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Retrospective Validation of the San Francisco Syncope Rule for prediction of short-term serious outcomes in adult syncope patients

By

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Thesis submitted to the School of Graduate Studies and Research in partial fulfillment of the requirements for the M.Sc. degree in Epidemiology

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ABSTRACT

CONTEXT: Syncope is defined as sudden transient loss of consciousness with spontaneous, complete recovery. Syncope is usually associated with loss of postural tone leading to falling. Syncope is a common problem in the emergency department constituting 1% - 5% of annual visits and 1% - 3% of admissions to the hospital. Disposition of syncope patients is very challenging to the emergency physician as a small proportion of patients will suffer death or other life threatening serious outcomes including arrhythmias, myocardial infarction, gastrointestinal bleeding, pulmonary embolism, stroke and subarachnoid hemorrhage. Of the various risk stratification instruments available, the San Francisco Syncope Rule is the only one that has been prospectively derived and validated, included all serious outcomes, focuses on short-term outcomes rather than long-term outcomes and adhered to the accepted guidelines for developing a clinical decision rule. Performance of this clinical decision rule in the Canadian population is not known. This thesis is on retrospective validation of the San Francisco Syncope rule. The study will also attempt to refine the rule if needed and collect basic epidemiological characteristics of syncope patients presenting to a tertiary care emergency department.

OBJECTIVES: (1) To assess the performance of the San Francisco Syncope Rule when applied retrospectively to Canadian syncope patients. (2) To assess the potential impact on resource utilization (in the form of admission rates) if the San Francisco Syncope Rule was applied in Canada. (3) To determine, if needed, the potential for refining the San Francisco Syncope Rule to improve its performance. (4) To describe the basic epidemiological characteristics of emergency department syncope visits to a tertiary care emergency department.

DESIGN: Retrospective chart review of consecutive adult syncope patients who presented to the emergency department between August 2005 and January 2007. The five variables for the San Francisco Syncope Rule and an additional 131 variables were abstracted.

SETTING: An urban Canadian tertiary care emergency department.

STUDY POPULATION: Patients were identified using the Canadian National Ambulatory Care Reporting System (NACRS) database which captures data on all patients visiting Canadian emergency departments. We reviewed charts of patients whose presenting complaint or primary or secondary diagnoses were syncope, pre-syncope, fainting, black out, loss of consciousness, fall, collapse, seizure or light-headedness. Adult patients (age ≥ 16 years) who fulfilled the definition of syncope and who had an Ottawa residential address were included. Patients with
prolonged loss of consciousness for more than 5 minutes, loss of consciousness not witnessed or not clearly established, any change in the mental status from baseline on regaining consciousness, loss of consciousness due to seizure or due to alcohol or illicit drug abuse or due to head trauma (i.e. trauma the initial event), significant associated trauma requiring admission and those transferred from another hospital for workup of syncope were excluded.

**MAIN OUTCOME MEASURES:** The main outcome of the study was to evaluate the performance characteristics of the San Francisco Syncope Rule in its ability to predict serious outcomes within 30 days. The outcome was a composite serious outcome that included any one of the serious outcomes: death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant bleeding anywhere, any procedural intervention to treat a related cause of syncope, any condition causing/likely to cause a return emergency visit or hospitalization for a related event within 30 days.

**DATA ANALYSIS:** Abstracted data was analyzed for the sensitivity and specificity of the San Francisco Syncope Rule. Actual admission rates to the hospital of included patients and hypothetical rate if the rule were applied was also calculated. Univariate analysis of all predictor variables was performed. A new preliminary clinical decision rule was derived using logistic regression and recursive partitioning. Data analysis was done using SAS and KnowledgeSEEKER.

**RESULTS:** 505 patient visits were included in the study. 49 (9.7%) of these visits were associated with serious outcomes with 22 (44.9%) occurring in the emergency department and 27 (55.1%) occurring outside the emergency department either during their inpatient stay or outside the hospital. The sensitivity and specificity of the San Francisco Syncope Rule for all serious outcomes was 90% (95% CI 78, 95) and 40% (95% CI 39, 41), for the serious outcomes occurring after discharge from the emergency department was 96% (95% CI 82, 99) and 40% (95% CI 39, 40). 12.3% of the study patients were admitted to the hospital. The rule would have required 63% of the study patients to be admitted. Exploration for refining the rule yielded a preliminary decision rule by recursive partitioning with 3 variables: (1) Age ≥ 65 years, (2) Lowest emergency department systolic blood pressure < 80 mm of Hg and (3) abnormal electrocardiogram [defined as non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm),
significant atrioventricular block (second and third degree), bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities]. This preliminary rule had a sensitivity 100% ((95% CI 93, 100) and 53% (95% CI 52, 53) for predicting serious outcomes within 30 days of the emergency visit for syncope. Using this new rule will require 52% of the patients to be admitted to the hospital. Syncope and pre-syncope were common complaints presenting to the emergency department accounting for 1% of all emergency visits.

CONCLUSION: The San Francisco Syncope Rule did not perform as well as previously reported. It is feasible to develop a better clinical decision rule based on the San Francisco Syncope Rule to improve the sensitivity and specificity. It also possible to prospectively clarify and improve the performance the 'abnormal electrocardiogram' variable.
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CHAPTER 1: BACKGROUND

1.1 Introduction to the problem
Syncope is one of the common presenting complaints to the Emergency Department (ED) accounting for 1% to 3% of medical admissions and 1% to 5% of emergency department visits. (1-5) The Emergency Department evaluation of patients with syncope is problematic on two fronts – one is that they are often asymptomatic on arrival and the other is that the differential diagnosis is extensive ranging from very benign causes to life-threatening ones. (6)

In the past few years there has been research done on ways to predict serious (adverse/life threatening) outcomes in syncope patients. There are five risk stratification instruments available in the literature. (7-13) Of the five available instruments, the San Francisco Syncope Rule is the only one that has been prospectively derived and validated, included all serious outcomes in the short-term and has adhered to the accepted guidelines for developing a decision rule. (14)

The first goal of this study is to retrospectively validate the ability of the San Francisco Syncope Rule (SFSR) to predict short-term serious outcomes occurring after discharge from the emergency department in Canadian adult syncope patients. The second goal is to evaluate the impact of the rule on resource utilization in the form of admission rates. The third goal is to collect additional variables to explore if needed the possibility refining the SFSR to improve its sensitivity and specificity. The fourth goal is to collect basic epidemiological characteristics of emergency department visits, admission rates and outcomes for syncope in Ottawa, Canada.

1.2 Introduction to Syncope
1.2.1 Definition
The term “Syncope” is derived from the Greek words, ‘syn’ – meaning ‘with’ and ‘kopto’ – meaning ‘I cut’ or ‘I interrupt’. (15) Syncope is defined as sudden and transient loss of consciousness, usually associated with loss of postural tone leading to falling.
Onset is rapid and recovery is spontaneous, complete and prompt. The underlying mechanism of syncope is transient global cerebral hypoperfusion. (16-19) Pre-syncope is a condition where the patient feels that syncope is imminent, but recovers before losing consciousness.

Syncope should be differentiated from other conditions that closely mimic it. In epilepsy, hypoglycemia, intoxications consciousness is truly lost but the mechanism is not cerebral hypoperfusion. In ‘psychogenic pseudo-syncope’, cataplexy, drop attacks consciousness is only apparently lost. In others there is no loss of consciousness or there is persistent altered level of consciousness as in falls, cerebrovascular accident/transient ischemic attack, coma, delirium, vertigo. (20)

Prodromal symptoms like light-headedness, nausea, sweating, weakness or visual disturbances may be present. Patients usually are not able to provide the accurate duration of loss of consciousness but typical episodes last approximately 20 seconds. One study in adolescents showed that the average duration was 12 seconds (range 5-22). (18)

1.2.2 Epidemiology and cost of syncope
In the Framingham Study 7814 people living in Framingham, Massachusetts, United States of America underwent serial examination and follow-up from 1971 to 1998. (21) Eight hundred and twenty-two of them had at least one syncopal episode during the study period and thereby the incidence of at least one syncopal episode is 6.2 per 1000 person-years. Assuming a constant incidence rate over time, the authors calculated a 10-year cumulative incidence of 6% and life-time prevalence (person living an average 70 years) of 42%. But the authors found that incidence is not constant as people age and it increases steeply after 70 years of age. The study reported a syncope rate of 11 per 1000 person-years for both sexes for ages 70-79 and 17 per 1000 person-years for men and 19 per 1000 person-years for women at age ≥ 80. Another study reported a syncope incidence rate of 6% per year with a recurrence rate of 30% for older people living in long-term care institutions. (22) Syncope accounts for 1% to 3% emergency department visits and hospital admissions. (1-5, 12)
National Ambulatory Medical Care Survey showed 6.7 million syncope-related visits to the United States emergency departments during a 10-year period from the year 1991 to 2000. (23) This accounted for 0.77% of the total emergency department visits and 2% of the total admissions from the emergency department were due to syncope during this period. Sun et al reported an estimated annual cost of US$ 2.4 billion due to syncope-related admissions. (24) There is no Canadian data available for syncope-related emergency department visits, admission rates or cost of syncope-related admissions.

Recurrence is common and patients with recurrent syncope do not have higher mortality rates or sudden death rates but they do have poor functional status and poor quality of life as with other chronic diseases as in rheumatoid arthritis and other chronic medical or mental illnesses. (4, 25-27) 6% of patients sustain major injuries like fracture and 29% suffer minor injuries like laceration and bruises. (25)

In summary, most studies indicate that syncope is a common problem in the community, in those with multiple medical problems, in the elderly particularly for those residing in long-term care institutions and in health-care delivery settings including the Emergency Department. Syncope affects functioning, quality of life and costs the health-care system substantially.

1.2.3 Pathophysiology

The pathophysiology behind syncope is global hypoperfusion. A minimum oxygen flow of 3.0-3.5 milliliters of oxygen per 100 grams of brain tissue per minute is required to maintain consciousness in humans. This translates to a cerebral blood flow of 50-60 milliliters per 100 grams of brain tissue per minute or 12-15% of the resting cardiac output in healthy young people. (28-30) Sudden loss of cerebral blood flow for 6-8 seconds is sufficient to cause syncope. (16)

Cerebral perfusion is largely dependent on systemic arterial pressure which in turn is dependent on cardiac output and peripheral vascular resistance. (31) Conditions that reduce cardiac output such as low blood volume, arrhythmias or valvular diseases can
cause syncope. With respect to vascular resistance, excessive vasodilatation can cause syncope as in neurally-mediated syncope and autonomic dysfunction due to diseases or medications. (32)

The following mechanisms protect the brain from hypoperfusion: (15)

(i) Cerebral autoregulation - This mechanism ensures adequate blood flow to the brain when there is fluctuation in systemic blood pressures thereby ensuring adequate blood flow at lower blood pressures while protecting the cerebral vasculature from very high pressures and increase in intracranial pressure due to vascular congestion.

(ii) Cerebral chemoreceptors - These receptors cause vasodilation of the cerebral blood vessels when the oxygen levels are low or when the carbon dioxide levels are high thereby ensuring adequate oxygen supply to the brain and prompt removal of excess carbon dioxide.

(iii) Carotid baroreceptors - Situated at the entrance to the brain in the common carotid arteries these receptors modulate the heart rate, cardiac contractility, systemic vascular resistance and systemic circulatory dynamics to ensure adequate blood flow to the brain.

(iv) Kidney and other hormones maintain total body fluids and therefore blood volume.

The chances of failure of the above mechanisms are greatest in the elderly and those with underlying medical problems. (19, 33)

### 1.2.4 Causes of syncope

On the basis of the physiological mechanisms responsible for the cerebral perfusion described in the previous section, the causes of syncope can be classified into the following groups:

1. Neurally-mediated (reflex/reflex-mediated) syncope: In normal circumstances physical and emotional stresses lead to increased sympathetic tone. In neurally-
mediated syncope, there is initially increased sympathetic tone which is inappropriately withdrawn and replaced with increased vagal tone leading to reflex vasodilatation and/or bradycardia. This in turn leads to cerebral hypoperfusion. The physical stresses include pain, cough, micturition, instrument playing. Carotid sinus syndrome/hypersensitivity is also a neutrally-mediated syncope when pressure or manipulation due to tight collar, turning head or shaving stimulates the carotid baroreceptors leads to increased vagal tone. The classical vasovagal syncope is a neurally mediated syncope.

2. Cardiac syncope: Inability of the heart to maintain adequate cardiac output and thereby adequate cerebral perfusion is the pathophysiological mechanism underlying cardiac syncope. Cardiac etiology of syncope can be further subdivided into structural causes and causes due to rhythm disturbances.

i) Structural heart disease: Structural heart diseases can cause syncope when the demands exceed the ability of the heart. Underlying structural heart disease is a concern when patients suffer syncope during exertion. Structural heart diseases that cause syncope include valvular heart diseases such as aortic stenosis, tricuspid stenosis and mitral stenosis, non-valvular conditions such as cardiomyopathy, pulmonary hypertension, congenital heart disease, myxoma, pericardial disease, aortic dissection, pulmonary embolism, myocardial ischemia and myocardial infarction.

ii) Dysrhythmias: Both bradyarrhythmias and tachyarrhythmias can lead to syncope. Low heart rates associated with sinus node disease, Stokes-Adams attack, 2nd or 3rd degree heart block and pacemaker malfunction lead to syncope. High heart rates associated with supraventricular or ventricular tachycardia, atrial fibrillation/flutter, ventricular fibrillation and torsades de pointes can cause syncope.

3. Orthostatic hypotension causing syncope: In normal individuals, on assuming upright posture from supine position the pooling of blood in the lower extremities causes a drop in cerebral perfusion. The carotid baroreceptors stimulate the autonomic nervous system causing increased sympathetic output and decreased parasympathetic output. This causes the both the blood pressure and cardiac
output to be increased, thereby restoring cerebral perfusion. While a small drop in blood pressure when standing from supine position is physiological, orthostatic hypotension has traditionally been described as fall in systolic blood pressure more than 20 mm of Hg after 2 minutes of standing. (34) Failure of the above mentioned compensatory mechanism leads to cerebral hypoperfusion and syncope. Such failure of the autonomic nervous system can be primary as seen in elderly or secondary to medications (beta blockers, calcium channel blockers), neurological disorders (diabetes, spinal cord injuries) and volume depletion due to poor intake or diuretics. One study showed that 5-55% of patients who had another etiology for syncope had an orthostatic systolic blood pressure drop of more than 20 mm of Hg. (34) As a result to attribute orthostatic hypotension as the cause of syncope patients must have both fall in systolic blood pressure and symptoms on standing.

4. **Medication induced syncope:** Antihypertensives, beta blockers, calcium channel blockers, cardiac glycosides, diuretics, antidysrhythmics, antipsychotics, antiparkinsonism drugs, antidepressants, phenothiazines and nitrates can cause syncope. Substances alcohol and cocaine when used or abused can also cause syncope. (35) The underlying mechanism responsible for syncope varies with each drug and some cause syncope by multiple mechanism. Antihypertensives, calcium channel blockers and nitrates can cause excessive vasodilation. Beta blockers blunt the autonomic response to carotid baroreceptors, beta blockers and calcium channel blockers decrease the heart’s chronotropic and ionotropic response to orthstatic stress. Diuretics can cause hypovolemic. Cardiac glycosides and antidysrhythmics can cause syncope with their proarrhythmic properties.

5. **Neurologic syncope:** Transient cessation of blood flow to the reticular activating system during transient ischemic attacks can cause syncope.

6. **Psychogenic syncope:** Psychogenic causes may or may not be associated with cerebral hypoperfusion. Hyperventilation associated with anxiety disorders can lead to hypocarbia profound vasoconstriction and syncope. Other psychiatric
disorders such as conversion disorder, somatization disorder and breath-holding spells can also lead to syncope.

7. **Steal syndromes**: Rarely congenital constriction of the subclavian artery proximal to the origin of the vertebral artery can lead to a lower and fixed amount of blood flow. Exercising the ipsilateral arm leads to diversion of most of blood flow to the arm causing less blood flow through the vertebral artery leading to cerebral hypoperfusion and syncope.

The problem is that in a given patient the cause may not clearly fit into any of these categories or multiple mechanisms may be in play. (36-39) In population based studies among all patients with syncope a mean of 17% have a final diagnosis of reflex-mediated syncope (including situational syncope), 11% orthostatic hypotension, 3% medication induced, 7% have neurological etiology, 3% have structural cardiac diseases, 14% cardiac arrhythmias, 1% psychiatric and 39% with unknown etiology. (1, 2, 4, 40-43) In emergency department based studies the distribution of the final diagnosis for reflex-mediated syncope ranges from 40-63%, orthostatic hypotension from 2-8%, medication induced 0-4%, cardiac causes 4-13%, psychiatric causes 1-4%, steal syndromes <1%, multifactorial in 2% and unknown etiology 13-38%. (42, 44)

1.2.5 Prognosis

As per the Framingham study death rates are 1.31 times higher, non-fatal myocardial infarction/death from coronary heart disease 1.27 times higher and fatal/non-fatal stroke 1.06 times higher in syncope patients than in non-syncope patients. (21) Cardiac syncope is associated with increased one-year mortality rate (18-33%) while it is lower for non-cardiac syncope (0-12%) or unexplained syncope (6%). One-year sudden death rate is 24% in cardiac syncope group and 3-4% in the other two groups. (1-5) Even after adjustments for baseline rates for heart and other diseases, cardiac syncope was an independent predictor of mortality and sudden death in patients with syncope. But the mortality rates were not significantly different in patients with similar severity of heart disease between those who had syncope and those without syncope. (45) Patients with advanced heart failure (defined as ejection fraction of 20% or less) have higher risk of
sudden death at one-year than those without advanced heart failure immaterial if the cause of syncope is cardiac or not. (46)

Young healthy syncope patients with normal EKG and no structural heart disease (11), patients with neurally mediated syncope (47) and orthostatic hypotension due to transient problems (such as volume depletion, drug induced) have excellent prognosis. Unexplained syncope has intermediate prognosis between neurally mediated syncope and cardiac syncope. In addition to the mortality risks, syncope patients are at risk for physical injury and also suffer employment and life-style restrictions.

1.3 Syncope in Emergency Department
Evaluation of syncope as a symptom is very challenging as the etiology is wide ranging from very benign causes (as in vasovagal syncope and situational causes like cough syncope or post-micturition syncope) to life threatening ones including arrhythmia, myocardial infarction (and other structural cardiac diseases), pulmonary embolism, occult hemorrhage, subarachnoid hemorrhage, transient ischemic attack (precedes stroke) and occult sepsis. (48-51) Underlying disorders may require procedural intervention such as dialysis, pacemaker insertion, surgery for valvular heart disease or ruptured abdominal aortic aneurysm or ruptured spleen or ruptured ectopic pregnancy and undetected causes such as arrhythmias can lead death in the short-term. In Emergency Department based studies the short-term serious outcomes reported (within 7 or 30 days) were: death 0.4% - 0.7%, myocardial infarction 0.4 - 4.9%, arrhythmias 3.2 - 7.1%, pulmonary embolism 0.2 - 0.7%, hemorrhage 1.0 - 1.8%, subarachnoid hemorrhage 0.1 - 0.4%, stroke 0.4 - 1.0%, sepsis 0.2 - 0.4% and readmission to hospital 0.3 - 0.7%. (7, 9, 52, 53) As a result syncope is often referred to as “low-risk/high-stakes” symptom – with physicians admitting the low-risk patients because of high stakes of the unidentified underlying life threatening conditions that are treatable with medications, transfusions, interventions and/or devices. (54) Patients for whom the underlying cause is life-threatening that is clearly evident in the emergency department, they need a thorough evaluation and even hospitalization for further work-up and treatment. While in other cases when the cause is benign all that is needed a thorough history, physical examination and these patients can
be discharged home. But for the most part patients do not fit the above two categories and pose a huge management dilemma as the cause of syncope may not be evident during the emergency visit.

Routine lab tests (blood count, electrolytes, glucose and cardiac enzymes) rarely yield useful information, but can be useful in patients with occult hemorrhage, arrhythmias due to electrolyte abnormalities, hypoglycemia and undetected myocardial infarction. Computed Tomography (CT) scan of the head does not yield any results in uncomplicated syncope. A series of studies involving 195 patients showed that CT scan of head identified etiology in 4% of patients, but all of them did not have true syncopal episode as they had focal neurological signs or a witnessed seizure. (1, 5, 41, 55, 56) If the cause of syncope is found after this initial evaluation then treatment is directed towards the etiology of syncope but more commonly these investigations yield no answers.

Disposition of these patients is a difficult task for the emergency physician as he or she has to balance the discharge of these patients from the emergency department in the face of potential life threatening outcomes. A survey among North American physicians identified syncope as the second most common decision problem. (57) Most patients get admitted because of concern about life-threatening outcomes. The evaluation, investigations ordered and admission rates are highly variable among ED physicians, institutions and countries. (54, 55, 58-61) When admitted these patients receive little or no further diagnostic tests. (62, 63) Because of inefficient use of expensive hospital resources a more cost effective approach is needed. (55, 60, 64-68) The guidelines available for admission are very conservative and lack clear evidence or criteria and may even lead to increase in admission rates. (10, 12, 15, 69, 70)

The presenting population is very heterogeneous both with respect to demographics and clinical characteristics. The prognosis varies depending on the cause and associated comorbidities. (3, 5) Extensive work has been done on diagnostic workup and treatment of syncope patients. (69-71) Even with intensive diagnostic testing 20% to 50% of syncope
patients will have no cause identified but at the same time high-risk patients have a
mortality rate as high as 57% within the first year. (1, 5, 10, 41, 44) Standardized
evaluation improves diagnostic yield but still for majority of patients no objective cause
of syncope is found in the Emergency Department or after an inpatient admission. (72)
As a result the focus shifted on risk stratification of these patients rather than finding the
cause of syncope. (11, 73)

1.3.1 Decision to Admit and Emergency Department/Hospital Overcrowding
The decision to admit syncope patients to the hospital is often not evidence-based. There
has been considerable controversy among emergency physicians, internists, cardiologists
and neurologists regarding the indications for admission. The decision to admit is a
complex issue with many low-risk patients getting admitted just for a brief period of
clinical observation and monitoring with no adverse outcomes and no etiology detected
thereby needlessly consuming valuable in-patient resources. These patients are being
admitted because of concerns about life-threatening causes. On the hand those who
needed to be admitted have been discharged from the ED to suffer serious outcomes
outside the hospital.

From the health care system prospective in this era of emergency department
overcrowding patients wait several hours in the emergency department before they can
get treatment. There is huge variation among physicians in the work-up of syncope
patients as there are no studies available in this area. (54, 55, 58-61) This leads to further
overcrowding in the emergency department. Health care resources are scarce and due to
already rampant hospital overcrowding we cannot admit everyone. At the present time,
patients wait in the emergency department several hours or even days to get an inpatient
bed. So we have to be very selective in our admissions and use inpatient resources
efficiently.

There is very high consensus among physicians regarding an urgent need for robust and
rigorously done studies to clarify the criterion for investigation and admission of syncope
patients. (57, 74) Such a study will identify which syncope patients need further
investigation and this can started in the triage area itself. Such a strategy will decrease wait time in the emergency department and improve patient flow. The study will also lead to better use of inpatient resources.

1.4 Methodological Standards for Clinical Decision Rules
Clinical decision rules are developed to reduce the uncertainty in medical decision making. A decision rule is usually derived from original research and can be defined as a decision making tool that incorporates variables from the history, physical examination and/or some simple investigations. The decision rules help clinicians with management decisions. Reported methodological standards for their development and validation can be summarized as follows: (75-78)

i) There must be a need for a decision rule because of the prevalence of the clinical condition and current practice; such need must be a belief among physicians practicing in that area.

ii) The outcome or diagnosis to be predicted must be clearly defined. Assessment of the outcome should be made without knowledge of the predictor variables.

iii) The clinical findings to be used as predictors must be clearly defined and standardized, clinically sensible and their assessment must be done in a blinded fashion.

iv) The reliability or reproducibility of the predictors must be clearly demonstrated.

v) To increase generalizability the subjects in the study should be selected without bias and should represent a wide spectrum.

vi) The mathematical techniques for deriving the rules must be clearly explained.

vii) Decision rules should be clinically sensible: have a clear purpose, be relevant, demonstrate content validity, be concise, and easy to use in the intended clinical application.

viii) The accuracy of the decision rule in classifying patients with (sensitivity) and without (specificity) the targeted outcome should be demonstrated.

ix) Prospective validation on a new set of patients is an essential test of a new decision rule. Unfortunately, many clinical decision rules are not prospectively validated to determine their accuracy, reliability, clinical sensibility, or potential impact on practice. This validation process is very important because many statistically derived rules or
guidelines fail to perform well when tested in a new population. (79-81) The reason for this poor performance may be statistical (i.e., over fitting or instability of the original derived model), or may be due to differences in prevalence of disease or differences in the population or differences in how the decision rule is applied. (82-84) The methodological standards for a validation study are the same.
x) Implementation phase (to demonstrate the true effect on patient care) is the ultimate test for a decision rule. (85)

1.5 Risk stratification of syncope patients – Literature Review
There have been both original studies and clinical guidelines published to predict serious outcomes in ED syncope patients. (7-13) There is one rule the “San Francisco Syncope Rule” (7), one guideline the “American College of Emergency Physicians’ Guideline” (12), one risk stratification system using historical and EKG factors (11) (all three from the United States), one risk score the “OESIL risk score” (10) (from Europe) and one arrhythmia risk score derived in Europe and validated in the US (13) for predicting arrhythmia alone that have been published to aid the emergency physicians in risk stratification. But the studies either involve small group of patients in only one setting, or they are designed to predict only certain outcomes or not widely accepted or not known to the emergency physician. (7-9, 13, 11) The “American College of Emergency Physicians’ Guidelines” is purely a clinical practice guideline based on available evidence and also heavily on expert opinion. (12) This is not a clinical decision rule and is not based on original research. A synopsis of the available instruments and how they perform against the methodological standards for clinical decision rules is given below.

1.5.1 The San Francisco Syncope Rule
The San Francisco Syncope Rule (SFSR) was derived from and validated on emergency department syncope patients. (7) The rule was derived to predict short-term serious outcomes within 7 days of the initial emergency visit. The study was conducted in San Francisco, USA and had 96% sensitivity and 62% specificity. The same study prospectively compared the emergency physicians versus SFSR in their ability to predict serious outcomes within 7 days and the need for admission to hospital. (8) Both had the
ability to predict all serious outcomes but the SFSR had the potential to decrease hospital admissions by 10%. The rule was then prospectively validated. But during the validation phase the outcomes were measured at 30 days after the initial emergency visit. At this phase the rule had a sensitivity of 98% and specificity of 56% and also had the potential to decrease admissions by 7%. (9)

The SFSR has five clinical variables as predictors of short-term serious outcomes. The clinical variables can be easily remembered with a pneumonic CHESS. The variables are history of Congestive Heart Failure, Hematocrit <30% (0.300 in SI units), Electrocardiogram abnormalities (non-sinus rhythm or new changes compared with previous electrocardiogram), Shortness of Breath as one of the complaints and Systolic Blood Pressure<90 mm Hg at triage. Presence of any one of these predictor variables puts the patient at ‘high risk’ for short-term serious outcomes and therefore the study recommends these patients be admitted to the hospital.

The final clinical decision rule was derived by recursive partitioning. A total of 50 variables were analyzed. Those variables that were significantly associated with short-term serious outcomes at 10% significance level in univariate analysis and had a kappa >0.5 were included for the multivariate analysis by recursive partitioning to develop the above clinical decision rule. Addition of a variable age older than 75 would have increased the sensitivity of the rule in the derivation cohort to 100% but in order to avoid the specificity dropping from 62% to 44% (to avoid the misclassification of 108/684 patient visits as high risk when they never experienced an adverse serious outcome) the authors decided to leave this age variable out of the final decision rule.

Evaluating the study based on the methodological standards for decision rules, the study performed well in most areas except a few. Though the outcomes were well defined, they could have been better defined. The outcome ‘significant hemorrhage’ is defined as one with a detected source of bleeding and that required transfusion. Now with the threshold for transfusions being very high there could be considerable bleeding in a patient with syncope but could have not got transfusions. We consider ‘Hospitalization for a related
event within 30 days’ as a soft outcome as sometimes patients get admitted because of social issues. The biggest problem in this study is the way the variable ‘abnormal electrocardiogram’ is defined – non-sinus rhythm or any new changes. We further received clarification from the author of the original study, Dr. Quinn, regarding application of the variable in the absence of an old electrocardiogram. The original study classified electrocardiograms with any changes as abnormal electrocardiogram in the absence of an old electrocardiogram. The phrase ‘any new changes’ can be interpreted in various ways leading to poor reproducibility. Lastly the rule was derived and validated only in one centre when our study was started. But overall this is the leading clinical decision rule for risk stratification of emergency syncope patients as it is only rule that addresses all the short-term serious outcomes and one of the few rules that have both been prospectively derived and validated.

1.5.2 The OESIL (Osservatorio Epidemiologico Sulla Sincope Nel Lazio) Risk Score

The OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) risk score was also derived from and validated on emergency department syncope patients. The scoring system does not predict short-term serious outcomes but was derived to predict mortality within the first twelve months after initial evaluation. (10) As a result this scoring system has not been of much use to the emergency physicians in deciding disposition of the patient. The study was conducted in the Lazio region of Italy. The variables in the scoring system were derived by multivariate logistic regression and included age >65 years, previous history of cardiovascular disease (previous structural heart disease or congestive heart failure or peripheral arterial disease or stroke or transient ischemic attack), absence of prodromes before the syncopal episode and abnormal electrocardiogram.

Abnormal electrocardiogram in this study was defined as presence of any one of the abnormalities: atrial fibrillation, atrial flutter, supraventricular tachycardia, multifocal atrial tachycardia, premature supraventricular or ventricular contractions that are frequent and repetitive, ventricular tachycardia, paced rhythms, II or III degree atrioventricular
block, bundle branch block, intraventricular conduction delay, left or right ventricular hypertrophy, left axis deviation, previous myocardial infarction or ST-T wave changes diagnostic or suggestive of ischemia. Non-specific repolarization ST-T wave changes were not considered abnormal.

One point was given for each variable and the arithmetic sum was the total score ranging from 0 to 4. The 12 month all-cause mortality for the derivation and validation cohorts for the different scores were: 0.8% and 0.6% for a score of 1, 19.6% and 14% for score of 2, 34.7% and 29% for a score of 3, 57.1% and 52.9% for a score of 4 respectively. The 12 month all-cause mortality for both cohorts was 0% for a score of 0. For all comers with a score of 0 and 1 there were no deaths until 275 days and only one after that until 12 months.

Overall it is a very good study and fulfilled all the criteria for the methodological standards, but the biggest problem is emergency physicians are more interested in short-term serious outcomes and not one year deaths. So this risk score is of very little use to emergency physicians.

1.5.3 The American College of Emergency Physicians’ Clinical Policy
The American College of Emergency Physicians (ACEP) in 2001 issued a clinical guideline for management of emergency department syncope patients. (12) The guideline was a review and critical appraisal of articles obtained by MEDLINE search using the term ‘syncope’ from 1985 to 1998. The articles were graded on their strength of evidence from classes I to III based on sample size, methodology and validity of the conclusions. Studies were downgraded if there were significant flaws or biases in the study. If the study was downgraded below class III, then they were not included in the guideline development. Based on the strength of evidence, the college came out with three levels of recommendation A, B and C. The criteria for the class of evidence and levels of recommendation are given in Figure 1. The recommendation of the college for admission of emergency department syncope patients is given in Figure 2.
Critically appraising this guideline, it must be clearly understood it is not based on original research and is not a clinical decision rule. So the criteria for methodological standards cannot be applied to this study. This guideline cannot even be classified as a systematic review as only English MEDLINE was searched for 13 years (only until the year 1998) and whatever evidence that was found in these articles got into the guideline. Also there was no level A recommendations (no articles with strong evidence were identified for admission of syncope patients) and only recommendation at levels B and C.

Another retrospective American study found that application of the above level B recommendations yielded high sensitivity (100%) and specificity (81%) for identifying patients with cardiogenic syncope and would have reduced admissions from 57.5% to 28.5%. (86) Application of level C recommendations did not offer any advantage.

1.5.4 Sarasin's arrhythmia risk score
Sarasin et al develop a risk-score to predict arrhythmias in syncope patients admitted to the hospital after their initial emergency department evaluation was negative. The duration of follow-up varied for each patient as it was the duration they were admitted to the hospital. (13) A cohort of 175 patients with unexplained syncope from University of Geneva Medical School, Geneva, Switzerland between 1998 and 2000 was used to derive the risk score. The same cohort was used for cross-validation. External validation was done retrospectively using a cohort from the University Medical Center, Pittsburgh, US between the years 1989 and 1991. The validation cohort predates the derivation cohort by 10 years. The three variables that predicted arrhythmias in unexplained syncope patients were abnormal electrocardiogram, history of congestive heart failure and age more than 65 years.

The electrocardiogram was considered abnormal if any one of the abnormalities including atrial fibrillation, sinus pause \( \geq 2 \) and \( < 3 \) seconds, sinus bradycardia \( > 35 \) and \( \leq 45 \) beats per minute, conduction abnormalities (bundle branch block, second-degree Mobitz type I atrioventricular block, bifascicular block), signs of ventricular hypertrophy or multiple premature ventricular beats or previous myocardial infarction were present.
Abnormalities worse than the above were considered diagnostic of the cause of syncope and included sinus pause \( \geq 3 \) seconds, sinus bradycardia \( \leq 35 \) beats per minute, atrial fibrillation with slow ventricular response defined as RR interval \( \geq 3 \) seconds, Mobitz type II atrioventricular block, complete atrioventricular block or symptomatic/sustained (\( \geq 30 \) seconds) ventricular tachycardia. Minor abnormalities such as I degree atrioventricular block, non-specific ST-T wave abnormalities, sinus tachycardia and premature atrial contractions were considered normal.

Areas under the Receiver Operator Characteristics (ROC) curves were 0.88 (95\% CI – 0.84 to 0.91) for the derivation cohort, 0.84 (95\% CI 0.77 to 0.91) after cross-validation within the same cohort and 0.75 (95\% CI 0.68 to 0.81) for the external validation cohort. The risk of arrhythmias in derivation cohort ranged from 0\% to 60\% for those with no risk factors versus all risk factors respectively. The results for the validation cohort for the same parameters were 2\% to 27\%.

Applying the standards for clinical decision rule derivation, it was a good idea to study the syncope patients after they have left the emergency department but the patients who were discharged home were not included. This is serious bias in this study and prevents generalization of the results. Duration of follow-up of the syncope patients is not known and no further follow-up after discharge from the hospital ward was done. Overall this study is not of much value to the emergency physician for risk stratification.

1.5.5 Martin’s risk stratification model

Martin et al developed the very first risk stratification system from emergency department syncope patients for the emergency physicians way back in 1997. This study developed a model to predict arrhythmias or 1-year death using 252 patients for derivation and 374 patients for validation. (11) The patients were recruited from the University of Pittsburg Medical Center, Pittsburg, US. Clinical, laboratory, ECG and cardiac monitoring data were collected. Follow-up was done at 3 month intervals for 3 years. Logistic regression and Cox proportional hazards models were used to identify important risk factors. The predictors of death or arrhythmia at one-year were abnormal.
emergency department electrocardiogram, previous history of ventricular arrhythmia, previous history of congestive heart failure or if the patient is older than 45 years of age. Abnormal electrocardiogram is defined as presence of any one of atrial fibrillation, atrial flutter, multifocal atrial tachycardia, junctional or paced rhythms, frequent or repetitive runs of premature ventricular contractions or ventricular tachycardia, left axis deviation, bundle branch block, intraventricular conduction delay, left or right ventricular hypertrophy, PR interval < 10 seconds, previous myocardial infarction, II or III degree atrioventricular block. Isolated sinus bradycardia or sinus tachycardia and non-specific ST-T wave abnormalities were considered normal.

Arrhythmias or death within one year occurred in 7.3% and 4.4% in patients with no risk factors and in 80.4% and 57.6% patients with three of four risk factors in the derivation and validation cohorts respectively.

This was the first study to attempt risk stratification of emergency department syncope patients and was methodological very good. The study defined outcomes at 1-year which is of less interest to the emergency physician, was limited only to arrhythmias/death and did not address the short-term outcomes. Also study required any patient over 45 years of age to be admitted. As a result this risk stratification system was not used by emergency physicians.

1.6 Rationale for the study
There has been considerable variation in practice among physicians with respect to admission of ED syncope patients. (54, 55, 58-61) Equally there has been considerable variation in the guidelines published and some of them are not based on research but on consensus. There have been a few studies published in the recent years but all of them are fraught with deficiencies and problems.

The San Francisco Syncope Rule is the only one that has been prospectively derived and validated, included all serious outcomes in the short-term and has adhered to the accepted guidelines for developing a decision rule. (14) The study showed reduction in admission
rates in the US, but may possibly increase admission rates in other countries where the baseline admission rates are lower than the US. There are criticisms about the broad nature of the variables (any ECG abnormalities and shortness of breath in any form as a complaint by the patient or elicited by the emergency physician) and about variations in follow-up days in the two cohorts. The rule was derived to predict short-term outcomes at 7 days but was prospectively validated for predicting outcomes at 30 days and was based on a moderate sample size. The study has been conducted in only one site - a tertiary care ED in the US and further studies are required to assess generalisability.

The fact that low-risk patients (scores of 0 and 1) in the OESIL risk score derivation and validation did not suffer outcome of death is useful in the ED, but this study has low sensitivity, does not address all the other important serious outcomes including arrhythmias that are important to the emergency physician and outcome of death at 12 months is too long from the ED perspective.

The ACEP guideline was partly based on research and more based on consensus. It was not based on original research and was neither prospectively derived nor prospectively validated, has very poor specificity and increases admission rates. (14)

Sarasin’s arrhythmia risk score predicts only arrhythmias in unexplained syncope patients with no clear information on the duration of follow-up. It has not prospectively validated, only retrospectively validated using a cohort that predates the derivation cohort by ten years and has poor specificity.

Martin’s risk stratification model predicts only the two adverse outcomes – death and arrhythmia at one year which is very distant for the emergency physician. It might lead to increased admission rates. It is not widely accepted and also not well known to the emergency physicians.
There are a few studies that have examined the outcomes such as mortality and arrhythmias of patients admitted to hospital after syncope but there are hardly any studies that report the outcomes in patients discharged from the ED.

The ideal clinical decision rule is one that has been derived and validated as per the above mentioned methodological standards (section 1.4) in a large number of patients. The usefulness in a specific population (i.e. Canadian population) can be assessed only by studies done in that population. There is neither an ideal clinical decision rule that is available for syncope nor there are Canadian studies in this area. Experts in several countries are working on this topic and in the premier Emergency Medicine conferences like the SAEM (Society of Academic Emergency Medicine) scientific sessions this topic attracts lots of attention. There is considerable controversy among emergency physicians about which variables should be included in the rule. Though the SFSR is the leading rule in the pack, still there is lot of room for further development on this topic.

Before attempting to reinvent the wheel and developing a new rule a very useful first step is to evaluate and possibly refine the SFSR – the leading clinical decision rule to predict short-term serious outcomes in adult ED syncope patients.

In Canada based on the US data we can estimate that there are probably 100,000 visits per year due to syncope and costs in the tens of millions of health-care dollars (65, 87, 88). There have been no risk stratification studies done in Canada either in the form of new strategies or as an application of pre-existing rule or scoring system. There are no published studies to date or readily available data on the incidence, Emergency Department visits, hospitalization rates, length of stay, outcomes or resource utilization due to syncope in Canada. In the Canadian context it is being assumed that to decrease health-care costs, patients are being discharged though they might have a higher risk of developing serious outcomes. If this prediction rule does well in the Canadian population it has the potential of predicting these serious outcomes. The rule might also change the use of health care resources in either way, but if there are over utilized there is a potential to decrease the use of resources.
Hence there is a need to study the usefulness of this rule to predict short-term serious outcomes in syncope patients in the Canadian context and also evaluate its effect on resource utilization.

Ideally the validation and refinement should be done by a prospective study. Such an endeavor will require lot of time and money. Also there is lack of literature in this area in the Canadian context. With all these consideration and with an aim to finish the master’s thesis, we concluded that a pilot study be done retrospectively to validate and attempt to refine the rule despite the weakness of the design. If the results are promising, we aim to use the results of this study to further launch future prospective studies. This pilot work will also convince the grant agencies regarding the feasibility of prospective studies.
CHAPTER 2: GOALS AND OBJECTIVES

2.1 Goals
The primary goal of this study is to retrospectively assess the accuracy of the San Francisco Syncope Rule to predict short-term serious outcomes occurring after discharge from the emergency department. Other goals include studying the impact on resource utilization if the San Francisco Syncope Rule was used, possibility of refining the San Francisco Syncope Rule and collection of basic epidemiological data about syncope in a tertiary care ED in Ottawa, Canada.

2.2 Specific Objectives
1. To determine the sensitivity and the specificity of the San Francisco Syncope Rule to predict short-term serious outcomes in Canadian ED syncope patients when applied retrospectively (particular those outcomes occurring after discharge from the emergency department).
2. To assess the potential impact on resource utilization (in the form of admission rates) if the San Francisco Syncope Rule was applied in Canada.
3. To determine, if needed, the potential for refining the San Francisco Syncope Rule to improve both sensitivity and specificity.
4. To describe the basic epidemiological characteristics of emergency department visits, admission rates, outcomes and resource utilization due to syncope in a tertiary care ED in Canada.
CHAPTER 3: METHODS

3.1 Study Design
The study was a retrospective cohort study conducted by reviewing charts of patients presenting with syncope to the Emergency Department.

3.2 Study Setting
We conducted the study at the Ottawa Hospital Civic Campus Emergency Department, Ottawa, Canada. The study site is an urban adult tertiary care Emergency Department with approximately 60,000 visits annually and staffed by certified emergency physicians certified either by Royal College of the Physicians and Surgeons of Canada or College of Family Physicians' of Canada Emergency Medicine certification. We chose this site as there was a separate chart room for the emergency visits located next to the emergency department. This will lead to less number of charts being unavailable due to other clinic appointments or other emergency/non-emergency department research projects.

3.3 Study Period
We reviewed charts of adult syncope patients who visited the emergency department between August 1st 2005 and January 31st 2007.

3.4 Study Population
Patients were identified using the Ottawa Hospital health records database which uses the Canadian National Ambulatory Care Reporting System (NACRS). The NACRS database captures data on all patients visiting Canadian emergency departments. Trained personnel in medical records review charts of all patients visiting the emergency department and enter the chief complaint, primary and secondary diagnoses for these patients. We reviewed the emergency department charts of patients whose presenting complaint or primary or secondary diagnoses were syncope, pre-syncope, fainting, black out, loss of consciousness, fall, collapse, seizure or light-headedness. Patients who fulfilled the inclusion criteria and had no exclusion criteria were included in the study. Eligibility was assessed by the principal investigator without knowledge of the patient’s outcome status.
3.4.1 Inclusion criteria

1. Age ≥ 16 years.
2. Patient must have an Ottawa residential address. The thinking behind this is that patients with an Ottawa residential address will return to one of the hospitals in the city of Ottawa if any adverse event were to occur. It will be extra-ordinarily difficult to follow-up patients who are not from Ottawa to confirm occurrence of any serious outcome.
3. Patient must fulfill the definition of syncope: sudden, transient loss of consciousness usually associated with loss of postural tone; onset is rapid; recovery is spontaneous, prompt and complete with no residual neurological deficit. A previously done quality control study by our group highlighted the difficulty in differentiating pre-syncope patients from dizziness, falls, lightheadedness and unwell feeling retrospectively.

The San Francisco Syncope Rule study included patients with both syncope and pre-syncope during the derivation and validation phases. A quality control project done by us prior to this study showed that based on retrospective data, it will be very difficult to differentiate pre-syncope from other symptoms including dizziness, light-headedness and unwell feeling. So we chose to exclude pre-syncope patients to avoid contamination with non-syncope patients.

Patients were included regardless of whether they were admitted as inpatients or discharged from the emergency department.

3.4.2 Exclusion criteria

The reasons for excluding these patients are given in the paragraph below.

1. Prolonged loss of consciousness more than 5 minutes.
2. Loss of consciousness not witnessed or clearly established.
3. Any change in the mental status from baseline on regaining consciousness.
4. Loss of consciousness due to seizure.
5. Loss of consciousness due to alcohol or illicit drug abuse.
6. Loss of consciousness due to head trauma, i.e. trauma the initial event.
7. Significant associated trauma requiring admission to a specialty due to the trauma.
8. Transfer from another hospital for workup of syncope.

Syncope is usually associated with brief loss of consciousness (usually few seconds to few minutes). Because of the dramatic nature of the symptom, patients' families have a tendency to overestimate time by few minutes. On the other hand if the duration of loss of consciousness is longer, then the patient might not have suffered syncope. So we chose a 5-minute cut off arbitrarily to exclude patients with other disorders. If loss of consciousness was not witnessed or was not clear then it could have been seizure or dizziness rather than syncope, so these patients were excluded. Mental status changes after regaining consciousness is usually associated with seizure and so these patients were excluded. Patients who have been drinking or using illicit drugs have several factors such as dehydration, head injury, mental status changes due to substance abuse that transient cerebral hypoperfusion may not be the only pathological basis of their loss of consciousness and so have been traditionally excluded. Head injuries can sometimes lead to a brief loss of consciousness by mechanisms different from cerebral hypoperfusion and so were excluded. Patients who sustain significant trauma have interplay of several factors that when they suffer serious outcomes it might be difficult to differentiate if the adverse outcome was due to syncope or the trauma. When patients are transferred from another hospital, important variables such as the triage and serial blood pressures, electrocardiograms, cardiac monitoring data might not be available. Also if the patients do not have an Ottawa residential address follow-up for occurrence of serious outcomes might be difficult, so these patients were excluded.

3.5 Visit Definition
The first visit during the study period and any visit after 30 days of a previous visit were defined as an initial visit. Any visit within 30 days of an initial visit was defined as a return visit. For patients with more than one initial visit, we included all visits and we used patient visits in our analysis rather than patients. The logic behind this is because the
common thread among these visits is only the past medical history and may be medications taken by the patient. All other variables vary from one visit to another visit. The etiology for the same patient might be very different in each visit; during the first patient might have presented with syncope due to gastrointestinal bleeding while during the second visit the cause might have been atrioventricular block.

3.6 Data Abstraction

The data abstraction forms for the initial visit and return visit were developed, reviewed by three experienced emergency medicine specialists who are also researchers and two renowned cardiologists working on syncope. The forms are shown in Appendix 1 and Appendix 2.

Data abstraction was done both by the principal investigator and a research assistant. Both were blinded to the outcomes at this stage of data abstraction. Data abstraction was done in paper data abstraction forms. The research assistant was trained by a 3-hour didactic session. In half of the included patient visits, the principal investigator extracted all the data. In the other half of the included visits, the principal investigator determined the eligibility of the patient to be included in the study. The research assistant then extracted patient demographics, medical history, medications, and vital signs recordings both in the pre-hospital setting and in the ED and laboratory values. The rest of the data—reading the ambulance electrocardiogram rhythm strip, extracting emergency department electrocardiogram results and outcomes were done by the principal investigator. The research assistant abstracted the first 25 charts in the presence of the principal investigator. After the trial run, all data abstracted by the research assistant were reviewed by the principal investigator at the end of the day.

3.6.1 Predictor variables abstracted

We enrolled patients who met the inclusion criteria and had no exclusion criteria. The principal investigator and/or research assistant extracted data from the Ambulance Call Report and all sections of the emergency department Record of Treatment (including the triage, emergency nurse, emergency physician, and consultant notes). We also reviewed
results of investigations available in the chart and in the hospital electronic health record, including laboratory, diagnostic imaging, and ECG. We explicitly collected the predictor variables for the San Francisco Syncope Rule and additional variables of potential value to refine the rule, from pre-hospital evaluation/treatment, history, physical examination and investigations. We chose these additional variables based on prior studies and expert opinion. (11, 13, 15, 89) The experts who determined the relevance of the additional variables were two cardiologists (one who has been working on syncope for several years) and four experienced emergency physicians. Each variable had a standardized definition, was collected in a standardized fashion and was given a yes, no or not available value. For predictor variables that had more than one value due to repeat measurements, the worst clinical value was recorded.

A second emergency physician different from the principal investigator abstracted data for inter-observer agreement.

3.6.2 San Francisco Syncope Rule variables abstracted
The predictor variables in the San Francisco Syncope Rule were
1. History of Congestive Heart Failure,
2. Hematocrit < 0.300,
3. ECG Abnormalities (any non-sinus rhythm or any new changes compared with previous ECG. If old ECG was not available then presence of any abnormalities resulted in this variable becoming positive),
4. Shortness of Breath as one of the complaints, and
5. Systolic Blood Pressure<90 mm of Hg at triage.

For the study we used cardiologists’ interpretation of the electrocardiogram as it was readily available. Ideally one should use the electrocardiogram in the clinical context of the patient. We could have had one emergency physician interpret all electrocardiograms and another performs inter-rater agreement of at least 10% of the electrocardiograms. Studies have shown poor inter-rater agreement on interpreting abnormalities in the
electrocardiogram (7, 52, 53). Due to time constraints and better interpretation by cardiologists’ we decided to use the cardiologists’ interpretation of the electrocardiogram.

3.6.3 Additional variables abstracted
The additional variables collected based on literature review and expert opinion are given below.

3.6.3.1 Variables from history
1. Age,
2. Sex,
3. Prodromal symptoms - presence of any symptom including nausea, vomiting, dizziness, pain, hot, cold, cough, urination, visual disturbances, sweating, shortness of breath, palpitations, incontinence or neurological symptoms - tingling, numbness prior to loss of consciousness,
4. Association with exertion,
5. Palpitations at any time,
6. History of paroxysmal nocturnal dyspnea, orthopnea,
7. History of coronary artery disease, arrhythmias (atrial or ventricular), cardiomyopathy, valvular heart disease, hypertension, diabetes, cerebrovascular accident, transient ischemic attack or peripheral arterial disease,
8. Past syncopal episodes, and
9. Medications taken by the patient: diuretics, anti-arrhythmics, digoxin, direct vasodilators, nitrates, sublingual nitroglycerine just before the syncopal episode, beta blockers, alpha blockers, combined alpha beta blockers and calcium channel blockers.

3.6.3.2 Variables from pre-hospital evaluation/treatment
Data extracted from Ambulance Call Report included:
1. The first, the last and the lowest blood pressure readings recorded by Emergency Medical Services personnel,
2. Results of finger prick glucometer readings,
3. Any treatment given by ambulance personnel including intravenous fluids and medications.

4. 12-lead electrocardiogram characteristics:
   a. Rhythm (Sinus or non-sinus; if non-sinus specify if it is supraventricular tachycardia, multifocal atrial tachycardia, atrial fibrillation or flutter, ventricular tachycardia – sustained or non-sustained, ventricular fibrillation, junctional or idioventricular rhythm),
   b. Rate,
   c. Presence of paroxysmal atrial contractions/paroxysmal ventricular contractions and their frequencies, atrioventricular block and its type if present, presence of right bundle branch block, left bundle branch block, left anterior/posterior fascicular block or intraventricular conduction delay,
   d. Presence of left ventricular hypertrophy, right ventricular hypertrophy, left axis deviation, right axis deviation, old myocardial infarction, ST segment and T wave changes consistent with ischemia, secondary ST – T wave changes (defined as ST-T wave changes that are not consistent with ischemia but are typically due to medications, electrolyte imbalances, conduction defects, arrhythmias or pulmonary disease), non-specific ST – T wave changes (defined as ST-T wave changes that are not consistent with ischemia or secondary ST-T wave changes), non-specific repolarization abnormalities, and

6. Any ambulance monitor abnormalities – abnormalities that are not evident in the 12-lead electrocardiogram.

3.6.3.3 Variables from examination

Data extracted from the Emergency Department Record of Treatment:

1. Pulse rate at triage and prior to leaving the Emergency Department,
2. Oxygen saturation at triage and prior to leaving the Emergency Department,
3. Respiratory rate at triage and prior to leaving the Emergency Department,
4. Blood pressure (both systolic and diastolic) at triage, prior to leaving the Emergency Department and lowest blood pressure in the serial measurements taken in the Emergency Department,

5. Postural blood pressure readings – supine, sitting, standing,

6. Cardio respiratory findings (murmur, rales, wheezes or reduced air entry to the lungs), and


3.6.3.4 Variables from investigations
Data extracted from Emergency Department record of treatment and hospital electronic health record:

1. Glucometer readings in the emergency department,

2. Lab values: Hemoglobin, hematocrit, sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, creatine kinase, troponin, calcium and magnesium,

3. Electrocardiogram characteristics as described above and:
   a. Was it reported by a cardiologist?
   b. Corrected QT interval value, and
   c. Abnormalities on continuous cardiac monitoring – abnormalities that are not evident in the 12-lead electrocardiogram.

4. Carotid sinus massage results, if done, and

5. Computed tomogram of head, if done (new and clinically important abnormalities). New and clinically important abnormalities were defined as the abnormality detected is the cause of syncope or is a consequence of syncope itself or the fall associated with the syncope. All chronic findings are classified as non-significant.

3.6.3.5 Disposition variables abstracted
Data about the disposition of the patient was also collected from the ED record of treatment, i.e. admission or discharge or death in the ED.
3.6.3.6 Variables abstracted for Inter-Observer Agreement

Ten percent of the included visits (52 patient visits) were randomly selected by using computerized random number generator for inter-rater agreement. Data extraction was performed by another emergency physician different from the candidate. Two emergency physicians were involved in data abstraction for inter-observer agreement and each abstracted data from 26 patient visits. A one hour orientation was given regarding study protocol and data abstraction sheet. Interobserver agreement for variables that have high probability of abstraction errors related to patient eligibility and the rule (i.e. inclusion/exclusion criteria, history of congestive heart failure and shortness of breath) were measured using kappa coefficient with 95% CIs. Interobserver agreement for age, sex, laboratory values, vital signs – blood pressure and glucometer measurements was not calculated. As the electrocardiograms were already read by a cardiologist, the second emergency physician was asked only to comment if the electrocardiogram was either normal or abnormal as defined by the San Francisco Syncope Rule. The inter-observer agreement data abstraction form is shown in Appendix 3.

3.7 Outcome measures abstracted

The outcomes measured were the serious outcomes as listed and defined in the San Francisco Syncope Rule study. The final outcome was a composite serious outcomes that included any one of death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant bleeding anywhere, any procedural intervention to treat a related cause of syncope, any condition causing/likely to cause a return emergency visit or hospitalization for a related event within 30 days. Data were collected both for occurrence of the adverse outcomes and place of occurrence of the outcomes, i.e. in the emergency department prior to discharge, inside the hospital as an in-patient, or outside the hospital as detected by a return visit to the hospital or through review of hospital medical records or provincial coroner’s records. While we collected serious outcomes that occurred both in the ED and after discharge from the ED (i.e. either while the patient was admitted in the hospital or at home after discharge from the ED/hospital), we were very interested in the ability of the San Francisco Syncope Rule to predict the serious outcomes occurring after ED discharge.
3.7.1 Definitions of outcomes
Each component of the composite serious outcome has been clearly defined by the San Francisco Syncope Rule study and we used the same definitions as given below.

a) Death: Death from any cause. Confirmation of death was done both by confirming that the patient is not dead in 30 days by detecting a visit to the hospital 30 days after the initial emergency department visit and with records from the provincial coroner’s office.

b) Myocardial infarction: Defined as an elevation in troponin or electrocardiogram changes consistent with ischemia/infarction and with an accompanying diagnosis of myocardial infarction. It must have been confirmed by the emergency physician or cardiology service or the most responsible physician in the patient’s chart.

c) Arrhythmia: Defined as any rhythm abnormalities (previously known or new) captured on monitoring and thought to have had a temporal relationship to the symptom or that required treatment.

d) Pulmonary embolism: Diagnosis made by ventilation-perfusion (VQ) scan, computed tomography scan of the chest or angiography. If it was low probability as per the VQ scan then the patient should have received or should have been considered for treatment.

e) Stroke: Defined by presence of persistent neurological deficit and the symptoms were temporally related to the syncope episode.

f) Subarachnoid hemorrhage: Confirmed by computed tomography/magnetic resonance imaging of the brain with or without spinal fluid analysis by lumbar puncture.

g) Significant hemorrhage: Defined as detected source of bleeding and that required transfusion.

h) Any procedural intervention to treat a related cause of syncope: Any patient who undergoes an acute intervention that would have caused them to return if they have been discharged will be considered to have had a serious outcome. Examples of acute interventions include: dialysis, pacemaker insertion, surgery for valvular heart disease, balloon-pump insertion, use of vasopressors, surgery to treat an abdominal aortic aneurysm, surgery for ruptured spleen, surgery for ruptured ectopic pregnancy, endoscopic treatment of esophageal varices or upper gastrointestinal bleeding or chest
tube/pig tail catheter insertion for pneumothorax. Monitoring of patients, medication changes or rehydration was not considered as acute intervention.

i) Any condition causing or likely to cause a return emergency visit: Patients with return visits related to the previous syncope visit and admitted or developed any of the above outcomes will be considered to have had an adverse outcome. If the return visit was related but they were again discharged without any acute intervention then they will not be considered as having sustained an adverse outcome.

j) Hospitalization for a related event within 30 days: Defined as hospitalization for syncope or any other related symptom within 30 days of an initial visit.

3.8 Outcome Assessment

Assessment for occurrence of adverse outcomes within 30 days of the index visit was performed regardless of whether patients were discharged from the Emergency Department or admitted to hospital. If the patient was admitted, the in-patient chart was reviewed. If the patient was discharged from the emergency department or from the inpatient service (prior to 30 days), we searched for evidence of return visits to the Emergency Department, any outpatient clinic visits and inpatient hospital admissions that occurred at any of the local adult hospitals (the Ottawa Hospitals, Montfort Hospital and Queensway-Carleton Hospital) within the 30 days after the index visit. If return visits occurred, records were review to determine if these visits were related to the initial syncope visit. If the return visit was related, a full chart review was conducted to see if any cause for syncope was found, if there was any procedural intervention done to treat the cause of syncope, if any serious outcomes occurred, or if the patient was hospitalized.

The outcomes were assessed using the following documents available at the Ottawa Hospitals, The Montfort Hospital and the Queensway-Carleton Hospital:

a) Emergency department health records
b) Hospital health records – outpatient clinic records and inpatient admission records
c) Computerized hospital patient tracking and record system.

Death records from all the hospitals and the provincial coroner’s office were reviewed.
Final determination of adverse outcome occurrence was confirmed independently by two emergency medicine specialists of whom at least one had no knowledge of the patient’s status for the predictor variables. In the event of disagreement, a third emergency medicine specialist without knowledge of the patient’s predictor variable status adjudicated the occurrence of the outcome.

3.9 Sample Size
The sample size required for validation of decision rules was based on the sensitivity of the San Francisco Syncope rule. Sample size to obtain previously achieved sensitivity levels within a reasonable bound is given by the formula (90)

\[ N = \frac{16p(1-p)}{B^2} \]

where \( p \) is the best estimate of sensitivity available and \( B \) is the bound on the error of estimation. The bound of error of estimation and the sample size in turn are dependent on the prevalence of serious outcomes in the syncope population. Lower the rate of adverse outcomes, higher the sample size. The previous best estimate of sensitivity for the San Francisco syncope rule is between 96% and 98%. Conservatively taking 96% as the sensitivity and with the bound on error of estimation of sensitivity as 2.5%, the sample size can be calculated as follows:

\[ N = \frac{16 \times 0.96 \times 0.04}{(0.025)^2} = 983 \text{ patient visits.} \]

As the retrospective refining of the San Francisco Syncope rule is similar to deriving another decision rule, for multivariate analysis roughly about 10 adverse events are required for each predictor variable in the model when deriving a decision rule. Previous studies have reported an adverse outcome rate of about 11.5 – 13.7%. (7, 9) About half of these adverse outcomes happen outside the emergency department. The derivation study did not report the rate of serious outcomes occurring after discharge from the emergency department. But based on the validation study we can estimate it as 5.75%. (7) The validation study reported this at 6.8%. (9) For a rule with 5 variables we can estimate that a sample size of 870 patient visits with 50 serious outcomes occurring outside the emergency department is required for the study.
Going with the higher of the two numbers - 983 patient visits and at very conservative estimate of adverse event rate of 5.75% outside the emergency department, there will be 57 adverse events occurring outside the emergency department with this sample which will be enough to validate and refine the rule. Due to time constraints for conducting a master's thesis, we arbitrarily chose a smaller sample size of 500 patient visits with at least 20 adverse outcomes occurring after discharge from the emergency department.

3.10 Data analysis

3.10.1 Data entry and verification:
All data collected by the research assistant was checked by the principal investigator before data entry. A Statistical Analysis Software (SAS) based database for the study was created by the professionals at the Ottawa Health Research Institute (OHRI) Methods Centre. All data from the completed paper study forms were entered into the database by data entry professional. The data entry and management system had built-in range and logic checks on the data. Accuracy of data collection and entry was further checked by regular frequency reports and visual checks. Any queries were clarified by reviewing the original treatment record.

3.10.2 Validation of the San Francisco Syncope Rule
We decided to exclude patient visits that had one of the predictor variables for the rule unavailable and suffered serious outcomes. We decided to do as assuming the missing variable as ‘yes’ or ‘no’ will artificially alter the sensitivity and specificity. To use a the highest number of patient visits for calculating the classification performance of the rule, for the patients who had a missing predictor variable and did not suffer serious outcomes, if any one of the predictor variable was ‘yes’ the rule was ‘positive’ and if all the available predictor variables were ‘no’ we assumed the rule was ‘negative’.

Sensitivity and specificity with 95% confidence intervals for the rule in its ability to predict all serious outcomes and those occurring after ED discharge were calculated. We
also calculated kappas with 95% confidence intervals for the variables collected for inter-
observer agreement.

3.10.3 Impact on Resource Utilization
We calculated the proportion of patient visits that rule predicted as ‘high risk’ and
thereby will require admission to the hospital. We calculated the actual admission rate of
syncope patients in the study site by abstracting disposition details from the patients’
charts. Comparison of the hypothetical admission rate if the rule was used to the actual
admission rate among the included patient visits gave us a measure of the impact on
resource utilization the rule will have if implemented.

3.10.4 Refining the San Francisco Syncope Rule
We performed univariate analysis to select variables for further analysis. Prediction
models were developed both using multivariate logistic regression and recursive
partitioning.

3.10.4.1 Univariate Analysis
Univariate analysis was done using SAS software to determine the association of all
predictor variables (i.e. the San Francisco Syncope Rule variables and the additional
variables collected) to any one of the composite adverse outcomes. The appropriate
univariate technique was selected based on the type of data. For nominal variables, chi-
square or Fisher’s exact test was used. For continuous variables, unpaired 2-tailed t-test
using separate or pooled variance estimates were used as appropriate. Only predictor
variables with a p-value < 0.2 were considered for further analysis.

3.10.4.2 Multivariate Analysis
Model to predict the occurrence of any of the composite outcomes was done using two
multivariate techniques, logistic regression and recursive partitioning. The final model
was aimed for nearly 100% sensitivity, improved specificity if possible, clinical
acceptability and sensibility.
Logistic Regression: Logistic regression was performed using SAS (Version 9.1) statistical software. Initial logistic regression was done with variables having a p-value of < 0.20 in the univariate analysis and those that made clinical sense. If required, variables with more missing values were removed to make the model more stable with narrow confidence intervals for the odds ratios. An assumption was made that predictor variables such as electrocardiogram, blood pressure measurements or laboratory values are within normal limits in patient visits missing these predictor variables. We did this for two reasons, first reason is it will avoid the risk of losing a large number of patient visits from the final model and the second reason is it will also give an opportunity to divide the predictor variables into categories for use in the model. Dividing the predictor variables into categories will make the model simple for use near the bedside without requiring computational aids for complex formulas. The p-value for the predictor variables to enter the model was set at 0.05 and the p-value for these variables to stay in the model was set at 0.1, else they were removed from the model. For the final models developed by logistic regression the odds ratio for the variables in the model with their 95% confidence intervals, the co-efficients for the variables in the model, the ‘c’ statistic (a measure of area under the curve if a receiver operator characteristic curve were to be plotted) and the Homer-Lemeshow goodness of fit were calculated. Interaction among the predictor variables was assessed by inspection in the model. Sensitivity and specificity of the final models with 95% confidence intervals were calculated by applying them to the original dataset.

Recursive Partitioning: Recursive partitioning was done using KnowledgeSEEKER (Version 2.1) software. Developers of clinical decision rules in the past have preferred recursive partitioning over logistic regression as it is more suitable to classify one outcome group at the expense of the other [i.e. high sensitivity is more important than overall accuracy]. (7, 91, 92) Similar to logistic regression, only predictor variables with a p-value of < 0.20 in the univariate analysis and made clinical sense were considered for recursive partitioning. For the same reasons indicated above in logistic regression, the same assumption was made that predictor variables were in the normal range if they were unavailable in patient visits. The variables used to dichotomize in the decision tree
formed the final model. The final models created were then applied to the original data set to obtain sensitivity and specificity with 95% confidence intervals.

3.10.5 Epidemiological Characteristics
Descriptive statistics were used to describe patient characteristics. Percentages were used for dichotomous variables. For continuous variables, means and standard deviations or medians and interquartile ranges were used as deemed appropriate.

During the study period the proportion of visits to the emergency department due to syncope, number of initial visits and return visits, and proportion of patients arriving by ambulance were calculated. The percentage of patients undergoing further investigations (laboratory, electrocardiogram and computed tomography of the brain) was also calculated. Data was analyzed for outcome measures such as admission rates, proportion of patients suffering outcomes inside and outside the emergency department, and timing of occurrence of outcomes after ED discharge.

3.11 Ethical Concerns
The study protocol was approved by the Ottawa Hospital Research Ethics Board prior to data abstraction. There were no ethical concerns expressed by the board. As patients were not contacted, the ethics board approved the project without requiring informed consent from patients included. As follow-up was done in all the other local hospitals in Ottawa, ethics approval was also obtained from the Queensway-Carleton Hospital and the Montfort Hospital prior to data abstraction from these hospitals. An independent study number was assigned for each patient and the link between the study number and the patient identification was housed separately and securely. A password protected database of the predictor variables was created, but patient identifiers in form of names, hospital unique number, and Ontario Health Insurance Plan (OHIP) number were deleted from all records. The copies of research ethics approval documents from all the local Ottawa hospitals are shown in Appendix 4-6.
CHAPTER 4: RESULTS

4.1 Study Flow
During the study period, 936 patient visits due to syncope or syncope-related symptoms were screened for eligibility. Of these 936 patient visits, 168 (17.9%) visits were by patients who did not have an Ottawa residential address, 181 patient visits (19.3%) were due to pre-syncope (with no loss of consciousness) or other non-syncopal illnesses such as falls, light-headedness and 2 patient visits (0.2%) were by pediatric patients with age less than 16, so were excluded. The study flow is illustrated in Figure 3. Five hundred and eighty-five patient visits (62.5%) met the inclusion criteria, of which 34 patient visits (3.6%) were excluded as they met the exclusion criteria. Twenty-five patient visits (2.6%) could not be included as 13 left the Emergency Department before seeing a physician and 12 records of treatment could not be located. As a result, 505 patient visits (53.9%) of the 936 visits screened, were included in the study.

4.2 Characteristics of Included Patient Visits

4.2.1 Demographics
The mean age of the cohort that was included in the study was 58.5 years with ages ranging from 16 to 101 years [Table 1]. Two hundred and fifty-four (50.3%) of the total visits were by females. Ambulance was the mode of arrival for 354 patient visits (70.1%). The 505 patient visits during the study period were made by 490 patients.

4.2.2 Clinical Characteristics
The clinical features of the present syncopal episode, medical history, medication profile and physical examination characteristics of the included patients are given below.

4.2.2.1 Characteristics of the Present Episode:
The episode of syncope was associated with a prodrome in 367 patient visits (73.0%) [Table 1]. Shortness of breath was present in 54 patient visits (10.7%). Syncope occurred during exertion in 28 patient visits (5.5%) and in 16 visits (3.2%) there were associated palpitations.
4.2.2.2 Medical History:
Among the pre-existing medical problems in the cohort, hypertension was most common, present in 174 patient visits (34.5%) followed by coronary heart disease in 99 patient visits (19.6%) and diabetes in 65 patient visits (12.9%). History of congestive heart failure was present in 30 patient visits (5.9%), arrhythmia in 58 patient visits (11.5%), valvular heart disease in 14 patient visits (2.8%) and cardiomyopathy in 5 patient visits (1.0%). Twenty nine patient visits (5.7%) had a previous history of stroke and 27 patient visits (5.4%) had previous history of transient ischemic attack. Of the 362 patient visits with information on previous syncope, 204 (56.4%) have had previous syncope [Table 1].

4.2.2.3 Medication Profile of Included Patients:
In 213 visits (42.2%), patients were already on some medications with diuretics being the most common in 114 patient visits (22.6%), followed by beta-blocker in 95 patient visits (18.8%) and calcium channel blocker in 65 patient visits (12.9%) [Table 2]. Nitroglycerine patch was one of the medications that the patient was on in 15 patient visits (3.0%) and nitroglycerine spray in 42 patient visits (8.3%). In 12 patient visits (2.4%) nitrospray was used prior to the syncopal episode. In 14 visits (2.8%) patients were already on digoxin. The reminder of the medications relevant to syncope which include anti-arrhythmics, direct vasodilators, oral nitrates, alpha blockers and combined alpha/beta blockers were uncommon in less than 2% of the visits. Names of medications were not known in 11 patient visits.

4.2.2.4 Physical Examination Findings of Included Patients:
At triage the included patient cohort had a mean heart rate, mean respiratory rate, mean systolic blood and diastolic blood pressures within the normal values for an adult but the ranges were quite wide particularly for the heart rate and both the triage and the lowest Emergency Department blood pressures [Table 3].

4.2.3 Management and Outcomes
Laboratory blood tests and electrocardiogram were done during majority of the visits - 448 visits (88.7%) and 470 visits (93.1%) respectively [Table 4]. Most of the
electrocardiograms (91.1%) also had a cardiologists' interpretation available in the patient’s medical record. A substantial portion 123 visits (24.4%) had Computerized Tomography (CT) of the head done but only 4 (0.8%) had any new and clinically important abnormalities detected in the scan.

Only 62 patient visits (12.3%) resulted in admissions to the hospital with the majority being discharged home [Table 5]. Table 6 shows the final diagnosis of the included patients at the end of their emergency department visit. Syncope NYD (cause Not Yet Determined) was the most common final diagnosis in 247 patient visits (48.9%) followed by vasovagal syncope in 155 patient visits (30.7%). Medications were the cause of syncope in 18 patient visits with majority (12 patient visits) due to the use of nitroglycerine spray just prior to syncope. Other less common causes for the syncope are listed in Table 6.

Table 7 shows all serious outcomes suffered by the study patients and the place of occurrence of these outcomes within 30 days of their initial visit. Forty-nine visits (9.7%) suffered serious outcomes with 22 serious outcomes (44.9%) occurring during the emergency department visit and 27 serious outcomes (55.1%) occurring outside the emergency department. Cardiac syncope was the most common serious outcome present in 26 visits (53.1%) occurring equally inside and outside the emergency department. Cardiac outcome was also the most common serious outcome occurring outside the emergency department. Twenty-nine visits (59.2%) had procedural intervention done to correct the cause of syncope with pacemaker insertion being the most common procedure done in 18 patient visits (36.7%). There were 5 patient visits that resulted in death with 3 occurring outside the emergency department.

### 4.3 Validation of the San Francisco Syncope Rule

All five predictor variables for the San Francisco Syncope Rule were available in 422 patient visits (83.6%). Hematocrit was the most common variable not available in 68 patient visits (13.5%) followed by electrocardiogram in 35 patient visits (6.9%). Only
two visits (0.4%) did not have the shortness of breath variable. The presence, absence and unavailability of the predictor variables in this validation cohort are given in Table 8.

Comparison of the groups with and without all the predictor variables is given in Table 9. The group without all the predictor variables was younger with a mean age of 38.3 years versus 62.4 years in the group with all the predictor variables. Overall the group without all variables had lesser medical problems such as congestive heart failure (0% versus 7.1% in the group with all variables available), coronary artery disease, arrhythmia, diabetes, hypertension and transient ischemic attack. They also had lesser preponderance of unfavourable clinical characteristics such as hematocrit less than 300, abnormal electrocardiogram, history of shortness of breath, triage systolic blood pressure less than 90 mm of Hg, presently taking any medication, arrival by ambulance, presence of cardiac murmur or rales or decreased air entry on auscultation, any blood tests done, non-sinus rhythm on electrocardiogram, new and clinically important abnormalities on computerized tomography of the head and admissions to the hospital. In the group without all the predictor variables, the most common final diagnosis was vasovagal syncope (74.7% versus 21.1% in the group with all variables). The most common final diagnosis in the group with all variables was syncope NYD (cause Not Yet Determined) in 62.6% versus 25.3% in the group without all predictor variables.

There were 48 serious outcomes (98%) in the group which had all the predictor variables available and only one (2%) in the group without all predictor variables. The only serious outcomes in the group without all the predictor variables was a patient who had syncope at home and had a large melena stool and had a cardiorespiratory arrest on arrival to the hospital. Advanced Cardiac Life Support measures were instituted by the Emergency Department staff. The patient was connected a cardiac monitor which showed ventricular fibrillation. Patient had a systolic blood of 66mm of Hg and diastolic blood pressure of 43mm of Hg in the ambulance. Blood work done on this patient showed the patient has had significant bleeding with haemoglobin of 50 grams per litre and the hematocrit of 0.168. This patient also had an elevated troponin T of 0.08 micrograms per litre. This patient had all the San Francisco Syncope Rule variables except the emergency
department electrocardiogram, which was not possible due to on-going resuscitation efforts. This patient died in the emergency department.

4.3.1 Inter-observer Agreement for San Francisco Syncope Rule variables
Inter-observer agreements were calculated for appropriate inclusion of patients into the study and for the San Francisco Syncope rule variables with high probability of abstraction errors - history of congestive heart failure, history of shortness of breath and abnormal electrocardiogram. Inter-observer agreements were not done for the variables that have low probability of abstraction errors such as hematocrit less than 0.300 and triage systolic blood pressure less than 90 mm of Hg. The kappa values with the 95% confidence intervals are shown in Table 10. There was very good agreement for inclusion of patients in the study and for the pertinent San Francisco Syncope rule variables.

4.3.2 Classification Performance of the San Francisco Syncope Rule
Excluding the patient with the serious outcome and without all the predictor variables, we calculated the sensitivity and specificity of the San Francisco Syncope Rule. We calculated the classification performance of the rule for both all the serious outcomes and those occurring after discharge from the Emergency Department.

For all serious outcomes we found the sensitivity of the rule was 90% (95% CI 78, 95) with the rule missing 5 serious outcomes [Figure 4]. The specificity of the rule was 40% (95% CI 39, 41). Of the five serious outcomes that the rule missed, four occurred in the emergency department and one outside the emergency department.

We found that the San Francisco Syncope Rule had better sensitivity for serious outcomes occurring after discharge from the Emergency Department [Figure 5]. The sensitivity was 96% (95% CI 82, 99) and the specificity was 40% (95% CI 39, 40).
4.3.3 Description of the serious outcomes missed by the San Francisco Syncope Rule

Outcomes in the emergency department:
Patient one had normal electrocardiogram as per the rule criteria but showed sinus pauses as long as 15 seconds in the cardiac monitor. This patient had a temporary pacer inserted in the emergency department and was admitted. There were no further interventions done in the hospital and this patient was discharged with a final diagnosis of neurally mediated syncope. Patient two had a sensation of palpitations followed by syncope resulting in facial injuries. This patient had a normal electrocardiogram as per rule, but had a history of paroxysmal atrial fibrillation. In the emergency department she was documented to have a run of atrial fibrillation on cardiac monitoring followed by a 4 second pause during which she was extremely dizzy. This was followed restoration of normal sinus rhythm. This patient was admitted and had a permanent pacemaker inserted. Patient three presented with syncope and had a normal electrocardiogram as per the rule but had profound bradycardia with sinus pauses on cardiac monitor. This patient was one of four who had a new and clinically important finding on the Computerized Tomography of the head in the form of frontal lobe mass with vasogenic edema. The patient underwent brain biopsy and was discharged home. Patient four, the last serious outcome that was missed by the rule in the emergency department was a young patient who developed chest tightness without shortness of breath and had a syncopal episode. Chest x-ray showed left spontaneous pneumothorax in this patient and had a pigtail catheter inserted in the emergency department. The patient was admitted and underwent thoracoscopic apical bleb resection and partial pleurectomy.

Outcomes outside the emergency department:
Patient one described above returned after 37 days of his previous syncope visit with another episode of syncope. This time again the electrocardiogram was normal as per the rule criteria and was discharged home only for the patient to return 4 hours later with another episode of syncope. The patient was admitted and telemetry showed profound sinus bradycardia with a sinus pause of 32 seconds. This patient had permanent pacemaker inserted.
4.4 Impact on Resource Utilization if the San Francisco Syncope Rule was used

We calculated that 63% of all patients will have to be admitted to the hospital if the San Francisco Syncope Rule was used as a risk stratification instrument to predict serious outcomes in adult syncope patients. This is in contrast to the present admission rate of 12.3%. So using the rule at its present form will lead to about a five-fold increase in admissions rate for syncope patients.

4.5 Potential for Refining the San Francisco Syncope Rule

We collected an additional 131 more extra variables to explore the possibility of refining the rule and improving both the sensitivity and the specificity. Of the additional variables collected, 34 were historical variables, 24 variables were related to ambulance/emergency department vital signs, 3 were related to interventions by ambulance personnel, 5 were physical examination variables, 48 variables were related to ambulance/emergency department electrocardiogram and cardiac monitoring, 15 were laboratory variables and one variable each for computed tomography of the head and carotid sinus massage.

4.5.1 Univariate Analysis

The entire cohort of included patients was divided into two groups – those with and without outcomes. The relationship between all the variables collected and the outcomes was analyzed by comparing the proportion of patients with the variable in the two groups.

The univariate association of demographic and medical history variables with serious outcomes is given in Table 11. Patients with serious outcomes were older (mean age 74.5 years versus 56.8, p = <0.0001) and more likely to arrive in the emergency department by ambulance (85.7% versus 68.4%, p = 0.01). These patients are also more likely to have difficulty breathing (24.5% versus 9.3%, p = 0.0044) around the syncopal episode and more likely to be on any medication from the list of medications in the data abstraction form. Patients with serious outcomes are more likely to suffer from congestive heart failure, coronary heart disease, arrhythmia, diabetes, hypertension and peripheral arterial disease than those without serious outcomes.
The correlation of various ambulance blood pressures and paramedic interventions with serious outcomes is given Table 12. Mean lowest systolic blood pressure and securing intravenous access in the ambulance were significantly associated with serious outcomes.

The relationship between ambulance electrocardiogram strip variables and serious outcomes are enlisted in Table 13. Presence of atrial flutter, left bundle branch block, left posterior fascicular block, ischemic ST-T wave changes and cardiac monitor abnormalities were significantly associated with occurrence of serious outcomes.

The comparison of the means of the vital signs at triage and prior to discharge, orthostatic vital signs, and lowest blood pressures recorded during the emergency department stay and proportion of patients with abnormal physical examination findings among the groups with and without serious outcomes is given in Table 14. Patients with serious outcomes had lower mean values at triage for oxygen saturation, systolic and diastolic blood pressures. The patients with serious outcomes had higher last mean respiratory rate, lower last mean oxygen saturation and lower last mean systolic and diastolic blood pressures. They also had higher sitting mean systolic and diastolic blood pressures which could not be explained. Lowest mean systolic and diastolic blood pressures recorded during the stay in the emergency department was significantly lower in the group with serious outcomes. Rales or crackles and decreased air entry in the chest was significantly more common in the group with serious outcomes.

Among the blood tests hemoglobin, hematocrit were significantly lower, potassium, blood urea nitrogen, creatinine and troponin were significantly higher in the group with serious outcomes [Table 15].

The group with serious outcomes had longer duration of the corrected QT interval (456.3 milliseconds versus 432.9 milliseconds) and significantly more proportion of patients with non-sinus rhythm, atrial fibrillation, atrioventricular block, right bundle branch block, left bundle branch block, left posterior fascicular block, ST-T wave changes consistent with ischemia, secondary ST-T wave changes in the emergency department
electrocardiogram and cardiac monitor abnormalities [Table 16]. Univariate correlation of combined electrocardiogram variables with the serious outcomes was also analyzed. Presence of bifascicular block (defined as presence of right bundle branch block and either left anterior fascicular or left posterior fascicular block), any bundle branch block with first degree atroventricular block and significant atroventricular block (defined as presence of second or third degree atroventricular block) was significantly higher in the group with serious outcomes.

Apart from the additional variables, we also performed univariate correlation of the San Francisco Syncope Rule variables with the serious outcomes and found that all five variables in the rule are significantly associated with serious outcomes. The results with the p-values are given in Table 17.

4.5.2 Multivariate Logistic Regression

4.5.2.1 Initial Logistic Regression Model:
All predictor variables that had a p-value of 0.2 or less in the univariate analysis and that made clinical sense were offered to the initial model. More patient visits had electrocardiogram done in the emergency department than electrocardiogram strips by paramedics (470 versus 223). The electrocardiograms done in the emergency department were of better quality, complete with all the 12 leads and interpreted by a cardiologist. The ambulance electrocardiogram strips were often incomplete, poor in quality with lot of artifacts and interpreted by the candidate. So we decided to use the emergency department electrocardiogram variables and not the ambulance electrocardiogram strip variables. Only 42 patient visits had the variables ‘sitting systolic and diastolic blood pressures’ and also were unexplainably higher than ‘supine systolic and diastolic blood pressures’ so were not entered into model. Similarly ‘carotid sinus massage’ was done only during 2 patient visits, was not included in the model. The variable ‘troponin’ is also an outcome variable so was not included in model development. The initial model derived used only 9 observations due to missing values. The results are shown in Appendix 7.
4.5.2.2 Model Development:
The variables with more missing values ‘last emergency department respiratory rate’, ‘last emergency department oxygen saturation’, ‘lowest ambulance systolic blood pressure’ and ‘lowest ambulance diastolic blood pressure’ were removed and analysis was tried again. The results are given as ‘Model A’ in Appendix 8. The results show that the model is still using only 24 patient visits data and unstable with electrocardiogram parameters showing wide confidence intervals.

The continuous laboratory values of hemoglobin, sodium, potassium, glucose, blood urea nitrogen, creatinine, and calcium were removed and the logistic regression was run again. The model was better with 336 patient visits used to develop the model. The results are shown as ‘Model C’ in Appendix 8. The variable ‘presently in congestive heart failure’ has wide confidence limits and the Hosmer and Lemeshow Goodness-of-Fit test is significant with a p value of 0.04 indicating improper fitting in the model.

The variable ‘presently in congestive heart failure’ was removed and the derived variables ‘bifascicular block’, ‘any bundle branch block + first degree atrioventricular block’ and ‘significant atrioventricular block’ were introduced into the model and analyzed again. The results are shown as ‘Model D’ in Appendix 8. Important electrocardiogram abnormalities such as ‘non-sinus rhythm’ and ‘significant atrioventricular block’ did not make into the model. ‘Non-sinus rhythm’ defined as supraventricular tachycardia or multifocal atrial tachycardia or atrial flutter or atrial fibrillation or junctional rhythm or idioventricular rhythm and significant atrioventricular block is defined as presence of second or third degree heart block.

So we sought to define the all electrocardiogram abnormalities under one variable ‘abnormal electrocardiogram’. We developed 9 different combinations of abnormalities to be used in the model with other non-electrocardiogram variables (Appendix 9). Also since we want physicians to use the model at the bedside, we split the continuous variables into categories within the range of values in the cohort. This also will eliminate the need for computational aids to use the final model. Age was split by every 5 years.
from 35 years to 75 years. For example patients with age 35 years and above were designated as age35 variable present and those below age 35 years as age35 variable absent. Triage oxygen saturation values were categorized at values below 88, 89, 90 and 92%. Triage and the lowest systolic blood pressures were divided into categories with values below the cut-offs at 80, 90 and 100 mm of Hg and triage diastolic blood pressure with values below 40, 50, 60 and 70 mm of Hg. Hemoglobin levels were made into categories with values lesser than 100, 110, 120 and 130 grams per liter. Hematocrit was made into categories with values less than 0.300, 0.290, 0.280, 0.270, 0.260 and 0.250. Potassium values were made into categories of more than 5, 5.5, 6 and 7 millimoles per liter. Creatinine values were categorized as those more than 100, 120, 140 and 160 micromoles per liter. Blood urea nitrogen values were split as those with and without values above 10, 12.5 and 15 millimoles per liter. The emergency department electrocardiogram rates were categorized at rates above 95, 100, 105 and 110 per minute. Duration of corrected QT interval was split every 50 milliseconds from more than 350 milliseconds to 450 milliseconds, by every 25 milliseconds from 450 milliseconds to 625 milliseconds and we also added one more category for more than 460 milliseconds as it is presently considered the upper limit of normal value. The 9 different of abnormal electrocardiograms which constitute varying combinations of abnormalities of the components of the electrocardiogram and the new categorical variables were tried in various combinations.

4.5.2.3 Important predictor variables for the Final Model:
The variables ‘history of coronary artery disease’, ‘history of diabetes’, ‘history of hypertension’, ‘history of cerebrovascular accident’, ‘history of peripheral arterial disease’, ‘arrival by ambulance’, ‘triage oxygen saturation’ categories, ‘last emergency department systolic blood pressure’, ‘last emergency department diastolic blood pressure’, ‘lowest emergency department diastolic blood pressure’ and all the categories for variables ‘age less than 70 years’, ‘triage diastolic blood pressure greater than 90 mm of Hg’, ‘hemoglobin’, ‘hematocrit’, ‘sodium’, ‘potassium’, ‘glucose’, ‘blood urea nitrogen’ less than 15 millimoles per liter, ‘creatinine’, and ‘calcium’ were found to be not significant consistently in all the models and were removed. The variables ‘lowest
emergency department systolic blood pressure’ less than 80 and 90 mm of Hg were also consistently making to the model instead of the categories of ‘triage systolic blood pressure’. The variable ‘decreased air entry’ did make to the model a few times but because of concern about the inter-observer agreement we decided to keep it out of the model. This variable will be included in future studies with interobserver agreement measurements. The variable ‘history of congestive heart failure’ and ‘hematocrit’ less than 300 never made it to any of models, but we decided to keep it as it was part of the San Francisco Syncope Rule. Among the electrocardiogram combinations, abnormal electrocardiogram types 7, 9 and 10 performed better in combination with other variables.

4.5.2.4 Final models developed:
Based on the above considerations, the variables ‘age more than 70 years’, ‘age more than 75 years’, ‘history of congestive heart failure’, ‘history of shortness of breath’, ‘history of arrhythmia’, ‘lowest emergency department systolic blood pressure’ less than 80 and 90 mm of Hg, ‘triage diastolic blood pressure’ less than 50 mm of Hg, abnormal electrocardiograms 7 and 9, ‘hematocrit’ less than 300 and ‘blood urea nitrogen’ more than 15 millimoles per liter were offered for the final models. The p value for variables to enter the model was set at 0.05 and to stay in the model was set at 0.10. The model was tried both with forward selection and backward elimination techniques. As explained in the methods section, an assumption was made that the above mentioned predictor variables considered for the final models are within normal limits in patient visits missing these predictor variables for reasons explained in that section.

The derivation of the final four multivariate logistic regression models is given in Appendix 10. Due to the above assumption all final models used all the 505 patient visits in the study. The final four models with the ‘c’ statistic for the model and odds ratios for their component predictor variables are given in Table 18. Both the forward selection and the backward elimination techniques yielded the same models. All the models derived include the variable ‘history of shortness of breath’ and ‘blood urea nitrogen’ greater than 15 millimoles per liter. All models also had the variable ‘lowest emergency department systolic blood pressure’ categorized at less than 80 or 90 mm of Hg and either abnormal
electrocardiogram 7 or 9 depending on what was offered to the model. Final models 1 and 2 include the age variables more than or equal to 70 and 75 years respectively. In the final model 4 we substituted the variable ‘lowest emergency department systolic blood pressure’ less than 90 mm of Hg with the variable ‘lowest emergency department systolic blood pressure’ less than 80 mm of Hg. All the final four models were very close in their prediction abilities. The ‘c’ statistic was best for model 3 at 0.876 followed by models 1 and 2 at 0.871. Model 4 had the lowest ‘c’ statistic at 0.850. Of the four models, we selected model 2 based on the ‘c’ statistic and the sensitivity and specificity given below.

4.5.2.5 Sensitivity, Specificity and Homer-Lemeshow Goodness of Fit for the Final four models:
The final four models were applied to the same dataset to derive the sensitivity and specificity of the final models (Table 19). These were exactly the same the sensitivity and specificity given in the classification tables with the probability cut off levels for each of the final models. The sensitivities ranged from 84% to 98% and specificity from 48% to 73%. As sensitivity was highest at 98% in model 2 we chose this as our final model. The specificity was modest at 48%. The p values for the goodness of fit show none were significant indicating good fitting of the model.

4.5.2.6 Final logistic regression model:
The final regression model chosen included the variables: age more than or equal to 70 years, history of shortness of breath, lowest emergency department systolic blood pressure less than 90 mm of Hg, abnormal electrocardiogram [defined as presence of any: non-sinus rhythm, significant atrioventricular block, any bundle branch block with first degree atrioventricular block, bifascicular block, ST-T wave changes consistent with ischemia or emergency department cardiac monitor abnormalities] and blood urea nitrogen more than 15 millimoles per liter. As the co-efficients for the predictor variables in the regression model were almost equal, each variable in the model will be given equal weight. Presence of any of the predictor variables will make the rule positive and put the patient at high risk for serious outcomes in the following 30 days. This model was chosen on the basis of statistical modelling ensuring clinically important variables were
included, that the model made clinical sense and had the best possible sensitivity. The final model had a sensitivity of 98% and specificity of 48% to predict serious outcomes within 30 days. The receiver operating characteristic curve for the final selected logistic regression model had an area under the curve of 0.871 in comparison to the San Francisco Syncope Rule receiver operating characteristic curve which had an area of 0.703 under the curve. The receiver operating characteristic curves for the final logistic regression model selected and the San Francisco Syncope Rule are shown in Figures 6 and 7.

4.5.3 Recursive Partitioning
As with multivariate logistic regression, we included variables that had a p value of less than 0.2 and clinically sensible. Also as recursive partitioning requires categorical variables; continuous variables were converted to categorical variables and offered to the model. As with logistic regression, we used the emergency department electrocardiogram variables instead of the ambulance emergency strip variables for the same reasons cited above. The variables offered to the model include: categories of ‘age’ variable, ‘arrival by ambulance’, ‘history of shortness of breath’, ‘presently on any medication’, ‘history of congestive heart failure’, ‘history of coronary artery disease’, ‘history of arrhythmia’, ‘history of diabetes’, ‘history of hypertension’, ‘history of cerebrovascular accident’, ‘history of peripheral arterial disease’, ‘lowest ambulance diastolic blood pressure’ in categories, emergency department examination variables – categories of ‘triage oxygen saturation’, ‘triage systolic blood pressure’, ‘triage diastolic blood pressure’, ‘last respiratory rate’, ‘last oxygen saturation’, ‘last systolic blood pressure’, ‘last diastolic blood pressure’, ‘lowest systolic blood pressure’, ‘lowest diastolic blood pressure’, presence of ‘rales’ or ‘decreased air entry’, categories of lab values – ‘hemoglobin’, ‘hematocrit’, ‘sodium’, ‘potassium’, ‘blood urea nitrogen’, ‘creatinine’ and ‘abnormal electrocardiogram types 1 to 9’. As explained in the methods section, an assumption was made that the above mentioned predictor variables considered for the model are within normal limits in patient visits missing these predictor variables for reasons explained in that section. Due to this assumption all final models used all the 505 patient visits in the study and none of the visits were deleted due to missing values.
4.5.3.1 Models derived by recursive partitioning:
The two models derived by recursive partitioning with their sensitivities and specificities are given in Table 20. The two rules were identical except the definition of abnormal electrocardiogram. Abnormal electrocardiogram type 7 includes the secondary ST-T wave changes while abnormal electrocardiogram type 9 does not include it. The sensitivities are the same but the rule containing abnormal electrocardiogram type 9 has a slightly better specificity and so was selected as the final rule. The decision trees for the two models and the calculations for sensitivity and specificity are given in Appendix 11.

4.5.3.2 Final Rule based on recursive partitioning:
The decision tree in derivation of the preliminary rule by recursive partitioning is given in Figure 8. The three variables that made it to the rule are: abnormal electrocardiogram (See appendix abnormal electrocardiogram type 9 for definition), lowest emergency department systolic blood pressure less than 80 mm of Hg and age ≥ 65 years [Figure 9]. The classification performances for the new preliminary rule for all outcomes and for outcomes that occur outside the emergency department are given in Figures 10 and 11. For all outcomes the rule has a sensitivity of 100% (95% CI 93, 100) and a specificity of 53% (95% CI 52, 53). When applied to the current cohort the admission rate would be 52%. For outcomes occurring outside the emergency department the rule has a sensitivity of 100% (95% CI 88, 100), a specificity of 53% (95% CI 52, 53) and result in 50% of patients being admitted.

4.6 Frequency and Outcomes of syncope in a tertiary care emergency department
A total of 90,036 visits to the Civic Campus Emergency Department occurred during the study period. Of the 936 visits screened, 905 visits (1.0%) were due to syncope or pre-syncope. Of these, 150 visits were due to pre-syncope and 505 patient visits (53.9%) met the eligibility criteria and were included in the study. The 505 patient visits during the study period were made by 490 patients with 97% making one initial visit, 14 patients (2.8%) making two initial visits and 1 patient (0.2%) making three initial visits [Table 1]. Apart from these 505 initial visits, 20 visits (4.1%) were return visits as these patients
returned to the Emergency Department within 30 days of their initial visit. Majority of the patients (354 patient visits, 70.1%) arrived by ambulance to the emergency department. Two hundred and four patient visits (40.4%) have had previous syncope with one previous episode in 86 visits (17.0%), two previous episodes in 29 patient visits (5.7%), three in 11 visits (2.2%) and four or more previous episodes in 43 patient visits (8.5%).

Majority had blood tests (448 visits, 88.7%) and electrocardiogram (470 visits, 93.1%) done [Table 4]. One hundred and twenty-three visits (24.4%) had Computerized Tomography (CT) of the head done but only 4 (0.8%) had any new and clinically important abnormalities detected in the scan. New and clinically important abnormalities were defined as the abnormality detected is the cause of syncope or is a consequence of syncope itself or the fall associated with the syncope. All chronic findings were classified as non-significant.

The final diagnosis at the end of their ED visit for the 505 patient visits in the study is shown in Table 6. Syncope NYD (cause Not Yet Determined) was the most common final diagnosis in 247 patient visits (48.9%) followed by vasovagal syncope in 155 patient visits (30.7%). Medications were the cause of syncope in 18 patient visits with majority (12 patient visits) due to the use of nitro-glycerine spray [Table 6]. Other diagnoses were less common. Twenty-two patient visits were associated with serious outcomes in the emergency department.

Sixty-two patient visits (12.3%) resulted in admission to the hospital [Table 5]. Forty-nine patient visits were associated with serious outcomes with 22 (44.9%) occurring in the emergency department and 27 (55.1%) occurring outside the emergency department. List of serious outcomes and their place of occurrence is given in Table 7. Cardiac syncope was the most common serious outcome present in 26 visits (53.1%) occurring equally inside and outside the emergency department. Cardiac outcome was also the most common serious outcome occurring outside the emergency department. Sinus node dysfunction and third degree heart block were very common and lead to pacemaker
insertion as the most common procedural intervention done in 18 patient visits (36.7%). Twenty-nine visits (59.2%) had procedural intervention done to correct the cause of syncope. Hemorrhage requiring transfusion was the next common outcome in 8 patient visits (16.3%). Five patient visits had a return visit within 30 days and were hospitalized for a syncope related problem. There were 5 patient visits that resulted in death with 3 occurring outside the emergency department.

The time of occurrence of outcomes outside the emergency department is given in Figure 12. The bar graph shows that 18 (67%) of the 27 serious outcomes outside the emergency department occurred within 7 days, with 17 (63%) happening within 5 days of the index visit.

4.7 Emergency Physicians’ Performance in Predicting Short-term Serious Outcomes
Though not part of our analysis, we analyzed the proportion of adverse outcomes missed by the emergency physicians in our study. Of the 27 serious outcomes that occurred after ED discharge, 8 (29.6%) of the patients were not referred to other specialities for admission and suffered serious outcomes in the community or were detected during their return visit. The 8 outcomes missed by the emergency physicians include: 1 death, 3 pacemaker insertions for complete heart blocks or sinus pauses, 2 had to be hospitalized during their return visit, 1 patient had to be cardioverted for atrial fibrillation and 1 stroke. We were not able to calculate the sensitivity and specificity of the emergency physicians’ ability to predict the serious outcomes as we did not collect information if the patient was referred to a speciality for consultation.
CHAPTER 5: DISCUSSION

To our knowledge this is largest validation study outside the United States and the second largest of all validation studies. About 500 patient visits were included in the study and 10% of the patients suffered serious outcomes within 30 days with more than half of these outcomes occurring after the patient has left the emergency department. The sensitivity and specificity of the San Francisco Syncope Rule was lower than reported in the original study. Implementing the rule will greatly increase the admission rates in this era of emergency department and hospital overcrowding. Of the total emergency department visits 1.0% was due to syncope and pre-syncope which is comparable to the previous published literature (1-5). As part of refining the San Francisco Syncope Rule, this is the first study to explore the relationship between the various electrocardiogram variables and the outcome. Our exploration for refining the rule shows it is feasible to develop a better clinical decision rule based on the San Francisco Syncope Rule with improved sensitivity and specificity.

5.1 Enrolment

During the chart review care was taken to review all consecutive patients presenting with syncope-like symptoms for inclusion in the study. By doing so we removed any systematic bias that might have occurred in inclusion of the patients in the study. The inter-observer agreement results indicated a very high degree of correlation for inclusion of patients into the study.

With respect to retrieving charts for review, we encountered problems pulling charts in the year 2005 as all charts were stored in archives. The original protocol indicated that charts would be reviewed from June 30, 2006 going backwards in time to meet the sample size requirement. Due to inability to locate charts in archives, 12 records of treatment were not available. As a result we stopped retrospective review of charts as of August 1st, 2005 and commenced the chart review from July 1st, 2006 going forwards to fulfill the sample size. This allows a continuous block of time for the study. Data collection was done on all charts who met the inclusion/exclusion criteria during the
study period except for the 12 charts which could not be located. This could have happened for various reasons including charts being out of archives at the request of patients, for clinic appointments, for other research projects or incorrect filing. We do not believe that there was any systematic reason for charts being unavailable, and so should not influence the results.

5.2 Performance of the San Francisco Syncope Rule and Comparison to the other San Francisco Syncope Rule validation studies

There are total of six external validation studies reported in the literature validating the San Francisco Syncope Rule. (52, 53, 93-96) Four studies are from the United States (52, 53, 95, 96), one from Australia (93) and one from the United Kingdom (94). Of these six studies, full text articles were available only for four studies. (52, 53, 93, 94) Two studies from the United States have only abstracts published in conference proceedings. (95, 96)

The sensitivity and specificity of the San Francisco Syncope Rule for predicting all serious outcomes in our study was 90% and 40% respectively. For serious outcomes occurring outside the emergency department the rule had a sensitivity of 96% and specificity of 40%. These values were lower than that was reported in the original derivation and validation study. The derivation study was done to predict serious outcomes at 7 days and had a sensitivity of 96% and a specificity of 62%. (7) During validation phase the rule was tested for its ability to predict serious outcomes at 30 days and had a sensitivity of 98% and a specificity of 58%. (9) Of the two United States studies that were published, Sun et al validated the rule in the south-western region of the United States and Birnbaum et al validated the rule in the north-eastern region of the United States. (52, 53) Sun et al reported a sensitivity of 89%, specificity of 42% for all serious outcomes and sensitivity of 69% sensitivity, specificity of 42% for serious outcomes outside the emergency department. Birnbam et al reported a sensitivity of 74%, specificity of 57% for all serious outcomes and sensitivity of 68% for serious outcomes occurring outside the emergency department. Specificity of the rule for serious outcomes occurring outside the emergency department was not reported in this study. External validation of the rule in Australia by Cosgriff et al showed the rule had a
sensitivity of 90% and a specificity of 57% for all serious outcomes. Reed et al externally validated the rule in the United Kingdom where the rule had a sensitivity of 100% for all serious outcomes. The specificity of the rule in this study was not reported. External validation studies both from the United Kingdom and Australia did not report the performance of the rule for serious outcomes occurring outside the emergency department. Both published abstracts validating the rule for which full text articles were not available, are from the north-eastern region of the United States. The sensitivities reported were 77% and 91%; specificities were 38% and 54% for all serious outcomes. Both abstracts did not report the classification performance of the rule for serious outcomes occurring outside the emergency department.

**Reasons for variation in the results**

The primary reason for these differences in the performance of the rule is related to the interpretation of the variable ‘abnormal electrocardiogram’. The variable ‘abnormal electrocardiogram’ in the San Francisco Syncope Rule study was defined as ‘any non-sinus rhythm’ or ‘any new electrocardiogram changes’ in comparison to the previous electrocardiogram. We further received clarification from the author of the original study, Dr. Quinn, regarding application of the variable in the absence of an old electrocardiogram. The original study classified electrocardiograms with any changes as abnormal electrocardiogram in the absence of an old electrocardiogram. Without clearly defined criteria, there could be wide differences in interpretation of this variable. This is evident from the wide variation in proportion of patients fulfilling the criteria for ‘abnormal electrocardiogram’ in the different studies. Quinn et al in his derivation study reported 32% of patients had ‘abnormal electrocardiogram’, Birnbaum et al reported 31%, Cosgriff et al reported 21% and we report 56%. To complicate matters further, Sun et al in their study defined electrocardiogram as abnormal by their own preset criteria as they anticipated problems with availability of old electrocardiograms. They reported 37% of the electrocardiograms as abnormal in this study. The high proportion of electrocardiograms classified as abnormal in our study could be due to the use of the cardiologists’ reporting all new abnormalities and automatically comparing to an old electrocardiogram electronically available while other studies reported interpretation by
the emergency physician. While this is strict application of the variable as defined by the original study, all studies including the San Francisco studies used emergency physicians’ judgement to label the electrocardiogram as abnormal. We feel that any component of the rule must be clearly defined for application. Poor agreement for the variable ‘abnormal electrocardiogram’ within the reported studies is evident from the kappa values of 0.55 for non-sinus rhythm and 0.68 for any new electrocardiogram changes in the San Francisco Syncope Rule derivation study, kappa of 0.50 and 0.53 for the variable ‘abnormal electrocardiogram’ in the study by Sun and Birnbaum respectively. Once again our study had a high kappa likely due to the use of cardiologists’ interpretation rather than the emergency physicians’.

A second reason for the differences among the studies might be the duration of follow-up after syncope. The San Francisco Syncope Rule study in its validation phase and our study were the only two studies which validated the performance of the rule to predict adverse outcomes 30 days after syncope, while the rest of the studies validated the rule for predicting adverse outcomes 7 days after syncope.

The third reason is due to variation in proportion of patients suffering serious outcomes, particularly the proportion of serious outcomes occurring outside the emergency department. Our study had 49 (9.7% of included patients) serious outcomes with 27 (55.1%) occurring outside the emergency department. The derivation study by Quinn et al showed that 11.5% of patient visits resulted in serious outcomes and the proportion of serious outcomes occurring outside the emergency department was not reported. In the validation phase, 13.7% of patient visits resulted in serious outcomes with 50% occurring outside the emergency department. Sun et al reported a total adverse outcome rate of 11.7% with 29% occurring outside the emergency department, while Birnbaum et al reported 8.6% total serious outcomes with 26% happening outside the emergency department. Both studies that reported a high proportion of outcomes occurring outside the emergency department had follow-up for 30 days after syncope instead of the 7 days. Reed et al reported serious outcome rate of 8.1% in the United Kingdom at 7 days, while two published abstracts in the United States reported 13.1% (Schladenhaufen et al) and
26% (Stracner et al). None of these three studies reported occurrence of serious outcomes outside the emergency department. As described above there is fair variation in the proportion of patients suffering serious outcomes particularly those who suffer outcomes after discharge from the emergency department.

Apart from the above reasons, there were differences in the ways the studies were conducted that could be sources of selection bias and be responsible for the variation in the results. Our study did not include pre-syncope patients because of difficulty differentiating retrospectively pre-syncope patients from those with dizziness, light headedness and falls. The study by Sun et al recruited prospectively a convenience sample of patients only between 8am and 10pm, excluded patients with advance care directives not to resuscitate or intubate and also patients with no follow-up. Birnbaum et al included only patients with age 21 years or older and also only those with follow-up.

5.3 Comparison to the other Models

In 1997 Martin et al derived and validated the first risk stratification system in emergency department syncope patients to predict arrhythmia or 1-year mortality. (11) It was not used by emergency physicians. In 2003 Colivicchi et al derived and validated risk factors for 1-year mortality in emergency department syncope patients. (10) Though a well conducted study, it was not used by emergency physicians as we are more interested in the short-term serious outcomes and not 1-year outcomes. Also in 2003 Sarasin et al developed risk factors for serious arrhythmia. (13) This risk stratification system is also not widely used by emergency physicians. As indicated in our previously presented study, the San Francisco Syncope Rule has become the leading clinical decision rule known or used by emergency physicians for risk stratification of adult syncope patients as it is the only one that has prospectively derived, validated and predicts short-term serious outcomes which of interest to the emergency physicians. (14) All the other risk classification systems have not been externally validated further and are not used by emergency physicians.
5.4 Impact on Resource Utilization

Admission rates for emergency department syncope patients vary widely across different parts of the world. Admission rates to the hospital from the emergency department in our study are the lowest reported in the western world at 12.3%. Admission rates for syncope patients reported in the two United States external validation studies were 51% and 83%, admission rates in the United Kingdom was 44% and in Australia was 35%. (52, 53, 93, 94) Our study shows that admission rates would increase by five-fold if the San Francisco Syncope Rule is implemented. The health-care system in Canada will not be able to cope with such an increase in admission rates as it is already been overstretched with limited resources and hospital/ED overcrowding. A newly developed clinical decision rule is required to improve our ability to predict serious outcomes that occur after discharge from the emergency department without such huge increase in admission rates.

5.5 Refining the San Francisco Syncope Rule

Due to retrospective nature of the study and large number of missing values, the univariate analysis is potentially methodologically weak. We were able to identify variables that are important in predicting serious outcomes in adult syncope patients.

5.5.1 Potentially Important Predictor Variables

The following predictor variables appear not only to be important, but also clinically and statistically significant for future prospective studies.

Age and history of the present episode:

‘Age’ as a continuous variable in univariate analysis was found to be significantly associated with serious outcomes in our study. Also the variables ‘age 65 years or more’ and ‘70 years or more’ made it to the final recursive partitioning and logistic regression models respectively. The San Francisco Syncope Rule derivation study considered ‘age more than 75 years’ as a variable in the rule to increase sensitivity from 96% to 100%. But as the specificity would drop from 62% to 44%, the age variable was not included. (7) Colivicchi et al found in their study that ‘age more than 65 years’ was associated with increased risk of death in 1 year. (10) Martin et al reported that ‘age more than 45 years’
was associated with increased risk of arrhythmias and 1-year mortality. (11) Sun et al found that ‘age 60 years or more’ was associated with short-term serious outcomes in syncope patients. (97) ‘Age’ is an important predictor variable and must be collected in future studies.

Our study showed that ‘arrival by ambulance’ was significantly associated by univariate analysis with serious outcomes in the short-term. But it may be considered clinically not sensible or relevant, and also did not make it to the final models derived by both recursive partitioning and logistic regression techniques.

Presence of ‘shortness of breath’ around the syncopal event was significantly associated with serious outcomes in the San Francisco Syncope Rule study. (7) In our study, ‘shortness of breath’ was found to be significant in univariate analysis and is one of the variables in the final logistic regression model but did not make it to the final recursive partitioning model. Future studies are required to address the pathophysiologic mechanisms that make ‘shortness of breath’ an important predictor of serious events.

Absence of ‘prodrome’ found to be significant predictor of death at one year by Colivicchi et al, was not found to be a significant predictor of short-term serious outcomes in our study and the San Francisco Syncope Rule study. (7, 10) A prospective study by Oh et al also concluded that none of the symptoms associated with syncope was a predictor of one year mortality in syncope patients. Only underlying cardiac disease was a predictor of 1-year mortality in this study. (73) The conclusion that absence of ‘prodrome’ is not a predictor of serious outcomes can be tested in future prospective studies.

**Pre-existing medical conditions:**
‘History of congestive heart failure’ was significantly associated with serious outcomes in univariate analysis in our study and in the San Francisco Syncope Rule study. (7) This variable was part of the San Francisco Syncope Rule but did not make it to the final models in our study. Other studies also have shown that ‘presence of congestive heart
failure' was associated with arrhythmias and death after syncope. (11, 13) Middlekauff et al showed that syncope in patients with advanced congestive heart (defined as ejection fraction less than 30%) was associated with high risk of sudden death. (89) In another related study the same author showed that history of syncope in patients with very advanced heart failure (ejection fraction of 20% ± 7%) was associated with sudden death independent of whether the etiology of syncope was cardiac or non-cardiac. (46) Though the variable 'congestive heart failure' did not make to the final model in our study, it is a very important variable. This variable needs further exploration as studies indicate severity of congestive heart failure may be more important than just the disease itself.

Pre-existing 'coronary artery disease', 'arrhythmia', 'hypertension' and 'diabetes' were significantly associated with serious outcomes in both our study and the San Francisco Syncope Rule study. (7) But none of the variables were part of the final model in both studies. This can be tested in future larger prospective studies.

Kapoor et al and Colivicchi et al showed that 'cardiovascular disease' is a very strong predictor of mortality in syncope patients older than 60 years and 65 years respectively. (10, 98) Kapoor et al also showed increased risk of sudden death in elderly syncope patients with cardiovascular disease. (98) The variable 'cardiovascular disease' must be collected in future prospective studies.

Though pre-existing 'peripheral arterial disease' was significantly associated with serious outcomes in univariate analysis, the number of patients had the disease was very small and also the variable did not make it to the final models. This can be further tested in future studies.

Variables from pre-hospital treatment:
'Lowest diastolic blood pressure', and on the electrocardiogram strip 'presence of non-sinus rhythm', 'left bundle branch block', 'left posterior fascicular block' and 'secondary ST-T wave changes' were significantly associated with serious outcomes in univariate analysis in our study. Due to incomplete and poor quality of the electrocardiogram strips,
our analysis indicates that usefulness of pre-hospital data may be limited to detection of transient electrocardiographic abnormalities such as atrioventricular block, non-sinus rhythm including atrial and ventricular arrhythmias. A large prospective study can clarify this question further.

**Vital signs:**
‘Triage and last emergency department systolic and diastolic blood pressures’ were important predictors of serious outcomes in our study. ‘Triage systolic blood pressure less than 90 mm of Hg’ is one of the variables in the San Francisco Syncope Rule. (7) More importantly lowest systolic blood pressure was a better predictor of serious outcomes in our study than the ‘triage systolic blood pressure’. ‘Lowest systolic blood pressure less than 90 mm of Hg’ is part of our final logistic regression model and ‘lowest systolic blood pressure less than 80 mm of Hg’ is part of our final recursive partitioning model. Sun et al in their prospective validation study suggested that as clinicians are influenced by lowest blood pressure values, serial blood pressure measurements need to be explored. (52)

Though ‘triage and last emergency department oxygen saturation and respiratory rate’ were found to be significant in univariate analysis, the difference in the mean values was not clinically significant among those with and without the outcomes. This can be explored further in future studies.

**Physical Examination findings:**
Presence of ‘rales’ (also known as ‘crackles’) and ‘decreased air entry’ on lung auscultation were significantly associated with serious outcomes in our study. The variable ‘rales’ did not make to the final models but ‘decreased air entry’ did make to a few preliminary models. But, because of concern regarding inter-observer variability, we decided not to include this variable in the final model development stages. The San Francisco Syncope Rule study also found ‘rales’ to be significant in univariate analysis but kappa was low at 0.48 and so was not included in multivariate analysis. The study did not collect the variable ‘decreased air entry’. Clinically it is more difficult to ascertain
‘decreased air entry’ than presence of ‘rales’. The variable ‘decreased air entry’ and ‘rales’ can be further tested in future prospective studies.

Laboratory values:
Among the laboratory investigations, values of ‘hemoglobin’, ‘hematocrit’, ‘potassium’, ‘blood urea nitrogen’ and ‘creatinine’ were significant in univariate analysis in our study. In the San Francisco Syncope Rule study, ‘hematocrit less than 0.300’ was significant and made to the final rule but the study did not collect the other laboratory parameters. In our study, ‘blood urea nitrogen more than 15 millimoles per liter’ made it to the final logistic regression model. All these laboratory values along with historical variable ‘renal failure’ should be collected in future prospective studies.

Emergency Department Electrocardiogram variables and Cardiac Monitor abnormalities:
The following emergency department electrocardiogram variables were significantly associated with serious outcomes in univariate analysis: presence of ‘non-sinus rhythm’, ‘atrioventricular block’, ‘right bundle branch block’, ‘left bundle branch block’, ‘left posterior fascicular block’, ‘ST-T wave changes consistent with ischemia’, ‘secondary ST-T wave changes’, ‘cardiac monitor abnormalities’, ‘bifascicular block’, ‘any bundle branch block + first degree atrioventricular block’, ‘significant atrioventricular block’ and mean ‘corrected QT interval’. The San Francisco Syncope Rule used the characteristics of ‘non-sinus rhythm’ and ‘any new changes’ to define the variable ‘abnormal electrocardiogram’. The study also did not include cardiac monitor abnormalities in predicting serious outcomes. Our study included all the important abnormalities under the variable ‘abnormal electrocardiogram’ and found sensitivity and specificity were better for the final models. Also area under the curve was higher for our final logistic regression model than for the San Francisco Syncope Rule. Further prospective studies need to be done to test the components of the variable ‘abnormal electrocardiogram’ and their combined performances, the inter-rater reliability for diagnosing electrocardiogram abnormalities among cardiologists and emergency physicians including ‘bifascicular block’ and to characterise the emergency syncope patients who require cardiac
monitoring. Defining the relationship of the various electrocardiogram abnormalities to the short-term serious outcomes is likely to be the biggest contribution of this study to the literature on risk stratification of emergency department syncope patients.

5.5.2 Reliability of Predictor Variables
We assessed inter-rater reliability only for the variables ‘shortness of breath’, ‘history of congestive heart failure’ and ‘abnormal electrocardiogram’ with cardiologists’ interpretation also available with the electrocardiogram. We do not feel the need to assess kappas for the reported values of age, blood pressures and laboratory values. Inter-rater reliability of rest of important predictor variables (i.e. ‘prodrome’, ‘history of coronary artery disease’, ‘history of arrhythmia’, history of any cardiovascular disease’, presence of ‘rales’ or ‘decreased air entry’ on lung auscultation, ‘Is the patient presently in congestive heart failure?’, emergency department and ambulance ‘electrocardiogram abnormalities’) were not assessed and need to be assessed in future prospective studies as kappas were available only for few variables in the literature.

5.5.3 Models Derived using Multivariate Logistic Regression
Although the models that we derived by logistic regression were fairly good, we found a few disadvantages with them. The 95% confidence intervals for the odds ratio estimates for the variables ‘blood urea nitrogen more than 15 millimoles per litre’, ‘abnormal electrocardiogram type 7’ and ‘lowest emergency department systolic blood pressure less than 90 mm of Hg’ were wide likely due to the sample size and distribution. As the coefficient for the variables in the final model selected were varied, the relative weights of the variables in the model were also different. Using the model as a clinical decision rule by giving equal weight leads to gross approximation of the model. For accurate short-term risk prediction, computational aids will be required to accurately use this model. This is a serious disadvantage for emergency physicians who would like to use clinical decision aides in the bedside and would lead to lesser use of the clinical decision rule.
5.5.4 Models Derived using Recursive Partitioning
We found recursive partitioning superior for developing a clinical decision rule as it offers a method of model development without the disadvantages listed above when using logistic regression model. The clinical decision rule that we derived using recursive partitioning was more parsimonious with only 3 variables, easy to use in the bedside and can be remembered using a pneumonic ‘ABC’ standing for the 3 variables: ‘A’ for age variable - ‘Age 65 years or more’, ‘B’ for ‘Blood pressure’ - ‘lowest emergency department systolic blood pressure less than 80 mm of Hg’ and ‘C’ for cardiogram abnormalities - defined as presence of any of the following: non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm), significant atrioventricular block (second and third degree), bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities. The model derived by recursive partitioning also had better classification performance for both sensitivity and specificity. The confidence intervals for the sensitivity and specificity were also narrow. Other authors also have found that recursive partitioning was more suitable for clinical decision rule development than logistic regression. (7, 91, 92)

5.6 Frequency and Outcomes of Syncope in the Emergency Department
The frequency of visits in our study by patients with syncope/pre-syncope is comparable to the previously reported frequencies. (1-5) Most patients arrived by ambulance to the emergency department and few patients made more than one visit. The rate of serious outcomes incurred by these syncope patients is also comparable to previously published studies. (7-9) Most patients did undergo investigations with blood tests, electrocardiogram and computed tomogram (CT) of the head. The yield of CT head in these patients is very low and further studies are required to clarify the need for CT head in syncope patients. Syncope NYD (cause not yet determined) is the most common final diagnosis followed by vasovagal syncope. Medications were cause of syncope in a small group (3.6%) of the patients. Our study confirms that syncope is common problem in the emergency department and about 1 in 10 of these patients are at risk for serious outcomes and about half of these occur after discharge from the ED. A robust clinical decision rule
better than the San Francisco Syncope Rule to risk-stratify patients presenting with this common ED problem will be very useful in the future.

5.7 Study Strengths
This was the largest study to validate the San Francisco Syncope Rule outside the United States and the second largest of all validation studies. Our study was the only one to explore the possibility of refining the San Francisco Syncope Rule and define 'abnormal electrocardiogram'. We reviewed consecutive patients and included only those who fulfilled the definition of syncope. We thoroughly evaluated all records of treatment — emergency medical services, nursing, emergency physician(s) and specialist(s) for collecting the predictor variables. We undertook extra steps in the form of reviewing records of all local hospitals and the provincial coroner's office for improving follow-up. All outcomes were verified by another emergency physician. The protocol of our study was very similar to the San Francisco Syncope Rule study. We used the same definitions for the outcomes as in the original study. The percentage of syncope visits to the emergency department, mean age of the included patients, their medical history, proportion of patients sustaining all outcomes and outcomes outside the emergency department are all comparable to the San Francisco Syncope Rule study. (7, 9)

When conducting this study, we strictly followed the methodological standards for the retrospective studies known in the literature. (99-101) The 15 different criteria identified in three separate studies in the literature as the methodological standards for medical records review are given in Figure 13. Evaluating our study against these standards, we find that we had very clear objectives before the beginning of the study. Apart from the principal investigator, there was one other abstractor who completed only part of the abstraction form and this research assistant was appropriately trained. The inclusion and exclusion criteria were clearly defined before the study was started. We used standardized abstraction forms with clear definition of the predictor and outcome variables. The principal investigator and the abstractor met at least once a week to review performance and all data abstracted by the research assistant was double checked by the principal investigator at the end of the day. Both the abstractors were blinded to the
outcomes at the steps of eligibility assessment and data extraction. Inter-observer reliability was tested for the eligibility criteria and pertinent San Francisco Syncope rule variables. Case identification was precisely done using National Ambulatory Care Reporting System (NACRS) database. We included very broad screening criteria to avoid missing eligible patients. We used consecutive sampling method to include patients in the study. During the analysis phase we assumed that the variables were absent in patient visits with missing variables and we also excluded variables with lot of missing data in the multivariate analysis. Ethics approval was obtained from all the hospitals before the study was commenced. Sample size was calculated a priori and the study was funded by a small grant from the Department of Emergency Medicine, University of Ottawa. So our study did fulfill all the 15 criteria for the methodological standards for medical records review.

Evaluating our study against the methodological standards for the clinical decision rules, the outcome and the predictor variables were clearly defined prior to the data abstraction. The predictor variables for which kappas were assessed show high reproducibility of these variables. The study population was selected without any bias. We described clearly the mathematical methods used for deriving the rule. Our goal was clear and the topic was clinically relevant. Because the rule is preliminary and the study is retrospective the rule was not able to fulfill the rest of criteria for the methodological standards. This study demonstrates the feasibility for deriving a prospective rule. Though the preliminary rule is sensible the variables might be refined or different after the prospective study. Once the final rule is derived from future prospective studies it can be tested if it is concise, easy to remember, how well it validates in the same (internal validation) and in a different population (external validation). In summary given the study is an exploration, it fulfills some of the basic criteria for the methodological standards for clinical decision rules and some of the advanced criteria cannot be fulfilled until future prospective studies are conducted.
5.8 Study Limitations

Many of the limitations in this study are due its retrospective nature. We included only patients with Ottawa residential address. Though there was a possibility of selection bias, we did this to improve our ability to follow-up of patients for occurrence of serious outcomes. We also excluded pre-syncope patients as there was difficulty in our pilot study to differentiate the pre-syncope patients from those with dizziness, light headedness and falls. While this avoided contamination by non-syncopal patients, this can also be source of selection bias. Pre-syncope patients could have been included if the study was prospectively conducted.

Important clinical information may not have been elicited or recorded by the medical personnel delivering care and the information in the patient’s chart may have been misinterpreted by the extractors. For example, if ‘loss of consciousness’ was not recorded the patient visit could have been inappropriately excluded from the study. Due to missing data, the resulting analysis is possibly weak. Prodromal symptoms might not have been properly recorded and could have affected its ability to differentiate those patients with serious outcomes. Hematocrit was not available in 13.7% of the patient visits, electrocardiogram in 6.9% and ‘history of shortness of breath’ in 0.4% of the patient visits. While this could have affected to some extent model development by both logistic regression and recursive partitioning, it probably had little effect on calculating sensitivity of the San Francisco Syncope Rule. The specificity calculated might be inappropriately high as we assumed that the San Francisco Syncope Rule variables were negative in those patients who were missing the variables for the rule. Cardiologists’ interpretation of the electrocardiogram was used in the study. This can be problem, as emergency physicians may not be able to interpret the electrocardiogram at the same level. This can be particularly true for the characteristic ‘bifascicular block’ which requires diagnosing the ‘left anterior fascicular block’ or ‘left posterior fascicular block’ both of which can be extremely difficult. There might be more variability between emergency physicians than cardiologists. While every effort was made to check health records in local hospitals to ensure follow-up, still follow-up for serious outcomes might not be complete. Patients might have been not from Ottawa and could have given an
Ottawa address which might have been a friend’s or relative’s address. Patients could have been living in Ottawa when suffering the syncopal episode and could have moved or could have been visiting elsewhere after the syncope and sustained serious outcomes. Though these are possible, they are unlikely and therefore will not influence the results of our study. Inter-observer reliability was not calculated for all predictor variables except for the pertinent San Francisco Syncope Rule variables. This could affect the appropriate risk classification of patients by the new preliminary clinical decision rule.

5.9 Need for a Clinical Decision Rule for Emergency Department adult syncope patients

Syncope is a common cause for emergency department visit. As we have indicated in the introduction it is a ‘low risk/high stakes’ symptom as patients are asymptomatic on arrival while they are at risk for serious outcomes. The differential diagnosis is also extensive. These problems that the emergency physicians face are evident by the results of our study which shows that our emergency physicians failed to predict 30% serious outcomes occurring outside the emergency department. All these patients were discharged home to suffer these events. In our study and in one external validation study conducted in the United States the best available clinical decision rule for predicting short-term serious outcomes in adult syncope patients, the San Francisco Syncope Rule did not perform as well as previously reported. (95) The rule performed poorly in two other external validation studies in the United States. (52, 53) One external validation study from the United Kingdom and another from Australia showed that the sensitivity of the rule was only as good as present clinical practice but admission rates would be increased if the rule was implemented. (93, 94) Hence there is a need for a robust and well developed clinical decision rule to predict all short-term serious outcomes occurring after discharge from the emergency department in adult syncope patients.

5.10 Future directions and feasibility of a prospective study

Our study shows that a prospective study to derive a clinical decision rule is feasible. We believe that the rule must be derived to mainly predict serious outcomes outside the emergency department. With about 800 syncope-related visits per year to the emergency
department at one study site, about 10% serious outcomes rate overall and about 5% outside the emergency department reported in our study, it is feasible to derive prospectively a clinical decision rule with 3 to 6 variables. This will require roughly a maximum of 60 serious outcomes outside the emergency department. A prospective study for one year at the two emergency departments of the Ottawa Hospital will provide enough patients to perform the study. All the pertinent variables can be prospectively collected and at least in 10% of the visits the variables will be collected by a second observer to provide adequate inter-rater reliability.

Once derived, the rule can be validated both internally and externally. During the derivation and validation phases the time to decide disposition of syncope patients can be collected and compared. If the rule performs well in the validation phase and prevents patients from suffering serious outcomes outside in the community, the rule can be implemented into clinical practice.

5.11 Importance and Relevance
Physicians in general and emergency physicians in particular find it difficult to decide which syncope patients are at risk of serious outcomes in the short-term and therefore need admission for further in-patient investigations. This is evident from the results of our study. We can reduce the risk of serious outcomes occurring outside the hospital by admitting most of the syncope patients as done in the United States. (52, 53) But with a public payer system in Canada, in all countries in this era of hospital overcrowding and to reduce strain on patients and their families’ admissions to hospitals must be wisely utilized with clear purpose. This will also avoid waste of precious health care dollars.

Developing a clinical decision rule will be useful to emergency physicians and other physicians not only to identify patients who are at risk of serious outcomes occurring outside the hospital but also to quickly decide on the disposition of syncope patients and thereby decrease time spent in the emergency department. This will improve flow of patients in the emergency department and reduce emergency department overcrowding.
This will also help community family and emergency physicians to help identify patients who need admission or transfer to a tertiary care facility.

5.12 Conclusions

We found that the San Francisco Syncope Rule did not perform as well as previously reported in our syncope patients. Implementing the rule will greatly increase the admission rates that the health care system in Canada will not be able to cope. While attempting to refine the San Francisco Syncope Rule, our study has identified very important variables that predict short-term serious outcomes in adult syncope patients. Our study also shows that it is feasible to develop a clinical decision rule that will perform better than the San Francisco Syncope Rule. Epidemiological data from our study confirms that syncope is a common problem in the emergency department with a substantial proportion of these patients at risk for serious outcomes.

We also attempted and defined the characteristics of the variable ‘abnormal electrocardiogram’ which can be tested and refined in future prospective studies. Our study found that in some syncope patients the cause was evident only by cardiac monitoring and not from the electrocardiogram. Future study should also address which syncope patients need cardiac monitoring in the emergency department.

Data from our study shows that it is possible to clearly identify electrocardiogram characteristics that are associated with outcomes by future prospective studies.

The rule derived in the present study is a preliminary rule and has been derived retrospectively. Future prospective studies are needed for deriving and validating a new clinical decision rule before it can be used by emergency or non-emergency physicians. It is feasible to perform such prospective studies with adequate sample size.
Table 1
Baseline demographic and clinical characteristics of 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient visits N = 505 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age in years - Mean</td>
<td>58.5</td>
</tr>
<tr>
<td>- Range</td>
<td>16-101</td>
</tr>
<tr>
<td>Female</td>
<td>254 (50.3)</td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>354 (70.1)</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>490</td>
</tr>
<tr>
<td>Patients with - One initial visit</td>
<td>490 (97.0)</td>
</tr>
<tr>
<td>- Two initial visits</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>- Three initial visits</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Patients with return visits</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
</tr>
<tr>
<td>History of any prodrome** (N=503)</td>
<td>367 (73.0)</td>
</tr>
<tr>
<td>History of exertional syncope</td>
<td>28 (5.5)</td>
</tr>
<tr>
<td>History of palpitations</td>
<td>16 (3.2)</td>
</tr>
<tr>
<td>History of shortness of breath* (N=503)</td>
<td>54 (10.7)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>30 (5.9)</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>99 (19.6)</td>
</tr>
<tr>
<td>History of arrhythmia</td>
<td>58 (11.5)</td>
</tr>
<tr>
<td>History of valvular heart disease</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>History of cardiomyopathy</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>65 (12.9)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>174 (34.5)</td>
</tr>
<tr>
<td>History of cerebro vascular accident</td>
<td>29 (5.7)</td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>27 (5.4)</td>
</tr>
<tr>
<td>Past history of syncope** (N=362)</td>
<td>204 (56.4)</td>
</tr>
<tr>
<td>Number of previous episodes^</td>
<td></td>
</tr>
<tr>
<td>- One</td>
<td>86 (23.8)</td>
</tr>
<tr>
<td>- Two</td>
<td>29 (8.0)</td>
</tr>
<tr>
<td>- Three</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>- ≥ Four</td>
<td>43 (11.9)</td>
</tr>
</tbody>
</table>

* Data not available for 2 visits. **Data not available for 143 visits. ^Data not available for 35 visits

^ Nausea, vomiting, dizziness, any pain, hot, cold, cough, urination, visual disturbances, sweating, shortness of breath, palpitations, incontinence and neurological symptoms - tingling, numbness.
### Table 2
Medication profile of 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Medications* (&gt;1 medication in some)</th>
<th>N = 505 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On any medication</td>
<td>213 (42.2)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>114 (22.6)</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>Direct vasodilators</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Oral nitrates</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Nitroglycerine patch</td>
<td>15 (3.0)</td>
</tr>
<tr>
<td>Nitroglycerine spray</td>
<td>42 (8.3)</td>
</tr>
<tr>
<td>Use of nitroglycerine spray just prior to syncopal episode</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>95 (18.8)</td>
</tr>
<tr>
<td>Combined alpha and beta-blocker</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>65 (12.9)</td>
</tr>
</tbody>
</table>

* Name of medications not known in 11 cases

### Table 3
Physical Examination Findings of 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Examination Findings†</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triage Mean Heart Rate (N=497)</td>
<td>75.3</td>
<td>17.4</td>
<td>18-190</td>
</tr>
<tr>
<td>Triage Mean Respiratory Rate (N=392)</td>
<td>17.4</td>
<td>2.8</td>
<td>9-32</td>
</tr>
<tr>
<td>Triage Mean Systolic Blood Pressure (N=502)</td>
<td>126.6</td>
<td>23.7</td>
<td>66-208</td>
</tr>
<tr>
<td>Triage Mean Diastolic Blood Pressure (N=485)</td>
<td>72.3</td>
<td>13.2</td>
<td>38-115</td>
</tr>
<tr>
<td>Lowest Mean Systolic Blood Pressure (N=502)</td>
<td>117.7</td>
<td>22.3</td>
<td>47-208</td>
</tr>
<tr>
<td>Lowest Mean Diastolic Blood Pressure (N=502)</td>
<td>66.6</td>
<td>14.3</td>
<td>15-105</td>
</tr>
</tbody>
</table>
Table 4
Management of 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Management</th>
<th>N = 505 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Blood tests done</td>
<td>448 (88.7)</td>
</tr>
<tr>
<td>Electrocardiogram done</td>
<td>470 (93.1)</td>
</tr>
<tr>
<td>Electrocardiogram read by cardiologist</td>
<td>460 (91.1)</td>
</tr>
<tr>
<td>Carotid sinus massage done</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Computerized Tomography of head done</td>
<td>123 (24.4)</td>
</tr>
<tr>
<td>New and clinically important abnormalities</td>
<td>4 (0.8)</td>
</tr>
</tbody>
</table>

* The abnormality must be new and clinically important – defined as the abnormality detected is the cause of syncope or is a consequence of syncope itself or the fall associated with the syncope. All chronic findings are classified as non-significant.

Table 5
Disposition and Outcomes of 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Disposition/Outcomes</th>
<th>N = 505 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted</td>
<td>62 (12.3)</td>
</tr>
<tr>
<td>Associated with serious outcomes</td>
<td>49 (9.7)</td>
</tr>
<tr>
<td>Serious outcomes in the Emergency Department</td>
<td>22 (44.9)</td>
</tr>
<tr>
<td>Serious outcomes outside the Emergency Department</td>
<td>27 (55.1)</td>
</tr>
</tbody>
</table>
### Table 6
Final Diagnosis for the 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>N = 505 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope NYD</td>
<td>247 (48.9)</td>
</tr>
<tr>
<td>Vasovagal syncope</td>
<td>155 (30.7)</td>
</tr>
<tr>
<td>- Situational syncope</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Medication related syncope</td>
<td>18 (3.6)</td>
</tr>
<tr>
<td>- Nitroglycerine spray induced syncope</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Diarrhoea/Dehydration</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Serious outcomes in the Emergency Department *</td>
<td>22 (4.4)</td>
</tr>
<tr>
<td>Other causes*</td>
<td>44 (8.7)</td>
</tr>
</tbody>
</table>

\* For list of serious outcomes please refer to the next table, Table 7.

\* Other causes are list of conditions not primarily responsible for syncope but could have contributed to the symptom. Such conditions include angina, allergic reaction, bronchitis, pneumonia, congestive heart failure, febrile illness, hyponatremia, hypokalemia, hyperglycaemia, pregnancy, pseudo seizure, restless legs syndrome, urinary tract infection, vertigo, viral illness and weakness not yet diagnosed.
Table 7
Occurrence of Serious Outcomes in 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Serious Outcomes (Some had &gt; 1 outcome)</th>
<th>ALL N=49 (%)</th>
<th>IN ED N=22 (%)</th>
<th>OUTSIDE ED N=27 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 (10.2)</td>
<td>2 (4.1)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>Significant haemorrhage*</td>
<td>8 (16.3)</td>
<td>5 (10.2)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>4 (8.2)</td>
<td>1 (2.0)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Brain Tumor</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Hospitalization for related event</td>
<td>5 (10.2)</td>
<td>0 (0)</td>
<td>5 (10.2)</td>
</tr>
<tr>
<td>Cardiac Syncope</td>
<td>26 (53.1)</td>
<td>13 (26.5)</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>- Profound bradycardia</td>
<td>4 (8.2)</td>
<td>2 (4.1)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>- New/uncontrolled Afib</td>
<td>3 (6.1)</td>
<td>2 (4.1)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>- Sinus node dysfunction</td>
<td>9 (18.4)</td>
<td>6 (12.2)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>- Third degree AV block</td>
<td>6 (12.2)</td>
<td>5 (10.2)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>- Coronary angio/CABG</td>
<td>2 (4.1)</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>- Pacer insertion</td>
<td>18 (36.7)</td>
<td>8 (16.3)</td>
<td>10(20.4)</td>
</tr>
<tr>
<td>- Ventricular fibrillation</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Arrhythmia unspecified</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Procedural interventions done</td>
<td>29 (59.2)</td>
<td>17 (34.7)</td>
<td>12 (24.5)</td>
</tr>
<tr>
<td>- Pacer insertion</td>
<td>18 (36.7)</td>
<td>8 (16.3)</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>- GI scope alone</td>
<td>4 (8.2)</td>
<td>3 (6.1)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>- GI Endoscopic treatment</td>
<td>3 (6.1)</td>
<td>2 (4.1)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>- Chest tube insertion</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Cardioversion for Afib</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>- Dialysis for hyperkalemia</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Biopsy of brain tumor</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Thoracoscopic surgery</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

† All percentages reported as a proportion of total of 49 serious outcomes

* All patients with significant haemorrhage were due to upper gastrointestinal bleeding.

^ Afib = Atrial Fibrillation. AV = Atrioventricular. GI = Gastrointestinal

Ω Unspecified arrhythmia was found to be the cause of death in this patient by autopsy

€ Same outcomes listed both under cardiac syncope and procedural intervention.

* Epinephrine injection or laser treatment.
Table 8
Presence, absence or unavailability of the San Francisco Syncope Rule variables in the 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Positive (%)</th>
<th>Negative (%)</th>
<th>Not Available (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of CHF</td>
<td>30 (5.9)</td>
<td>475 (94.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematocrit &lt; 300</td>
<td>15 (2.8)</td>
<td>421 (83.4)</td>
<td>69 (13.7)</td>
</tr>
<tr>
<td>Abnormal Electrocardiogram^</td>
<td>283 (56.0)</td>
<td>187 (37.0)</td>
<td>35 (6.9)</td>
</tr>
<tr>
<td>History of Shortness of Breath</td>
<td>54 (10.7)</td>
<td>449 (88.9)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Triage SBP&lt;90 mm of Hg</td>
<td>25 (4.9)</td>
<td>480 (95.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

All variables available

Yes = 422 (83.6)  
No = 83 (16.4)

*Some patient visits had more than one variable present.

^ As defined in the San Francisco Syncope Rule Study: Any non-sinus rhythm or any new changes on the electrocardiogram

CHF = Congestive Heart Failure
SBP = Systolic Blood Pressure
Table 9
Comparison of patients with and without all the predictor variables for the San Francisco Syncope Rule in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>No [N=83] (%)</th>
<th>Yes [N=422] (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>38.3</td>
<td>62.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>52 (62.6)</td>
<td>202 (47.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>0 (0)</td>
<td>30 (7.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>2 (2.4)</td>
<td>97 (23.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of arrhythmia</td>
<td>3 (3.6)</td>
<td>55 (13.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>4 (4.8)</td>
<td>61 (14.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>7 (8.4)</td>
<td>167 (39.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>0 (0)</td>
<td>27 (6.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hematocrit &lt; 300</td>
<td>1 (1.3)</td>
<td>14 (3.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abnormal EKG*</td>
<td>25 (32.1)</td>
<td>258 (61.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of shortness of breath</td>
<td>8 (9.8)</td>
<td>46 (10.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>Triage SBP &lt;90 mm of Hg</td>
<td>5 (6.0)</td>
<td>20 (4.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>On any medication</td>
<td>10 (12.1)</td>
<td>192 (45.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>41 (49.4)</td>
<td>313 (74.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac murmur</td>
<td>2 (2.4)</td>
<td>46 (10.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rales on lung auscultation</td>
<td>1 (1.2)</td>
<td>36 (8.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Decreased air entry</td>
<td>0 (0)</td>
<td>22 (5.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Laboratory blood tests done</td>
<td>27 (32.5)</td>
<td>422 (100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-sinus rhythm in EKG</td>
<td>0 (0)</td>
<td>38 (9)</td>
<td>0.03</td>
</tr>
<tr>
<td>CT head abnormalities^</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admitted</td>
<td>0 (0)</td>
<td>62 (14.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasovagal Syncope</td>
<td>62 (74.7)</td>
<td>89 (21.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serious Outcomes</td>
<td>1 (1.2)</td>
<td>48 (11.4)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* As defined in the San Francisco Syncope Rule Study: non-sinus rhythm or any new changes on the electrocardiogram

^ Abnormality must be both new and clinically important: Defines as the abnormality detected is the cause of syncope or is a consequence of syncope itself or the fall associated with the syncope. All chronic findings are classified as non-significant.

EKG = Electrocardiogram
SBP = Systolic Blood Pressure
CT = Computerized Tomography
Table 10
Inter-observer agreement of inclusion into the study, presence of variables congestive heart failure, shortness of breath and abnormal electrocardiogram in the 52 patient visits selected for review in the 18-month retrospective study

<table>
<thead>
<tr>
<th></th>
<th>Kappa</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion into the study</td>
<td>0.98</td>
<td>0.88, 0.99</td>
</tr>
<tr>
<td>History of CHF</td>
<td>0.85</td>
<td>0.57, 1.00</td>
</tr>
<tr>
<td>History of Shortness of Breath</td>
<td>0.90</td>
<td>0.70, 1.00</td>
</tr>
<tr>
<td>Abnormal Electrocardiogram^</td>
<td>0.84</td>
<td>0.70, 0.97</td>
</tr>
</tbody>
</table>

^ As defined in the San Francisco Syncope Rule Study: Any non-sinus rhythm or any new changes on the electrocardiogram

CHF = Congestive Heart Failure
Table 11
Univariate Correlation of Demographic and Historical variables with Serious Outcomes in 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>No [N=456] (%)</th>
<th>Yes [N=49] (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>56.8 (23)</td>
<td>74.5 (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>50.9</td>
<td>44.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>312 (68.4)</td>
<td>42 (85.7)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Historical Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prodrome ^a (N=455, 48)</td>
<td>123 (27.0)</td>
<td>13 (27.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>History of exertional syncope</td>
<td>26 (5.7)</td>
<td>2 (4.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>History of palpitations</td>
<td>14 (3.1)</td>
<td>2 (4.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>History of shortness of breath ^b (N=454, 49)</td>
<td>42 (9.3)</td>
<td>12 (24.5)</td>
<td>0.0044</td>
</tr>
<tr>
<td>History of paroxysmal nocturnal dyspnea</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>0.74</td>
</tr>
<tr>
<td>History of orthopnea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of previous syncope ^* (N=322, 40)</td>
<td>182 (56.5)</td>
<td>22 (55)</td>
<td>1.00</td>
</tr>
<tr>
<td>Presently on any medications</td>
<td>180 (39.5)</td>
<td>33 (67.4)</td>
<td>0.0008</td>
</tr>
<tr>
<td>History of Congestive Heart Failure</td>
<td>22 (4.8)</td>
<td>8 (16.3)</td>
<td>0.0012</td>
</tr>
<tr>
<td>History of Coronary Artery Disease</td>
<td>82 (18.0)</td>
<td>17 (34.7)</td>
<td>0.0051</td>
</tr>
<tr>
<td>History of Arrhythmia</td>
<td>45 (9.8)</td>
<td>13 (26.5)</td>
<td>0.0005</td>
</tr>
<tr>
<td>History of Valvular Heart Disease</td>
<td>12 (2.6)</td>
<td>2 (4.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>History of Cardiomyopathy</td>
<td>5 (1.1)</td>
<td>0 (0)</td>
<td>0.46</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>54 (11.8)</td>
<td>11 (22.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>150 (32.9)</td>
<td>24 (48.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of Cerebro Vascular Accident</td>
<td>24 (5.3)</td>
<td>5 (10.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>History of Transient Ischemic Attack</td>
<td>24 (5.3)</td>
<td>3 (6.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>History of Peripheral Arterial Disease</td>
<td>2 (0.4)</td>
<td>2 (4.1)</td>
<td>0.0063</td>
</tr>
</tbody>
</table>

^a Data not available for 2 cases. ^b Data available for only 362 visits.
^ Nausea, vomiting, dizziness, any pain, hot, cold, cough, urination, visual disturbances, sweating, shortness of breath, palpitations, incontinence and neurological symptoms - tingling, numbness
Table 12
Univariate Correlation between Emergency Medical Services Physical Findings, Intervention variables and Serious Outcomes in 354 patient visits with syncope who arrived by ambulance to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serious Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No [N=312] (SD)</td>
</tr>
<tr>
<td><strong>Physical Examination Findings [mm of Hg]</strong></td>
<td></td>
</tr>
<tr>
<td>Mean first Systolic Blood Pressure (N=325)</td>
<td>118.8 (26.8)</td>
</tr>
<tr>
<td>Mean first Diastolic Blood Pressure (N=283)</td>
<td>69.8 (13.8)</td>
</tr>
<tr>
<td>Mean last Systolic Blood Pressure (N=324)</td>
<td>121.5 (20.0)</td>
</tr>
<tr>
<td>Mean last Diastolic Blood Pressure (N=300)</td>
<td>72.1 (11.2)</td>
</tr>
<tr>
<td>Mean lowest Systolic Blood Pressure (N=325)</td>
<td>111.7 (23.4)</td>
</tr>
<tr>
<td>Mean lowest Diastolic Blood Pressure (N=293)</td>
<td>67.9 (13.0)</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Glucometer Reading</td>
<td>7.4 (2.4)</td>
</tr>
<tr>
<td>Securing Intravenous access (%)</td>
<td>132 (45.67)</td>
</tr>
<tr>
<td>Infusion of any fluids (%)</td>
<td>44 (15.2)</td>
</tr>
</tbody>
</table>
Table 13
Univariate Correlation between Emergency Medical Services Electrocardiogram strip variables and Serious Outcomes in 223 patient visits with ambulance rhythm strips in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>No</th>
<th>Yes</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency Medical Services Electrocardiogram Strip (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Heart Rate (SD)</td>
<td>73.3 (16.3)</td>
<td>72.6 (25.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Non-sinus rhythm</td>
<td>12 (6.0)</td>
<td>3 (12.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>- Atrial Flutter</td>
<td>0 (0)</td>
<td>1 (4.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>- Atrial Fibrillation</td>
<td>10 (5.1)</td>
<td>2 (8.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Atrioventricular Block</td>
<td>14 (7.1)</td>
<td>2 (8.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Premature Atrial Contractions</td>
<td>5 (2.5)</td>
<td>0 (0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Premature Ventricular Contractions</td>
<td>9 (4.6)</td>
<td>1 (4.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>Intraventricular conduction defect</td>
<td>5 (2.5)</td>
<td>1 (4.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Right Bundle Branch Block</td>
<td>12 (6.0)</td>
<td>3 (12.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Left Bundle Branch Block</td>
<td>2 (1.0)</td>
<td>4 (16.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left Anterior Fascicular Block</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Left Posterior Fascicular Block</td>
<td>1 (0.5)</td>
<td>2 (8.0)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>4 (2.0)</td>
<td>0 (0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Right Ventricular Hypertrophy</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Left Axis Deviation</td>
<td>4 (2.0)</td>
<td>0 (0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Old Myocardial Infarction</td>
<td>5 (2.5)</td>
<td>0 (0)</td>
<td>0.42</td>
</tr>
<tr>
<td>ST-T changes consistent with ischemia</td>
<td>10 (5.1)</td>
<td>4 (16.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-specific ST-T wave changes</td>
<td>25 (12.6)</td>
<td>6 (24.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-specific repolarisation changes</td>
<td>2 (1.0)</td>
<td>0 (0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Secondary ST-T wave changes</td>
<td>2 (1.0)</td>
<td>2 (8.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Any cardiac monitor abnormalities</td>
<td>80 (36.0)</td>
<td>16 (55.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
### Table 14
Univariate Correlation of Emergency Department Physical Examination variables and Serious Outcomes in 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serious Outcomes</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No [N=456]</td>
<td>Yes [N=49]</td>
<td>p value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triage Vital Signs (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Heart Rate (N=450, 47)</td>
<td>74.9 (15.7)</td>
<td>79.7 (28.8)</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Respiratory Rate (N=357, 35)</td>
<td>17.3 (2.6)</td>
<td>18.1 (3.9)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Oxygen Saturation (N=384, 42)</td>
<td>98.2 (2.0)</td>
<td>96.1 (4.3)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Systolic Blood Pressure (N=453, 49)</td>
<td>127.3 (23.0)</td>
<td>120.0 (28.9)</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Diastolic Blood Pressure (N=437, 48)</td>
<td>72.8 (12.7)</td>
<td>67.5 (16.8)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic Vital Signs (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine mean Systolic Pressure (N=55, 2)</td>
<td>122.0 (19.6)</td>
<td>118.0 (12.7)</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine mean Diastolic Pressure (N=55, 2)</td>
<td>68.8 (13.2)</td>
<td>76.0 (9.9)</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting mean Systolic Pressure (N=40, 2)</td>
<td>122.9 (19.0)</td>
<td>157.5 (47.4)</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting mean Diastolic Pressure (N=40, 2)</td>
<td>67.6 (10.4)</td>
<td>100.0 (5.7)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing mean Systolic Pressure (N=58, 2)</td>
<td>121.3 (18.6)</td>
<td>121.5 (58.7)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing mean Diastolic Pressure (N=57, 2)</td>
<td>72.5 (13.4)</td>
<td>72.5 (30.0)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs prior to discharge (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last mean Heart Rate (N=399, 46)</td>
<td>74.5 (14.6)</td>
<td>76.4 (16.4)</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last mean Respiratory Rate (N=361, 41)</td>
<td>17.1 (2.4)</td>
<td>18.6 (4.4)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last mean Oxygen Saturation (N=347, 41)</td>
<td>98.0 (1.9)</td>
<td>97.3 (2.4)</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last mean Systolic Pressure (N=414, 46)</td>
<td>130.8 (21.8)</td>
<td>123.8 (24.9)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last mean Diastolic Pressure (N=412, 46)</td>
<td>69.8 (12.2)</td>
<td>63.0 (15.5)</td>
<td>0.0006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Emergency Department Blood Pressures (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest mean Systolic Pressure (N=453, 49)</td>
<td>119.3 (20.9)</td>
<td>103 (28.9)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest mean Diastolic Pressure (N=447, 48)</td>
<td>67.3 (13.9)</td>
<td>60.2 (16.0)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination Findings (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any murmur</td>
<td>41 (9.0)</td>
<td>7 (14.3)</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales/Crackles</td>
<td>26 (5.7)</td>
<td>11 (22.5)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze/Rhonchi</td>
<td>10 (2.2)</td>
<td>3 (6.1)</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Air Entry</td>
<td>14 (3.1)</td>
<td>8 (16.3)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 15
Univariate Correlation of Emergency Department Blood Test variables and Serious Outcomes in 436 emergency department syncope visits with laboratory investigations in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serious Outcomes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (SD)</td>
<td>Yes (SD)</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Blood tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (N=387, 49)</td>
<td>136.8 (16.6)</td>
<td>123.4 (27.9)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (N=387, 49)</td>
<td>0.40 (0.05)</td>
<td>0.37 (0.08)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Sodium (N=380, 49)</td>
<td>137.8 (4.0)</td>
<td>137.0 (3.6)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Potassium (N=371, 48)</td>
<td>3.9 (0.5)</td>
<td>4.1 (0.5)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Chloride (N=379, 49)</td>
<td>101.7 (8.2)</td>
<td>101.5 (4.9)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Glucose (N=372, 46)</td>
<td>6.8 (2.4)</td>
<td>7.9 (3.2)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Blood Urea Nitrogen (N=376, 49)</td>
<td>6.2 (3.7)</td>
<td>13.1 (9.7)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Creatinine (N=375, 49)</td>
<td>96.0 (38.6)</td>
<td>136.7 (97.7)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Creatine Kinase (N=246, 35)</td>
<td>125.4 (153.0)</td>
<td>120.7 (121.5)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Troponin (N=157, 24)</td>
<td>0.02 (0.02)</td>
<td>0.04 (0.05)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Calcium (N=54, 11)</td>
<td>2.3 (0.1)</td>
<td>2.2 (0.1)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Magnesium (N=48, 10)</td>
<td>0.88 (0.09)</td>
<td>0.86 (0.12)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Glucometer Reading (N=25, 3)</td>
<td>8.2 (3.6)</td>
<td>7.0 (1.8)</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>
Table 16: Univariate Correlation of Emergency Department Electrocardiogram variables and Serious Outcomes in 470 emergency department syncope visits with electrocardiogram in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serious Outcomes No [N=422] (%)</th>
<th>Serious Outcomes Yes [N=48] (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Heart Rate (SD)</td>
<td>69.4 (14.5)</td>
<td>75.4 (27.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-sinus rhythm</td>
<td>28 (6.6)</td>
<td>10 (20.8)</td>
<td>0.0017</td>
</tr>
<tr>
<td>- Supraventricular Tachycardia</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>- Atrial Flutter</td>
<td>1 (0.2)</td>
<td>1 (2.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>- Atrial Fibrillation</td>
<td>19 (4.5)</td>
<td>6 (12.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>- Junctional rhythm</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>- Idioventricular rhythm</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>- Ectopic / Paced rhythm</td>
<td>8 (1.9)</td>
<td>0 (0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Atrioventricular Block</td>
<td>29 (6.9)</td>
<td>8 (16.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Premature Atrial Contraction (PAC)</td>
<td>22 (5.2)</td>
<td>5 (10.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>- Number of PACs (SD)</td>
<td>1.2 (0.9)</td>
<td>1 (0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Premature Ventricular Contraction (PVC)</td>
<td>18 (4.3)</td>
<td>4 (8.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>- Number of PVCs (SD)</td>
<td>1.2 (0.6)</td>
<td>2.3 (1.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>Intraventricular conduction defect</td>
<td>6 (1.4)</td>
<td>1 (2.1)</td>
<td>0.72</td>
</tr>
<tr>
<td>Right Bundle Branch Block</td>
<td>26 (6.2)</td>
<td>12 (25.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left Bundle Branch Block</td>
<td>9 (2.1)</td>
<td>9 (18.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left Anterior Fascicular Block</td>
<td>10 (2.4)</td>
<td>3 (6.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Left Posterior Fascicular Block</td>
<td>0 (0)</td>
<td>2 (4.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>47 (11.1)</td>
<td>7 (14.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>Right Ventricular Hypertrophy</td>
<td>5 (1.2)</td>
<td>1 (2.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Left Axis Deviation</td>
<td>35 (8.3)</td>
<td>6 (12.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Right Axis Deviation</td>
<td>9 (2.1)</td>
<td>2 (4.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>Old Myocardial Infarction</td>
<td>36 (8.5)</td>
<td>4 (8.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>ST-T changes consistent with ischemia</td>
<td>34 (8.1)</td>
<td>9 (18.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-specific ST-T wave changes</td>
<td>45 (10.7)</td>
<td>7 (14.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Non-specific repolarisation changes</td>
<td>6 (1.4)</td>
<td>0 (0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Secondary ST-T wave changes</td>
<td>8 (1.9)</td>
<td>4 (8.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Corrected QT interval (SD)</td>
<td>432.9 (33.4)</td>
<td>456.3 (48.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiac monitor abnormalities</td>
<td>40 (9.4)</td>
<td>19 (39.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bifascicular block^</td>
<td>4 (0.9)</td>
<td>5 (10.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any bundle branch block + I^ block</td>
<td>3 (0.7)</td>
<td>4 (8.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Significant atrioventricular block^</td>
<td>0 (0)</td>
<td>3 (6.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

^Defined as presence of right bundle branch block and either left anterior fascicular or left posterior fascicular block. I^ block = First degree atrioventricular block. § Defined as presence of second or third degree atrioventricular block
Table 17
Univariate Correlation of San Francisco Syncope Rule variables and Serious Outcomes in 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serious Outcomes (%)</th>
<th></th>
<th></th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No [N=456]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Congestive Heart Failure</td>
<td>22 (4.8)</td>
<td></td>
<td></td>
<td>0.0012</td>
</tr>
<tr>
<td>Hematocrit &lt; 0.300 (N=388, 49)</td>
<td>7 (1.8)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abnormal electrocardiogram</td>
<td>245 (58.1)</td>
<td></td>
<td></td>
<td>0.0003</td>
</tr>
<tr>
<td>Triage Systolic Blood pressure &lt; 90</td>
<td>16 (3.5)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of shortness of breath* (N=454, 49)</td>
<td>42 (9.3)</td>
<td></td>
<td></td>
<td>0.0044</td>
</tr>
</tbody>
</table>
Table 18: Odds Ratios of the clinical variables in the final four logistic regression models to predict serious outcomes derived from 505 patient visits with syncope to the Emergency Department in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variables in Model</th>
<th>Co-efficient (95%CI)</th>
<th>Odds Ratio (95%CI)</th>
<th>C statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td>0.871</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.298</td>
<td>2.1 (1.0, 4.2)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>0.36</td>
<td>3.7 (1.6, 8.6)</td>
<td></td>
</tr>
<tr>
<td>History of Shortness of breath</td>
<td>0.65</td>
<td>4.3 (1.8, 10.3)</td>
<td></td>
</tr>
<tr>
<td>Lowest ED SBP&lt;90</td>
<td>0.72</td>
<td>5.2 (2.5, 10.6)</td>
<td></td>
</tr>
<tr>
<td>Abnormal Electrocardiogram9*</td>
<td>0.82</td>
<td>8.1 (3.0, 22.3)</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;15</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td>0.871</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.379</td>
<td>2.1 (1.0, 4.6)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 70</td>
<td>0.39</td>
<td>3.5 (1.5, 8.2)</td>
<td></td>
</tr>
<tr>
<td>History of Shortness of breath</td>
<td>0.63</td>
<td>4.6 (1.9, 11.0)</td>
<td></td>
</tr>
<tr>
<td>Lowest ED SBP&lt;90</td>
<td>0.76</td>
<td>4.9 (2.4, 10.0)</td>
<td></td>
</tr>
<tr>
<td>Abnormal Electrocardiogram9*</td>
<td>1.03</td>
<td>7.9 (2.8, 21.3)</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;15</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td>0.876</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.613</td>
<td>3.2 (1.4, 7.7)</td>
<td></td>
</tr>
<tr>
<td>History of Shortness of breath</td>
<td>0.59</td>
<td>4.5 (1.8, 11.0)</td>
<td></td>
</tr>
<tr>
<td>Lowest ED SBP&lt;90</td>
<td>0.75</td>
<td>10.5 (4.8, 23.1)</td>
<td></td>
</tr>
<tr>
<td>Abnormal Electrocardiogram7^</td>
<td>1.18</td>
<td>7.2 (2.6, 20.0)</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;15</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td></td>
<td></td>
<td>0.850</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.329</td>
<td>3.2 (1.4, 7.6)</td>
<td></td>
</tr>
<tr>
<td>History of Shortness of breath</td>
<td>0.58</td>
<td>15.1 (4.4, 51.2)</td>
<td></td>
</tr>
<tr>
<td>Lowest ED SBP&lt;80</td>
<td>1.36</td>
<td>6.2 (3.0, 12.7)</td>
<td></td>
</tr>
<tr>
<td>Abnormal Electrocardiogram9*</td>
<td>0.91</td>
<td>9.2 (3.2, 26.4)</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;15</td>
<td>1.11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abnormal Electrocardiogram9 is defined as presence of any of the following: non-sinus rhythm, significant atrioventricular block, bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities.

^ Abnormal Electrocardiogram7 is non-sinus rhythm or significant atrioventricular block or right bundle branch block with first degree atrioventricular block or left bundle branch block or any left fascicular block or secondary ST-T changes.

ED SBP = Emergency Department Systolic Blood Pressure.

¶Final model selected
Table 19
Sensitivity, Specificity and Homer-Lemeshow Goodness of Fit of the final four logistic regression models to predict serious outcomes derived from the 18-month retrospective study

<table>
<thead>
<tr>
<th>Model (Variables included)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Goodness of Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1* (Age ≥75, history of shortness of breath, lowest ED SBP &lt; 90, abnormal EKG9°, BUN &gt; 15)</td>
<td>96%</td>
<td>52%</td>
<td>0.385</td>
</tr>
<tr>
<td>Model 2** (Age ≥70, History of shortness of breath, lowest ED SBP &lt; 90, abnormal EKG9°, BUN &gt; 15)</td>
<td>98%</td>
<td>48%</td>
<td>0.281</td>
</tr>
<tr>
<td>Model 3*** (History of shortness of breath, lowest ED SBP &lt; 90, abnormal EKG7^, BUN &gt; 15)</td>
<td>92%</td>
<td>66%</td>
<td>0.902</td>
</tr>
<tr>
<td>Model 4**** (History of shortness of breath, lowest ED SBP &lt; 80, abnormal EKG9£, BUN &gt; 15)</td>
<td>84%</td>
<td>73%</td>
<td>0.497</td>
</tr>
</tbody>
</table>

Sensitivities and specificities are calculated by applying the models to the dataset. ED SBP = Emergency Department Systolic Blood Pressure. BUN = Blood Urea Nitrogen. EKG = Electrocardiogram.

* Final model selected

** Variables offered to model 2: Same variables offered to model 1 except age changed from ≥75 to ≥70.

*** Variables offered to model 3: Same variables offered to model 1 except specification of abnormal electrocardiogram changed from 9 to 7 (see below for description).

**** Variables offered to model 4: Same variables offered to model 1 except lowest emergency department systolic blood pressure changed from <90 to <80mm of Hg.

£ Abnormal Electrocardiogram is defined as presence of any of the following: non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm), significant atrioventricular block (second and third degree), bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities.

^ Abnormal Electrocardiogram is non-sinus rhythm or significant atrioventricular block (both as detailed above) or right bundle branch block with first degree atrioventricular block or left bundle branch block or any left fascicular block or secondary ST-T changes.
Table 20
Models derived to predict serious outcomes by recursive partitioning with their sensitivity and specificity in the 18-month retrospective study

<table>
<thead>
<tr>
<th>Variables in the model/rule</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule 1 ( Age ≥65, lowest ED SBP &lt; 80, abnormal EKG7)</td>
<td>100% (93, 100)</td>
<td>52% (51, 52)</td>
</tr>
<tr>
<td>Rule 2† ( Age ≥65, lowest ED SBP &lt; 80, abnormal EKG9)</td>
<td>100% (93, 100)</td>
<td>53% (52, 53)</td>
</tr>
</tbody>
</table>

Sensitivities and specificities are calculated by applying the models to the dataset. ED SBP = Emergency Department Systolic Blood Pressure. BUN = Blood Urea Nitrogen. EKG = Electrocardiogram.

†Final model selected


‡Abnormal Electrocardiogram9 is defined as presence of any of the following: non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm), significant atrioventricular block (second and third degree), bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities.

^ Abnormal Electrocardiogram7 is non-sinus rhythm or significant atrioventricular block (both as detailed above) or right bundle branch block with first degree atrioventricular block or left bundle branch block or any left fascicular block or secondary ST-T changes.
Figure 1
Criteria for the different classes of evidence and the levels of recommendation in the guideline published by the American College of Emergency Physicians' (12)

CLASSES OF EVIDENCE

CLASS I: Studies were given this high grade if they were intervention studies, prospective cohort studies (even if observational) and if they were meta-analysis of only randomized clinical trials.

CLASS II: Retrospective cohort studies, case-controlled studies and meta-analysis involving non-randomized trials were given this grade.

CLASS III: Cross-sectional studies that were descriptive, case series, case reports and publications of consensus panels were given this grade.

LEVELS OF RECOMMENDATION

LEVEL A: If the studies answered the question of need for admission of syncope patients with high degree of certainty on the basis of class I studies or overwhelming class II studies then level A recommendation was given.

LEVEL B: If there was moderate degree of certainty based on class II studies or overwhelming class III studies then level B recommendation was given.

LEVEL C: If the studies were at a preliminary stage or were inconclusive or were conflicting or if there was no evidence available and the recommendation was based on consensus of the panel developing the guideline then a recommendation of class C was given.
Figure 2
American College of Emergency Physicians’ recommendations for admission of emergency department syncope patients (12)

**Level B recommendations**
Admit if any of the following present:

1. If there is a ‘history of congestive heart failure’ or ‘history of ventricular arrhythmias’
2. If the signs and symptoms are indicative of an acute coronary syndrome diagnosis.
3. If there is ‘significant congestive heart failure’ or ‘significant valvular heart disease’ on examination of the patient.
4. If there are electrocardiogram findings consistent with ischemia, arrhythmia, prolonged QT interval or bundle branch block.

**Level C recommendations**
Consider admission if any of the following present:

1. If the patient is older than 60 years.
2. If there is a ‘history of coronary artery disease’ or a ‘history of congenital heart disease’ in the patient.
3. If there is a ‘family history of unexpected sudden death’.
4. If a young patient sustained an exertional syncope with no clear cause.
Figure 3
Flow of study patients in the 18-month retrospective validation of the San Francisco Syncope Rule study

Total visits screened (N=936)

- Not from Ottawa = 168
- Not syncope = 181
- Paediatric patients (Age < 16) = 2

Visits that met inclusion criteria (N=585)

- Prolonged Loss of Consciousness / prolonged confusion after the event = 13
- Alcohol or drug related = 14
- Head trauma leading to syncope = 4
- Significant trauma leading to hospitalization = 3

Eligible patient visits (N=530)

- Left before seen by physician = 13
- Record of treatment not available = 12

Patient visits included (N=505)
Figure 4
Classification performance of the San Francisco Syncope Rule for all serious outcomes in the 18-month retrospective validation study

<table>
<thead>
<tr>
<th>SFSR Rule</th>
<th>Serious Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>43</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
</tr>
</tbody>
</table>

Sensitivity = 90% (95% CI 78, 95)
Specificity = 40% (95% CI 39, 41)

Percentage of patients in this cohort that would have been admitted if the San Francisco Rule were used 63%

Figure 5
Classification performance of the San Francisco Syncope Rule for serious outcomes occurring outside the Emergency Department in the 18-month retrospective validation study

<table>
<thead>
<tr>
<th>SFSR Rule</th>
<th>Serious Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>26</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
</tbody>
</table>

Sensitivity = 96% (95% CI 82, 99)
Specificity = 40% (95% CI 39, 40)

Percentage of patients in this cohort that would have been admitted if the San Francisco Rule were used 62%
Figure 6
Receiver Operating Characteristic curve for the final logistic regression model developed for predicting serious outcomes in adult syncope patients in the 18-month retrospective study.

ROC Curve

Area under curve=0.871
Figure 7
Receiver Operating Characteristic curve for the San Francisco Syncope Rule for predicting serious outcomes in adult syncope patients in the 18-month retrospective study

ROC Curve for San Francisco Syncope Rule Performance

Area under curve = 0.703
Figure 8
Decision tree in the derivation of the new preliminary clinical decision rule with abnormal electrocardiogram*, lowest emergency department systolic blood pressure < 80mm of Hg and age ≥ 65.

* Abnormal EKG9 = Abnormal Electrocardiogram9 is defined as presence of any of the following: non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm), significant atrioventricular block (second and third degree), bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities.

ED SBP = Emergency Department Systolic Blood Pressure
Adult patients presenting with syncope to the emergency department are at risk of serious outcomes in the next 30 days if they have any one of the following:

Age ≥ 65 years
Lowest emergency department systolic blood pressure < 80 mm of Hg
Abnormal electrocardiogram*

*Abnormal Electrocardiogram is defined as presence of any of the following: non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm), significant atrioventricular block (second and third degree), bifascicular block, first degree atrioventricular block in the presence of left or right bundle branch block and cardiac monitor abnormalities
Figure 10
Classification performance of the preliminary rule developed by recursive partitioning to predict all serious outcomes in adult syncope patients

<table>
<thead>
<tr>
<th>Preliminary Rule</th>
<th>Serious Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>49</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
</tbody>
</table>

Sensitivity = 100% (95% CI 93, 100)
Specificity = 53% (95% CI 52, 53)

Percentage of patients in this cohort that would have been admitted if the New Rule were used: 52%

Figure 11
Classification performance of the preliminary rule developed by recursive partitioning to predict serious outcomes outside the Emergency Department in adult syncope patients

<table>
<thead>
<tr>
<th>Preliminary Rule</th>
<th>Serious Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>27</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
</tbody>
</table>

Sensitivity = 100% (95% CI 87, 100)
Specificity = 53% (95% CI 52, 53)

Percentage of patients in this cohort that would have been admitted if the New Rule were used: 50%
Figure 12
Time of occurrence of outcomes outside the Emergency Department in the 18-month retrospective validation of the San Francisco Syncope Rule study
Figure 13
Methodological Standards for Medical Records Review

Three separate studies identified 14 different criteria as the methodological standard for retrospective studies. In 1996, Gilbert et al proposed 8 criteria that must be mentioned in a emergency medicine research study involving chart review. They are listed below:

1. Clear hypothesis/aim – There must be a clear hypothesis/aim before the start of the study.
2. Abstractor training – Abstractors must be trained before they start data abstraction.
3. Case selection – Inclusion and exclusion criteria must have been clarified before beginning the study.
4. Definition of the variables – All the variables that will be used in the study must have been clearly defined before commencing the study.
5. Standard Abstraction form – The study should have used a standard abstraction form to ensure conflicting, ambiguous, missing or unknown data are handled the same way.
6. Meetings – Abstractors and study co-ordinators must have met periodically to resolve disputes and review coding rules.
8. Blinding – Abstractors must be blinded to the hypothesis and/or outcomes.
9. Inter-rate agreement – Studies should perform and report correlation coefficient for variables with high probability of abstraction errors.

In 2005, Worster et al and Badcock et al proposed an additional 6 criteria (4 and 2 respectively):

10. Case identification – The study explain the method of identification of potential cases from the database or medical records.
11. Sampling method – Was there any sampling method used for inclusion in the study?
12. Management of missing data – The analysis must explain how missing data were dealt with.
13. Ethics Approval – Ethics approval must have been obtained before the study was conducted.
14. Sample Size – Appropriate sample size calculation must have been done before the start of the study.
15. Funding disclosure – Funding source must be disclosed when presented or published.
8. REFERENCES


90. Wells GA. Sample size calculation for clinical decision rule.


Appendix 1: Data abstraction form – Initial visit

RETROSPECTIVE VALIDATION OF THE SFSR – Initial visit

Subject # _________ Data Abstracted by PI ______ RA_______ Date entry ______

DEMOGRAPHICS:
Patient initials _______ Date of visit (dd/mm/yy) _____________
Date of birth (dd/mm/yy) ____________
Sex O M O F
Type of visit: O Initial O 1 O 2 O 3 O 4 O 5
O Return. (If return visit, must be within 30 days of initial visit)– use return visit form.
Hospital: O TOHC O TOHG Chart # ____________
• Pt. from Ottawa O Y O N If no, excluded ---------------------------EXCLUSION

INITIAL PRESENTATION:
• Definition of syncope fulfilled O Y O N O Unknown
The patient will be included if ‘yes’ only, if not, patient excluded----------------EXCLUSION

• Exclusion criteria: Prolonged altered LOC (usually < 5min) O Y O N
Alcohol/illicit drug related (Substances caused syncope) O Y O N
Syncope due to head trauma (First injury occurred then syncope) O Y O N
Significant trauma (Admission to Ortho/trauma/surgery) O Y O N
If yes for any of the above four then EXCLUDED ---------------------------EXCLUSION
No exclusions by above three criteria -------------------------------INCLUDED

SFSR:
History of Congestive Heart Failure O Y O N O NA
Hematocrit < 0.300 O Y O N O NA
Abnormal EKG* O Y O N O NA
Pt. complaint of Shortness of Breath O Y O N O NA
Triage Systolic Blood Pressure< 90 O Y O N O NA
*Any non-sinus and any new changes
All variables available O Y O N NA = Not Available

HISTORY:
Prodrome: O Nausea O Vomiting O Dizziness O Chest pain O Abd. pain O Sweating
O Others (Specify) ___________________ O NA
Past episodes O Y O N O No info. If yes, # of previous episodes _______ O Several O NA
Exertional syncope O Y O N O NA
Palpitations O Y O N O NA
Paroxysmal Nocturnal Dyspnea (PND) O Y O N O NA
Orthopnea O Y O N O NA
Coronary Artery Disease (CAD)  O Y  O N  O NA
Arrhythmia  O Y  O N  O NA
Cardiomyopathy  O Y  O N  O NA
Valvular Heart Disease  O Y  O N  O NA
Diabetes  O Y  O N  O NA
Hypertension (HTN)  O Y  O N  O NA
Cerebrovascular accident (CVA)  O Y  O N  O NA
Transient Ischemic Attack (TIA)  O Y  O N  O NA
Peripheral Arterial Disease (PAD)  O Y  O N  O NA
Other  

MEDICATIONS:  Unknown O

Diuretics  O Y  O N  If yes, specify code
Anti-arrhythmics  O Y  O N  If yes, specify code
Digoxin  O Y  O N
Direct vasodilators  O Y  O N  If yes, specify code
Nitrates PO  O Y  O N  If yes, specify code
Nitropatch  O Y  O N
Nitroglycerine sublingual  O Y  O N  Did the pt. have it just prior to syncope? O Y O N
Alpha-blockers  O Y  O N  If yes, specify code
Beta-blockers  O Y  O N  If yes, specify code
Combined alpha & beta blockers  O Y  O N  If yes, specify code
Calcium Channel Blockers  O Y  O N  If yes, specify code

EXAMINATION:

<table>
<thead>
<tr>
<th></th>
<th>Triage</th>
<th>Last ED value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Rate</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>O2 sat</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Room air</td>
<td>O</td>
<td>Room air</td>
</tr>
<tr>
<td>Home O2 at ___L/min</td>
<td></td>
<td>Home O2 at ___L/min</td>
</tr>
<tr>
<td>O2 at ___L/min</td>
<td>O No info</td>
<td>O2 at ___L/min</td>
</tr>
<tr>
<td>NRB</td>
<td>O</td>
<td>NRB</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>______</td>
<td>______</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>PreEMS/Home</th>
<th>1 EMS value</th>
<th>Last EMS value</th>
<th>Triage</th>
<th>Supine</th>
<th>Sitting</th>
<th>Standing</th>
<th>Last ED value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
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<tr>
<td>DBP</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Worst EMS value</th>
<th>Worst ED value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>DBP</td>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

ARRIVAL BY AMBULANCE  O Y  O N
EMS SHEET AVAILABLE  O Y  O N

ANY INTERVENTIONS BY EMS:
IV Start  O Y  O N
Fluids  O Y  O N  Type_____  Amount_____
Medications:  O Y  O N
Epinephrine  O  Concentration 1:1000  O  1:10,000  O  Amount_____  IV  O  IM  O  SC  O
Atropine  O  Amount_____  IV  O  IM  O  SC  O
Others:  Type_______  Amount/Route____________

EMS RHYTHM STRIP  O NOT DONE  O NO INFO  O NORMAL  O ABNORMAL
Rhythm:  O Sinus  O Non-sinus  O Sinus arrhythmia  Rate  ___.___
If non-sinus, specify:  O SVT  O MAT  O Aflutter  O Afib  O VT  O Vfib
  O Junctional  O Idioventricular rhythm  O Others______________
AV block  O Y  O N  If yes; check one  O I  O II 1  O II 2  O III
PACs  O Y  O N  If yes; number per sec____
PVCs  O Y  O N  If yes; number per sec____
Intraventricular conduction defect  O Y  O N
RBBB  O Y  O N
LBBB  O Y  O N
LAFB  O Y  O N
LPFB  O Y  O N
LVH  O Y  O N
RVH  O Y  O N
LAD  O Y  O N
RAD  O Y  O N
Old MI  O Y  O N
ST-T wave changes consistent with ischemia  O Y  O N
Non-specific ST-T wave changes  O Y  O N
Non-specific repolarization abnormalities  O Y  O N
Secondary ST-T wave changes  O Y  O N
Others__________________
Any abnormality in EMS monitor  O Y  O N  O No Info  Specify______________

Any murmur  O Y  O N  O NA
Rales/crackles  O Y  O N  O NA
Wheeze/rhonchi  O Y  O N  O NA
Decreased air entry  O Y  O N  O NA

INVESTIGATION:  O NOT DONE
Hb  _______  Glucose  _______.  Ca  _______.
Hct  _______  BUN  _______.  Ion. Ca  _______.
Na _______.  Creatinine _______.  Mg _______.
K _______.  CK _______.  Glucometer EMS _______.
Cl _______.  Troponin _______.  Glucometer ED _______.

EKG:  O NOT DONE
Cardiologist opinion  O Y  O N  O NORMAL  O ABNORMAL
Rhythm:  O Sinus  O Non-sinus  O Sinus arrhythmia  Rate  ___.___
If non-sinus, specify:  

SVT  MAT  Aflutter  Afib  VT  Vfib  
Junctional  Idioventricular rhythm  Others  

AV block:  

Y  N  If yes; check one  I  II 1  II 2  III  

PACs:  

Y  N  If yes; number per sec  

PVCs:  

Y  N  If yes; number per sec  

Intraventricular conduction defect  

Y  N  

RBBB  

Y  N  

LBBB  

Y  N  

LAFB  

Y  N  

LPFB  

Y  N  

LVH  

Y  N  

RVH  

Y  N  

LAD  

Y  N  

RAD  

Y  N  

Old MI  

Y  N  

ST-T wave changes consistent with ischemia  

Y  N  

Non-specific ST-T wave changes  

Y  N  

Non-specific repolarization abnormalities  

Y  N  

Secondary ST-T wave changes  

Y  N  

Others  

QTC  msec (If given in seconds, multiply by 1000. For eg. If it is 0.42 sec, it is 420 msec)  

Any abnormality in ED monitor  

Y  N  

Carotid sinus massage done  

Y  N  

Abnormal  

Y  N  

CT HEAD Abnormalities (New & Clinically important)  

Y  N  NOT DONE  

IS PT. PRESENTLY IN CHF  

Y  N  MAY BE  

ADMITTED Admission chart reviewed  

Y  N  

OUTCOMES:  

Y  N  

DEATH:  

Y  N  

Confirming no death: Visit to any hospital 30 days since the initial visit  

Y  N  

If No for previous line, need - Review of death records (Coroner's office)  

Y  N  

MYOCARDIAL INFARCTION:  

Y  N  

Troponin elevated  

Y  N  

Level:  

ECG changes consistent with MI  

Y  N  

ARRHYTHMIA:  

Y  N  

Non-sinus rhythm (previously known or new) captured on monitoring and thought to have had a temporal relationship to the symptom or that required treatment.  

Y  N  

Sinus pause ≥ 3 seconds  

Y  N  

Sinus bradycardia ≤ 35 beats per minute  

Y  N  

Symptomatic supraventricular tachycardia  

Y  N  

Atrial fibrillation with slow ventricular response (RR interval > 3 seconds)  

Y  N  

Atrial fibrillation with fast ventricular response  

Y  N  

Mobitz type II second degree heart block  

Y  N  

Complete heart block  

Y  N  

Symptomatic or sustained (≥ 30 seconds) ventricular tachycardia  

Y  N
Ventricular Fibrillation 
○ Y ○ N 
Pacemaker malfunction. 
○ Y ○ N 
Others _________________________________

PULMONARY EMBOLISM: 
○ Y ○ N 
(Diagnosis made by VQ scan, computed tomography scan of the chest or angiography. If it was low probability VQ then the patient should have received or should have been considered for treatment)

STROKE: 
○ Y ○ N 
(Defined by presence of persistent neurological deficit and the symptoms were temporally related to the syncope episode)

SUBARACHNOID HEMORRHAGE: 
○ Y ○ N 
(Confirmed by computed tomography/magnetic resonance imaging of the brain with or without spinal fluid analysis by lumbar puncture)

SIGNIFICANT HEMORRHAGE: 
○ Y ○ N 
(Defined as syncope associated with detected source of bleeding that is significant and that required transfusion)

ANY PROCEDURAL INTERVENTION TO TREAT A RELATED CAUSE OF SYNCOPE: ○ Y ○ N 
(Any patient who undergoes an acute intervention that would have caused them to return if they have been discharged will be considered to have had a serious outcome. Monitoring of patients, medication changes or rehydration will not be considered as acute intervention.)

Dialysis 
○ Y ○ N 
Reason______________________

Pacemaker insertion 
○ Y ○ N 
Reason______________________

Surgery for valvular heart disease 
○ Y ○ N 
Reason______________________

Balloon-pump insertion 
○ Y ○ N 
Reason______________________

Use of vasopressors 
○ Y ○ N 
Reason______________________

Surgery to treat an abdominal aortic aneurysm 
○ Y ○ N 
Reason______________________

Surgery for ruptured spleen 
○ Y ○ N 
Reason______________________

Surgery for ruptured ectopic pregnancy 
○ Y ○ N 
Reason______________________

Endoscopic treatment of esophageal varices. 
○ Y ○ N 
Reason______________________

Others _________________________________ 
Reason______________________

ANY CONDITION CAUSING/LIKELY TO CAUSE RETURN EMERGENCY VISIT:○ Y ○ N Patients with related return visits and admitted or developed any of the above outcomes will be considered to have had an adverse outcome. But if the return visit was related but they were again discharged without any acute intervention then they will not be considered as having developed an adverse outcome.

HOSPITALIZATION FOR A RELATED EVENT WITHIN 30 DAYS: ○ Y ○ N 
Defined as hospitalization for an event that would have caused the syncope within 30 days of the index visit.

CAUSE FOR SYNCOPE FOUND ○ Y ○ N 
FINAL DIAGNOSIS: Subjective ○ Objective ○
○Syncope NYD ○ Vasovagal Syncope ○ Neuralgic Syncope ○ Cardiac syncope ○ Orthostatic hypotension ○ Micturition syncope ○ Others _________________________________
Appendix 2: Data abstraction form – Return Visit Form

RETROSPECTIVE VALIDATION OF THE SFSR – RETURN VISIT FORM

Subject # ________  Data Abstracted by PI ___ RA___

DEMOGRAPHICS:
Patient initials ______  Date of birth (dd/mm/yy) |__|__|__|
Sex  O M  O F
Hospital:  O TOHC  O TOHG  O QCH  O MF  Chart # ________
Date of return visit (dd/mm/yy) |__|__|__|  Number of return visit  O 1  O 2  O 3  O 4  O 5

INITIAL PRESENTATION: If presentation is not syncope, go directly to HISTORY
Definition of syncope fulfilled  O Y  O N  O Unknown

Exclusion criteria: Prolonged altered LOC (usually < 5min)  O Y  O N
Alcohol/illicit drug related (Substances caused syncope)  O Y  O N
Syncope due to head trauma (First injury occurred then syncope)  O Y  O N
Significant trauma (Admission to Ortho/trauma/surgery)  O Y  O N

SFSR:
<table>
<thead>
<tr>
<th>Variable</th>
<th>Y</th>
<th>N</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Congestive Heart Failure</td>
<td>O</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Hematocrit &lt; 0.300</td>
<td>O</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Abnormal EKG*</td>
<td>O</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Pt. complaint of Shortness of Breath</td>
<td>O</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Triage Systolic Blood Pressure &lt; 90</td>
<td>O</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>*Any non-sinus and any new changes</td>
<td>O</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>

All variables available  O Y  O N  NA = Not Available

HISTORY:
Prodrome:  O Nausea  O Vomiting  O Dizziness  O Chest pain  O Abd. pain  O Sweating
O Others (Specify) ________  O NA
Exertional syncope  O Y  O N  O NA
Palpitations  O Y  O N  O NA
Paroxysmal Nocturnal Dyspnea (PND)  O Y  O N  O NA
Orthopnea  O Y  O N  O NA
Coronary Artery Disease (CAD)  O Y  O N  O NA
Arrhythmia  O Y  O N  O NA
Cardiomyopathy  O Y  O N  O NA
Valvular Heart Disease  O Y  O N  O NA
Diabetes  O Y  O N  O NA
Hypertension (HTN)  O Y  O N  O NA
Cerebrovascular accident (CVA)  O Y  O N  O NA
Transient Ischemic Attack (TIA)  O Y  O N  O NA
Peripheral Arterial Disease (PAD)  O Y  O N  O NA
Others

MEDICATIONS: Unknown O

Diuretics O Y O N If yes, specify code___
Anti-arrhythmics O Y O N If yes, specify code___
Digoxin O Y O N
Direct vasodilators O Y O N If yes, specify code___
Nitrates PO O Y O N If yes, specify code___
Nitropatch O Y O N
Nitroglycerine sublingual O Y O N Did the pt. have it just prior to syncope? O Y O N Alpha-blockers O Y O N If yes, specify code___
Combined alpha & beta blockers O Y O N If yes, specify code___
Calcium Channel Blockers O Y O N If yes, specify code___

EXAMINATION:

<table>
<thead>
<tr>
<th>Triage</th>
<th>Last ED value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Rate</td>
<td>Room air</td>
</tr>
<tr>
<td>O2 sat</td>
<td>Home O2 at ___ L/min</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>O2 at ___ L/min</td>
</tr>
<tr>
<td></td>
<td>No info</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First EMS value</th>
<th>Last EMS value</th>
<th>Triage</th>
<th>Supine</th>
<th>Sitting</th>
<th>Standing</th>
<th>Last ED value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worst EMS value</th>
<th>Worst ED value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
</tr>
</tbody>
</table>

ARRIVAL BY AMBULANCE O Y O N
EMS SHEET AVAILABLE O Y O N

ANY INTERVENTIONS BY EMS:

IV Start O Y O N
Fluids O Y O N Type_____ Amount_____

Medications: O Y O N
Epinephrine Concentration 1:1000 1:10,000 Amount ____ IV O IM O SC O
Atropine Amount ______ IV O IM O SC O
Others: Type______ Amount/Route ___________

EMS RHYTHM STRIP O NOT DONE O NO INFO O NORMAL O ABNORMAL
Rhythm: O Sinus O Non-sinus O Sinus arrhythmia Rate ___________
If non-sinus, specify:  
- SVT  
- MAT O Aflutter O Afib  
- VT O Vfib  
- Junctional  
- Idioventricular rhythm  
- Others  

AV block  
- Y O N  
If yes; check one  
- I II 1 II 2 III  
If yes; number per sec  

PACs  
- Y O N  
If yes; number per sec  

PVCs  
- Y O N  
If yes; number per sec  

Intraventricular conduction defect  
- Y O N  

RBBB  
- Y O N  
LBBB  
- Y O N  
LAFB  
- Y O N  
LPFB  
- Y O N  
RVH  
- Y O N  
LVH  
- Y O N  
LAD  
- Y O N  
RAD  
- Y O N  
Old MI  
- Y O N  

ST-T wave changes consistent with ischemia  
- Y O N  

Non-specific ST-T wave changes  
- Y O N  

Non-specific repolarization abnormalities  
- Y O N  

Secondary ST-T wave changes  
- Y O N  

Others  

Any abnormality in EMS monitor  
- Y O N  
No Info  
Specify  

Any murmur  
- Y O N  
Rales/crackles  
- Y O N  
Wheeze/rhonchi  
- Y O N  
Decreased air entry  
- Y O N  

INVESTIGATION:  
- NOT DONE  

<table>
<thead>
<tr>
<th>Hb</th>
<th>Glucose</th>
<th>Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct</td>
<td>BUN</td>
<td>Ion. Ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>Creatinine</td>
<td>Mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>CK</td>
<td>Glucometer EMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>Troponin</td>
<td>Glucometer ED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EKG:  
- NOT DONE  

Cardiologist opinion  
- Y O N O NORMAL O ABNORMAL  
Rhythm:  
- Sinus  
- Non-sinus  
Sinus arrhythmia  
Rate  

If non-sinus, specify:  
- SVT  
- MAT O Aflutter O Afib  
- VT O Vfib  
- Junctional  
- Idioventricular rhythm  
- Others  

AV block  
- Y O N  
If yes; check one  
- I II 1 II 2 III  
If yes; number per sec  

PACs  
- Y O N  
If yes; number per sec  

PVCs  
- Y O N  
If yes; number per sec  

Intraventricular conduction defect  
- Y O N  
RBBB  
- Y O N  

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Abnormal ST-T wave changes consistent with ischemia
Non-specific ST-T wave changes
Non-specific repolarization abnormalities
Secondary ST-T wave changes
QTc [_____] msec (If given in seconds, multiply by 1000. For eg. If it is 0.42 sec, it is 420 msec)

Others
Any abnormality in ED monitor
Carotid sinus massage done
CT HEAD Abnormalities (New & Clinically important)
IS PT. PRESENTLY IN CHF
ADMITTED Admission chart reviewed
OUTCOMES: O Y O N
DEATH: Confiming no death: Visit to any hospital 30 days since the initial visit
If No for previous line, need - Review of death records (Coroner's office)
MYOCARDIAL INFARCTION:
Troponin elevated
ECG changes consistent with MI
ARRHYTHMIA:
Non-sinus rhythm (previously known or new) captured on monitoring and thought to have had a temporal relationship to the symptom or that required treatment.
Sinus pause ≥ 3 seconds
Sinus bradycardia ≤ 35 beats per minute
Symptomatic supraventricular tachycardia
Atrial fibrillation with slow ventricular response (RR interval > 3 seconds)
Atrial fibrillation with fast ventricular response
Mobitz type II second degree heart block
Complete heart block
Symptomatic or sustained (≥ 30 seconds) ventricular tachycardia
Ventricular Fibrillation
Pacemaker malfunction.
Others
PULMONARY EMBOLISM:
(Diagnosis made by VQ scan, computed tomography scan of the chest or angiography. If it was low probability VQ then the patient should have received or should have been considered for treatment)

STROKE: O Y O N
(Defined by presence of persistent neurological deficit and the symptoms were temporally related to the syncope episode)

SUBARACHNOID HEMORRHAGE: O Y O N
(Confirmed by computed tomography/magnetic resonance imaging of the brain with or without spinal fluid analysis by lumbar puncture)

SIGNIFICANT HEMORRHAGE: O Y O N
(Defined as syncope associated with detected source of bleeding that is significant and that required transfusion)

ANY PROCEDURAL INTERVENTION TO TREAT A RELATED CAUSE OF SYNCOPE: O Y O N
(Any patient who undergoes an acute intervention that would have caused them to return if they have been discharged will be considered to have had a serious outcome. Monitoring of patients, medication changes or rehydration will not be considered as acute intervention.)

Dialysis O Y O N Reason
Pacemaker insertion O Y O N Reason
Surgery for valvular heart disease O Y O N Reason
Balloon-pump insertion O Y O N Reason
Use of vasopressors O Y O N Reason
Surgery to treat an abdominal aortic aneurysm O Y O N Reason
Surgery for ruptured spleen O Y O N Reason
Surgery for ruptured ectopic pregnancy O Y O N Reason
Endoscopic treatment of esophageal varices. O Y O N Reason
Others O Y O N Reason

ANY CONDITION CAUSING/LIKELY TO CAUSE RETURN EMERGENCY VISIT: O Y O N
Patients with related return visits and admitted or developed any of the above outcomes will be considered to have had an adverse outcome. But if the return visit was related but they were again discharged without any acute intervention then they will not be considered as having developed an adverse outcome.

HOSPITALIZATION FOR A RELATED EVENT WITHIN 30 DAYS: O Y O N
Defined as hospitalization for an event that would have caused the syncope within 30 days of the index visit.

CAUSE FOR SYMPTOM FOUND O Y O N
FINAL DIAGNOSIS: Subjective O Objective O
O Syncope NYD O Vasovagal Syncope O Neurogenic Syncope O Cardiac syncope O Orthostatic hypotension O Micturition syncope O Others

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Appendix 3: Inter-Observer Agreement form

INTER-OBSERVER RELIABILITY

Subject No. ____

Pt. from Ottawa O Y O N If no, excluded -------------------------------------EXCLUSION

INITIAL PRESENTATION:
• Definition of syncope fulfilled O Y O N O Unknown
  The patient will be included if ‘yes’ only, if not, patient excluded---------------------EXCLUSION

• Exclusion criteria:
  Prolonged altered LOC (usually < 5min) O Y O N
  Alcohol/illicit drug related (Substances caused syncope) O Y O N
  Syncope due to head trauma (First injury occurred then syncope) O Y O N
  Significant trauma* (Admission to Ortho/trauma/surgery) O Y O N
  If yes for any of the above four then EXCLUDED ---------------------EXCLUSION

No exclusions by above three criteria -------------------------------------INCLUDED

<table>
<thead>
<tr>
<th>SFSR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Congestive Heart Failure O Y O N O NA</td>
</tr>
<tr>
<td>Abnormal EKG* O Y O N O NA</td>
</tr>
<tr>
<td>Pt. complaint of Shortness of Breath O Y O N O NA</td>
</tr>
<tr>
<td>*Any non-sinus and any new changes</td>
</tr>
</tbody>
</table>
Appendix 4: Research Ethics Board approval – The Ottawa Hospital

Dr. Venkatesh Thiruganasambandamoorthy
25 Dossetter Way
Ottawa, ON
K1G 4S3

Dear Dr. Thiruganasambandamoorthy:

Re: Protocol # 2007037-01H  Retrospective Validation of San Francisco Syncope Rule (SFSR) for Prediction of Short Term Serious Outcomes in Adult Syncope Patients

Protocol approval valid until -  Tuesday, January 15, 2008

I am pleased to inform you that your protocol for chart review was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and approved. No changes, amendments or addenda may be made in the protocol without the OHREB review and approval.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board
Tuesday, February 12, 2008

Dr. Venkatesh Thiruganasambandamoorthy
25 Dossetter Way
Ottawa, ON
K1G 4S3

Dear Dr. Thiruganasambandamoorthy:

RE: Protocol# - 2007037-01H   Retrospective Validation of San Francisco Syncope Rule (SFSR) for Prediction of Short Term Serious Outcomes In Adult Syncope Patients

Renewal Expiry Date - Wednesday, February 11, 2009

I am pleased to inform you that your Annual Renewal Request (listed above) was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made in the protocol or the consent form without the OHREB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

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

Encl.

/jm
Appendix 5: Research Ethics Board approval – The Queensway-Carleton Hospital

Queensway Carleton Hospital

April 16, 2007

Dr. Venkatesh Thiruganasambandamoorthy
Emergency Physician
Queensway Carleton Hospital
25 Dossetter Way
Ottawa, ON K1G 4S3

RE: Study 07-02 Retrospective validation of San Francisco Syncope Rule (SFSR) for prediction of short-term serious outcomes in adult syncope patients

Dear Dr. Venk,

I am pleased to inform you that the Consent’s and Research Committee has reviewed the above named protocol at it’s recent meeting held April 5, 2007 and has granted full approval for conduct of this study at QCH.

This approval will expire in one year, April 30, 2008 and two months prior to the expiry date the committee requires that you complete a Continuing Review Form at which time you may request an extension to the approval if required. Should you have any questions please do not hesitate to contact me.

On behalf of the Committee, I extend best wishes for a successful study.

Sincerely,

D. Crowe Ph.D., C. Psych
Chair, Consent’s & Research Committee

DC:ml
cc: Dr. Mary Brown, Chief of Staff
    Ms. M. Sgarbiosa, Manager of Health Records
Queensway Carleton Hospital

July 9, 2008

Dr. Venkatesh Thiruganasambandamoorthy
Emergency Physician
Queensway Carleton Hospital
25 Dufferin Way
Ottawa, ON K1G 4S3

RE: Study 07-02 Retrospective validation of San Francisco Syncope Rule (SFSR) for prediction of short-term serious outcomes in adult syncope patients

Dear Dr. Venk,

This is to advise that we are in receipt of the Continuing Review Form regarding the above named study and your request for extension of approval for this study.

The Consents & Research Committee does not meet again until September, 2008 but I am, on behalf of the Committee authorized to extend approval for a period of one year expiring July, 2009. Please note that the Continuing Review Form contains a request for a summary of progress. We would appreciate this summary at your earliest convenience.

Thank you,

D. Crowe Ph D., C. Psych.
Chair, Consents & Research Committee

DC:ml
cc:-Dr. Andrew Falconer, Chief of Staff
- Ms. M. Sgarbossa, Manager of Health Records
Le 29 novembre 2007

Dr Venkatesh Thiruganasambandamoorthy
Emergency Physician
Department of Emergency Medicine
The Ottawa Hospital
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9

OBJET : « Retrospective Validation of San Francisco Syncope Rule (SFSR) for Prediction of Short-Term Serious Outcomes in Adult Syncope Patients »

Docteur,

La présente est pour vous informer de la décision du Comité de recherche de l'Hôpital Montfort en ce qui a trait à votre recherche citée en rubrique. Le Comité de recherche a consulté le Comité d'éthique avant de prendre la décision finale. Votre projet de recherche à l'Hôpital Montfort est accepté sujet aux conditions suivantes :

- Que l'équipe de chercheurs établisse un moyen de bien identifier les patients qui pourraient participer à ce projet de recherche afin de faciliter le travail au service des archives cliniques de l'Hôpital Montfort.

Les modalités de fonctionnement de ce projet ont été discutées avec Mme Carmen Bercier du service d'informations cliniques et support décisionnel et se résument comme suit :

- Vous nous envoyez la liste des patients participant (nom, numéro RASO, date de naissance, période des visites recherchées) en format Excel, protégé par un mot de passe envoyé séparément;
- Nous vérifions si le patient s'est présenté au service d'urgence dans la période étiquetée,
- Si le patient s'est présenté, nous inscrivons tous les diagnostics reliés à cette visite (code de la CIM 10);
- Nous avons besoin d'un délai d'un mois pour retourner la liste de patients;
- Vous venez revoir les dossiers des patients sélectionnés;
- Dans un deuxième temps vous nous enverrez une autre liste de patients.

De plus, vous êtes demandé de nous fournir un sommaire des résultats de votre projet de recherche.
Nous vous remercions de l'intérêt que vous portez à la recherche au sein de l'Hôpital Monfort et nous vous souhaitons le succès dans votre étude.

Veuillez agréer, docteur, l'assurance de nos meilleurs sentiments.

Dr Harvey Barkun
Président du Comité de recherche

c.c. Mme Carmen Bercier, gestionnaire analyste, informations cliniques et support décisionnel
    Mme Diane Poirier, directrice par intérim, informations cliniques et support décisionnel
    M. Brian Malcolmson, vice-président associé, affaires académiques
    Dr André Bilodeau, vice-président, affaires académiques
Appendix 7: Multivariate logistic regression – Initial logistic regression model

Variables offered to the initial logistic regression model:

Age as a continuous variable, history of congestive heart failure, history of shortness of breath, history of coronary artery disease, history of arrhythmia, history of diabetes, history of hypertension, history of cerebrovascular accident, history of peripheral arterial disease, arrival by ambulance, lowest systolic and diastolic blood pressure in the ambulance, triage systolic blood pressure, triage diastolic blood pressure, triage oxygen saturation, rales and decreased air entry on physical examination, last emergency department respiratory rate, last emergency department oxygen saturation, last and the lowest emergency department systolic and diastolic blood pressures and patient presently in congestive heart failure.

Laboratory values for haemoglobin, sodium, potassium, glucose, blood urea nitrogen, creatinine, troponin and calcium.

Emergency electrocardiogram features: non-sinus rhythm, duration of the corrected QT interval presence of premature atrial contractions, premature ventricular contractions, atrioventricular block, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, ST-T wave changes consistent with ischemia, secondary ST-T wave changes and cardiac monitor abnormalities.

Results of the initial logistic regression model – Model A:

| Number of Observations Read | 505 |
| Number of Observations Used | 9 |

<table>
<thead>
<tr>
<th>Step</th>
<th>Effect Entered</th>
<th>DF</th>
<th>Number In</th>
<th>Score Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Variable Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ekg_lbbb</td>
<td>1</td>
<td>1</td>
<td>9.0000</td>
<td>0.0027</td>
<td>EKG: LBBB</td>
</tr>
</tbody>
</table>
Appendix 8: Multivariate logistic regression – Model development

The variables with more missing values ‘last emergency department respiratory rate’, ‘last emergency department oxygen saturation’, ‘lowest ambulance systolic blood pressure’ and ‘lowest ambulance diastolic blood pressure’ were removed and analysis was tried again.

Model A:

<table>
<thead>
<tr>
<th>Step</th>
<th>Effect Entered</th>
<th>DF</th>
<th>Number In</th>
<th>Score Chi-Square</th>
<th>Pr &gt; ChiSq</th>
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<td>1</td>
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<td>EKG: LBBB</td>
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<td>2</td>
<td>8.2949</td>
<td>0.0040</td>
<td>EKG: RBBB</td>
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<td>wed_dbp</td>
<td>1</td>
<td>3</td>
<td>6.1928</td>
<td>0.0128</td>
<td>Worst ED value: dbp</td>
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</table>

<table>
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<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
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<td>wed_dbp</td>
<td>1.212</td>
<td>0.945 – 1.553</td>
</tr>
<tr>
<td>ekg_rbbb</td>
<td>&lt;0.001</td>
<td>&lt;0.001 – 18.187</td>
</tr>
<tr>
<td>ekg_lbbb</td>
<td>&lt;0.001</td>
<td>&lt;0.001 – &gt;999.999</td>
</tr>
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</table>

Model C:

The continuous laboratory values of hemoglobin, sodium, potassium, glucose, blood urea nitrogen, creatinine, troponin and calcium were removed and the logistic regression was run again.
<table>
<thead>
<tr>
<th>Step</th>
<th>Effect Entered</th>
<th>DF</th>
<th>Number In</th>
<th>Score Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Variable Label</th>
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<tbody>
<tr>
<td>1</td>
<td>triage_o2sat</td>
<td>1</td>
<td>1</td>
<td>24.2955</td>
<td>&lt;.0001</td>
<td>Examination: At triage- O2 sat</td>
</tr>
<tr>
<td>2</td>
<td>chfpresent</td>
<td>2</td>
<td>2</td>
<td>18.0721</td>
<td>0.0001</td>
<td>IS PT. PRESENTLY IN CHF?</td>
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<td>ekg_anyabnedm</td>
<td>2</td>
<td>3</td>
<td>17.4967</td>
<td>0.0002</td>
<td>EKG: Any abnormality in ED monitor</td>
</tr>
<tr>
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<td>ekg_lbbb</td>
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<td>4</td>
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<td>0.0012</td>
<td>EKG: LBBB</td>
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<tr>
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<td>wed_sbp</td>
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<td>5</td>
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</table>

**Odds Ratio Estimates**

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<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
</tr>
</thead>
<tbody>
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<td>1.002, 1.056</td>
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<td>&gt;999.999</td>
<td>&lt;0.001, &gt;999.999</td>
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<td>ekg_rbbb</td>
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<tr>
<td>ekg_anyabnedm</td>
<td>5.747</td>
<td>1.769, 18.668</td>
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</table>
Model D:

The variable "presently in congestive heart failure" was removed and the derived variables "bifascicular block", "any bundle branch block + first degree atrioventricular block" and "significant atrioventricular block" were introduced into the model and analyzed again.

<table>
<thead>
<tr>
<th>Step</th>
<th>Effect Entered</th>
<th>DF</th>
<th>Number In</th>
<th>Score Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Variable Label</th>
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<tr>
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<td>triage_o2sat</td>
<td>1</td>
<td>1</td>
<td>24.2955</td>
<td>&lt;.0001</td>
<td>Examination: At triage- O2 sat</td>
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Appendix 9: Defining abnormal electrocardiogram for the new preliminary rule

All abnormal electrocardiogram definitions based on Emergency Department electrocardiogram and include: non-sinus rhythm (supraventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, junctional rhythm, idioventricular rhythm), significant atrioventricular block (second and third degree), ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities.

Abnormal Electrocardiogram1 is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities:
Sinus arrhythmia, presence of premature atrial contractions, presence of premature ventricular contractions, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block and secondary ST-T wave changes.

Abnormal Electrocardiogram2 is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities:
Presence of premature atrial contractions, presence of premature ventricular contractions, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block and secondary ST-T wave changes.

Abnormal Electrocardiogram3 is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities:
Presence of premature ventricular contractions, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block and secondary ST-T wave changes.

Abnormal Electrocardiogram4 is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities:
Presence of premature atrial contractions, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block and secondary ST-T wave changes.

Abnormal Electrocardiogram5 is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities:
Right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block and secondary ST-T wave changes.

Abnormal Electrocardiogram6 is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities:
Right bundle branch block, left bundle branch block, left anterior fascicular block and left posterior fascicular block.

**Abnormal Electrocardiogram** is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities: (Right bundle branch block + first degree atrioventricular block), left bundle branch block, left anterior fascicular block, left posterior fascicular block and secondary ST-T wave changes.

**Abnormal Electrocardiogram** is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities: (Right bundle branch block or left bundle branch block + first degree atrioventricular block), bifascicular block and secondary ST-T wave changes.

**Abnormal Electrocardiogram** is defined as presence of any of the following in addition to non-sinus rhythm, significant atrioventricular block, ST-T wave changes consistent with ischemia and emergency department cardiac monitor abnormalities: (Right bundle branch block or left bundle branch block + first degree atrioventricular block) and bifascicular block.
Appendix 10: Multivariate logistic regression – The Final four logistic regression models

Model 1:
Variables offered to the model: Age ≥ 75 years, history of congestive heart failure, history of shortness of breath, history of arrhythmia, lowest emergency department systolic blood pressure < 90mm of Hg, triage diastolic blood pressure < 50mm of Hg, abnormal EKG9 (see appendix 10), hematocrit < 300 and blood urea nitrogen > 15mmol/L.

```
proc logistic data=newdata.newsfsr descending;
ods rtf file="C:\Documents and Settings\Administrator\Desktop\New Reports\model84_&_SYSDATE9..rtf";
  class AGE75 (ref='0') HIS_CHF(ref='0') SOBl(ref='0') HIS_ARRH(ref='0')
  WED_SBP90(ref='0') TRIAGE_DBP50(ref='0')
  ABNEKG9(ref='0') HEMATOCRIT300(ref='0') BUN15(ref='0');
  model outcome = age75 his_chf sob1 his_arrh
  wed_sbp90 triage_dbp50
  abnekg9 hematocrit300 bun15
  / outroc=roc84 details lackfit rsq ctable pprob = (.01 to .05 by .01)
  selection=forward sle=0.05 sls=0.10;
  output out=regdiagnost1 pred=pi;
  title 'Model84';
run;
ods rtf close;
```

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### Odds Ratio Estimates

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### Association of Predicted Probabilities and Observed Responses

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### Hosmer and Lemeshow Goodness-of-Fit Test

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Model 2:
Variables offered to the model: Age ≥ 70 years, history of congestive heart failure, history of shortness of breath, history of arrhythmia, lowest emergency department systolic blood pressure < 90 mm Hg, triage diastolic blood pressure < 50 mm Hg, abnormal EKG (see appendix 10), hematocrit < 300 and blood urea nitrogen > 15 mmol/L.

```
proc logistic data=newdata.newsfsr descending;
ods rtf file="C:\Documents and Settings\Administrator\Desktop\New Reports\model85_&SYSDATE9..rtf";
class AGE70 (ref='0') HIS_CHF(ref='0') SOBl(ref='0') HIS_ARRH(ref='0') WED_SBP90(ref='0') TRIAGE_DBP50(ref='0') ABNEKG9(ref='0') HEMATOCRIT300(ref='0') BUN15(ref='0');
model outcome = age70 his_chf sobl his_arrh wed_sbp90 triage_dbp50 abnekg9 hematocrit300 bun15
/ details lackfit rsq ctable pprob = (.01 to .05 by .01) selection=forward sle=0.05 sls=0.10;
output out=regdiagnostl pred=pi;
Title 'Model85';
run;
ods rtf close;
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### Odds Ratio Estimates

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### Association of Predicted Probabilities and Observed Responses

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### Hosmer and Lemeshow Goodness-of-Fit Test

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**Model 3:**

Variables offered to the model: Age ≥ 75 years, history of congestive heart failure, history of shortness of breath, history of arrhythmia, lowest emergency department systolic blood pressure <90mm of Hg, triage diastolic blood pressure <50mm of Hg, abnormal EKG7 (see appendix 10), hematocrit <300 and blood urea nitrogen >15mmol/L.
**proc logistic**
data=newdata.newsfsr descending;
ods rtf file="C:\Documents and Settings\Administrator\Desktop\New Reports\model87 &SYSDATE9..rtf";
class AGE75 (ref='0') HIS_CHF(ref='0') SOB1(ref='0') HIS_ARRH(ref='0')
WED_SBP90(ref='0') TRIAGE_DBP50(ref='0')
ABNEKG7(ref='0') HEMATOCRİT300(ref='0') BUN15(ref='0');
model outcome = age75 his_chf sob1 his_arrh
wed_sbp90 triage_dbp50
abnekg7 hematocrıt300 bun15
/ details lackfit rsq ctable pprob = (.01 to .05 by .01) selection=forward
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output out=regdiagnost1 pred=pi;
Title 'Model87';
run;
ods rtf close;

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### Association of Predicted Probabilities and Observed Responses

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### Hosmer and Lemeshow Goodness-of-Fit Test

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</tr>
<tr>
<td>0.040</td>
<td>45</td>
<td>154</td>
<td>68.7</td>
</tr>
<tr>
<td>0.050</td>
<td>44</td>
<td>154</td>
<td>68.5</td>
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</tbody>
</table>

Model 4:
Variables offered to the model: Age $\geq$ 75 years, history of congestive heart failure, history of shortness of breath, history of arrhythmia, lowest emergency department systolic blood pressure <80mm of Hg, triage diastolic blood pressure <50mm of Hg, abnormal EKG (see appendix 10), hematocrit <300 and blood urea nitrogen >15mmol/L.

```
proc logistic data=newdata.newsfmr descending;
ods rtf file="C:\Documents and Settings\Administrator\Desktop\New Reports\model88_&SYSDATE9..rtf";
class AGE75 (ref='0') HIS_CHF(ref='0') SOBl(ref='0') HIS_ARRH(ref='0')
WED_SBP80(ref='0') TRIAGE_DBP50(ref='0')
ABNEKG9(ref='0') HEMATOCRIT300(ref='0') BUN15(ref='0');
model outcome = age75 his_chf sobl his_arrh
wed_sbp80 triage_dbp50
abnekg9 hematocrit300 bun15
/ details lackfit rsq ctable pprob = (.01 to .05 by .01) selection=forward
sle=0.05 sls=0.10;
output out=regdiagnost1 pred=pi;
Title 'Model88';
run;
ods rtf close;
```

<table>
<thead>
<tr>
<th>Step</th>
<th>Effect Entered</th>
<th>DF</th>
<th>Number In</th>
<th>Score Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Variable Label</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>wed_sbp80</td>
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<td>1</td>
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<td>abnekg9</td>
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<td>2</td>
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<td>&lt;.0001</td>
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<tr>
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<td>bun15</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>sobl</td>
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<td>4</td>
<td>7.3740</td>
<td>0.0066</td>
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<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
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<tbody>
<tr>
<td>sobl</td>
<td>3.210</td>
<td>1.352 7.625</td>
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<tr>
<td>wed_sbp80</td>
<td>15.077</td>
<td>4.434 51.269</td>
</tr>
<tr>
<td>abnekg9</td>
<td>6.187</td>
<td>3.012 12.708</td>
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</table>
### Association of Predicted Probabilities and Observed Responses

<table>
<thead>
<tr>
<th></th>
<th>Percent Concordant</th>
<th>Somers' D</th>
<th>Percent Discordant</th>
<th>Gamma</th>
<th>Percent Tied</th>
<th>Tau-a</th>
<th>Pairs</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>77.1</td>
<td>0.700</td>
<td>7.0</td>
<td>0.833</td>
<td>15.9</td>
<td>0.123</td>
<td>22344</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

### Partition for the Hosmer and Lemeshow Test

<table>
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<th>Group</th>
<th>Total</th>
<th>outcome = 1</th>
<th>outcome = 0</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>1</td>
<td>339</td>
<td>8</td>
<td>8.74</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>1</td>
<td>2.51</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>11</td>
<td>10.97</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>29</td>
<td>26.78</td>
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### Hosmer and Lemeshow Goodness-of-Fit Test

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>DF</th>
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</thead>
<tbody>
<tr>
<td>1.3978</td>
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<td>0.4971</td>
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### Classification Table

<table>
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<tr>
<th>Prob Level</th>
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<th>Incorrect</th>
<th>Percentages</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Event</td>
<td>Non-Event</td>
<td>Sensitivity</td>
</tr>
<tr>
<td></td>
<td>Event</td>
<td>Event</td>
<td>Correct</td>
</tr>
<tr>
<td>0.010</td>
<td>49</td>
<td>0</td>
<td>456</td>
</tr>
<tr>
<td>0.020</td>
<td>49</td>
<td>0</td>
<td>456</td>
</tr>
<tr>
<td>0.030</td>
<td>41</td>
<td>331</td>
<td>125</td>
</tr>
<tr>
<td>0.040</td>
<td>41</td>
<td>331</td>
<td>125</td>
</tr>
<tr>
<td>0.050</td>
<td>41</td>
<td>331</td>
<td>125</td>
</tr>
</tbody>
</table>

### Appendix 11: Recursive Partitioning – Models Derived:

Rule 1: Age≥65, wed_sbp<80, abnegk7
Sensitivity = \frac{a}{c1}; (use exact Binomial confidence intervals instead of these)
Specificity = \( \frac{d}{c2} \); (use exact Binomial confidence intervals instead of these)

Positive Predictive Value (PPV) = \( \frac{a}{r1} \); (use exact Binomial confidence intervals instead of these)

Negative Predictive Value (NPV) = \( \frac{d}{r2} \); (use exact Binomial confidence intervals instead of these)

Rule 2: \( \text{Age} \geq 65, \text{wed_sbp} < 80, \text{abnekg9} \) – THE FINAL MODEL SELECTED

\[
\begin{array}{c|c|c|c}
\text{Outcome} & 0.00 & 456 & 90.30 \% \\
\hline
\text{abnekg9} & 1.00 & 49 & 9.70 \% \\
\hline
\text{Total} & 505 & 100.00 \% \\
\end{array}
\]

\[
\begin{array}{c|c|c|c}
\text{Outcome} & 0.00 & 372 & 95.38 \% \\
\hline
\text{wed_sbp80} & 1.00 & 18 & 4.62 \% \\
\hline
\text{Total} & 390 & 77.23 \% \\
\end{array}
\]

\[
\begin{array}{c|c|c|c}
\text{Outcome} & 0.00 & 368 & 97.10 \% \\
\hline
\text{age65} & 1.00 & 11 & 2.90 \% \\
\hline
\text{Total} & 379 & 75.05 \% \\
\end{array}
\]

* Outcome Occurred | Outcome did not Occur | Totals
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor Present or Dx Test Positive</td>
<td>49 = a</td>
<td>214 = b</td>
</tr>
</tbody>
</table>

| 150 |
Risk Factor Absent or Dx Test Negative

\[
\begin{align*}
\text{Risk Factor Absent or Dx Test Negative} & \quad 0 = c \quad 242 = d \quad 242 = r_2 \\
\text{Totals} & \quad 49 = c_1 \quad 456 = c_2 \quad 505 = t
\end{align*}
\]

Sensitivity = \(a/c_1\); (use exact Binomial confidence intervals instead of these)

\[
\begin{array}{ccc}
1.000 & 0.929 & 1.000 \\
0.531 & 0.523 & 0.531 \\
0.186 & 0.173 & 0.186 \\
1.000 & 0.986 & 1.000
\end{array}
\]

Specificity = \(d/c_2\); (use exact Binomial confidence intervals instead of these)

Positive Predictive Value (PPV) = \(a/r_1\); (use exact Binomial confidence intervals instead of these)

Negative Predictive Value (NPV) = \(d/r_2\); (use exact Binomial confidence intervals instead of these)