Clinical Prediction Rule for Treatment Change Based on Echocardiogram Findings in Transient Ischemic Attack and Non-Disabling Stroke

By

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Abstract

The goal of this study was to derive a clinical prediction rule for transient ischemic attack (TIA) and non-disabling stroke to predict a treatment change based on echocardiogram.

Methods: We conducted a cohort sub-study for TIA and non-disabling stroke patients collected over five years from 8 Emergency Departments. We compiled a list of 27 potential predictors to look for treatment change based on echocardiogram findings. We used a univariate, logistic regression and recursive partitioning analysis to develop the final prediction model.

Results: The frequency of treatment change was seen in 87 (3.1%) of 2804 cases. The final model contains six predictors: age less than 50 years old, coronary artery disease history, history of heart failure, any language deficit, posterior circulation infarct and middle cerebral artery infarct on neuroimaging.

Conclusions: We have developed a highly sensitive clinic prediction rule to guide in the use of echocardiogram in TIA and non-disabling stroke.

Executive Summary

Introduction: There is a lack of evidence-based guidelines demonstrating which patients will benefit the most from receiving an echocardiogram in transient ischemic attack (TIA) and non-disabling stroke patients. Many patients will have to wait days to weeks before completing this test, and some may have a recurrent ischemic event before this tests completion. The goal of this study was to derive a clinical prediction rule for transient ischemic attack (TIA) and non-disabling stroke to predict a treatment change based on echocardiogram.

Methods: We conducted a prospective cohort sub-study for TIA and non-disabling stroke patients collected over five years from 8 Emergency Departments. We compiled a comprehensive list of 27 potential predictors to look for treatment change based on echocardiogram findings. A univariate analysis was performed to determine the association between the potential predictors and treatment change based on echocardiogram findings. Only significant predictors were eligible for multivariable analysis. We followed two mathematical multivariable analysis methods of both logistic regression and recursive partitioning analysis. In attempt to assess the internal validity of our logistic regression final model, a 5000 bootstrapping assessment was performed.

Results: The frequency of treatment change was seen in 87 (3.1%) of 2804 cases. The final model of both logistic regression and recursive partitioning analysis contains the same six predictors: age less than 50 years old, coronary artery disease history, history of heart failure, any language deficit, posterior circulation infarct and middle cerebral artery infarct on neuroimaging. Our model had a good discriminatory power with C-statistics of 0.77 (95%CI 0.7-0.8). The final model showed a sensitivity of 94.3% (95% CI 87.1 % to 98.1 %), a specificity of 35.4%

(95% CI 33.6% to 37.3%) and a negative predictive value of 99.5% (95% CI 98.8 % to 99.8%).

Conclusions: We developed a highly sensitive prediction rule that will help identify high-risk patients for a treatment change based on echocardiogram findings.

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Table of Contents

List of Table

List of Figures

CHAPTER 1: INTRODUCTION

When a transient ischemic attack (TIA) or a non-disabling stroke occurs, efforts are made to prevent subsequent stroke by screening for the source of the ischemic event. An embolism from the heart is a common cause of a brain ischemic event; therefore many patients who have suffered a TIA or a non-disabling stroke will undergo cardiac ultrasound imaging (echocardiogram) to identify a potential cardioembolic source.[1] Such tests are not often readily available, primarily because of limited resources. Thus, many patients will have to wait days to weeks before completing this test, and some may have a recurrent ischemic event before this tests completion. Moreover, there is a lack of evidence-based guidelines demonstrating which patients will benefit the most from receiving an echocardiogram. The overall goal of this study was to derive a clinical prediction rule determining which patients with a TIA or a non-disabling stroke require an echocardiogram resulting in a treatment change based on its findings.

1.1 Rationale for the Study

Among clinicians, we identified a practice variation in echocardiogram use. These variations included both the initial type of echocardiogram used and the indication of a more advanced echocardiogram (i.e., transesophgeal echocardiogram (TEE)). Performing an echocardiogram in all TIA/non-disabling stroke patients may needlessly overwhelm our healthcare system and increase healthcare costs. If a prediction tool is developed, clinicians can order echocardiograms efficiently and thusly prevent subsequent strokes.

1.2 Goals and objectives

1.2.1 To derive a clinical prediction rule for patients with TIA and non-disabling stroke to predict an abnormal echocardiogram requiring a change in treatment

1.2.2 To determine the incidence of subsequent stroke in patients with abnormal echocardiogram findings compared to the incidence in those with normal echocardiogram findings in the 90 days following a TIA or a non-disabling stroke.

1.2.3 To determine the incidence rate of subsequent stroke within 90 days stratified, by the etiology of the TIA or the non-disabling stroke.

1.2.4 To compute the mortality rate within 90 days, stratified by the etiology of the TIA or the non-disabling stroke.

1.3 Description of chapters of this thesis

In the second chapter we will describe the background of TIA's and of non-disabling stroke including the following: definition, etiology, pathophysiology, epidemiology, and clinical presentation. A detailed review on the diagnostic utility, the yield, and the cost effectiveness of the work up of TIA or non-disabling stroke will be outlined. Finally, we will discuss potential predictors of cardioembolic TIA/non-disabling stroke, background on the dataset used to derive our prediction model, and outline the methodological standards used to develop our clinical prediction rule.

The third chapter is the methods section where our study population, sample size adequacy, process of data collection, and data analyses for each study objective is discussed. The univariate and multivariable analyses are described for the prediction model derivation. The multivariable analysis describes both the recursive partitioning and the logistic regression analysis used.

The fourth chapter, the results section, discusses study flow, descriptive statistics, frequency of abnormal echocardiogram structure, type of structure and treatment change made based on echocardiogram results, frequency of different types of

etiology of TIA or non-disabling stroke, reliability and the results of our study's four objectives. In particular, in the derivation of the prediction rule study objective, we discuss the results of the univariate analysis and the multivariable analysis of both the recursive partitioning and logistic regression analysis. We also report the prediction score scale as well as the bootstrapping results of the logistic regression model.

The final chapter is the discussion section, where we outline our studies strengths, weaknesses and limitations as well as discuss the future clinical and research implications.

CHAPTER 2: BACKGROUND AND REVIEW OF THE LITERATURE

2.1 Introduction to Transient Ischemic Attacks and Non-disabling Stroke

2.1.1 Definition of a Transient Ischemic Attack and an Ischemic Stroke

A transient ischemic attack (TIA) is defined by the World Health Organization (WHO) as a "focal neurological deficit lasting for less than 24 hours, presumed to be of vascular origin, and confined to an area of the brain or eye perfused by a specific artery".[2 3] In 2002, a group of experts proposed an alternative definition for TIA: "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia (i.e., inadequate tissue perfusion), with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction".[2] This alternative definition was further revised in 2009 by the American Stroke Association, where TIA was redefined as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction". [2] The newer definition emphasizes that the physiological nature of transient ischemia does not cause permanent brain damage. To prove the nature of ischemia, advanced neuroimaging is required; this is not often readily available in most Canadian Emergency Departments (ED).

The World Health Organization (WHO) defines stroke as "rapidly developing signs of focal (or global) disturbance of cerebral function lasting more than 24 hours".[4] This cerebral disturbance is caused by ischemia and leads to permanent brain damage.

A non-disabling stroke is defined as any mild, non-disabling symptom(s) with National Institutes of Health Stroke Scale (NIHSS) less than 3 secondary to ischemic stroke.[5]

2.1.2 Etiology of Transient Ischemic Attack (TIA) and Non-disabling Stroke

TIAs and non-disabling strokes can occur secondary to many etiologies including: 1) large vessel disease in 7–17% of cases; 2) cardioembolic in 21–29% of cases; 3) small vessel disease in 16–30% of cases; 4) cryptogenic (i.e., uncertain etiology) in 31–41% of cases; and 5) other causes in 1–7% of cases (Table 1).[6-11]

Large vessel disease results from either atherosclerosis or arterial dissection, both of which cause a narrowing of arterial blood flow and involve the internal carotid artery, the vertebro-basilar artery, or one of the arteries within the circle of Willis and its proximal branches.[6 12 13] Cardioembolic causes of TIA/non-disabling stroke occur with the presence of an abnormal cardio-aortic structure or function that predispose a clot to form within the heart or proximal aorta (Table 2).[10 14] Small vessel disease is a localized disease affecting small perforating arteries that supply blood to the brain.[15 16] Cryptogenic TIA/non-disabling stroke is an ischemic brain event that has an undetermined cause, despite extensive investigation.

Table 1. Other Causes of Transient Ischemic Attack/Non-Disabling Stroke
Abnormalities of thrombosis and hemostasis
Acute disseminated intravascular coagulation
Vasculitis
Cerebral venous thrombosis
Drug-induced stroke (e.g., from cocaine use)
Hyperviscosity syndrome
Hypoperfusion
Antiphospholipid syndrome
Vasospasm
Sickle cell disease

Table 2. Potential Cardioembolic Source of TIA/Non-Disabling Stroke
Left atrial appendage thrombus (LAAT)
Left ventricular thrombus
Left atrial myxoma
Vegetation
Valve dehiscence
Ventricular aneurysm
Aortic dissection
Ejection fraction <30%
Atrial fibrillation or flutter
Dilated cardiomyopathy
Left atrial appendage contrast (LAAC)
Atrial septal aneurysm (ASA)
Arthrosclerosis of ascending aorta
Patent foramen ovale
Valvular calcification

2.1.3 Pathophysiology of a Transient Ischemic Attack/ Non-disabling Stroke

In the cases of TIA/non-disabling strokes resulting from large vessel disease, the most common pathological culprit is an atherosclerotic plaque that ulcerates and leads to platelet aggregation and fibrin formation with subsequent thrombus or clot formation. The thrombus will narrow the affected artery or break down into smaller debris or emboli. An emboli can travel to more distant blood vessels within the brain, lodging itself within a cerebral artery and leading to a complete or partial blockage of cerebral blood flow.[12]

In addition, arterial dissection is considered an important cause of large vessel disease occurring with pre-existing arterial wall pathology (e.g., connective tissue disease), as it affects the arterial wall strength and integrity. As a result, the intimal wall (the innermost layer of the arterial wall) is torn. This defect allows for the accumulation of blood within the sub-intimal wall space. Subsequently, the dissection results in the formation of a pocket of blood within the arterial wall. This may lead to either a complete or an incomplete occlusion of cerebral blood flow.[13]

Cardioembolic sources of TIAs/non-disabling stroke occur with the presence of an abnormal cardiac source (Table 2) that predisposes an individual to thrombus formation, which can then be further broken down into smaller emboli.[14] Again, these emboli will travel distally and lodge within a cerebral artery leading to a decreased cerebral perfusion.[10] The causes of cardioembolic emboli are further explained in section 2.3 below.

Small vessel disease can result either from lipohyalinosis (i.e., intra-arterial wall necrosis of a small perforating artery as a result of a longstanding history of

hypertension or diabetes), from microartherosclerosis, or from a microemboli shower.[15] [16]

Cryptogenic TIAs/non-disabling stroke are those whose cause remains undetermined following full investigation. The unknown cause poses problems in determining the best course of treatment. This undetected cause of TIA/non-disabling stroke could arise from one of many factors including undetected occult atrial fibrillation (i.e., irregular heart rhythm resulting in pooling of blood within the heart and subsequent clot formation), undetected occult intra-cerebral large vessel disease, or an undetected abnormal cardiac structure that predisposes the individual to thrombus formation.[17] [18]

2.2 Epidemiology of Transient Ischemic Attack (TIA) and Non-disabling Stroke

TIAs account for 0.3% of all ED visits in the United States (US).[19] Their estimated yearly incidence in the U.S. general population is between 200,000–500,000.[20]

There are many risk factors for TIAs/non-disabling strokes, including hypertension, diabetes, smoking, hyperlipidemia, atrial fibrillation, a previous history of TIA or of stroke, heart failure, valvular heart disease, myocardial infarction and peripheral vascular disease.[21-23] The treatment of underlying risk factors can serve as a significant secondary preventative measure for subsequent stroke.[24]

Approximately one-third of strokes are preceded by a TIA event.[25] Stroke complications following an initial TIA is considered to be the fourth leading cause of death in North America.[26] The risk of subsequent stroke in the first 30 days following a TIA event is 5% among patients in Ontario, Canada.[21] The mortality rate following a TIA is 1.7%.[27] If a subsequent stroke occurs as the result of a cardioembolic source, the

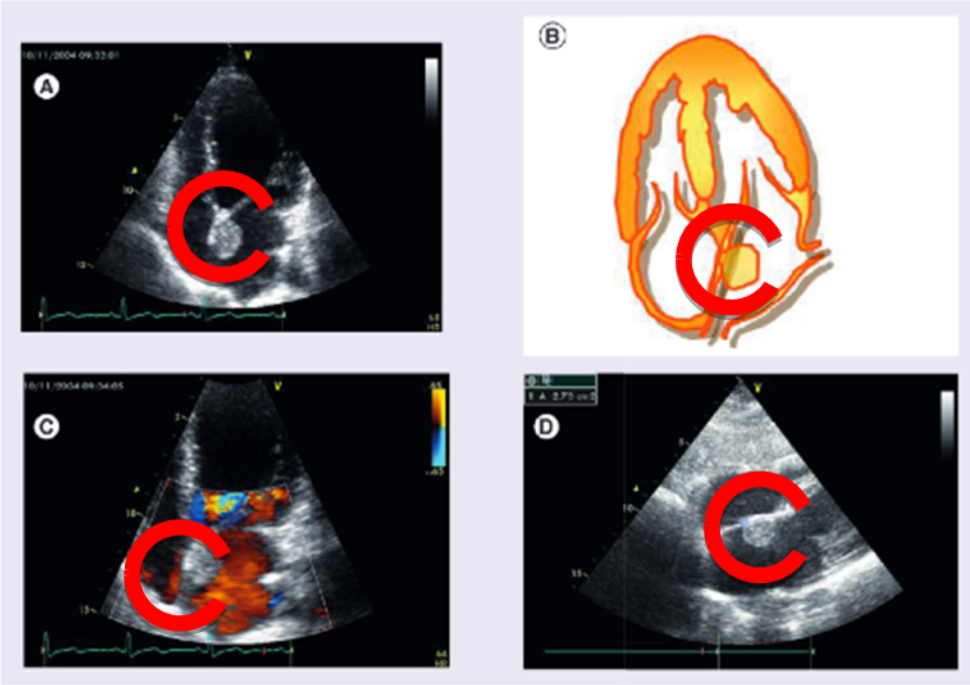
mortality and risk of stroke recurrence carries the highest rate among various causes of TIA, with a rate of 6–27% and 1–10% respectively.[28]

2.3 Cardioembolic Sources of TIA or Non-disabling Stroke

2.3.1 Atrial Source of Cardioembolic TIA or Non-disabling Stroke

The presence of a rhythm disturbance such as atrial fibrillation, atrial flutter, or sick sinus syndrome will interfere with normal blood flow through the atrial cardiac chamber. Consequently, blood stasis within the atrium will occur, leading to the formation of a left atrial thrombus formation in 10-20% of cases.[29] These thrombi may break down into smaller debris, called emboli, which can then travel to cranial arteries, causing either a TIA or a stroke. Atrial myxoma is another rare cardioembolic source of TIAs. It is a polypoid benign cardiac tumour that arises within the left atrium (Figure 1).[30 31] One-third of myxomas will ultimately embolize to the brain and cause a subsequent TIA or stroke.[29]

Figure 1. Atrial Myxoma



Adapted from; *Figure 7 of the following reference :Esposito R, et al. The role of echocardiography in the management of the sources of embolism. Future Cardiol. 2012;8(1):101-114*

2.3.2 Valvular source of cardioembolic TIA or non-disabling stroke

There are many etiologies of valvular heart disease (Table 3).[32] For example, valvular microbial seeding (more commonly known as infective endocarditis) may occur after bacteremia (i.e., " the presence of viable microorganisms in the bloodstream").[33] This valvular inflammation will result in the formation of infected thrombi within the affected valve, known as vegetation's.[34] The risk of subsequent stroke from an infective endocarditis vegetation is somewhere between 15 to 20%.[32]

Table 3. Valvular Heart Disease that Predisposes Thrombus Formation
Infective endocarditis
Rheumatic heart disease
Cardiomyopathy
Lupus
Myocardial infarction
Prosthetic valve with sub-therapeutic anticoagulation

2.3.3 Ventricular source of cardioembolic TIA or non-disabling stroke

The two most worrisome ventricular causes of cardioembolic TIAs/non-disabling strokes are left ventricular thrombi and ventricular aneurysms. Left ventricular thrombi are most commonly caused by a massive myocardial infarction (i.e., a large myocardial cell death or necrosis) or dilated cardiomyopathy (i.e., myocardial muscle weakness).[35] During the first month of post-myocardial infarction, 2–3% of patients will have a subsequent stroke, while the annual risk of stroke in dilated cardiomyopathy is 2–4%.[35,36]

Left ventricular aneurysm is a dyskinetic weakening of the ventricular wall, which can be caused by either myocardial infarction or trauma.[37] This kind of aneurysm predisposes a patient to thrombus formation, which may embolize and result in a stroke. Left ventricular aneurysms account for 10% of cardioembolic strokes.[38]

2.3.4 Septal source of cardioembolic TIA or non-disabling stroke

An atrial septal aneurysm (Figure 2) is an atrial septal segment measuring 15 mm in diameter that deviates 15 mm away from the remainder of the septum and is found in 0.2–4% of patients who undergo an echocardiogram.[39] The association of an atrial septal aneurysm with a patent foramen ovale increases the overall risk of TIA or stroke.[40] A patent foramen ovale (Figure 3) is a "hole between the left and right atria of the heart that fails to close naturally soon after a baby is born due to incomplete fusion of the

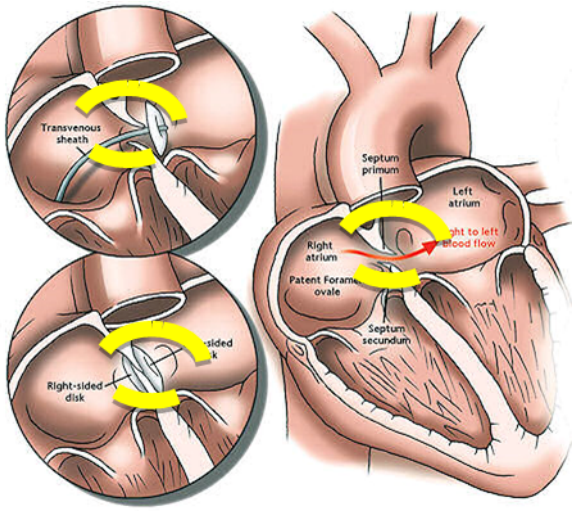
septum primum and foramen secundum".[30 41 42] The prevalence of a patent foramen ovale is between 27–35% in the general population.[43]

The mechanism of a TIA or non-disabling stroke with the coexistence of an atrial septal defect and patent foramen ovale is unique, especially with the presence of more distal emboli coming up from venous circulation. Under these conditions, emboli will pass from the right to the left side of the heart through the intra-atrial communication, thereby facilitating a cerebral embolization. However, an isolated patent foramen ovale may not necessarily facilitate this embolization process. Therefore, it is considered to be a low risk for cardioembolic TIA.[35]

Figure 2. Atrial Septal Aneurysm

Adapted from; *figure 1 of the following reference Olivares-Reyes A, Chan S, Lazar EJ et al. Atrial septal aneurysm: a new classification in two hundred five adults. J. Am. Soc. Echocardiogr.10,644–656 (1997)*

Figure 3. Patent Foramen Ovale



Adapted from the following website;
http://www.divernet.com/Training/training_general/160095/the_trouble_with_pfos.html

2.3.5 Aortic source of cardioembolic TIA or non-disabling stroke

Complex atherosclerosis of the aortic arch is a potential cause of TIA. It is defined as a protruding aortic atheroma >4 mm in length. The presence of such pathology increases the risk of cardioembolic stroke by three to nine-fold.[29]

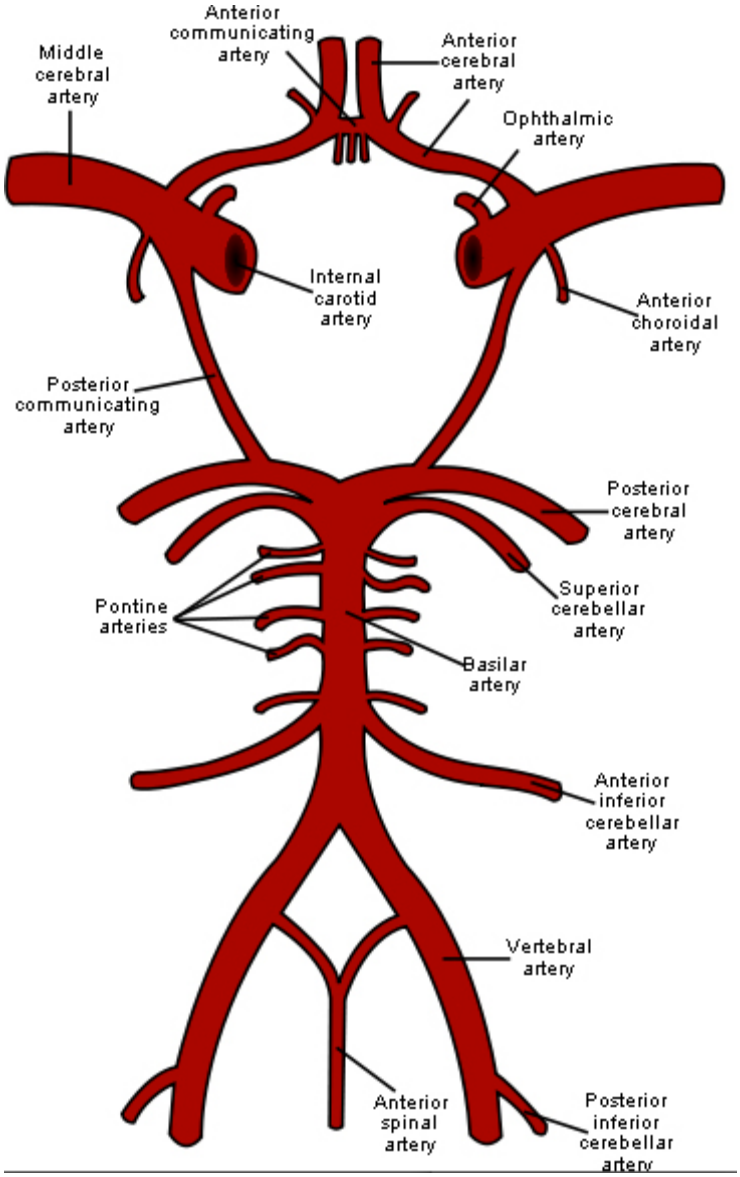
2.4 Presentation of Transient Ischemic Attack (TIA) or non-disabling stroke

A TIA/non-disabling stroke can have many different clinical presentations depending on the anatomical location of the blocked artery. Classically, it is divided into either anterior circulation or posterior circulation ischemic symptoms.

The anterior circulation of the brain's two hemispheres is divided into three large arteries and many small perforating arteries. The large arteries include the internal carotid artery, the anterior cerebral artery, and the middle cerebral artery. These all exist in pairs, one for each hemisphere (Figure 4). Similarly, the posterior circulation consists of three large arteries and many small perforating arteries. The large arteries are a pair of

vertebral arteries and a single basilar artery. The main small arteries are a pair of posterior cerebral arteries, a pair of superior cerebellar arteries and 2 pairs of inferior cerebellar arteries (Figure 4). As such, the clinical presentation will depend on which of these arteries is compromised.

Figure 4. Anatomy Of Cerebral Circulation



Adapted from; *wikipedia of the following link: http://en.wikipedia.org/wiki/Circle_of_willis*

2.4.1 Presentation of middle cerebral artery Transient Ischemic Attack (TIA) or non-disabling Stroke

When the occlusion is in the middle cerebral artery, the presentation varies based on the affected side. The left side will typically present with signs and symptoms of aphasia (i.e., the patient's inability to comprehend or express him or herself), a right homonomyous hemianopsia (i.e., a right-sided visual field defect or blindness), a right-sided weakness, and facial/extremity numbness. The right side will have a similar presentation, but affect the opposite side (i.e., neurological deficit are on the left side); however, there will often be no aphasia. Overall, when any middle cerebral artery is affected, the degree of limb weakness is more profound in the upper limb than in the lower.

2.4.2 Presentation of anterior cerebral artery Transient Ischemic Attack (TIA) or non-disabling Stroke

Any anterior cerebral artery ischemia will cause weakness and numbness contralateral to the affected artery. The degree of weakness secondary to the anterior cerebral artery's involvement is typically more profound in the lower limb compared to the upper.

2.4.3 Presentation of internal carotid Transient Ischemic Attack (TIA) or non-disabling Stroke

When the internal carotid artery is involved, it will lead to either a unilateral vision loss (known as amaurosis fugax) or a middle cerebral artery-like symptom.

2.4.4 Presentation of posterior circulation Transient Ischemic Attack (TIA) or non-disabling Stroke

When the vertebral artery is involved in the posterior circulation TIA/non-disabling stroke, a lateral medullary infarct (known as Wallenberg syndrome) will occur. This will cause vertigo (i.e., sensation of a spinning movement), hoarseness as well as pain and temperature sensory loss in the ipsilateral (i.e., same side as the cerebral ischemia) face and contralateral limb (i.e., paralysis of either side of extremities opposite to the cerebral ischemic site). Basilar artery ischemia will present with an altered mental status, alternating hemiparesis (i.e., alternating weakness in either limbs side), and a disconjugate gaze pattern (i.e., both eyes are unable to move in the same direction together). Also, if any cerebellar arteries are involved; symptoms of vertigo, nystagmus, and inability to coordinate limb movement or ataxia may be present. Lastly, ischemia caused by a posterior cerebral artery may lead to a contralateral homonymous hemianopsia (i.e., partial visual field defect of both eyes opposite to the affected posterior cerebral artery) in relation to the affected artery.[44,45]

2.4.5 Presentation of small vessel disease Transient Ischemic Attack (TIA) or non-disabling stroke

All small perforating arteries affected can present with a variety of symptoms depending on their anatomical location. The most common presentation of small vessel ischemia is usually isolated pure sensory or pure motor deficit contralateral to the affected side of the small artery.[44]

2.5 Investigation of TIAs or non-disabling Strokes

The main goal of TIA/non-disabling stroke work-up is to determine the ischemic event's cause, allowing for prompt initiation of specific treatment to prevent subsequent stroke or recurrent TIA.[46]

Patients with a TIA or non-disabling stroke undergo a comprehensive work-up, often including an echocardiogram. However, this work-up is expensive and has a low diagnostic yield.[46] Therefore, some experts recommend a stepwise approach, beginning with the least expensive, non-invasive option and progressing to the most expensive and invasive test. The decision to follow this approach will be based on the physician's level of confidence of the exact TIA or non-disabling stroke etiology.[46] The work-up typically consists of brain imaging, cranial artery imaging, cardiac work-up (i.e., Electrocardiogram, Holter monitor and echocardiogram) and blood work.[47] The level of evidence of the aforementioned work-up is outlined in the most recent 2014 Canadian Stroke Best Practice Recommendations (Table 4).[48]

Table 4. 2014 Canadian Best Stroke Practice Recommendations for TIA Work-Up		
Type of work up	Recommendation Level	Definition the level of recommendation
Cranial vascular imaging ⊓	A	Desirable effects clearly outweigh undesirable effects. Evidence from a meta-analysis or consistent findings from multiple randomized controlled trials.
Routine brain imaging ⍵	B	Desirable effects outweigh or are closely balanced with undesirable effects. Evidence from a single trial or consistent findings from multiple well-designed nonrandomized and/or non-controlled trials, and large observational studies.
Prolonged Holter monitor *	B	
Blood work	C	Group consensus and/or supported by limited research evidence.
Electrocardiogram	C	
Echocardiogram	C	

⊓: Either Doppler ultrasound, computed tomography angiography or magnetic resonance angiography was used
Ω: Either brain computed tomography or magnetic resonance imaging was used
Φ: The blood work included; complete blood count, electrolyte panel, glucose, glycated hemoglobin level, lipid profile, renal function tests, Alanine transaminase level and coagulation profile
***:** This applies for older patients with a presumed undetermined cardioembolic cause of ischemia who no evidence of atrial fibrillation on their initial electrocardiogram

2.5.1 Brain Imaging

The American Association's (AHA) recommendation is to perform brain imaging within 24 hours for all TIA or non-disabling stroke patients (level of evidence: class I-B) (for a definition of level of evidence, Table 5).[2 49] This is to rule out the presence of a new brain infarction (based on the new definition, this would be a stroke) or conditions that may mimic a TIA or non-disabling ischemic stroke, such as intracranial bleeding or a tumor.[46 50]

Table 5. Definition of Level of Evidence of the American Heart Association

Definition of Classes and Levels of Evidence Used in AHA Recommendations	
Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts
Diagnostic recommendation	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or ≥1 case-control studies or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

Adapted with permission of publisher from; *original table appearing in Stroke; 2009;40:2276–93.*

2.5.1.1 Brain Computed Tomography Scan (Brain CT scan)

Brain CT scan is the most commonly used imaging modality for TIA or non-disabling stroke patients. Some data suggest that the diagnostic yield of a brain CT scan is 1–5% to rule out conditions that can mimic a TIA.[2 50-52]

The advantages of performing a CT scan rather than another imaging modality like magnetic resonance imaging (MRI), is that a CT scan is fast, inexpensive and readily available to physicians in the ED. It is considered to be substantially sensitive, nearly 100%, for ruling out an intracranial bleed.[47 53] The disadvantages of CT include the subsequent exposure to radiation and its inability to detect lesions in the posterior

cranial fossa. Furthermore, it has a poor sensitivity, 20%, for detecting a new small infarct in early presenters.[47,54 55]

2.5.1.2 Brain Magnetic Resonance Imaging (Brain MRI)

Brain MRI is the preferred modality of brain imaging, when available.[49,56] An MRI can detect up to 31% of new infarcts relevant to cases diagnosed as TIA, as per the WHO definition.[57] The two types of MRI imaging are the conventional T2-Weighted MRI and the Diffusion-Weighted Imaging (DWI) MRI. The conventional MRI is considered to be more sensitive than a CT scan when detecting infarcts. Unfortunately, it is often unavailable due to high demand, comparatively long scanning times (5 minutes/CT scan versus 30 minutes/MRI scan) and it is unable to determine the infarct's acuity. On the other hand, the DWI MRI can assess the diffusion rate of water within each anatomical cranial location. In contrast to a traditional MRI, DWI MRI has the ability to determine both the age of the infarct and the presence or absence of ischemia in a patient with a recent onset of symptoms.[2 56] MRI is considered the superior imaging modality to assess the posterior cranial fossa with no radiation exposure. However, due to the limited availability of MRI, the longer imaging time, expensive cost, and the challenges in patients with claustrophobia or implanted metal, it is often not feasibly performed in an ED setting, nor is readily available within hours, days weeks or often months of the new TIA diagnosis.[2 47]

2.5.2 Cranial artery imaging

2.5.2.1 Overview

There are many imaging modalities used to screen and assess the cranial arteries. Doppler ultrasound is the most commonly used screening tool.[46] The choice of a more advanced imaging modality is based on the suspected type of pathology, the degree of

stenosis in the initial images (i.e., Doppler ultrasound), and whether surgical intervention is indicated.[2,46] The diagnostic performance of the available tests varies. Often, it depends on many pathological factors, such as the type of pathology present, its severity and the anatomical location of the culprit.[46 58] Anatomically, the cranial arteries are divided into extracranial arteries (i.e., arterial supply of the brain located outside the skull) and intracranial arteries (i.e., arterial blood supply of the brain within the skull).[46] The extracranial arteries consist of a pair of the internal carotid arteries (extracranial parts) and a pair of extracranial vertebral arteries. Furthermore, the intracranial arteries consist of a pair of intracranial internal carotid arteries, a pair of middle cerebral arteries, a pair of anterior cerebral arteries, a pair from the intracranial part of the vertebral artery and finally, a single basilar artery.[59]

Cranial artery screening is important in determining whether large vessel disease was the cause of the TIA or non-disabling stroke. Large vessel disease is most commonly caused by stenosis (arterial narrowing caused by an atherosclerotic plaques) secondary to atherosclerosis in the carotid artery. Assessing the degree of carotid artery stenosis is an important step; it is classified as either mild (for less than 50% stenosis), moderate (for 50–69% stenosis), severe (for 70–95% stenosis), critical (for 96–99% stenosis) or occluded (for 100% stenosis).[60] If more than 50% but less than 100% carotid artery stenosis is present and the lesion correlates with the clinical neurological deficits, there is good evidence that surgical correction may prevent subsequent stroke.[56]

2.5.2.2 Types of cranial imaging

i. Doppler ultrasound

Doppler ultrasound assesses vascular blood flow using sound waves. It is recommended by the American Heart Association (AHA) to assess the extracranial

arteries (which include two carotid arteries in the anterior brain circulation and two vertebral arteries in the posterior circulation) in all TIA patients within 24 hours of presentation (level of evidence is class I-A).

The goal of a Doppler ultrasound is to determine the degree of stenosis. If a >50% stenosis is present, advanced imaging is required (i.e., computed tomography angiography (CTA) or magnetic resonance angiography (MRA)). The reported sensitivity and specificity in detecting more than 50% stenosis is 88% and 76% respectively.[2]

Doppler ultrasound is non-invasive, relatively inexpensive, and lacks the harmful effects of radiation seen in other imaging modalities.[61] However, it has a poor diagnostic performance when detecting cranial artery dissection or a critical degree of carotid stenosis.[49]

ii. Computed tomography angiography (CTA)

Computed tomography angiography is the gold standard imaging technique for performing a comprehensive assessment of both intracranial and extracranial arteries using contrast dye.[46 49] It is the second most commonly performed imaging test for TIA or stroke patients. The AHA reserves CTA to assess the extent of carotid arthrosclerosis detected in the initial Doppler ultrasound, particularly for surgical-arterial revascularization candidates (level of evidence is Class IIa-B).[2 46 62]

The diagnostic yield to detect more than 70% carotid artery stenosis has been demonstrated as 4%.[63] The reported sensitivity and specificity to detect greater than 50% carotid stenosis is 77% and 94%, respectively, while for high degree stenosis, CTA has a sensitivity of 100%.[56 64] Additionally, CTA has the ability to rule out the possibility of

an arterial dissection.[46] However, it is an invasive test and is not suitable for patients with renal insufficiency or a contrast allergy.[64]

iii. Magnetic resonance angiography (MRA)

Magnetic resonance angiography (MRA) is an alternative modality to CTA. The sensitivity and specificity of MRA's detection of a carotid artery stenosis of greater than 50% is 82% and 97%, respectively.[64] Like CTA, MRA has a high diagnostic accuracy to diagnose a completely occluded carotid artery.

MRA has no risk of radiation or of contrast exposure. However, it is expensive and is not suitable for claustrophobic patients or those with implanted metal. Finally, MRA has a tendency to overestimate the presence of cranial artery stenosis.[47]

2.5.3 Cardiac work-up

A cardiac work-up is required to identify any abnormal cardiac rhythm or any structure that could serve as a potential source of either a cardioembolic TIA or non-disabling stroke.[35]

2.5.3.1 Electrocardiogram

An electrocardiogram is a transthoracic electrode that records the electrical activity of the heart. It includes heart rate and regularity of heart rate, and it provides some indication of the degree of myocardial damage. The goal is to detect the presence of an arrhythmia, such as atrial fibrillation, atrial flutter, or sick sinus syndrome. Atrial fibrillation is the most common and significant arrhythmia in TIA or stroke patients.[35] The American Heart Association recommends an electrocardiogram for all TIA patients (level of evidence is Class I-B). In the TIA work-up, the diagnostic yield of an electrocardiogram to diagnose atrial fibrillation is between 5–25%.[35 65] Furthermore, a serial electrocardiogram over a period of 72 hours may increase the diagnostic yield by

2.6-fold.[66] The use of a 24-hour continuous cardiac monitor may detect an additional 4–8.4% of atrial fibrillation cases.[43 65]

2.5.3.2 Holter monitor

A Holter monitor is a portable continuous cardiac electrical tracing device worn for 24 to 48 hours.[35] The diagnostic yield of Holter monitor is 4.6% to detect the presence of atrial fibrillation.[67] Due to lack of solid data, there is not a clear recommendation for the duration or for the indication of Holter monitoring.[68] Wallmann et al. demonstrated an association between premature atrial contractions (>70 times per 24-hour period) and occult atrial fibrillation. Therefore, extended Holter monitoring (i.e., >48 hours) may be beneficial for those with occult atrial fibrillation.[69]

A recent trial compared conventional Holter monitoring for 24 hours with a 30 day cardiac monitor, which revealed that a prolonged portable cardiac monitoring for 30 days is beneficial for those with an undetermined cause of TIA or stroke with an age older than 55 years. The prolonged portable cardiac monitoring was able to detect an additional 12.8% of occult atrial fibrillation.[70]

2.5.3.3 Echocardiogram

The current evidence for use of an echocardiogram in TIA or stroke patients is sparse and inconsistent. This has precluded advisory committees, such as the AHA, from providing clear guidelines for echocardiogram use. To our knowledge, there are no studies that have looked at clinical predictors correlating with echocardiogram findings resulting in deviation of treatment in the ED.

Types of echocardiogram

An echocardiogram can be either a transthoracic echocardiogram (TTE- a non-invasive cardiac ultrasound wherein the scan is performed through the chest wall) or a

transesophageal echocardiogram (TEE- a more invasive cardiac ultrasound where the scanning occurs through the esophagus). A TEE requires sedation to facilitate the scanning process.

Guidelines on the use of echocardiogram in TIA patients

The AHA has not outlined detailed recommendations for the use of echocardiogram in TIA patients (level of evidence is II-B). However, they stress the importance of using echocardiogram in patients with an undetermined source of TIA or of stroke.[2] The European Stroke Organization (ESO) guidelines state that the use of an echocardiogram is controversial (level of evidence III-B). They favour performing the scan if there is either: 1) a history or finding of cardiac disease; 2) a suspicion of a cardioembolic source of TIA; 3) suspicion of aortic disease; 4) suspicion of a paradoxical embolism; or 5) an undetermined source of TIA. Unfortunately, the guidelines are non-specific and are not comprehensive; they are primarily based on the opinions of experts.[71] Furthermore, there is also some degree of uncertainty about the ideal timeframe for performing the scan.[65] In the latest Canadian 2014 Stroke Best Practice Recommendations on the use of echocardiogram in TIA it stated that "Echocardiogram may be considered in cases where the stroke mechanism has not been identified".[48]

Diagnostic performance of echocardiogram in TIA or non-disabling Stroke patients

The ideal echocardiogram in TIA patients is controversial. Some experts recommend transesophageal echocardiogram (TEE) as the initial cardiac imaging for TIA or stroke patients that occur in either young patients (i.e., less than 50 years old) or

patients with a history of cardiac disease.[72] Others recommend using TTE as the initial modality to determine whether a TEE is indicated.[73]

Traditionally, TEE has been known as the modality of choice for detecting cardiac structural abnormalities located within the base of the heart. Those abnormal structures include atrial thrombus, patent foramen ovale, atrial septal aneurysm, and aortic arthromas.[74-78] Overall, TEE seems to be more sensitive than TTE in detecting potential cardioembolic structures.[42]

The diagnostic performance of an echocardiogram is variable. It is primarily influenced by the type and the site of the structural abnormality. Unfortunately, the literature lacks a comprehensive assessment of an echocardiogram's diagnostic performance for patients with TIA secondary to a cardioembolic source. Several studies have assessed the sensitivity of echocardiogram, which varies based on the type of echocardiogram and type of cardiac abnormality present (Table 6).[65 79-83]

Findings of an echocardiogram for TIA are classified by the European Stroke Organization into a major, a minor or an uncertain risk of cardioembolism for different cardiac abnormal structures or dysfunction (Table 7).[79] The overall most common abnormal echocardiogram finding in TIA patients is atrial fibrillation; however, for patients under the age of 50, the most common finding is a patent foramen ovale.[78]

TABLE 6. Sensitivity of Echocardiogram		
	Transthoracic Echocardiogram	**Transesophageal Echocardiogram**
Left atrial appendix thrombus	53–62%	93–100%
Patent foramen ovale	50%	89–100%
Vegetation	60%	85–90%
Left ventricular thrombus	72–95%	NAD

NAD: No Available Data.

Table 5. Level of Risks of Cardioembolism
Major risk of cardioembolism
Left atrial appendage thrombus (LAAT)
Left ventricular thrombus
Left atrial myxoma
Vegetation
Valve dehiscence
Ventricular aneurysm
Aortic dissection
Ejection fraction <30%
Atrial fibrillation
Atrial flutter
Dilated cardiomyopathy
Left atrial appendage contrast (LAAC)
Arthrosclerosis of ascending aorta
Minor or uncertain risk of cardioembolism
Atrial septal aneurysm (ASA)
Valvular calcification
Patent foramen ovale

Diagnostic yield and therapeutic implications of echocardiogram in TIA or stroke patients

The current literature on the diagnostic yield and therapeutic implication of echocardiogram in TIA patients is sparse and inconsistent (Table 8); the diagnostic yield differs from one study to another. Factors that may contribute to this variability include the baseline characteristics of the enrolled population (e.g., age, history of cardiac disease, and level of uncertainty on stroke etiology from some other work-up) (Table 8).[76 78 84-86] Generally, the trend shows a higher diagnostic yield when the cause of TIA is undetermined, when there is a history of cardiac disease, and with a younger patient population. In a systematic review by Kapral et al., the overall pooled estimate of the diagnostic yield of echocardiogram in stroke patients was 4% for transthoracic echocardiogram (TTE) and 11% for transesophageal echocardiogram (TEE).[82]

The therapeutic impact for the use of echocardiogram in TIA patients has a wide range, from 0– 22% (Table 9).[42 75 78 84 87-91] Only one study by Wolber et al. looked at the number needed to test in order to have a therapeutic impact on a patient with cerebral ischemia. As a result, the study showed the impact of using an echocardiogram was highest in a younger population and lowest in elderly patients, with an overall number needed to test of 14 (Table 10).[78]

Table 6. Diagnostic Yield of Echocardiogram		
Type of population	**Transthoracic Echocardiogram**	**Transesophageal Echocardiogram**
Uncertain etiology of TIA	15–30%	57%
No cardiac disease	0–19%	9–43%
Cardiac disease	0–38%	32–79%
Overall	0–50%	11–60%

Table 9. Therapeutic Impact of an Echocardiogram	
Type of echocardiogram	Therapeutic impact
Transesophageal echocardiogram	0–22.0%
Transthoracic echocardiogram	4–10.8%

Table 10. Number Needed to Test with Echocardiogram to Impact Patient Therapy	
Type of population	Transthoracic echocardiogram
Overall	14
Age >70	63
Age <50	6

Economic evaluation of echocardiogram in TIA or stroke patients

In 1997 the annual cost of stroke in the U.S. was reported between $15–30 billion.[92] Two economic evaluations have since been published on the use of echocardiogram in TIA or stroke patients. McNamara et al. conducted a cost-effective analysis using the Markov model. The analysis compared different strategies of echocardiogram use in TIA patients (Table 11). The result of the analysis showed that

the most expensive use was for patients who underwent transthoracic and transesophageal echocardiogram, with an initial cost of $686 USD per patient. The least expensive use was echocardiogram use for only high-risk patients with a cardiac disease, with the initial cost being $122 USD per patient for a TTE and $133 USD per patient for a TEE. Furthermore, when computing the benefit of anticoagulation in preventing subsequent stroke, performing only a TEE for all patients is the most efficient approach, with a lifetime cost effective ratio of $13,000 USD per quality of adjusted life years (Table 11).[92]

In 2007, Meenan et al. conducted a more recent economic evaluation of echocardiogram. The conclusion of this analysis was that no single strategy had shown to be more efficient than another.[93] We believe that developing a prediction model for potential cardioembolic sources requiring a treatment change will impact the cost-effectiveness of echocardiogram in daily practice.

Safety of transesophageal echocardiogram in TIA or stroke patients

Transesophageal echocardiogram is an invasive test, with potential for various complications (Table 12).[94] However, the overall risk of complications is low, around 0.7%, with a mortality rate of 0.009%.[82 95]

Table 11. Cost Effectiveness of Echocardiogram, comparing Different Usage Strategies

Proposed strategy	Initial cost (USD Per patient)	Lifetime cost-effectiveness ratio ($ value per QALY)
All TEE	$360	$13,000 Ω
All TTE	$330	$36,000–57,000 ⊓
All TTE followed by TEE	$686	$24,000–32,000
Selective in cardiac disease patients with either:		
1. TTE if negative, followed by TEE	$254	$24,000–32,000
2. TEE only	$133	$9,000 Ω
3. TTE only	$122	$36,000–57,000 ⊓

⊓: These patients group had the worst outcome
Ω: These patients group had best outcome
TEE: Transesophageal echocardiogram
TTE: Transthoracic echocardiogram
QALY: Quality of adjusted life year

Table 12. Potential Complications of Transesophageal Echocardiogram

Esophageal perforation
Gastrointestinal bleeding
Methemoglobinemia
Bronchospasm
Hypoxia
Non-sustained ventricular tachycardia
Atrial fibrillation
Hemoptysis

2.6 Potential Predictors of Cardioembolic TIA or stroke

A validated prediction model for cardioembolic TIA in the setting of the Emergency Department is non-existent in the current literature. However, several studies

have found a significant association between cardioembolic TIA and stroke through clinical and work-up findings. All of the associated variables were poorly predictive of a cardioembolic cause of TIA, having a positive predictive value of less than 50%.[96]

2.6.1 Potential clinical predictors of cardioembolic TIA

Several clinical characteristics have been associated with a cardioembolic source of TIA or stroke (Table 13).[14 35 36 96-102] Some were found to be more common than others. For instance, a maximal deficit at the onset (i.e., the timing of maximum neurological deficit occurring instantly at onset of symptoms) was found to occur in 50–80 % of cases.[35 101] Altered mental status was found in 20-30% of cases. Its presence increases the odds of a cardioembolic source of TIA/non-disabling stroke by a factor of 3.2.[36 99-101]

Experts in the field proposed several theories to explain the association between maximal deficit of symptoms and a cardioembolic source of TIA/non-disabling stroke. For example, maximal deficit symptoms at onset can occur due to a sudden onset of interrupted blood flow from the embolus.[35] These emboli can then migrate causing a repercussion and resulting in a rapid regression of symptoms.[28 96] Furthermore, symptom onset on exertion may be explained by the negative pressure created at exertion and can then predispose a patient to paradoxical embolization.[100] Cardioembolic TIA or stroke was found to be more common in certain age groups. Patients over 65 years old have a higher incidence because of their higher instance of atrial fibrillation.[96 102] In patients under 50 years old, a patent foramen ovale associated with atrial septal aneurysm is often the cause.[14] Blood pressure measurements may hint at the etiology of the TIA. Meurer et al. found that a systolic blood pressure of less than 150 mmHg increases the odds of a cardioembolic source of ischemia by a factor of 4.[97]

Table 13. Potential Clinical Predictors of a Cardioembolic Source of TIA

Age above 65 years
Age less than 50 years
Maximal deficit within 5 minutes of onset
Rapid regression of symptoms
Symptom onset at exertion or strain (e.g., coughing, bending, heavy lifting)
Altered mental status
Visual field defect
History of headache *
History of seizure Ω
Signs of neglect
Symptoms or signs of aphasia
Signs or symptoms of multi-territorial infarct
Presence of neurological syndrome of either:
Isolated aphasia
Wallenberg syndrome Π
Basilar artery syndrome
Symptom of cerebellar infarct Φ
Absence of lacunar-like symptom
Systolic blood pressure less than 150 mmHg
Other systemic ischemia (e.g., limb ischemia)
Cormorbidity
History of atrial fibrillation
Heart failure
Antiphospholipid syndrome
History of coronary artery disease

*: Headache is associated with 25% of cardioembolic TIA/stroke.

Ω: Seizure is associated with 12% of cardioembolic TIA/stroke.

Π: Wallenberg syndrome is a lateral medullary infarct that presents with sensory deficit of pain and temperature in the ipsilateral facial side of infarct and contralateral limb.

Φ: Cerebellar infarct is attributed to a cardioembolic source in 54–80% of cases.

2.6.2 Cranial imaging features of cardioembolic TIA/stroke

Several studies have recognized a specific imaging pattern site and feature associated with cardioembolic stroke. The right middle cerebral artery appears to be the most common site of cardioembolic stroke.[36 69] However, the posterior and anterior cerebral arteries also have a higher association with cardioembolic stroke.[14 98] An arterial wall injury may occur as result of the impact force caused by migrating emboli. Subsequent hemorrhagic transformation occurs in two-thirds of cardioembolic strokes (Table 14).[14 35 36 79 98 100]

Table 14. Imaging Findings Suggestive of Cardioembolic Stroke

Multi-territorial infarct
Hemorrhagic transformation of ischemic stroke
Presence of hyperdense sign *
Anterior or posterior cerebral site of infarct
Absence of carotid stenosis of more than 50%

*: Hyperdense sign is a thrombus seen within the middle cerebral artery

2.7 Management of cardioembolic TIA or stroke

The choice of treatment for TIA or stroke caused by a cardioembolic source is dependent on the etiology of the cardiac emboli.

2.7.1 Management of cardioembolic TIA or stroke caused by atrial fibrillation

Atrial fibrillation is the most common source of cardioembolic TIA or stroke.[35] The diagnosis made using either an ECG or a Holter monitor. The 2011 AHA guidelines recommend warfarin as the anticoagulant of choice. The anticoagulation effect of warfarin should be measured by an international normalized ratio (INR), a blood test assessing the degree of coagulation factor inhibition. The recommended level of INR for

these patients should be between 2 and 3. This will subsequently reduce the annual risk of stroke by 3%.[103]

Recently, several studies looked at newer forms of oral anti-coagulants (OAC) in stroke prevention for patients with atrial fibrillation.[104-107] The two types of OAC's are: direct thrombin inhibitors (e.g., Dabigatran) and factor Xa inhibitors (e.g., Rivaroxaban, Edoxaban and Apixaban). The most recent 2014 Canadian Stroke Best Practice Recommendations and the Canadian Cardiovascular Society recommend the use of new OAC over warfarin for stroke prevention in patients with atrial fibrillation.[48 108] The decision was made due to a favorable efficacy and safety of the new OAC. There was reproducible evidence of similar efficacy if not superiority of the newer OAC in stroke prevention with less risk of bleeding and some mortality benefit. Lastly, it offered more convenience to clinicians and patients with unrequired blood work monitoring of INR.[48 104-108]

2.7.2 Management of cardioembolic TIA or stroke caused by infective endocarditis

Antibiotics are the best treatment for infective endocarditis. The use of anticoagulation is contraindicated as it heightens the risk of hemorrhagic transformation, thus increasing mortality rates.[96]

2.7.3 Management of cardioembolic TIA or stroke caused by left ventricular dysfunction

The AHA gave an open recommendation for the use the following antiplatelet agents: aspirin with or without dipyridamole, clopidogrel, or anticoagulation (warfarin) in patients with left ventricular dysfunction as long as the ejection fraction is less than

35%.[103] With the presence of a left ventricular thrombus, anticoagulation should be initiated for a minimum of 3 months.[103]

2.7.4 Management of cardioembolic TIA or stroke caused by patent foramen ovale

The ideal treatment is unknown for patent foramen ovale or atrial septal aneurysm detected in TIA patients. Anticoagulation and surgical patent foramen ovale closure is controversial. The 2011 AHA guidelines stress the importance of antiplatelet agents for such patients.[103] The European Stroke Organization (ESO 2010) guidelines recommend either the closure of a patent's foramen ovale surgically or anticoagulation if a concurrent atrial septal aneurysm is present if the patient is less than 55 years old, or there is a presence of concurrent venous thrombosis.[79] A recent change in the 2014 Canadian Stroke Best Practice Recommendations made a change where a surgical closure of patent foramen was no longer recommended.[48] This change was made based on a two recent trials comparing medical treatment (i.e., antiplatelet or anticoagulation) to percutaneous closure for patients with patent foramen ovale in cryptogenic TIA or stroke.[48 109 110] The results showed no mortality or morbidity (i.e., stroke prevention) benefit of surgical intervention over medical treatment.

2.7.5 Management of cardioembolic TIA or stroke caused by aortic atheroma

The treatment of aortic atheroma is controversial. Treatment options include lipid-lowering agents (3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors) combined with either an anticoagulant or an antiplatelet agent. Unfortunately, there are no large studies demonstrating the most effective treatment. The SPAF III trial was primarily designed to compare a dose-adjusted warfarin regimen to aspirin with a fixed dose of warfarin in patients with atrial fibrillation.[111] A post-hoc analysis of this

trial of 133 patients with an aortic atheroma was conducted. The results showed a significantly lower risk of embolism in those receiving dose-adjusted warfarin, with an absolute risk reduction of 13%.[111] Another 12 year retrospective cohort study consisting of 519 cases with an atheroma showed that a statin alone had protective effects from subsequent embolism, with an absolute risk reduction of 17% and number needed to treat of 6.[112]

2.8 Statement of Problem in Emergency Departments

When a TIA or a non-disabling stroke diagnosis is made in most Canadian emergency departments (ED's), a transthoracic echocardiogram may be ordered. A fraction of ordered echocardiograms will not be performed due to the lack of availability. Among those who are able to have the test, many will have the scan delayed from the time of their initial diagnosis. This will subsequently delay appropriate treatment, and may result in a stroke.

2.9 Overview of a clinical prediction rule

Clinical prediction rules are defined as "a decision making tool that is derived from original research (as opposed to a consensus-based clinical practice guideline) and incorporates 3 or more variables from the history, physical examination, or simple tests".[113] Clinical prediction rules have recently gained much attention among clinical researchers. These rules have successfully reduced the number of ordered tests, subsequently reducing cost, patient wait times, and the number of unnecessary tests performed.[114-116] There are six methodological steps to incorporate a prediction rule into clinical practice: identifying the need for a prediction model, derivation, validation, implementation, economic evaluation, and dissemination of the prediction model.

2.9.1 The methodological standards of clinical prediction rules:

The methodological standards follow a systematic approach for the development of a clinical prediction rule.[113 117 118] The following steps create an outline for its development:

Identifying the need for a prediction model

The need of a prediction rule is justified by a knowledge gap, significant practice variation, or an inefficient current practice for a common particular medical condition. This can be done through a systematic survey among experts and practicing clinicians.

Derivation

Derivation is the first stage in generating a prediction rule for a particular disease or test result. This requires several steps:

1. Clearly select and define several appropriate, potential predictors and provide a targeted outcome for each.
2. Determine a set of selection criteria (i.e., inclusion and exclusion criteria).
3. Calculate an appropriate sample size based on disease prevalence, targeted accuracy, number of potential predictors, and expected proportion of a given outcome. The accepted necessitates 5 to 10 positive outcomes for each potential predictor.[119]
4. The assessment of each potential predictor should be blinded from the outcome status to avoid observational bias.
5. Appropriate selection of final predictors that are easy to use, statistically significant, and clinically meaningful.
6. Mathematical definition of both univariate and multivariable analysis to follow (e.g., Pearson Chi-square, Fisher exact test, logistic regression or recursive partitioning analysis).

Validation

A prospective validation of the prediction model is an important step to determine accuracy, reliability, generalizability, impact, and incorporation of the model into clinical practice. At the end of this stage, investigators may refine some of the proposed variables to improve the overall performance of the prediction model.

Implementation

During this stage, the main goal is to assess the generalizability, the impact and the clinical acceptance of the selected model. Even if a model is successful in validation, major challenges may be found in incorporating this model into clinical practice. This can be attributed to a clinician's fear of missing a given diagnosis. The ideal method of assessing a model's success in implementation is through a before and after trial. Alternatively, a survey of physicians' attitude to assess their comfort, understanding and their satisfaction in using the model can be done.

Economic evaluation

Upon successful implementation of the prediction model, an economic evaluation should be done. This should assess three economic aspects: cost identification, cost benefit analysis, and cost effective analysis on the health care system.

Dissemination

This stage focuses mainly on strategic marketing of the prediction model. A publication in a scientific journal alone is often not sufficient enough to get clinicians familiar with the prediction rule. Disseminating the model via other means such as seminars, posters, mobile phone applications or pocket cards may be helpful.

2.10 Overview on the database we used of the TIA study

2.10.1 Study Design

The TIA study is a prospective cohort study of patients who presenting to one of the 8 participating Canadian Emergency Departments (EDs) with either TIA or non-disabling stroke.[120] The primary objective of the TIA study was to derive a highly sensitive, clinical prediction rule to identify high-risk patients for subsequent stroke or death in the first seven days following their initial hospital visit. Emergency physicians ordered initial TIA/non-disabling stroke investigations including an electrocardiogram, a brain MRI or a CT, echocardiogram, carotid artery imaging either during the initial emergency department visit or as an outpatient. Neurologists ordered additional tests based on their clinical judgment. A total of 3,906 patients were enrolled; 28% (N= 1,094) of the enrolled patients did not have an echocardiogram within the first 90 days following presentation.

2.10.2 Study Population

Seventy five percent of all eligible patients presenting to the participating EDs were enrolled in the TIA study. The eligibility criteria are as follows:

2.10.2.1 Inclusion Criteria

Any adult patient 18 years of age or older diagnosed with non-disabling ischemic stroke or TIA by the assessing neurologist or emergency physician. The WHO definition of TIA was used: a "focal neurological deficit lasting for <24 hours, presumed to be of vascular origin, and confined to an area of the brain or eye perfused by a specific artery". [3]

2.10.2.2 Exclusion Criteria

Patients were excluded based on the presence of any of the following:

Symptom onset greater than one week prior to assessment;

Diagnosis in ED of a completed stroke, defined as either a neurological deficit for longer than 24 hours, or cases who qualified for thrombolysis;

Presentation with a decreased level of consciousness (i.e., Glasgow Coma Scale score of less than 15);

Presence of any other documented cause for the deficit not attributed to TIA (e.g., hypoglycemia, seizure, electrolyte imbalance, migraine, transient global amnesia, etc.)

2.10.3 Study setting

The study was conducted at 8 tertiary university affiliated EDs:

i. The Ottawa Hospital, Civic Campus

ii. The Ottawa Hospital, General Campus

iii. Kingston General Hospital

iv. Hôpital de L'Enfant-Jesus (Quebec City)

v. Hotel Dieu Hospital (Kingston)

vi. Hamilton Health Sciences Centre: McMaster Site

vii. Hamilton Health Sciences Centre: Henderson Site

viii. Hamilton Health Sciences Centre: General Site

2.10.4 Study duration

All patients were enrolled over a 5-year period from October 2006 to October 2011.

CHAPTER 3: METHODS

3.1 Study targeted population

For the purposes of this project, a sub-study of the TIA prospective cohort was done to derive a prediction rule to determine whether a treatment change is indicated based on an abnormal echocardiogram. Patients who had an echocardiogram within the TIA study were targeted.

3.2 Sample size adequacy

Seven per cent of the sample size is estimated to have had a treatment change based on an abnormal echocardiogram. The appropriateness of the sample size selected is based on the bound of error estimation of the sensitivity of the clinical prediction rule (i.e., width of the 95%CI). The formula for this bound is $B=16p(1-p)/\sqrt{n}$. For N=536 and an anticipated sensitivity of 95% (p=0.95), the bound of error estimation is 0.045 (i.e., a lower 95% confidence limit of 90.5%). Based on consensus among our local expert panel (consisting of 2 emergency physicians and 1 neurologist), this would be an acceptable precision. For the model sensitivity, a precision between 90.5%-99.5% was also deemed acceptable. We estimated that 60 to 120 positive outcomes were needed to derive a stable prediction model and to conduct a valid multivariable analysis.

3.4 Data collection

A standardized data collection sheet was used (Appendix 1) to collect the following additional data (i.e., not contained in the original prospective cohort study): brain imaging results (CT or MRI scan), echocardiogram results, and the presence or absence of a treatment change based on the echocardiogram result. This information was

collected from both the original electronic imaging reports and the electronic or paper medical charts.

Data were entered as new variables in the existing TIA study database. The TIA database contained patient's baseline demographics (i.e., age, gender and comorbidity), presenting signs and symptoms, occurrence of subsequent stroke or death in the 90 days following presentation. In an effort to avoid misclassification, all variables already collected in the TIA database were verified by a research nurse using the notes from the patients' hospital visit attached to the original data collection form of the TIA study.

3.4 Data Analysis

3.4.1 Objective 1.2.1 analysis

Outcome definition

The outcome of our study is defined as any treatment change made based on an abnormal echocardiogram finding in patients with TIA or non-disabling stroke within the TIA study.

Outcome ascertainment

A comprehensive list of possible abnormal echocardiogram findings at risk cardioembolic events was compiled (Table 15). In order to ascertain each subjects outcome, the medical record had to clearly indicate a treatment change was made based on given abnormal echocardiogram findings. The type of treatment change was also outlined (Table16). We reviewed each hospital visit to ensure an accurate outcome ascertainment. If an outcome (i.e., treatment change based on the echocardiogram result) was unclear, the case was deferred to an expert panel consisting of two emergency physicians and one stroke neurologist. The reviewers of the outcome ascertainment were blinded to the status of the proposed predictors.

Table 15. Abnormal Cardiac Structures that Predispose Cardioembolic Causes of TIA that may lead to a Treatment Change
Left atrial appendage thrombus (LAAT)
Left ventricular thrombus
Left atrial myxoma
Vegetation
Valve Dehiscence
Ventricular aneurysm
Aortic dissection
Ejection fraction <30%
Atrial fibrillation
Atrial flutter
Dilated cardiomyopathy
Left atrial appendage contrast (LAAC)
Atrial septal aneurysm (ASA)
Arthrosclerosis of ascending aorta
Patent foramen ovale
Valvular calcification

Table 16. Type of Treatment Change Made Based on an Abnormal Echocardiogram Findings
Treatment change
Medical treatment
Surgical treatment
Both surgical and medical treatment
Type of Medical Intervention
Warfarin
New Oral Anticoagulants (NOACs)
Multiple anticoagulant
Other medical treatment
Multiple medical treatments
Type of Surgical Intervention
Patent foramen ovale closure
Atrial septal aneurysm repair
Multiple surgical intervention
Other

Potential predictor definitions:

A comprehensive list of 27 potential predictor variables were listed based on the expert opinions of two emergency medicine attending physicians and one stroke neurologist at our local centre (Table 17).

Table 17. Definitions of the Proposed Predictors of Treatment Change Made Based an Abnormal Echocardiogram

Variable number	Variable name	Definition
1.	Age ≤ 50 years old	Any age less than or equal to 50 years old
2.	History of heart failure	Any patients who previously had a formal diagnosis of heart failure
3.	Presence of valvular heart disease	Any patients who previously had a formal diagnosis of valvular heart disease
4.	Hypertension	Any patients who previously had a formal diagnosis of hypertension
5.	Atrial fibrillation	Any patients who previously had a formal diagnosis of atrial fibrillation
6.	Diabetes	Any patients who previously had a formal diagnosis of diabetes
7.	Current smoker	Any patients known to be a current smoker
8.	Dementia	Any patients who previously had a formal diagnosis of dementia
9.	Prior stroke	Any patients who previously had a formal diagnosis of stroke
10.	Carotid stenosis	Any patients who previously had a formal diagnosis of carotid artery stenosis
11.	Coronary artery disease	Any patients who previously had a formal diagnosis of coronary artery disease
12.	Hyperlipidemia	Any patients who previously had a formal diagnosis of hyperlipidemia
13.	Symptoms last more than 60 minutes	Any patient who experienced signs or symptoms of a deficit lasting more than 60 minutes

Variable number	Variable name	Definition
14.	Recurrent symptoms of TIA	Any patient who experienced recent reoccurring signs or symptoms of a deficit over a given time period
15.	Any language disturbance	Any signs or symptoms of either slurred speech or aphasia
16.	Lightheadedness	Any symptoms of dizziness
17.	Vertigo	A sensation of a false spinning movement
18.	Confusion	Acute loss of either short-term, long-term memory or disorientation
19.	Visual field defect	Acute partial or complete visual loss
20.	Diplopia	Sensation of double vision from history or during physical exam
21.	Signs of incoordination	Inability to coordinate body movement during physical examination
22.	Presence of audible murmur in cardiac exam	Presence of an audible abnormal heart sound between the phases of normal physiological heart sounds
23.	Presence of Atrial fibrillation or Flutter in Electrocardiogram (ECG)	Presence of atrial rhythm disturbance and irregularity evident in cardiac tracing
24.	ACA infarct	Presence of cerebral infarct in the Anterior cerebral artery territory
25.	MCA infarct	Presence of cerebral infarct in the middle cerebral artery territory
26.	Posterior circulation infarct	Presence of brain infarct in either posterior cerebral artery, vertebrobasilar artery or any cerebellar artery territory

Variable number	Variable name	Definition
27.	Presence of multi-territorial infarct on any kind of imaging	Presence of multiple arterial territory infarcts regardless of the acuity of either: 1. Presence of bilateral ACA, MCA, PCA or cerebellar infarcts 2. Presence of ACA with MCA, vertebrobasilar, cerebellar artery or PCA infarcts 3. Presence of MCA with vertebrobasilar, cerebellar artery or PCA infarcts 4. Presence of vertebrobasilar with cerebellar artery or PCA infarcts 5. Presence of cerebellar artery with PCA infarcts

ACA: Anterior Cerebral Artery
MCA: Middle Cerebral Artery
PCA: Posterior Cerebral Artery

Descriptive statistics

All baseline characteristics and echocardiogram findings are listed as either a proportion "if the variable was nominal" or as a mean with standard deviation "if the variable was continuous".

Mathematical method of Analysis

Univariate analysis

All listed variables in table 17 are nominal dichotomous. A univariate analysis was done to assess the strength of association between proposed predictors and our targeted outcome (i.e., treatment change made based on an abnormal echocardiogram finding). If the number of any cell within the 2x2 contingency table were less than 10% expected, a Fisher exact test was used to test for an association. If the number was large

(i.e., more than 10 subjects within each cell) a Pearson chi-square test was used to test for an association.

Handling missing data

A reviewer went to through the charts of all those with missing variables and looked for as much data as possible. The purpose was to verify the exact value of a given variable. This review included all emergency department physician notes, nurses triage notes, paramedics notes, and all consultation notes. All remaining missing variables were imputed as "not present" before conducting our multivariable analysis if they were small numbers of missing values (< 5%) assuming they were missed completely at random. This approach was taken in order to ensure a conservative approach is utilized, which does not favour the predictability of our model.

Reliability

A second independent reviewer recollected a randomly selected 10% (n=280) of our sample size in a separate data collection sheet (Appendix 2,3). We used kappa statistics to report the level of agreement. A kappa value greater than 0.6, was considered to be a good level of agreement.

Multivariable analysis

We used two different mathematical methods: binary logistic regression analysis and recursive partitioning analysis.

i. Logistic regression analysis

We utilized a regression analysis to produce a scoring system in order to divide our study subjects into high and low risk probability. This scoring system will help clinicians to determine the urgency with which echocardiogram must be performed in patients presenting with TIA and non-disabling stroke. A stepwise backward and

forward selection approach was followed. In order for a variable to be eligible to enter the model, the P-value must have been less than 0.2. The exclusion criterion for selection was the presence a P-value of more than 0.05. For the final model, the variable with the smallest beta coefficient was used to divide itself and all other beta co-efficient values. We created a scoring system by rounding all values to the nearest whole number. Each score translated into a probability of the targeted outcome. For each predictor, we reported the beta co-efficient, the score, and the odds ratio with its 95% confidence interval. A Goodness of Fit test was performed using the Hosmer Lemeshow test. A diagnostic check on our regression model for collinearity and confounding using Pearson's correlation coefficient was performed. All coefficients greater than or equal to ±0.5 were considered significantly collinear variables. These were not included in the multivariable analysis. In addition, we checked for outliers using standardized residual statistics. A residual value of more than ± 3 was considered to be an outlier and was removed to assess for changes in the model. Subject outliers were kept in the analysis if an outlier's effect was not identified or if a positive outcome was found (i.e., treatment change based on echocardiogram). The discriminatory power was assessed with a C-statistics test, using a 95% confidence interval value. For the purpose of internal validation of our final models, a 5000 bootstrapping assessment (a resampling technique) was performed to test the model's stability. The mean of beta coefficient of each variable and C-statistics will be reported.

ii. Recursive partitioning analysis

Recursive partitioning analysis is a type of Classification and Regression Tree (CART) modeling. We chose this approach to derive a highly sensitive decision tree in order to predict our study outcome. All variables that were clinically meaningful and had

a P-value equal or less than 0.05 in the univariate analysis, were eligible for inclusion in the model. All predictors with at least five positive outcomes predicted were kept in the model. The final choice of the model that favours the most specific and sensitive among candidate models was chosen.

3.4.2 Objective 1.2.2 analysis

We conducted an analysis to determine the risk of stroke for TIA patients within the first 90 days following diagnosis with both an abnormal and a normal echocardiogram. The relative risk (based on incidence risk estimates) with 95% confidence intervals, and a chi-squared test were used to compare the subsequent risk incidence of stroke in patients with an abnormal versus normal echocardiogram.

3.4.3 Objective 1.2.3 analysis

An analysis was conducted to determine the subsequent risk of stroke for each type of TIA etiology within the first 90 days following diagnosis, compared to all other TIA etiologies. The relative risk (based on incidence risk estimates) with 95% confidence intervals, and a chi square test were used to compare the subsequent risk incidence of stroke for each type of TIA etiology versus all other TIA etiologies.

3.4.4 Objective 1.2.4 analysis

An analysis determining the all-cause mortality for each type of TIA etiology in the first 90 days in comparison to all other types of TIA etiology was conducted. The relative risk (based on incidence risk estimates) with 95% confidence intervals, and a chi square test were used to quantify the comparison.

3.4.5 Software

The statistical analysis was done using IBM® SPSS® Statistics version 21 (SPSS Inc.; Chicago, IL) with the exception of the recursive partitioning analysis, where Knowledge SEEKER® version 8.3 (Angoss; Toronto, Canada) was utilized.

3.5 Ethical considerations

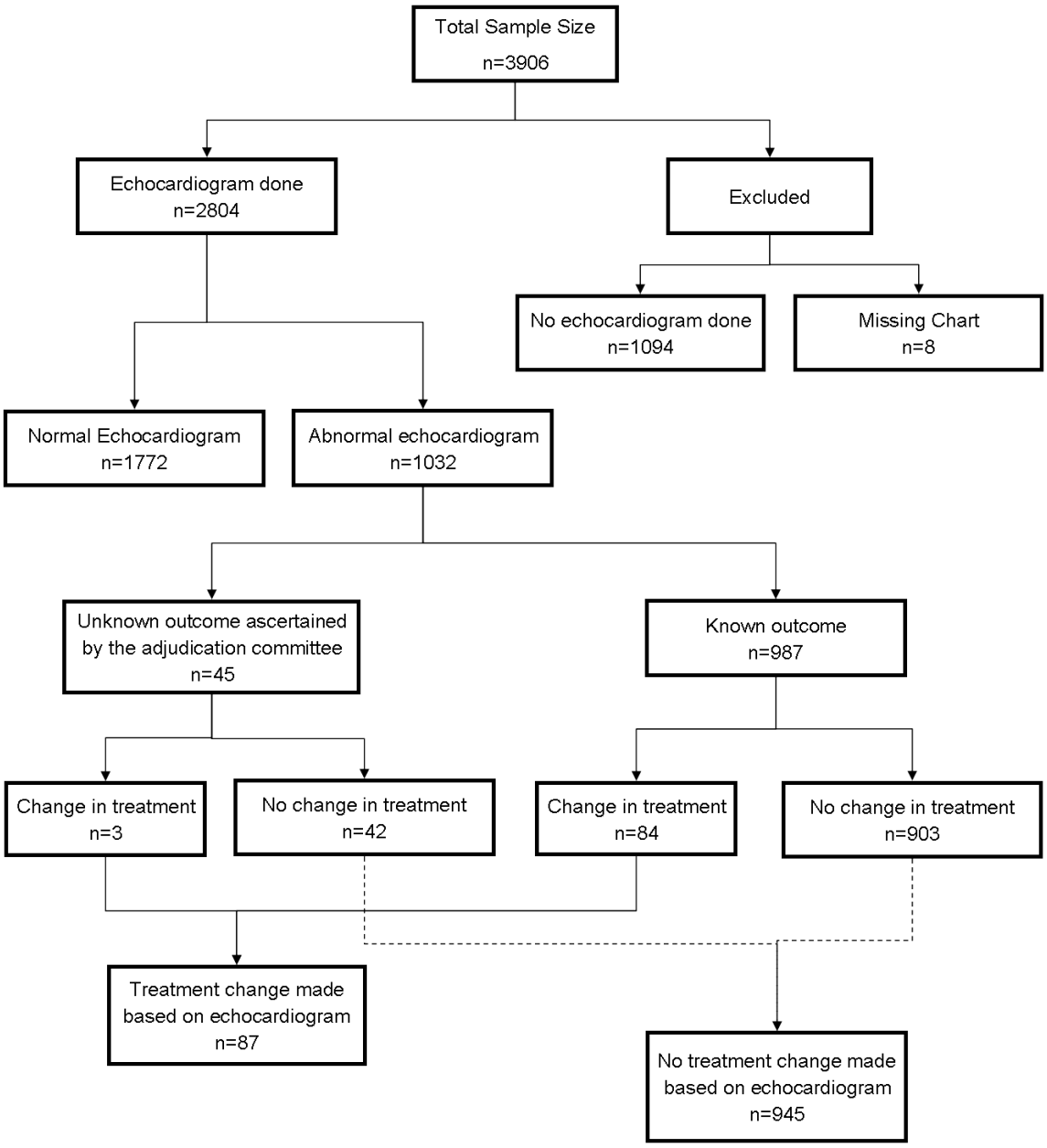
We obtained approval from The Ottawa Hospital Research Ethics Board prior to data collection for this sub-study (Appendix 4). Patients were identified with a unique subject number. To ensure patient privacy, the case record forms (CRFs) used did not contain any patient identification information. The CRFs was stored at the Ottawa Hospital Research Institute (OHRI), in a locked, secure place, accessible only by our research team members.

CHAPTER 4: RESULTS

4.1 Study Flow

An outline of our study flow is shown in Figure 5. Of the 3,906 patients in the TIA study, 71.9% (N=2,812) had an echocardiogram. We excluded 8 cases because of missing charts. A total of 2,804 were enrolled in our sub-study, of which 1,032 cases had an abnormal echocardiogram. Based on our calculation, we have obtained an adequate sample size. A total of 45 cases had an unknown outcome (Appendix 5). For these outcomes, our adjudication committee made ascertainment. Eighty-seven cases had a positive outcome (i.e., treatment change made based on an abnormal echocardiogram). Eighty-four of these cases were discovered in the patients follow-up visit note, while the adjudication committee ascertained the remaining 3 cases.

Figure 5. Patient Flow



4.2 Descriptive statistics

Table 18 outlines a list of baseline sub-study subjects' characteristics. The mean age of our sub-study was 67.7 years old with equal gender distribution. Less than one fifth (13%) of the TIA/non-disabling stroke cases in our study were young subjects (i.e., age were less than 50 years old). A proportion of 17.8% had a diagnosis of non-disabling stroke. The diagnosis of non-disabling stroke was made at their follow up visit where subsequent brain imaging revealed an occult infarct. The occult infarct was not revealed in the initial Emergency department Brain CT scan, due to the known limitation of this particular imaging modality. In this patient proportion with non-disabling stroke it was not possible to make the diagnosis in the Emergency Department, due to lack of readily available MRI for this particular cases.

When the comorbid conditions of our patients were assessed, we found that more than 50% of our study subjects had hypertension. Roughly one of fifth of our study cases had coronary artery disease and a similar proportion had diabetes. Atrial fibrillation and a prior history of stroke had fairly similar proportions of almost one tenth of patients. Heart failure, valvular heart disease, dementia, carotid artery stenosis as well as peripheral vascular disease had again very similar proportions of roughly 5%.

Table 18. Baseline Characteristics	
Variable	Overall study N=2804
Demographic	
Age (Mean) Range	67.7 (21-101)
Male	1,415 (50.5%)
Age less or equal to 50 years old	368 (13.1%)
Non–disabling stroke	499 (17.8%)
Comorbidity	
History of heart failure	80 (2.9%)
Presence of valvular heart disease	77 (2.7%)
Hypertension	1656 (59.1%)
Atrial fibrillation	216 (7.7%)
Diabetes	540 (19.3%)
Current smoker	362 (12.9%)
Dementia	69 (2.5%)
Prior stroke	315 (11.2%)
Carotid stenosis	97 (3.5%)
Peripheral vascular disease	106 (3.8%)
Coronary artery disease	485 (17.3%)
Hyperlipidemia	922 (32.9%)

4.3 Echocardiogram findings

In our study sample (Table 19) two types of echocardiogram were performed: transthoracic echocardiogram (99.2%) or transesophageal echocardiogram (8.5%). The choice of echocardiogram type of either transthoracic or transesophageal

echocardiogram was based on clinician discretion of how likely to find a cardioembolic structure. Almost one third of transthoracic echocardiograms included were abnormal; while more than half of transesophageal echocardiograms were abnormal.

The structures commonly found in transthoracic echocardiogram were valvular calcification (58.9%), atherosclerosis of ascending aorta (16.2%), patent foramen ovale (14.7%), atrial fibrillation (11.8%), and atrial septal aneurysm (6.6%). The common abnormalities found in transesophageal echocardiograms were patent foramen ovale (72.1%), atrial septal aneurysm (30.7%), atherosclerosis of ascending aorta (25.0%), and valvular calcification (7.1%).

Table 19. Echocardiogram Findings

Finding	Transthoracic Echocardiogram N= 2782(%)	Transesophageal Echocardiogram N=238(%)
Abnormal echocardiogram findings	982 (35.3%)	140 (58.8%)
Left trial appendage thrombus (LAAT)	4 (0.4%) *	1 (0.7%) Ω
Left ventricular thrombus	6 (0.6%) *	0 Ω
Left atrial myxoma	3 (0.3%) *	2 (1.4%) Ω
Vegetation	8 (0.8%) *	1 (0.7%) Ω
Valve dehiscence	1 (0.1%) *	0 Ω
Ventricular aneurysm	12 (1.2%) *	2 (1.4%) Ω
Aortic dissection	3 (0.3%) *	1 (0.7%) Ω
Ejection fraction <30%	27 (2.8%) *	1 (0.7%) Ω
Atrial fibrillation	116 (11.8%) *	3 (2.1%) Ω
Atrial flutter	6 (0.6%) *	0 Ω
Dilated cardiomyopathy	15 (1.5%) *	3 (2.1%) Ω
Left atrial appendage contrast (LAAC)	35 (3.6%) *	4 (2.9%) Ω
Atrial septal aneurysm (ASA)	65 (6.6%) *	43 (30.7%) Ω
Arthrosclerosis of ascending aorta	159 (16.2%) *	35 (25.0%) Ω
Patent foramen ovale	144 (14.7%) *	101 (72.1%) Ω
Valvular calcification	576 (58.9%)*	10 (7.1%) Ω
Transthoracic was consistent with transesophageal echocardiogram	110 (46.2%) Ω	

*** :** The proportions were calculated were out of abnormal transthoracic echocardiogram only (n=982)
Ω: The proportions were calculated were out of abnormal transesophageal echocardiogram only (n=140)

4.3.1 Type of treatment change made based on echocardiogram

The three types of treatment changes made for our study population were medical (57.5%), surgical (11.5%) or both medical and surgical treatment (31.0%) (Table 20). The types of common medical treatment changes were anticoagulation therapy in 76.1% of cases, or starting a new antiplatelet therapy (e.g., aspirin, clopidogrel) in 11.9% of our study. The anticoagulation therapies used were either oral or parenteral (i.e., injection). The oral anticoagulation used was warfarin (58.6%) or new oral anticoagulants (e.g., Dabigatran) in 2.3% of cases with a treatment change. Co-administration of both parenteral anticoagulants (i.e., Heparin) with an oral anticoagulant was administrated in 12.6% cases (Table 20).

Surgical interventions in our study included closure of patent foramen ovale, atrial septal aneurysm repair, valve replacement or aortic dissection/aneurysm repair. The most common surgical intervention, accounting for almost one third of the surgical interventions, was the closure of a patent foramen ovale (Table 20).

The treatment changes were made based on TTE in 52.9% of cases, while 47.1% were made based on TEE. The most common structure leading to a deviation in all types of treatment was patent foramen ovale with atrial septal aneurysm, seen in more than one third of cases. The second most common was an echocardiographic detection of atrial fibrillation or flutter in 18.4% of cases (Table 21).

Table 20. Type of Treatment Change Made Based on Echocardiogram Findings	
Treatment change	Frequency (%) n=87
Medical treatment	50 (57.5%)
Surgical treatment	10 (11.5%)
Both surgical and medical treatment	27 (31.0%)
Type of Medical Intervention	77 (89.5%)
Warfarin	51 (58.6%)
New oral anticoagulants (NOACs)	2 (2.3%)
Multiple anticoagulants	11 (12.6%)
Other	10 (11.5%)
Multiple medical treatments	3 (3.4%)
Type of Surgical Intervention	38 (43.7%)
Patent foramen ovale closure	32 (36.8%)
Atrial septal aneurysm repair	1 (1.1%)
Multiple surgical intervention	1 (1.1%)
Other	4 (4.6%)

Table 21. Type of Echocardiogram and Abnormal Findings that Made the Treatment Change

Variable	Treatment change N=87 (%)
Treatment change based on a diagnostic Test	
Transthoracic echocardiogram	46 (52.9%)
Transesophageal echocardiogram	41 (47.1%)
Abnormal findings that had a treatment change	
Atrial myxoma	1 (1.1%)
Left atrial appendage thrombus (LAAT)	1 (1.1%)
Left ventricular thrombus	3 (3.4%)
Vegetation	3 (3.4%)
Ventricular aneurysm	5 (5.7%)
Ejection fraction <30%	7 (8.0%)
Atrial fibrillation/flutter	16 (18.4%)
Patent foramen ovale with Atrial Septal Aneurysm (ASA)	33 (37.9%)
Atrial Septal Aneurysm (ASA) alone	2 (2.3%)
Patent foramen ovale alone	9 (10.3%)
Aortic dissection	1 (1.1%)
Aortic atheroma	6 (6.9%)

4.4 Reliability

All data collected included the proposed predictors in the model, echocardiogram findings and the treatment change made had a Kappa Value >0.60. (Table 22).

Table 22. The Level of Agreement of the Proposed Variable, Echocardiogram Result and if a Treatment Change was Made Based on Echocardiogram Findings

Variable name	Kappa Value n= 280
History of heart failure	0.65
Presence of valvular heart disease	1.0
Hypertension	0.77
Atrial fibrillation	1.00
Diabetes	1.00
Current smoker	0.72
Dementia	0.65
Prior stroke	1.00
Carotid stenosis	1.00
Coronary artery disease	1.00
Hyperlipidemia	0.82
Symptoms last more than 60 minutes	0.81
Recurrent symptoms	0.74
Any language disturbance	0.94
Lightheadedness	0.40
Vertigo	0.34
Confusion	1.00
Visual field defect	0.89
Diplopia	0.78
Signs of incoordination	0.63
Presence of audible murmur in cardiac exam	NA
Presence of Atrial fibrillation or flutter on electrocardiogram (ECG)	0.87
ACA infarct	0.70

Variable name	Kappa Value n=280
MCA infarct	0.65
Posterior circulation infarct	0.86
Presence of multi-territorial infarct in any kind of imaging	0.68
Transthoracic Echocardiogram result	0.96
Transesophageal Echocardiogram result	1.00
Treatment change based on echocardiogram findings	0.99

ACA: Anterior Cerebral Artery
MCA: Middle Cerebral Artery
NA: Not Assessed

4.5 Etiology of TIA or of non-disabling stroke

The most common cause of TIA and non-disabling stroke was cryptogenic, followed by small vessel disease. Cardioembolic sources were the third leading cause in 9.4% of cases, while large vessel disease was the fourth (Table 23).

Table 23. Etiology of TIA or Non-Disabling Stroke	
Etiology	Overall study N=2804(%)
Large Vessels Disease (LVD)	229 (8.2%)
Small Vessels Disease (SVD)	487 (17.4%)
Cardioembolic (CE)	264 (9.4%)
Cardioembolic (CE) with multiple etiologies	330 (11.8%)
Multiple etiologies	67 (2.4%)
Cryptogenic	675 (24.1%)
Cocaine induced	4 (0.1%)
Vasculitis	3 (0.1%)
Venous thrombosis	0
Unable to determine	139 (5.0%)
Not a TIA or stroke by neurology	931 (33.2%)
Other	4(0.1%)

4.6 Results of objective 1.2.1

4.6.1 Univariate analysis:

Eight out of 27 proposed predictors were eligible to enter the multivariable analysis (Tables 24A/24B). The 8 potential predictors were as follows: age less than or equal to 50 years old, history of heart failure, history of coronary artery disease, clinical presentation of any language deficit (either slurred speech or aphasia), findings of middle cerebral artery infarct on brain imaging, findings of any infract at posterior circulation territories in brain imaging, recurrent symptom of TIA and presence of multi-territorial infarcts on brain scan. All eligible variables had a P-value less than 0.2.

In 10 out of the 27 proposed predictors, a small proportion of missing values are present (Tables 24 A/ 24 B). These values were missing either because a given test was not performed or because the treating physician did not complete the study case record form.

Table 24 A. Univariate Analysis of Clinical Variable for Cases had a Treatment Change Based on Echocardiogram Findings

Variable	Treatment change N=87 (3.1%)	No treatment change N=2717 (96.9%)	P-value
Demographic			
Age(Mean) Range	61.16 (SD=17.0) (22-88)	67.89 (SD=14.1) (21-101)	0.002 §
Male	44 (50.6%)	1371 (50.5%)	1.00
Age less or equal to 50 years old	33 (37.9%)	335 (12.3%)	<0.001 Ω §
Final diagnosis of non-disabling stroke	29 (33.3%)	470 (17.3%)	<0.001 §
Comorbidity			
Heart failure	7 (8.0%)	73 (2.7%)	0.011 Ω §
Valvular heart disease	4 (4.6%)	73 (2.7%)	0.300
Hypertension	46 (52.9%)	1610 (59.3%)	0.268
Atrial fibrillation	6 (6.9%)	210 (7.7%)	1.00
Diabetes	18 (20.7%)	522 (19.2%)	0.681
Current smoker	9 (10.3%)	353 (13.0%)	0.625
Dementia	1 (1.1%)	68 (2.5%)	0.724
Prior stroke	8 (9.2%)	307 (11.3%)	0.729
Carotid stenosis	2 (2.3%)	95 (3.5%)	0.768
Coronary artery disease	22 (26.2%)	463 (17.1%)	0.039 Ω §
Hyperlipidemia	27 (31.0%)	895 (32.9%)	0.730
General clinical presentation characteristics			
Symptoms last more than 60 minutes Φ	53 (60.9%)	1599 (59.0%)	0.741
Recurrent symptoms ¥	19 (21.8%)	824 (30.5%)	0.096
Posterior circulation signs and symptoms			
Lightheadedness	21 (27.6%)	590 (24.0%)	0.496

Vertigo	6 (8.1%)	303 (12.4%)	0.367
Confusion	8 (10.5%)	324 (13.2%)	0.606
Visual field defect [λ]	8 (9.2%)	372 (13.7%)	0.267
Diplopia [μ]	4 (4.6%)	140 (5.2%)	1.00
Signs of incoordination [ξ]	9 (11.3%)	224 (8.8%)	0.423
Other signs and symptoms			
Any language disturbance (either slurred speech or aphasia)	47 (54.0%)	1138 (41.9%)	0.027 Ω §
Presence of audible murmur in cardiac exam [ς]	8 (9.3%)	178 (6.6%)	0.375

SD: Standard deviation
Ω: Eligible variables to enter to the multivariable analysis
§: Statistically significant association
Φ: Missing 5 values with no positive outcomes within those cases
γ: Missing 12 values with no positive outcomes within those cases
λ: Missing 11 values with no positive outcomes within those cases
μ: Missing 26 values with no positive outcomes within those cases
ξ: Missing 173 values with 7 positive outcomes within those cases
ς: Missing 29 values with 1 positive outcome within those cases

Table 24 A. Univariate Analysis of Work-Up Result for Cases had a Treatment Change Based on Echocardiogram Findings

Variable	Treatment change N=87 (%)	No treatment change N=2717 (%)	P-value
Diagnostic Test			
Electrophysiology Cardiac investigation			
Presence of Atrial fibrillation or Flutter in Electrocardiogram (ECG) ω	6 (7.1%)	143 (5.5%)	0.469
Cardiac imaging			
Any echocardiogram	87 (100.0%)	2717 (35.0%)	
Transthroacic Echocardiogram	84 (3.0%)	2698 (97.0%)	
Transesophageal Echocardiogram *	45 (18.9%)*	193 (81.1%) *	
Brain imaging (CT Scan /MRI scan) ϑ			
CT scan performed Δ	87 (100.0%)	2690 (99.0%)	
Abnormal CT scan §	22 (25.3%)	356 (13.1%)	
MRI performed ¶	35 (40.2%)	762 (28.0%)	
Abnormal MRI scan	15 (42.9%)	165 (21.7%)	
ACA infarct	1 (1.1%)	67 (2.5%)	0.723
MCA infarct	21 (24.1%)	222 (8.2%)	<0.001 α §
Acute MCA infarct	7 (8.0%)	98 (3.6%)	0.042 §
Non-acute MCA infarct	14 (16.1%)	126 (4.6%)	<0.001§

Posterior circulation infarct	17 (19.5%)	239 (8.8%)	0.002 α §
Acute posterior circulation infarct	4 (4.6%)	63 (2.3%)	0.152
Non-acute posterior circulation infarct	13 (14.9%)	176 (6.5%)	0.005 §
PCA infarct	7 (8.0%)	99 (3.6%)	0.044 §
Mid-brain Infarct	2 (2.3%)	37 (1.4%)	0.343
Cerebellar Infarct	9 (10.3%)	116 (4.3%)	0.014 §
Presence of multi-territorial infarct in either CT or MRI	6 (6.9%)	88 (3.2%)	0.069 α

CT: Computed Tomography,
ACA: Anterior Cerebral Artery,
MCA: Middle Cerebral Artery,
PCA: Posterior Cerebral Artery,
MRI: Magnetic Resonance Images
***:** The reported percentage is within patients who had transesphageal echocardiogram.
α: Eligible variables to enter to the multivariable analysis
§: Statistically significant association
ω: ECG was not performed in 136 cases, where had 3 cases with positive outcome
ϑ: No brain imaging of any kind was performed in 18 cases, where had not have a single case with a positive outcome
Δ: CT scan was not performed in 27 cases, where had not have a single case with a positive outcome
¶: MRI scan was not performed in 2007 cases, where had 52 cases with positive outcome

4.6.2 Multivariable analysis:

All eight eligible variables examined are binomial. A small proportion of the missing values (0.6%) were present in 4 of the eligible variables. Those four variables are recurrent symptom of TIA, findings of middle cerebral artery infarct on brain imaging, finding of any infract at posterior circulation territories on brain imaging, and the presence of multi-territorial infarcts on brain scan. None of the cases with missing values had a positive outcome (i.e., treatment change based on an abnormal echocardiogram) (Appendix 6). A correlation was seen between multiterritorial infarct and posterior circulation (Table 25). The Pearson correlation coefficient after rounding the number was approximately 0.5. Therefore, the multiterritorial infarct variable was excluded. Also, the recurrent symptoms of the TIA variable has affected the fitness of the model with a very large standard error when running the regression analysis, therefore it was excluded as well.

Table 25. Assessment for Collinearity Between Eligible Variables to Enter Multivariable Analysis

		Language disturbance	History of CAD *	History of HF α		Multiterritorial infarct	Posterior circulation infarct	MCA infarct β	Age ≤50
Language disturbance	**Pearson Correlation**	1	.044	.031		.033	.035	.129	.099
History of CAD*	**Pearson Correlation**		1	.165		.025	.055	.064	.127
History of HF α	**Pearson Correlation**			1		.016	.042	.031	.035
Multiterritorial infarct	**Pearson Correlation**					1	.450^	.323	.049
Posterior circulation infarct	**Pearson Correlation**						1	.100	.065
MCA infarct β	**Pearson Correlation**							1	.067
Age ≤50	**Pearson Correlation**								1

*: CAD is coronary artery disease
α: HF is heart failure
β: MCA is middle cerebral artery
^: Correlated variables; therefore, multiterritorial infarct variable is not eligible

4.6.2.1 Logistic regression analysis:

Six variables were included through a backward selection processes during the analysis. Further, using standardized residual statistics; we identified 62 cases as potential outliers. However, these cases had positive outcomes; therefore, they were kept in the model.

The final regression model had 6 predictors (Table 26), all of which had a P-value less of than 0.05. The most significant of the two predictors were age equal or less than 50 years old, with a P-value less than 0.001 and an odds ratio of 7.2, and the presence of a middle cerebral artery infarct on brain scan, with a P-value less than 0.001 and an odds ratio of 3.6. The least significant predictor was history of heart failure, with a P-value of 0.037 and an odds ratio of 2.3. The Hosmer-Lemeshow Goodness of the Fit test had a non-statistically significant result (P-value=0.49) leading to the conclusion that our model was fit. The final model had a good discriminatory power, with a C-statistic of 0.77 (Table 26 and Figure 6 for the ROC curve). The diagnostic performance (Table 27 and 28) of the model showed a sensitivity of 94.3% (95% CI 87.1 % to 98.1 %), a specificity of 35.4% (95% CI 33.6% to 37.3%) and a negative predictive value of 99.5% (95% CI 98.8 % to 99.8%).

Table 26. Final Logistic Regression Prediction Model

Variables	ß-coefficient	Standard error	Wald statistics	df	P value	Odds ratio	95% CI for OR	
							Lower	Upper
Past medical history of coronary artery disease	0.64	0.28	5.4	1	0.021	1.9	1.1	3.3
Past medical history of heart failure	0.94	0.45	4.4	1	0.037	2.6	1.1	6.1
Age less than 50 years old	1.96	0.26	59.4	1	<0.001	7.2	4.3	11.8
Any language deficit of either slurred speech or aphasia	0.52	0.23	5.1	1	0.024	1.7	1.1	2.6
CT or MRI finding of MCA infarct regardless of the acuity	1.29	0.28	21.2	1	<0.001	3.6	2.1	6.3
CT or MRI finding of posterior circulation infarct regardless of the acuity*	0.94	0.29	10.2	1	0.001	2.6	1.4	4.6
Intercept	-4.7	0.23	400.2	1	<0.001			
Hosmer-Lemeshow	0.49	df=4						
C-statistics	0.77	95%CI (0.72-0.82)						
Chi square	3.4	df=4						

***:** Posterior circulation infarct is either; posterior cerebral artery infarct, cerebellar or vertebro-basilar infarct
df: degree of freedom

Figure 6. Receiver Operating Curve for the Regression Model

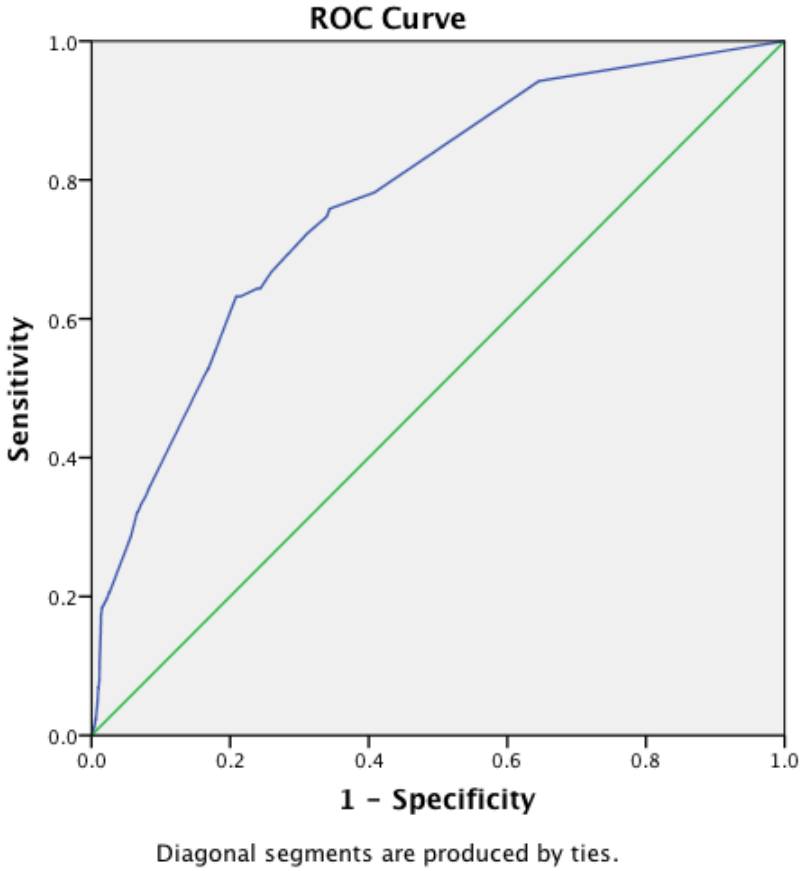


Table 27. Contingency Table for the Logistic Regression Model			
	Treatment change	**No treatment change**	**Total**
Predicted by the model	82	1754	1836
Not predicted by the model	5	963	968
Total	87	2717	2804

Table 28. Diagnostic Performance of the Final Logistic Regression Model					
Sensitivity 95%CI	**Specificity 95%CI**	**Positive likelihood ratio**	**Negative likelihood ratio**	**Positive predictive value**	**Negative predictive value**
94.3 % 95% CI (87.1 % to 98.1 %)	35.4 % 95% CI (33.6 % to 37.3 %)	1.5 95% CI (1.4 to 1.6)	0.16 95% CI (0.07 to 0.38)	4.5 % 95% CI (3.6 % to 5.5 %)	99.5 % 95% CI (98.8 % to 99.8 %)

The prediction model score

To simplify the use of our model we translated our prediction model into a score scale (Table 29, 30). The goal of the scale is to identify patients with TIA/non-disabling stroke at a high-risk of a treatment change based on echocardiogram findings. A score greater than 2 is identified as high-risk of treatment change with a probability of greater than 4% of positive outcomes (i.e., treatment change).

Table 29. Treatment Change Based on Echocardiogram Finding in TIA or Non-Disabling Stroke Prediction Score

Variables	Point
Past medical history of coronary artery disease	1
Past medical history of heart failure	2
Age less than 50 years old	4
Any language deficit of either slurred speech or aphasia	1
CT or MRI finding of MCA infarct regardless of the acuity	2
CT or MRI finding of posterior circulation infarct regardless of the acuity	2

Table 30. Probability of Treatment Change Made Based on Echocardiogram Findings in TIA or Non-Disabling Stroke Patients

Prediction score	Probability of treatment change based on echocardiogram	Risk level	Sensitivity	Specificity
0	0.96%	Low	100%	0%
1	1.6%	Low	94.3%	35.5%
2	2.6%	Low	75.9%	65.6%
3	4.3%	High	64.4%	75.6%
4	6.9%	High	51.7%	83.7%
5	11.1%	High	28.7%	94.2%
6	17.3%	High	17.2%	98.6%
7	25.8%	High	2.3%	99.4%
8	36.7%	High	0	99.9%
10	61.7%	High	0	99.9%

Internal validation

After bootstrapping (resampling) the logistic regression model 5000 times (Table 31), the bootstrapped beta coefficient and C-statistics values were similar to the beta values of the original model. This adds more internal validity than our derived model.

Table 31. Beta Coefficient Value Post 5000 Boot Strapping

Variable	Beta coefficient values of original model (SD)	Beta coefficient values of bootstrapped model (SD)
Any language deficit of either slurred speech or aphasia	0.52(0.22)	0.52(0.22)
Past medical history of Coronary artery disease	0.64(0.28)	0.634(0.29)
Past medical history of heart failure	0.94(0.4486)	0.86(0.70)
CT or MRI finding of posterior circulation infarct regardless of the acuity	0.94(0.29)	0.9312(0.32)
CT or MRI finding of MCA infarct regardless of the acuity	1.29(0.28)	1.29(0.30)
Age less than 50 years old	1.97(0.26)	1.986(0.26)
C-statistics	0.778 (95% CI 0.777-0.779)	0.771(95% CI 0.723-0.821)

4.6.2.2 Recursive partitioning analysis:

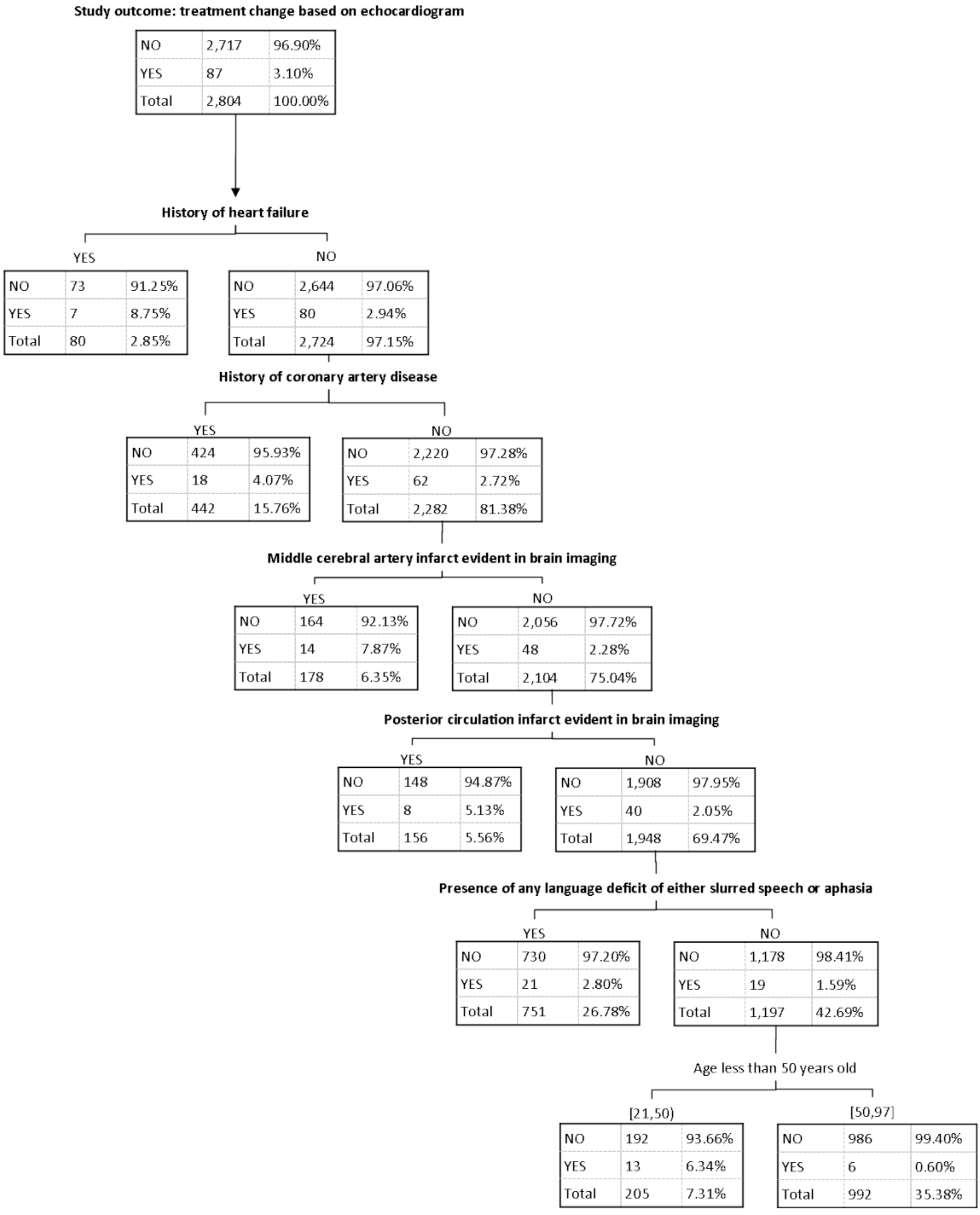
The same 6 eligible variables used in the logistic regression analysis were eligible for the recursive partitioning model. Further, all eligible variables were included in the model as they were able to predict at least 5 positive outcomes (See Figure 7). [115] The diagnostic performance of the recursive-partitioning model was similar to that of the logistical regression model (Table 32). The sensitivity, specificity and negative predictive value were 93.1%, 36.4 and 99.4% respectively.

The predictors of both recursive partitioning and logistic regression models were similar. There is a noted difference in the total number of cases classified as high risk for our study outcome. The recursive partitioning model classified 1812 cases to be a high risk while the logistic regression model classified 1836 cases as high risk for treatment change based on echocardiogram results. The small difference of (1.3%) of high-risk cases for our study outcome is expected given that the regression analysis mathematically classify high risk cases based on the weight of the beta coefficient value rather than the presence or absence of a given predictor of which the case in the recursive model is.

Table 32. Diagnostic Performance of the Recursive Partitioning Model

Sensitivity 95%CI	Specificity 95%CI	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value
93.1% 95% CI (85.6 to 97.4%)	36.3% 95% CI (34.5 to 38.1%)	1.5 95% CI (1.4 to 1.6)	0.19 95% CI (0.09 to 0.41)	4.5 % 95% CI (3.6 to 5.5%)	99.4% 95% CI (98.7 to 99.8%)

Figure 7. Decision Tree of Recursive Partitioning Analysis



4.7 Results of objective 1.2.2

In the case of an abnormal echocardiogram, the overall risk of subsequent stroke is 70% more than normal results. The risk of recurrent TIA showed no statistically significant difference when comparing across the two types of echocardiogram results. Furthermore, the risk of death is 4 times greater in cases with an abnormal echocardiogram compared to a normal result (Table 33).

Table 33. Relative Risk of 90 days Outcome of Mortality and Morbidity among Various Type Of TIA or Non-Disabling Stroke Etiology and Echocardiogram Result

	Subsequent stroke (95% CI)	Recurrent TIA (95% CI)	Death (95% CI)
Abnormal echocardiogram	1.7(1.1-2.5)	1.1(0.8-1.5)	4.1(1.9-8.6)
Large vessel disease etiology	3.3(2.1-5.2)	2.4(1.7-3.4)	0.7(0.2-2.9)
Cardioembolic etiology	2.9(1.9-4.7)	2.0(1.4-2.9)	7.6(3.9-14.8)
Multiple etiologies	0.9(0.2-3.6)	1.4(0.7-3.1)	1.2(0.2-8.9)
Small vessel disease etiology	1.7 (1.1-2.6)	1.1(0.8-1.6)	0.5(0.1-1.5)
Cryptogenic etiology	0.9(0.6-1.5)	1.48(1.09-2.00)	0.4(0.2-1.2)

4.8 Results of objective 1.2.3

Between TIA/non-disabling strokes, the risk of subsequent stroke or recurrent TIA was highest in among those with large vessel disease, (relative risk of 3.3), followed by cardioembolic etiology (relative risk of 2.9). However, looking at the morbidities (i.e., subsequent stroke or recurrent TIA) the relative risk confidence intervals among other various types of TIA/non-disabling stroke demonstrated no significant difference (Table 33).

4.9 Results of objective 1.2.4

There is a significant mortality difference noticed in cardioembolic TIA/non-disabling stroke, in comparison with other types of etiologies (Table 33). A cardioembolic TIA/non-disabling stroke has a 7-fold increase in mortality.

CHAPTER 5: DISCUSSION

5.1 Overview

A small proportion of TIA and non-disabling strokes patients in our prospective cohort (3.1%) had a treatment change made based on echocardiogram findings. More than half of the treatment changes were medical (i.e., anticoagulation or antiplatelet). The most common structural abnormality found causing a treatment change was a patent foramen ovale associated with an atrial septal aneurysm, seen in one third of cases (37.9%). Furthermore, a closure of a patent foramen ovale was the most common surgical intervention, which was seen in approximately one third of cases. A cardioembolic etiology was found to be the third most common cause of a TIA or non-disabling stroke.

In the univariate analysis, we discovered that 6 of the 27 clinical and non-clinical variables collected and analyzed were significantly associated with a treatment change based on echocardiogram findings. All six variables were included in the final prediction model. Predictors of a treatment change are the presence of the following: a middle cerebral artery infarct evident on Brain CT or MRI, a posterior circulation infarct evident on Brain CT or MRI, age less than 50 years old, a language deficit of either slurred speech or aphasia, a history of heart failure and a history of coronary artery disease.

We found both large vessel disease and cardioembolic etiologies of TIA had a significantly higher risk of subsequent stroke and recurrent TIA among the various etiologies in the first 90 days. Cardioembolic causes of TIA or non-disabling stroke carries the highest mortality rate with a seven fold higher risk of death in the first 90 days. Furthermore, the presence of an abnormal cardioembolic structure on the

echocardiogram has a higher risk of subsequent stroke and death in the first ninety days, by 1.5 fold and 4 fold respectively, in comparison to a normal echocardiogram result.

5.2 Previous studies

5.2.1 Overview

Menon et al, made the first attempt to derive a prediction rule in patients with stroke and TIA to predict a treatment change based on echocardiogram findings. They performed a retrospective chart review of 370 patients. The results showed that 6.2% of transthoracic echocardiogram instigated a change in treatment, while 11.1% of transesophageal echocardiograms resulted in a change in treatment. The results of the study demonstrated that male sex, abnormal ischemic changes on electrocardiogram and an embolic pattern on brain imaging of either an unexplained cortical infarct, a multiterritorial infarct or multiple cortical infarct in the same territory were significant predictors of treatment change based on the echocardiogram findings, with a C statistic of 0.7 (95% CI 0.59-0.80). The list of potential predictors was not comprehensive. The study was carried out in an in-patient setting, which increases the risk of selection bias. Furthermore, given that the study's retrospective design, it had the potential of introducing information bias.[121]

5.2.2 Rationale of each predictor

5.2.2.1 Age less than 50 years old

In our study, almost one tenth (13.2%) of our cases were young patients (i.e., age less 50 years old). We found young age to be the strongest predictor of a treatment change based on echocardiogram findings.

Unfortunately, the incidence of TIA cases in the young Canadian population has yet to be reported. However, the incidence of ischemic stroke among young Canadians (i.e., for age less than 54 years) is 13 in every 100,000 persons.[122]

In several studies, the proportion of potential cardioembolic sources of stroke are reported as higher in younger cases, ranging between 14% and 54%.[122-129] Another study found that non-cardioembolic causes of TIA, such as large or small vessel disease, are less common in the younger population.[130] As previously stated, a patent foramen ovale is the most common cardioembolic structure that led to a treatment change in our study. A postmortem study where an autopsy of 965 patients was performed found that the incidence of patent foramen ovales are highest among the younger population (i.e., first three decades of life) with an incidence of 34.3%, in comparison to older populations, of 20.2%.[131] The lack of certainty in determining a TIA source may be due to failure of the clinician to understand the diagnostic importance of the presence of a structural abnormality (e.g., a patent foramen ovale). This underscores the importance of performing an aggressive investigation (i.e., transesophageal echocardiogram) to search for potential cardioembolic sources in younger TIA patients.

5.2.2.2 Middle cerebral artery infarct evident in Brain CT or MRI

The second most powerful predictor of a treatment change is the presence of a middle cerebral artery (MCA) infarct evident on either a brain CT or an MRI. More than one third of our study cases showed evidence of an MCA infarct. Only one-tenth of cases with an MCA infarct had a treatment change based on the echocardiogram.

Paciaroni et al studied the correlation between the site of infarct and the etiology of stroke. The study included a spectrum of both disabling and non-disabling stroke. The results showed that an infarct involving the entire MCA was the most prevalent site of cardioembolic stroke in one fourth of cases, with an odds ratio of 1.85 (95% CI 1.36 to 2.61).[132]

5.2.2.3 Posterior circulation infarct evident on Brain CT or MRI

The presence of an infarct involving any of the posterior circulation territories is another predictor of a treatment change. Posterior territories include either the posterior cerebral artery, mid brain or cerebellum. Almost half of the study cases had evidence of an infarct in the posterior circulation. Six percent of these cases had a change in treatment based on echocardiogram findings.

Paciaroni et al found that a posterior circulation infarct is the second most common site of infarct in cardioembolic causes of stroke.[132] Another study by Martin et al aimed to correlate the type of etiology to vertebrobasilar ischemia. The results showed that almost one third of cases had an underlying cardioembolic etiology.[133]

5.2.2.4 Language deficit of either slurred speech or aphasia

The presence of a language deficit is the least effective predictor of our study outcome. More than one third of our study cases had a language deficit. Only 5% of them had treatment change based on the echocardiogram result.

Three cohort studies aimed to characterize the etiology of stroke in cases presenting with a language deficit. They consistently found a significant association between cardioembolic strokes and the presence of aphasia, with an odds ratio ranging from 1.6 to 2.3.[134-136]

5.2.2.5 History of coronary artery disease

Coronary artery disease is another important predictor, which accounted for almost one fifth of study cases. Only 7.7% had a treatment change based on echocardiogram findings.

A large data set, consisting of more than one and a half million patients, aimed to assess the predictors of post percutaneous cardiac intervention (PCI) cardioembolic stroke or TIA. The result showed that a history of coronary artery disease was a significant predictor of post PCI stroke or TIA, with an odds ratio of 1.56.[137]

5.2.2.6 History of heart failure

The presence of heart failure was found to be another predictor in our study. A small proportion of our sample had heart failure (2.8%). Only eight percent of them had a treatment change.

Witt et al conducted a cohort and found the annual rate of stroke to be 0.8% in patients with heart failure. The risk of stroke was found to be 17.4 times higher in patients with heart failure.[138] Furthermore, a meta-analysis of 26 studies aimed to

estimate the annual stroke rate of patients with heart failure, of which the results showed a pooled estimate rate of 18.4 per 1000 persons.

5.2.3 Morbidity and mortality of various etiologies of TIA or non-disabling stroke

Purroy et al conducted 2 cohort studies in Spain consisting of 1,525 cases of TIA, aiming to estimate the risk of subsequent stroke among various etiologies of TIA. The estimate result showed that large vessel disease had the highest risk of subsequent stroke in the first 90 days, with a significant hazard ratio of 3.8.[139 140] This result was consistent with our study results.

Unfortunately, there are no studies that looked at the mortality among various etiologies of TIA and non-disabling stroke. Similarily, no study looked at the mortality and morbidity of TIA patients who had abnormal echocardiogram results.

5.3 Strengths

Several strengths were identified in our cohort. To our knowledge, this is the first study that derived a prediction rule for the use of echocardiogram in TIA and non-disabling stroke patients in an Emergency Department setting. We are the first to assess mortality rates among various etiologies of TIA and non-disabling stroke, as well as the morbidity and mortality of TIA patients with an abnormal echocardiogram. This sets the cornerstone for future research in the management of TIA and non-disabling stroke. Moreover, our dataset is the largest Canadian multi-centric TIA and non-disabling stroke dataset date, which improves the overall generalizability and validity of our results. Furthermore, our prediction model has a high sensitivity with a very high negative predictive value, which makes it an attractive model for future validation. Additionally, with a high negative predictive value, further testing with echocardiograms will be eliminated for those who have no positive predictors upon successful validation.

5.4 Limitations

We recognized several limitations in the design, data collected and results of our study. The TIA study was not initially designed to derive our prediction model.[120] The primary goal of the TIA study was to derive and validate a prediction model to identify high-risk TIA patients for subsequent stroke.[120] Utilizing this dataset put our results at risk for a selection and information bias. However, we made every effort to list comprehensive potential predictors and collect additional data to complement the existing data. Therefore, we feel that this was no substantial limitation to our study. Another design limitation is the use of the old TIA definition rather the newer, tissue based one. This was due to lack of readily available MRI scanners in most Canadian Emergency Departments, which are required as per the newer definition. However, the definition we used is a more pragmatic, and therefore, we feel that the results were not greatly affected. Also, a proportion of our study subjects had a final diagnosis of non-disabling stroke (17.8%) based on a detected occult brain infarct in an MRI scan or persistent minor symptoms beyond 24 hours. The degree of symptom deficit was based on clinician discretion rather than quantifying the deficit using an objective scale. As a result, we may have misclassified a proportion of patients with true disabling stroke into a non-disabling class. Furthermore, one third of our study subjects were excluded because they did not have an echocardiogram performed. This may have led to a selection bias, which may have affected the validity of our study results. Also, a number of occult cardioembolic structures may have been missed since only 8.4% (n=238) had a transesophageal echocardiogram performed. This puts our study at risk for detection bias. Performing a transesophageal echocardiogram on every patient was simply not

feasible given its invasiveness, economic burden, and limited access. We feel that we were able to gather significant data from our 238 cases regardless.

A small proportion of our study data was missing. We made every effort to locate missing data from all available resources in the patient's health records. The study results had a small proportion of unknown outcomes. In order to resolve this, an expert panel reviewed and discussed each case thoroughly, and a decision on the outcome (i.e., treatment change based on echocardiogram) was made based on the most recent evidence and accepted international practice guidelines. Therefore, we believe this did not have a substantial impact on our results. Further, all 90 days hospital visit records have been reviewed rather than a standardized follow up to determine if a treatment change was made based on echocardiogram results. We recognize this may put our study results at risk of detection bias. Therefore, we made every effort to look at all subsequent hospital visits (i.e., beyond 90 days) for patients with abnormal echocardiogram. A standardized follow up will be undertaken in our future validation study. Moreover, our current outcome definition we considered the treatment change based on echocardiogram findings. We recognized using a management change definition would be more appropriate. For instance, the echocardiogram finding of left atrial enlargement increases the index of suspicion of the presence of an underlying occult paroxysmal atrial fibrillation. Such finding may prompt clinicians to order an ambulatory cardiac monitor to make the diagnosis of atrial fibrillation. Consequently, We will change the definition of our study outcome to predict management change rather than treatment in our future study.

Our prediction model has a poor specificity to our study outcome. However, we aimed to derive a highly sensitive model rather than a specific one. Sensitivity should take priority over specificity when deriving a prediction model given the consequence of missing a treatable cardioembolic source may include permanent disability or death.

Despite that patent foramen ovale closure was the most common treatment change made in our study population, a recent change, as previously mentioned, in the 2014 Canadian Stroke Best Practice Recommendations made a change where a surgical closure of patent foramen was no longer recommended .[48] This may have affected the acceptability of our study results. Unfortunately, we did not have any control over such practice changes during the course of our study period, however in the future validation of this study; significant consideration will be drawn to this.

5.5 Future implications

5.5.1 Research implication

This study sets the cornerstone for future validation of a prediction rule for treatment change based on echocardiogram results in patients with TIA or non-disabling stroke. Our study results frame the need for clarified practice guidelines and recommendations for this population.

5.5.2 Clinical implications

1. Our prediction model will help clinicians in recognizing high-risk patients that may need a treatment change based on their echocardiogram results.

This will promote better resource allocation, as well as highlight the urgency of performing an echocardiogram. Upon the detection of a cardioembolic structure, prompt treatment initiation may lead to better patient outcomes in preventing death and major disabling caused by stroke.

2. A prediction score greater than 2 deserves a greater effort to detect potential cardioembolic source of TIA.

Transthoracic echocardiogram may fail to detect potential cardioembolic structures. If so, we recommend, for high-risk patients with a prediction score more than 2 (See Table 30), to consider more advance cardiac imaging of transesophageal echocardiogram which may be valuable in detecting an occult cardioembolic structure in patients with undetermined TIA etiology.

3. High mortality rates of cardioembolic TIA deserve greater attention.

The factor that may have most significantly contributed to the high mortality of cardioembolic TIAs is the delay in work-up and treatment initiation.

5.6 Conclusion

Cardioembolic TIA and non-disabling stroke carry the highest mortality rate among various TIA etiologies. We developed a highly sensitive prediction rule that will help identify high-risk patients for a treatment change based on echocardiogram findings. Upon successful validation, clinicians will make better decisions on both resource utilization and treatment choices.

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Appendix 1: Case record form for Clinical Characteristics of Transient Ischemic Attack *in* Patients with an Abnormal Echocardiograms

Subject number:

Are there large vessels territorial infarcts in CT?

○Yes ○No ○CT not done

If yes specify Site of infarcts on CT:

□MCA: ○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□ACA: ○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□PCA: ○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□Cerebellar
○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□Verbrobasilar /midbrain
○Acute/Subacute ○ Old ○ Indeterminate

Are there large vessels territorial infarcts in MRI?

○Yes ○No ○MRI not done

If yes specify Site of infarcts on MRI:

□MCA: ○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□ACA: ○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□PCA: ○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□Cerebellar
○Right ○Left ○Both
○Acute/Subacute ○ Old ○ Indeterminate

□Verbrobasilar /midbrain
○Acute/Subacute ○ Old ○ Indeterminate

Presence of multiple acute/subacute territorial infarct involvement

□ Yes □ No

Type of echocardiogram:

Transthoracic Echocardiogram (TTE) □ Yes □ No

Transesophageal Echocardiogram (TEE) □ Yes □ No

If Transthoracic Echocardiogram (TTE) was done, was the result:

□ Normal □ Abnormal □ Unavailable report

If abnormal, specify:

Left atrial appendage thrombus (LAAT)	**☐ Yes**	**☐ No**
Left ventricular thrombus	**☐ Yes**	**☐ No**
Left atrial myxoma	**☐ Yes**	**☐ No**
Vegetation	**☐ Yes**	**☐ No**
Valve Dehiscence	**☐ Yes**	**☐ No**
Ventricular aneurysm	**☐ Yes**	**☐ No**
Aortic dissection	**☐ Yes**	**☐ No**
Ejection fraction <30%	**☐ Yes**	**☐ No**
Atrial fibrillation	**☐ Yes**	**☐ No**
Atrial flutter	**☐ Yes**	**☐ No**
Dilated cardiomyopathy	**☐ Yes**	**☐ No**
Left atrial appendage contrast (LAAC)	**☐ Yes**	**☐ No**
Atrial septal aneurysm (ASA)	**☐ Yes**	**☐ No**
Arthrosclerosis of ascending aorta	**☐ Yes**	**☐ No**
Patent foramen ovale	**☐ Yes**	**☐ No**
Valvular calcification	**☐ Yes**	**☐ No**

If Transesophageal Echocardiogram (TEE) was done, was the result :

☐ Normal ☐ Abnormal ☐ Unavailable report

If abnormal, specify:

Left atrial appendage thrombus (LAAT)	**☐ Yes**	**☐ No**
Left ventricular thrombus	**☐ Yes**	**☐ No**
Left atrial myxoma	**☐ Yes**	**☐ No**
Vegetation	**☐ Yes**	**☐ No**
Valve Dehiscence	**☐ Yes**	**☐ No**
Ventricular aneurysm	**☐ Yes**	**☐ No**
Aortic dissection	**☐ Yes**	**☐ No**
Ejection fraction <30%	**☐ Yes**	**☐ No**
Atrial fibrillation	**☐ Yes**	**☐ No**
Atrial flutter	**☐ Yes**	**☐ No**
Dilated cardiomyopathy	**☐ Yes**	**☐ No**
Left atrial appendage contrast (LAAC)	**☐ Yes**	**☐ No**
Atrial septal aneurysm (ASA)	**☐ Yes**	**☐ No**
Arthrosclerosis of ascending aorta	**☐ Yes**	**☐ No**
Patent foramen ovale	**☐ Yes**	**☐ No**
Valvular calcification	**☐ Yes**	**☐ No**

If TEE was done was it consistent with TTE result?

□ Yes □ No □ Uncertain

Based on the echocardiography finding, was there any treatment change?

□ Yes □ No □ Uncertain

If yes specify:

□ Start of a new anticoagulant

○Heparin ○Warfarin ○Dabigatran or similar

○Combination of above ○Other ---Specify

□ Surgical intervention

○Patent foramen ovale closure ○Aneurysm repair, ○Valve replacement,

○Myxoma surgical resection, ○Other specifiy-----

Completed by_____

Appendix 2: Inter-observer Case record form for Clinical Characteristics of Transient Ischemic Attack *in* Patients with an Abnormal Echocardiograms

Subject number:

Type of echocardiogram:

Transthoracic Echocardiogram (TTE)	☐ Yes	☐ No
Transesophageal Echocardiogram (TEE)	☐ Yes	☐ No

If Transthoracic Echocardiogram (TTE) was done, was the result :

□ Normal □ Abnormal □ Unavailable report

If abnormal, specify:

Left atrial appendage thrombus (LAAT)	□ Yes	□ No
Left ventricular thrombus	□ Yes	□ No
Left atrial myxoma	□ Yes	□ No
Vegetation	□ Yes	□ No
Valve Dehiscence	□ Yes	□ No
Ventricular aneurysm	□ Yes	□ No
Aortic dissection	□ Yes	□ No
Ejection fraction <30%	□ Yes	□ No
Atrial fibrillation	□ Yes	□ No
Atrial flutter	□ Yes	□ No
Dilated cardiomyopathy	□ Yes	□ No
Left atrial appendage contrast (LAAC)	□ Yes	□ No
Atrial septal aneurysm (ASA)	□ Yes	□ No
Arthrosclerosis of ascending aorta	□ Yes	□ No
Patent foramen ovale	□ Yes	□ No
Valvular calcification	□ Yes	□ No

If Transesophageal Echocardiogram (TEE)was done, was the result **:**

□ Normal □ Abnormal □ Unavailable report

If abnormal, specify:

Left atrial appendage thrombus (LAAT)	□ Yes	□ No
Left ventricular thrombus	□ Yes	□ No
Left atrial myxoma	□ Yes	□ No
Vegetation	□ Yes	□ No
Valve Dehiscence	□ Yes	□ No
Ventricular aneurysm	□ Yes	□ No
Aortic dissection	□ Yes	□ No
Ejection fraction <30%	☐ Yes	☐ No
Atrial fibrillation	□ Yes	□ No
Atrial flutter	□ Yes	□ No
Dilated cardiomyopathy	□ Yes	□ No
Left atrial appendage contrast (LAAC)	☐ Yes	☐ No

Atrial septal aneurysm (ASA)	□ Yes	□ No
Arthrosclerosis of ascending aorta	□ Yes	□ No
Patent foramen ovale	□ Yes	□ No
Valvular calcification	□ Yes	□ No

If TEE was done was it consistent with TTE result?

□ Yes □ No □ Uncertain

Completed by_____

Appendix 3: Inter-observer Case record form for Clinical Characteristics of Transient Ischemic Attack *in* Patients with an Abnormal Echocardiograms

Subject number:

Based on the echocardiography finding, was there any treatment change?
☐ Yes ☐ No ☐ Uncertain

If yes specify:
☐ medical treatment
☐ surgical intervention
☐ both medical and surgical treatment

If medical treatment was made specify:
○Heparin
○Warfarin
○Dabigatran or similar
○Multiple anticoagulant
○Other medical treatment specify---
○Multiple medical treatment

If surgical intervention was made specify:
○Patent foramen ovale closure
○Aneurysm repair,
○Valve replacement,
○Myxoma surgical resection,
○Other specifiy-----
○Multiple surgical intervention specify----

Completed by_____

Appendix 4: Ethics Approval

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

[redacted]

January 18, 2013

Dr. Abdulaziz Alsadoon

[redacted]

Dear Dr. Alsadoon:

Re: Protocol # 20120832-01H **Clinical Characteristics of Transient Ischemic Attack of Patients with Abnormal Echocardiograms**

Protocol approval valid until - January 17, 2014

Thank you for your e-mail dated January 18, 2013. I am pleased to inform you that this protocol (Thesis Research Proposal dated September 18, 2012) underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHREB's review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

[redacted]

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/cb

Appendix 5: Missing Outcome Adjudication Committee Decisions

Subject number	Abnormality	Panel decision
112186	Aortic atherosclerosis	No treatment change
310134	Patent foramen Ovale in TTE	No treatment change
710146	Atrial Fibrillation already in warfarin	No treatment
111430	Aortic arthrosclerosis and valve calcification	No treatment change
110701	Left atrial myxoma and PFO in TEE	Yes "surgical treatment"
113021	Aortic arthrosclerosis	No treatment change
111595	Isolated atrial septal aneurysm in TTE	No treatment change
210837	Isolated PFO in TEE	No treatment change
112185	Valvular calcification	No treatment change
112757	Aortic atherosclerosis	No treatment change
112979	Aortic arthrosclerosis and valve calcification	No treatment change
112777	Valvular calcification	No treatment change
211070	Valvular calcification	No treatment change
210490	Valvular calcification	No treatment change
111852	Left ventricular thrombus already on warfarin	No treatment change
112276	Valvular calcification	No treatment change
111302	Isolated PFO in TEE and TTE	No treatment change
111756	EF<30% and atrial fibrillation already on warfarin	No treatment change

111251	Vegetation	Yes “medical treatment”
112986	Aortic arthrosclerosis	No treatment change
112635	Valvular calcification	No treatment change
113337	Valvular calcification	No treatment change
113177	Valvular calcification	No treatment change
210082	Atrial fibrillation already on warfarin	No treatment change
112184	Valvular calcification	No treatment change
112109	Valvular calcification	No treatment change
211941	Valvular calcification	No treatment change
610071	Atrial fibrillation was detected in ECG first	No treatment change
110364	Valvular calcification	No treatment change
112181	Valvular calcification	No treatment change
310223	Valvular calcification	No treatment change
113040	Isolated PFO in TTE with none TIA final diagnosis	No treatment change
112045	Valvular calcification	No treatment change
710041	LV thrombus	Yes “medical treatment”
210802	Isolated PFO in TEE	No treatment change
113100	Valvular calcification	No treatment change
112044	Valvular calcification	No treatment change
211895	Valvular calcification	No treatment change
610011	Valvular calcification	No treatment change
212976	Left atrial appendage contrast no TEE with none TIA final diagnosis	No treatment change

111059	Left ventricular aneurysm already on warfarin	No treatment change
112835	Valvular calcification	No treatment change
111876	Aortic arthrosclerosis and valve calcification	No treatment change
210439	Atrial septal aneurysm in TTE with no TEE done with none TIA final diagnosis	No treatment change
113912	Valvular calcification	No treatment change

TTE: Transthoracic echocardiogram
TEE: Transesophageal echocardiogram
PFO: Patent foramen Ovale
EF: Ejection fraction
LV: Left ventricular

Appendix 6: Variables with missing data

Variable	Number of missing data	Reason of missing	Imputed	Reason of imputing the data
ECG	136	MCAR	No	
Recurrent symptoms	12	MCAR	Yes	Small number
Duration of symptoms more than 60 minute	5	MCAR	No	
Visual loss	11	MCAR	No	
Diplopia	26	MCAR	No	
Presence of murmur	29	MCAR	No	
Brain imaging	18	MCAR	Yes	Small number
Incoordination	173	MCAR	No	

MCAR: missing completely at random.

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Appendix 8: Funding Source

TOHAMO
The Ottawa Hospital Academic Medical Organization

March 21, 2013

Dear Dr. Perry:

Re: TOHAMO Innovation Fund Approval – 2013

TOHAMO is pleased to inform you that your project entitled *"Improving the Efficiency of Echocardiography following TIA"* has been approved for funding by both TOHAMO and the Innovation Fund Provincial Oversight Committee (IFPOC).

As outlined in TOHAMO's *Innovation Project Budget Policy*, TOHAMO will flow $80,075.00 funding as follows:

- Confirmation of REB Approval – 50%
- Submission of Year 1 Status Report – 25%
- Submission of Year 2 Status Report – 25%

The funds will be flowed to the Ottawa Hospital Research Institute (OHRI) and the Finance Department will establish a TOHAMO Innovation Cost Centre for your project. The use of the funds to support the project will be subject to review and audit by both TOHAMO and IFPOC. TOHAMO will regularly review your expenditures by accessing your cost centre using the OHRI Finance System.

To monitor the progress of your project and proceed with the next installment of your grant, TOHAMO requires you to submit a Status Report following Year 1 and again in Year 2. For your reference, please find attached the *Status Report* template. In the event that your project is tracking ahead of schedule or your timeline is shortened and you require earlier release of your TOHAMO project grant, you will need to make your request, in writing, to TOHAMO. Your request will be reviewed and you will be notified on the result of your request.

Attached please find a copy of the *TOHAMO Policy: Physician Remuneration*. Please ensure that you are familiar with this policy if you are considering physician remuneration.

In October 2012, IFPOC provided new guidelines for project completion timelines. Given that your project is one (1) year, you will be required to complete your project by no later than March 31, 2016. Attached is a copy of the *TOHAMO Policy: Innovation Project Timelines*.

Once you complete your project, a final report must be submitted to TOHAMO and IFPOC within 60 days of project completion. The *Final Report* template is attached for your reference.

If you have any questions, please do not hesitate to contact me directly at [redacted]. Congratulations on your Innovation project and good luck with your project!

Regards,

C. Colasante
Executive Director, TOHAMO

Attachments:
1. TOHAMO Policy: Innovation Project Budget
2. TOHAMO Policy: Physician Remuneration
3. Status Report Template
4. TOHAMO Policy: Project Timelines
5. Final Report Template