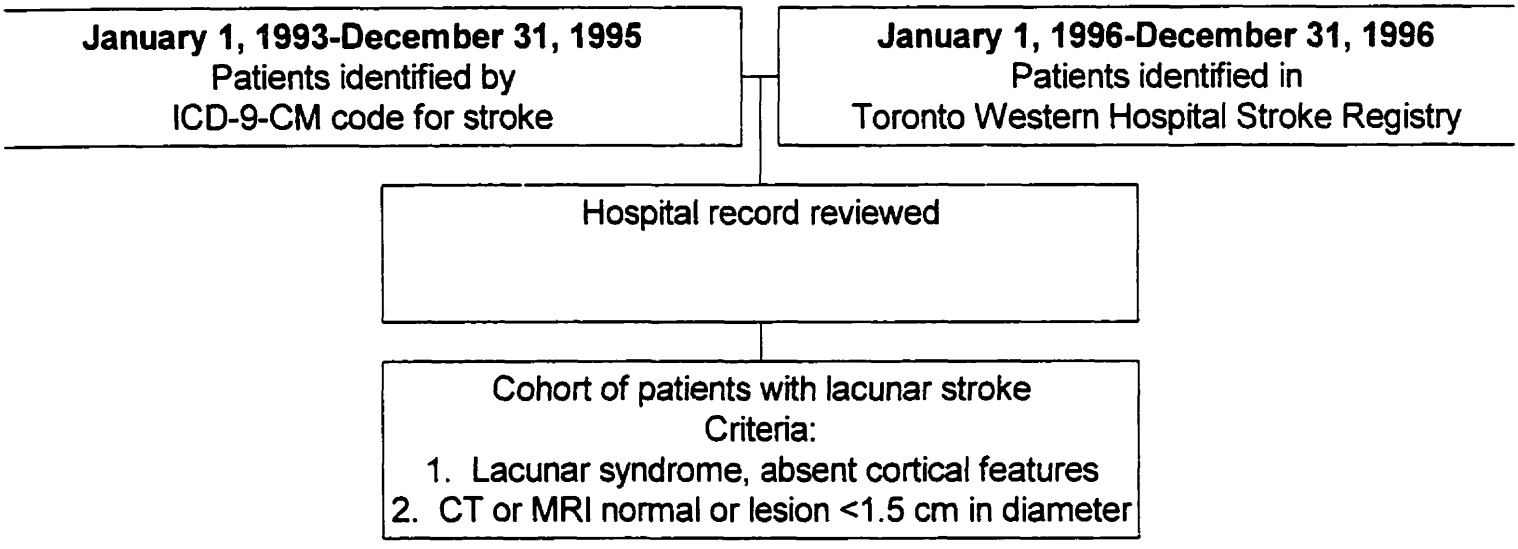


Figure 2: Linkage with Administrative Databases

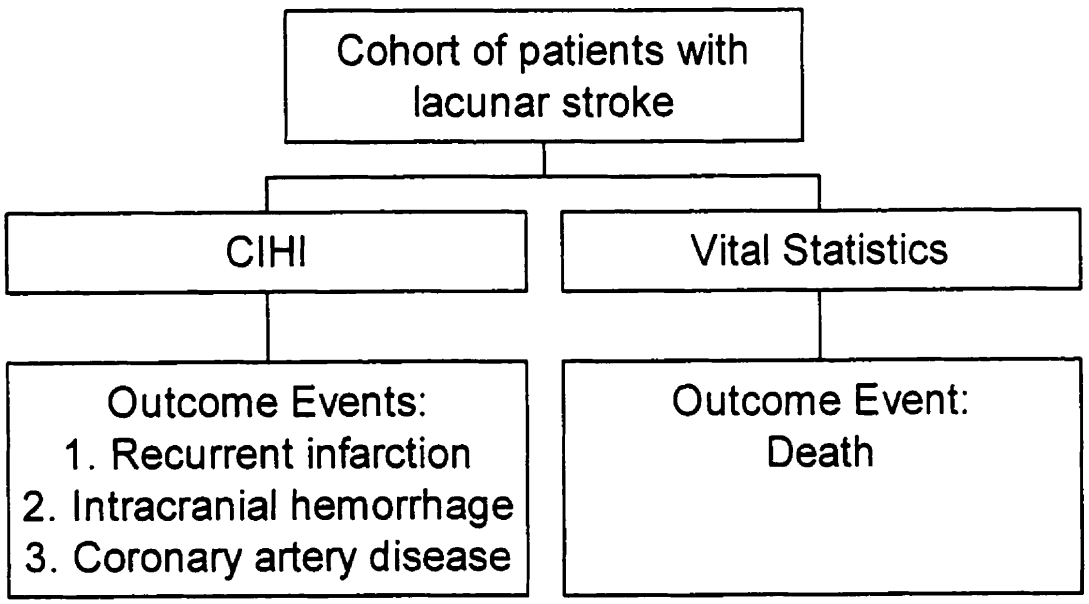


Figure 3: Survival of all patients

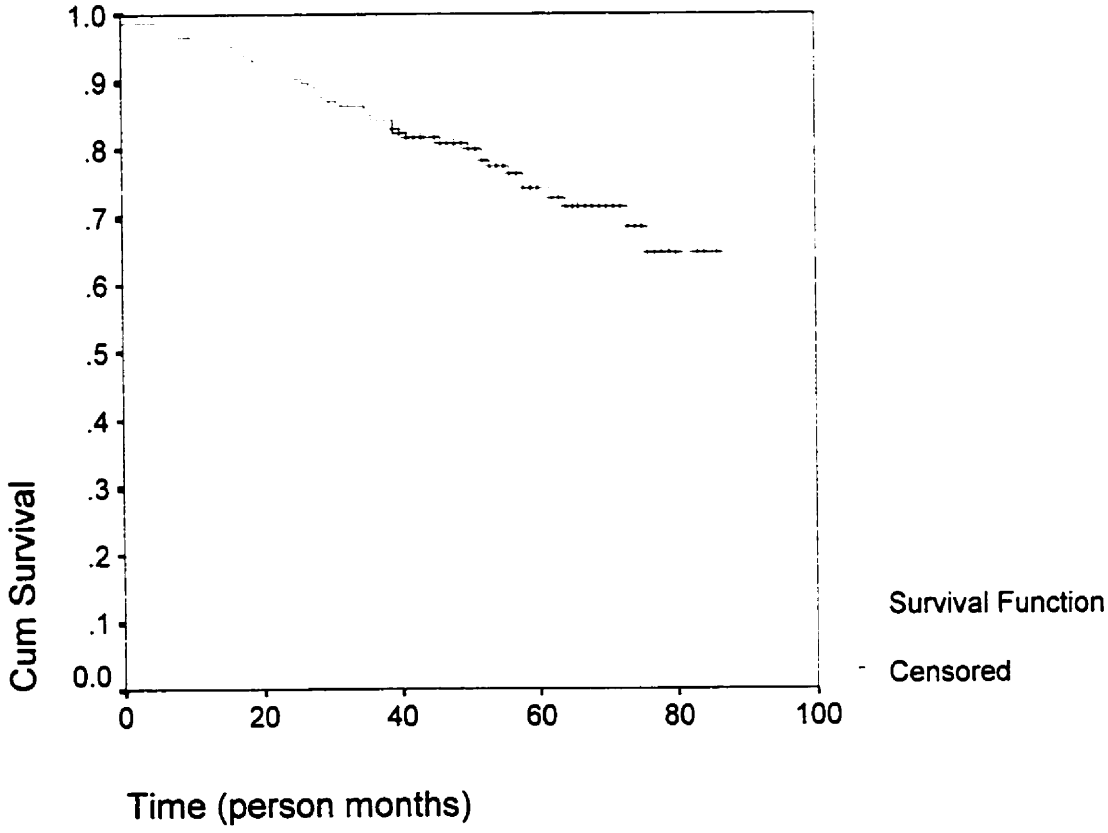


Figure 4: Comparison of survival of patients with first and recurrent stroke

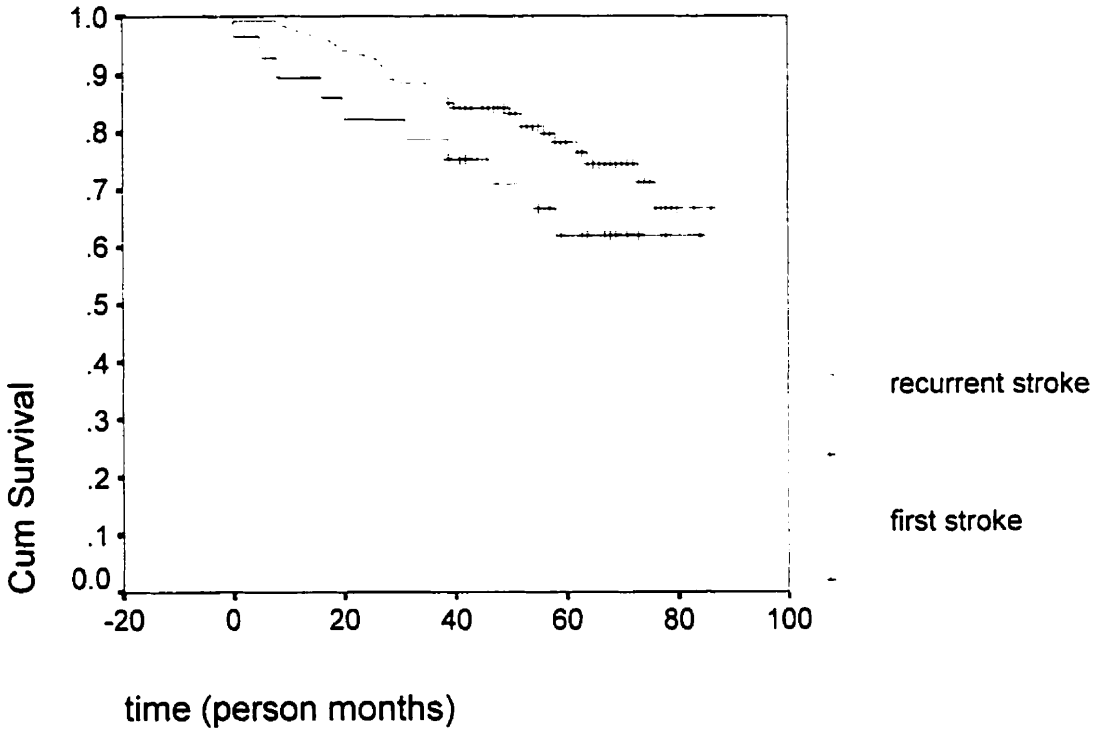


Figure 5: Comparison of survival between patients with and without embolic source

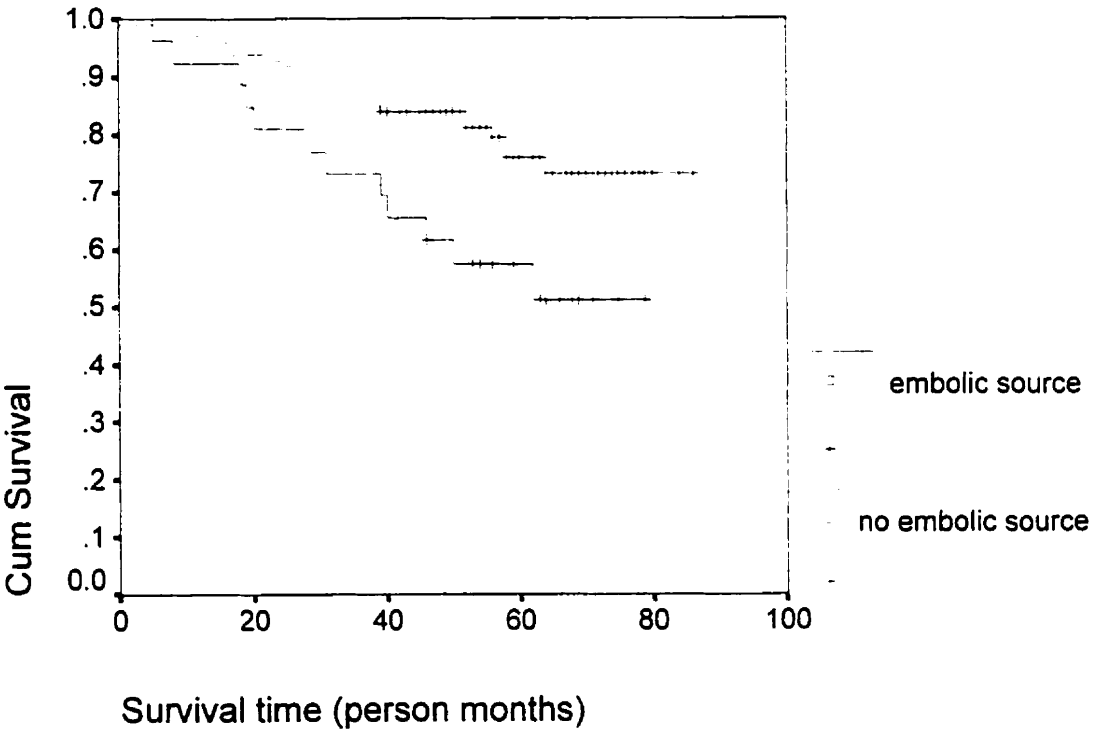


Figure 6: Stroke-free survival after lacunar stroke

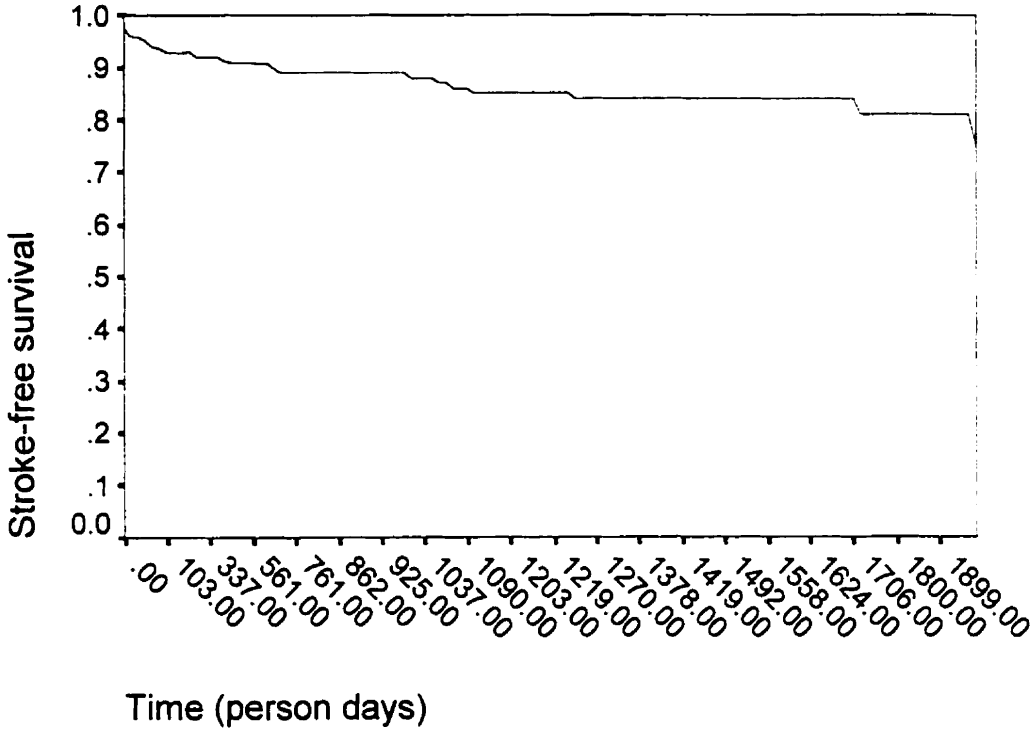
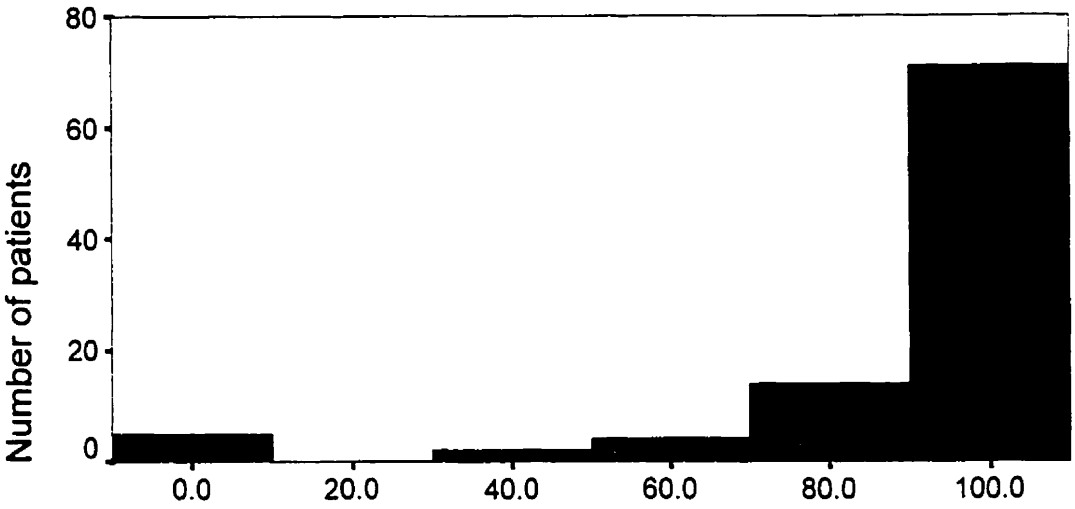


Figure 7: Functional outcome of patients with lacunar stroke



Barthel score

n=96

mean=88, median=100

Appendix 1

Stroke Investigations Unit
Toronto Western Hospital
399 Bathurst Street
MP 12-320
Toronto, Ontario
Telephone: (416) 603 5800 ext. 2445
March 28, 2000

Dear

I am a physician conducting a study on stroke. I am interviewing patients by telephone five to six years after their stroke to determine how well they are able to carry out their activities of daily living ie. walking, climbing stairs, feeding and dressing. This will hopefully lead to a better understanding of certain types of stroke. As part of my study, patients are contacted by telephone and asked a series of questions about their ability to care for themselves. This interview will require about ten to fifteen minutes.

You have been identified as a patient who was admitted to Toronto Western Hospital with a stroke between 1993 and 1996. You will be contacted in the next two to three weeks by telephone. If you agree to participate at this time, you or a family member will be asked a number of questions. Your responses will be confidential and your privacy will be respected.

Thank you in advance for your consideration.

Sincerely,

Dr. Cheryl Jaigobin