CURRENT MANAGEMENT OF TYPE 2 MI

by

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ABSTRACT

Background: Type 2 myocardial infarction (T2MI), or myocardial necrosis due to supply-demand mismatch, poses significant diagnostic and management challenges for clinicians. We conducted a detailed clinical characterization of management and outcomes of a large population of T2MI patients, comparing them to type 1 MI (T1MI) patients, to better characterize investigation, management and prognosis.

Methods and Results: Chart review was performed on all hospitalized troponin-positive patients in the Calgary Health Region between January 2007 and December 2008, identifying those diagnosed with type 1 and 2 MI. Additional data was obtained from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry and the Strategic Clinical Network for Cardiovascular Health and Stroke. Mortality was assessed at 30 days through to 4 years.

After age and sex matching, 756 patients with T2MI were included and compared with patients with T1MI. Patients with T2MI had infrequent, non-specific symptoms. An initial electrocardiogram (ECG) was not performed in 6%, and 1/3 did not have subsequent ECGs performed. Investigations were performed infrequently, with no patient undergoing angiogram. Evidence-based medical therapy was seldom prescribed, with 25.5% prescribed ASA and 17.3% statin. Outcomes were poor compared to patients with T1MI, with T2MI patients experiencing significantly greater 30-day through 4-year

mortality (30-day adjusted OR 6.59, 95% CI 3.47-12.53 and 4-year adjusted OR 1.65, 95% CI 1.23-2.22).

Conclusions: In this large cohort of patients diagnosed with T2MI, ECG changes were common, further investigation for coronary disease was uncommon, and outcomes were worse than patients diagnosed with T1MI, even after adjustment for comorbidities. Further research is required to determine appropriate management approaches and improve clinical outcomes of this vulnerable patient population.

PREFACE

This thesis is an original work by Deirdre O'Neill. Chapter 2, is an original research manuscript written by Deirdre O'Neill, along with co-authors, Danielle A. Southern, MSc, Matthew T. James, MD, PhD, Colleen Norris, PhD, Blair J. O'Neill, MD, and Michelle M. Graham, MD.

Deirdre O'Neill assisted in the design of the research project, interpreted the statistical analysis, independently performed relevant literature review and writing of the manuscript, as well as independently wrote chapter 1 and 3 of the thesis.

Danielle Southern and Colleen Norris assisted with statistical analysis and interpretation, Matthew T. James and Blair O'Neill assisted in editing of the manuscript and Michelle Graham was involved in the concept formation, design of the research project, interpretation of statistical analysis, aided in manuscript writing, and edited the thesis in its entirety – chapters 1, 2 and 3.

An abstract pertaining to this research project was presented at the Canadian Cardiovascular Congress previously. The manuscript portion (chapter 2 of the thesis) is currently submitted for publication.

The research project has been approved by the University of Alberta Research Ethics Board, Pro00011838.

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LIST OF ABBREVIATIONS USED

MI	Myocardial infarction
T1MI	Type 1 myocardial infarction
T2MI	Type 2 myocardial infarction
ECG	Electrocardiogram
APPROACH	Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease
ASA	Aspirin
OR	Odds ratio
CI	Confidence interval
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
ESC/ACCF/AHA/WHF	European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation
ACS	Acute coronary syndrome
PCI	Percutaneous coronary intervention
MINS	Myocardial Injury after Non-cardiac Surgery
MACE	Major Adverse Cardiac Events
SCN	Strategic Clinical Network
CT	Computerized Tomography
TRITON-TIMI-38	Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction trial
CASABLANCA	Catheter Sampled Blood Archive in Cardiovascular Diseases trial
VISION	Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study
ULI	Unique Lifetime Identifier

CHAPTER 1 INTRODUCTION

Over the past few decades, the development of serum biomarkers has revolutionized the diagnosis and care of cardiac patients. Currently, cardiac troponin is the biomarker used for detection of myocardial necrosis and diagnosis of myocardial infarction (MI).[1]

Troponin is a regulatory protein present in both cardiac and skeletal muscle. Troponin mediates muscle contraction by controlling the calcium-mediated interaction between actin and myosin.[2] The cardiac forms of troponin – cardiac troponin I and T, are more specific to the myocardium. The majority of cardiac troponin is intracellular and therefore, when troponin is detected in the serum, it is thought that some degree of myocardial damage has occurred.[3] Monoclonal antibodies to cardiac troponin are used to allow the detection of cardiac troponin I (cTnI) and cardiac troponin T (cTnT) in the serum, with high specificity.[2]

In 2000, the European Society of Cardiology and American College of Cardiology released a joint statement redefining myocardial infarction, recommending incorporating troponin into the diagnosis of MI.[4] In 2007, the Universal Definition of MI was created by the ESC/ACCF/AHA/WHF, which defined MI as the "detection of rise and/or fall of cardiac biomarkers above the 99th percentile of the upper reference limit" with evidence of ischemia.[1]

Additionally, they adapted the definition of MI to the increasing sensitivity of troponin assays by introducing the five types of MI, a classification which still exists in the most recent 2012 revision.[1,5]

Type 1 MI (T1MI) is spontaneous myocardial infarction, related to plaque rupture, ulceration or dissection which results in intraluminal thrombus occluding myocardial blood flow and myocardial necrosis.[1] Type 2 MI (T2MI) is myocardial infarction occurring when a condition other than coronary artery disease results in myocardial oxygen supply-demand mismatch.[1] In contrast, a type 3 MI is myocardial infarction resulting in sudden cardiac death and types 4a, 4b and 5 are myocardial infarctions related to percutaneous coronary intervention or coronary artery bypass surgery.[1]

1.1 Mechanism

The mechanism of T2MI is reflected by its definition, involving myocardial ischemia and necrosis due to an imbalance in myocardial oxygen supply and demand due to a cause other than atherosclerotic plaque rupture. At this time, little more than this is known about the pathophysiology of T2MI. It may be that underlying coronary artery disease is contributing in T2MI, however current angiographic data shows close to half of patients with T2MI have significant coronary artery disease (32-53%), with a similar percentage having non-obstructive coronary artery disease (36-46%).[6-9] Changes in myocardial oxygen demand can also occur as a result of alterations in wall tension, contractility, and heart rate.[8] Changes in myocardial oxygen supply occur as a result of alterations in

coronary blood flow and oxygen carrying capacity.[8] However, this may somewhat oversimplify the mechanism, as some patients with coronary artery disease can tolerate fairly major stressors, while others without evidence of coronary artery disease on angiogram may develop T2MI with what is thought to be physiology-demanding stressors. The pathophysiology is likely multifactorial, particularly in an older patient population with additional comorbidities.

1.2 Diagnosis

The diagnosis of T1MI is well-established, biomarker and clinically-based, and strong evidence guides its intervention and treatment. In contrast, T2MI has been associated with diagnostic uncertainty. No clear diagnostic criteria exist for T2MI and it is often quite difficult to discern T1MI from T2MI, as there is no pathophysiological or biomarker-based way to discriminate between the two. Additionally, the heterogeneous population involved and variety of disease processes resulting in supply-demand mismatch, contribute to a difficult and oftentimes uncertain clinical diagnosis.

Adding to the complexity of the diagnosis, in the third revision of the Universal definition of myocardial infarction, Thygesen et al differentiated another entity ("myocardial injury") from T2MI.[5] Myocardial injury is defined as a troponin elevation without clinical evidence of ischemia such as ECG changes or symptoms. However, studies of T2MI have shown that typical ischemic symptoms and ECG changes occur relatively infrequently, making the differentiation between T2MI and myocardial injury exceedingly difficult.[9-11]

Additionally, investigators have reported myocardial injury and T2MI populations to be similar in baseline characteristics and clinical outcomes, calling into question whether these two entities are in fact part of the same spectrum of disease.[10,12]

Overall, the clinical history and symptoms of T1MI and T2MI are not helpful in distinguishing these 2 entities. The literature supports a higher incidence of chest pain in those with T1MI as compared to T2MI, but a similar number of patients appear to present with dyspnea.[8-10,12-15] Electrocardiogram (ECG) is also unable to distinguish T1MI from T2MI. Common ECG findings in T2MI include ST segment depression and T wave inversion, but it is also common to present with no ischemic changes; all of which could be present in T1MI. Moreover, several reports in the literature confirm T2MI can present with ST elevation on ECG, with rates of 3.4-24%.[9,11,16-18] Therefore, no ECG pattern is specific to T1MI or T2MI, largely making ECG only interpretable as a part of the entire presentation, not as an independent diagnostic tool for MI.

Laboratory investigations are also of limited use in diagnosing T2MI. Literature shows that patients with T2MI more often have elevations in their creatinine, glucose, brain naturetic peptide (BNP) and lower hemoglobin levels as compared to T1MI, but these are again not helpful to differentiate T1MI and T2MI.[8,9,19] Troponin peak concentrations are usually higher in T1MI, but there is no reported cut off value over which increases the likelihood of T1MI, and no investigations into absolute or relative difference in peak and nadir troponin values have proven effective in distinguishing T1 and T2MI.[9,14,16,20] Interestingly, a promising method to discriminate between type 1 and 2 MI has been

described by Zahran and colleagues.[21] The investigators showed troponin is more proteolyzed after myocardial infarct, as cell death activates intracellular proteases, and the degree of proteolytic degradation increased with increasing severity of myocardial injury. The highest type of proteolytic digestion was in ST-elevation MI and the lowest was in T2MI.[21] Therefore proteolytic degradation of troponin may aid in confirming T2MI.

Saaby and colleagues have proposed using specific criteria to diagnose T2MI, in an effort to make the diagnosis more universally applied.[16] However, this definition has not been validated further and therefore has not been accepted in the literature or guidelines. Other authors have used angiographic evidence of plaque rupture to differentiate type 1 and 2 MI; however, performing an invasive procedure is not a practical tool for widespread diagnosis of T2MI and it is possible to have T1MI without finding angiographic evidence of plaque rupture.[8]

Although specific criteria for T2MI would reduce physician confusion and aid in making research in this area more reproducible, other authors, including ourselves, believe that due to the heterogeneous population and disease processes involved, T2MI needs to be evaluated on an individual basis, with the current Universal Definition applied.[8,16,17,22] For example, a patient with significant coronary artery disease would require less supply/demand mismatch to sustain a T2MI than a person with no underlying obstructive coronary disease.[8,23] Therefore, the current literature supports the fact that no one

symptom, sign or test is helpful to diagnose T2MI – the diagnosis is best made on an individual basis, taking into account all available clinical history and investigations.

1.3 Epidemiology

Understanding of the epidemiology of T2MI is limited by the fact that it is a relatively new diagnosis that is still lacking wide acceptance in clinical use and discrepancies in definitions.[8] Most of the current literature on T2MI is retrospective in nature, with reported incidence between 1.6-35.2%.[9,12,13,16,20, 24-27]

There are currently two prospective studies on T2MI. Both studies involved patient populations with known atherosclerotic disease and therefore could have higher risk of T2MI than the general population. The TRITON-TIMI-38 study followed 12,608 patients after acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) for 15 months.[19, 28] These patients were randomized to receiving prasugrel or clopidogrel post-PCI. The investigators reported 3.5% of patients experienced T2MI over the follow-up period. The CASABLANCA study followed patients who underwent coronary or peripheral angiography for a mean follow-up of 41 months and found that 12.2% of patients experienced T2MI over the follow-up period.[19] Thus, it appears the occurrence of T2MI is frequent.

The typical patient with T2MI is older, with incidence increasing with age.[10] Shah and colleagues found that the incidence of T2MI is less than T1MI in individuals under the

age of 75 years (60 vs 124 per 100,000 persons), however this trend reversed and in individuals over the age of 75 years, incidence of T2MI was higher than T1MI (1008 vs 750 per 100,000 persons).[10] Other investigators have found that patients with T2MI are more likely to be female, to have a lower left ventricular ejection fraction and more numerous comorbidities.[6,9,11,16] On multivariable regression, the CASABLANCA study found several factors, including older age, lower systolic blood pressure, history of coronary artery disease, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, nitrate use, abnormal glucose, to all be independent predictors of T2MI, emphasizing the medical complexities of these patients.[19] Additionally, Stein et al found that those with T2MI were more likely to have impaired functional levels (defined by the treating physician as normal, mildly impaired and significantly impaired) than T1MI counterparts (45.7% vs 17%, $p<0.0001$).[11] Therefore, T2MI is a disease of older, more medically complex patients, which would therefore influence treatment options and prognosis.

1.4 Management

Unlike T1MI, there is a lack of prospective evidence and no guidelines or consensus statements to guide treatment of T2MI. It is established that acute treatment should involve correcting the underlying supply-demand imbalance – whether that be by volume resuscitation, administration of blood products, respiratory support, rate control, etc.[3,8,23,29] The role of secondary prevention of coronary artery disease or cardiovascular risk reduction in this population is less clear however.[29] No medication has been shown to

be effective in reducing morbidity or mortality post-T2MI. The VISION trial provided evidence that pre-operative use of statins was associated with lower risk of myocardial injury after non-cardiac surgery (MINS), as well as lower risk of all-cause mortality and cardiac mortality, prompting the question of whether the same could be true in T2MI.[30]

At time of discharge, T2MI patients have been shown to receive fewer cardiac medications, as compared to patients with T1MI, likely due to a lack of evidence to support their use.[6,9,10,11,17] However, Baron and colleagues showed that even when patients with T2MI were known to have significant coronary artery disease, they were less likely to be treated with aspirin or statin than T1MI patients, which must at least in part be reflective of the clinical confusion over this diagnosis.[9]

As well, despite the lack of direct evidence for secondary prevention, there is a high prevalence of cardiovascular risk factors in this population. Furthermore, CASABLANCA showed an increased risk of subsequent adverse cardiovascular events in this population, therefore risk factor modification could be considered as a treatment strategy in T2MI.[8,19]

Similarly, the role of risk stratification post-T2MI is another area of uncertainty. It has been shown that patients with T2MI are less likely to undergo coronary angiography than those with T1MI, but also that they are less likely to have culprit lesions identified when they do undergo this procedure.[9,11,16] Baron et al found 42% of those with T2MI had non-obstructive coronary artery disease or normal coronary arteries on angiogram, while this

was only the case in 7% of T1MI patients.[9] With the older average age of patients with T2MI and the more numerous comorbidities in this population, an additional concern does exist for increased risk for procedural complications, therefore careful weighing of the individual risks and benefits would be required before deciding to proceed with angiogram.

Shah and colleagues investigated whether lowering troponin cut off for diagnosis of MI would impact the investigation, management or prognosis of type 1 and type 2 MI.[10] They found that there was an increased use of healthcare resources and improved prognosis in T1MI, whereas in T2MI, it resulted in more numerous cardiology referrals, echocardiograms and angiograms, without any change in treatment or prognosis. Therefore, at this point in time, we feel each patient's management should be considered on an individual basis. Future studies investigating medical management and risk stratification and their impact on prognosis are required in order to properly assess and treat this patient population.

1.5 Prognosis/Outcome

Once again, prognosis associated with T2MI has been variably reported, however, overall the literature suggests that type 2 MI is more than just a troponin elevation, it has important prognostic consequences.[6,10-14,17-19,25-27] Patients who have a T2MI are significantly more likely to have subsequent adverse events, as compared to those without such a diagnosis.[17,19] In the median 3.4-year follow-up of the CASABLANCA study,

12.2% sustained a T2MI during the follow up.[19] These patients had higher rates of subsequent major adverse cardiovascular events (MACE) compared to those without T2MI during the follow-up (53.7 vs 21.1 per 100 person/years, p<0.001). The rates of MACE in those with T2MI were similar to that of patients who sustained a T1MI over the same follow-up period. Additionally, on multivariate analysis, T2MI was found to be a significant predictor of risk of future MACE (HR 1.9, 95%CI 1.46-2.48).[19] Similarly, Landes et al found that the risk of MACE at 30-days, 1-year and 5-years was similar after T2MI or T1MI.[17]

Type 2 MI has also been found to result in an increased risk of short and long-term mortality, with many authors finding the mortality rate after T2MI higher than that after T1MI.[10,11,13,17] Investigators have found one-, two- and three-year mortality after T2MI to be alarmingly high, with Sarkisan and colleagues reporting a 3-year mortality rate of 63%.[6,10,12] Shah et al found 1-year mortality to be higher after T2MI than T1MI, with a relative risk of 2.31(95%CI 1.98-2.69).[10] Other authors are in agreement that both in the short and long-term, all-cause mortality is higher after T2MI than T1MI.[11,13,14,17]

Of significance, the majority of studies on T2MI report all-cause mortality rather than cardiac mortality, introducing the question of whether the patients are dying due to their multiple comorbidities, or due to cardiac issues. The CASABLANCA study, however, did report both all-cause death and cardiac death, finding both to occur as frequently after T2MI as after T1MI (all-cause death: 17.9 vs 21.1 per 100 person years, CV death 14.3 vs 15.6 per 100 person years).[19] This suggests that patients with T2MI do have a

significant subsequent cardiovascular mortality risk, in addition to the risk associated with their significant comorbidities and more advanced age. Therefore, T2MI is a clinical syndrome associated with significant morbidity and mortality rates similar to or greater than that of acute coronary syndrome.

Overall, T2MI is highly prevalent and associated with significant morbidity and mortality. We sought to better characterize this diagnosis by gathering data on a large population of patients with T2MI in order to evaluate the current investigation, management and prognosis associated with this diagnosis.

CHAPTER 2 ORIGINAL MANUSCRIPT

2.1 Introduction

The Universal Definition of Myocardial Infarction was first proposed in 2007, identifying 5 types of myocardial infarction (MI).[1] Type 2 MI was defined as myocardial infarction secondary to supply-demand mismatch. However, the diagnosis of T2MI has been associated with clinical challenges. It is often difficult to discern Type I (T1MI) from T2MI based on clinical features. Additionally, T2MI is frequently encountered in heterogeneous populations, as the consequence of a variety of disease processes. Distinguishing between these entities is nonetheless essential, as management approaches are often significantly different.

Although T2MI is prevalent and associated with significant mortality, there are discrepancies in reported incidence, mortality and prognosis associated with this diagnosis, in part due to diagnostic ambiguity. Furthermore, there are no evidence-based treatment recommendations for T2MI.

We sought to better characterize T2MI by gathering data on a large, unselected population of patients with T2MI in order to evaluate the investigation, management and prognosis associated with this diagnosis.

2.2 Methods

2.2.1 Setting

Calgary is a city in Alberta with a population of 1,042,892 (2008 Census). The Calgary zone of Alberta Health Services has three major teaching hospitals, of which two are regional centers and one is a tertiary care center with cardiac catheterization and revascularization capabilities.

2.2.2 Data Collection

From January 1, 2007 to December 31, 2008, all troponin values above the reference range occurring during hospital admission within the Calgary Zone were identified. At the time of data collection, the Calgary Zone was measuring cardiac troponin T (cTnT). Patients whose primary residence was outside of the Calgary Zone or those transferred from institutions outside the region were excluded, as were those under the age of 18 years.

The cohort of interest were those patients for whom the attending medical team decided a cardiac troponin T measure was indicated, and there was a presumptive diagnosis of T2MI. As there is no ICD code at current for type 2 MI, this was determined by performing a retrospective chart review on every patient. This chart review was performed by an International Medical Graduate, fully trained in cardiology. The chart abstraction form used can be seen in the appendix. An experienced cardiologist, blinded to patient data and diagnosis, reinterpreted all electrocardiograms (ECG) performed around the time of the troponin elevation. Patients with types 3, 4a, and 4b MI were excluded.

The Alberta Provincial Project for Outcomes Assessment in Coronary Heart disease (APPROACH) registry was used to create an age- and sex-matched cohort of T1MI patients admitted during the same time as the T2MI patients.

Ethics approval was obtained by the Health Research Board at the University of Alberta. The ethics board granted a waiver of consent for this study, given the retrospective chart review and no patient contact.

2.2.3 Data Sources

The Alberta Provincial Project for Outcomes Assessment in Coronary Heart disease (APPROACH) registry is a clinical data-collection initiative, capturing all patients undergoing cardiac catheterization in Alberta since 1995, following them longitudinally to determine patient outcome.[31] The admission module of the APPROACH registry has tracked all patients admitted with acute coronary syndromes across Southern Alberta since 1994. The registry also contains detailed information regarding patient demographics, cardiac risk factors, comorbidities and results of cardiac catheterization and revascularization procedures. Comorbidities are subsequently verified through a data enhancement procedure to ensure data is accurate and there is no missing data.[32,33] Mortality data for all patients in the database is ascertained through quarterly linkage to the Alberta Bureau of Vital Statistics.

The Cardiovascular Health & Stroke Strategic Clinical Network (SCN) is an Alberta-wide team of healthcare professionals, researchers and policy makers who are

knowledgeable about cardiovascular health and work to improve its prevention, treatment and management, through accessing and supporting research. Through the SCN we obtained access to provincial administrative data identifying individual patient comorbidities, hospital readmissions and the completion of diagnostic tests including echocardiograms, myocardial perfusion scans and CT scans. The APPRAOCH, mortality and administrative data was linked using individual ULI number to ensure accuracy of all information.

2.2.4 Cardiac Troponin T Analysis

The cardiac troponin used in the Calgary Zone at this time was the Roche Troponin T assay, measured using the Elecsys 2010 Modular Analytics E170 system. It is an immunoassay for the in vitro quantitative measurement of troponin T, using two monoclonal antibodies specifically directed against human cardiac troponin T. The results are reported in μg/L. The lower detection limit for this assay is 0.010 μg/L, however, 0.030 μg/L is the troponin T concentration that can be reproducibly measured with an intermediate precision coefficient of variation of 10%, and the normal value is therefore reported as <0.030 μg/L. The measurement range is 0.03-40.0 μg/L.

2.2.5 Statistical Analysis

Patients identified as having a positive troponin due to T2MI were sex- and exact age-matched to patients with T1MI from the APPROACH registry. Baseline clinical characteristics were compared using chi-square tests, as was crude mortality. Cox regression models were used to compare mortality of patients with type 1 and 2 MI, with

adjustment for age, sex and Charlson comorbidity index[34-36]. Statistical analysis was performed with SAS 9.3 (Cary, NC) and a p value of <0.05 was defined as significant.

2.3 Results

From January 1, 2007 to December 31, 2008, 4,860 patients with a positive cardiac troponin T value were admitted to hospital in the Calgary Zone. Following chart review, 2,051 (42.2%) patients were identified as having a diagnosis of T1MI and 998 (20.5%) with T2MI. Those with type 3-5 MI were excluded. Following age and sex matching, 756 patients with T1MI and T2MI were included in the matched cohorts.

Prior to age and sex matching, the mean age of those with T2MI was 73.5 years (standard deviation 16.0) and no sex predominance was found, with 511 (51.2%) of T2MI patients being men. Baseline characteristics of the two age and sex matched cohorts are shown in Table 1. The T2MI cohort had significantly more comorbidities, including cerebrovascular disease, diabetes, heart failure, pulmonary and renal disease. Those with T1MI were significantly more likely to have hypertension, hyperlipidemia, to be an active smoker and to have undergone prior percutaneous coronary intervention.

Table 2 shows the admitting service of those patients admitted with T2MI. Of those with T2MI, 5.4% (n=41) of patients were admitted to a cardiology service, with the majority being inpatients on other services including internal medicine (n=272, 36.0%) and family medicine (n=193, 25.5%). Additionally, of those admitted to non-cardiology services, only 6 (0.8%) received a cardiology consultation to assist in management.

Symptoms documented at the time of troponin elevation are demonstrated in Table 2. Shortness of breath was most common, yet occurred in only 17% (n=129) of patients. Chest pain was documented in only 8.4% (n=64) of cases of T2MI.

Relevant laboratory and ECG findings are illustrated in Table 3. Troponin levels were significantly higher in patients with T1MI. Dynamic ECG changes were common in T2MI (20.1%, n=152). The most common ECG changes were T-wave changes (23.3%, n=176) and ST segment depression (12.8%, n=97). Lastly, patients with T2MI were more likely to have no ECG done at all, or no follow-up ECG performed.

None of the patients diagnosed with T2MI underwent coronary angiography during their index admission, compared to 80.4% (n=608) of the T1MI cohort ($p<0.0001$). T2MI patients underwent echocardiogram and CT chest to rule out pulmonary embolism significantly more often than their T1MI counterparts (23.7% vs. 3.0%, $p<0.0001$, 6.9% vs. 0%, $p<0.0001$, respectively).

Antiplatelet, anticoagulant and secondary prevention medications were infrequently prescribed in T2MI, with 24.3% (n=184) being prescribed aspirin, 22.9% (n=173) beta blocker and 17.6% (n=133) a statin agent (Table 4).

Table 5 shows mortality associated with T1MI and T2MI. Outcomes were significantly worse in patients with T2MI at 30-days, through to 4-years. There was no significant

difference in 30-day or 1-year readmission rates in the two cohorts. These differences in mortality were also seen following adjustment for age, sex, and baseline risk factor differences using the Charlson Comorbidity index. The Kaplan Meier survival curve demonstrating mortality in type 1 and 2 MI is shown in in Figure 1.

Independent predictors of 30-day mortality with T2MI are shown in Table 6. History of stroke, active malignancy and creatinine >200mmol/L were all found to be independent predictors of 30-day mortality in T2MI.

2.4 Discussion

In a large population of patients with troponin elevation, we found that one-fifth of troponin elevations (20.5%) were attributable clinically to T2MI. These patients frequently had ECG changes (20.1%), yet infrequently underwent further investigation for coronary artery disease. Additionally, their outcomes were poor, worse than patients diagnosed with T1MI, even after adjustment for comorbidities.

Estimates of the incidence of T2MI are variable, ranging from 1.6 to 35.2%.[9,13,15,16,20,24-27] This range likely reflects small sample sizes, heterogeneous populations with variable illness severity and most significantly, variability in diagnostic definitions in prior studies. It is often difficult to discriminate between T1MI and T2MI clinically, as there are no objective pathophysiological-or biomarker-based tests to assist in diagnostic differentiation.

Saaby *et al* reported a retrospective study identifying those with T2MI using an independently-created, specific definition, observing a prevalence of 24-26%.[16] This definition has not been further validated or universally accepted. Most other investigators have defined of T2MI on an individual basis, as we did through retrospective chart review of the clinical situation and impression of the healthcare team at the time of troponin elevation.[9,11,12,13,15,18,19,24-27,37,38]

Consistent with previous studies, our cohort with T2MI was older, with an average age of 73.5 years, with numerous comorbidities.[9,11,13,15,16,17,19,27] We did not find a female sex predominance, as other studies have.[9,14,16,18,27,39]

In our study, the majority of patients with a diagnosis of T2MI were admitted to family medicine and internal medicine. This is likely due to the age and comorbidities present in this population, as well as the fact that T2MI is a secondary diagnosis, with the cause of the supply-demand mismatch often being the primary admission diagnosis. Nonetheless, the rarity of cardiology consultation was striking (0.7%). This practice pattern is noteworthy, as literature shows that when myocardial infarction (MI) is treated by a generalist, cardiology consultation has been shown to result in equivalent treatment to when MI a specialist in cardiology is the primary care provider, suggesting cardiology consultation can standardize appropriate diagnosis, investigation and therapy.[40]

Symptoms were infrequently reported in patients diagnosed with T2MI. Additionally, the most common symptom documented was non-specific (dyspnea), consistent with other

investigators.[12,13,15] Baron *et al* found 85% of T1MI patients suffered chest pain at the time of diagnosis as compared to only 62% of those with T2MI.[9] Sandoval *et al* found a similar trend, with patients with T1MI being significantly more likely to present with typical cardiac symptoms than those with T2MI.[14] The relative paucity of symptoms and the non-specific symptoms that do develop with T2MI could contribute to missed diagnoses, similar to descriptions from studies of post-operative myocardial injury.[41]

As demonstrated by other authors, the maximal troponin associated with T2MI in our study was lower than in T1MI.[6,9,10,16] Unfortunately, T2MI cannot be diagnosed by absolute troponin, as a wide range of values are seen. Studies have assessed whether delta troponin values could be used to differentiate T1MI from T2MI, but this has also been unsuccessful in differentiating the two entities.[14] Smilowitz *et al* found the maximal troponin value in T2MI was important however, as T2MI patients with top quartile troponin values had a significantly higher in-hospital mortality.[37] This emphasizes that T2MI is not just a laboratory abnormality, but instead is a complex, poorly understood syndrome, associated with significant mortality risk.

As has been documented by other authors, cardiac medications were used infrequently in T2MI in our study, with aspirin being prescribed in only 25.5% and a statin in 16.7%.[6,9,11] In contrast, Javed *et al* reported no difference in medications prescribed to T1MI versus T2MI patients.[20] Despite the excellent evidence for numerous cardiac medications in acute coronary syndrome, their use in T2MI has not yet been established.

Although no patient in our cohort of T2MI underwent coronary angiography during index hospitalization, it has been previously reported that roughly half of patients with type 2 MI have significant coronary artery disease.[9,16] Ambrose *et al* found angiographic culprit lesions were uncommon in patients with T2MI; however, Landes and colleagues found angiographic evidence of plaque rupture in 29% of T2MI patients.[7,17] The CASA-BLANCA study found 61.2% and 47.7% of T2MI patients had >50% and >70% coronary stenosis in two or more coronary arteries, respectively.[19] Supply-demand ischemia does suggest that there may be some degree of underlying coronary artery disease, therefore medications for secondary prevention of coronary artery disease may be appropriate.[9,16,17,38] The lack of guidelines and clinical trials in this area leaves the prescribing of such medications to the discretion of individual clinicians.

Current literature on mortality in T2MI is limited by small population numbers, short-duration of follow-up, and diagnostic discrepancies. In our population, crude mortality in T2MI was high, approaching 40% at 4-years. This is significantly higher than that of T1MI patients when age and sex matched cohorts were compared, and is consistent with the findings of Saaby *et al*.[6] Even after adjustment for age, sex and baseline risk factor differences, we found mortality associated with T2MI remained greater than that associated with T1MI. Other investigators, while reporting lower mortality rates with T2MI than our study, also found worse outcomes compared to T1MI.[10,13,17,20]

We identified several comorbidities to be independent predictors of 30-day mortality in T2MI, including stroke, malignancy and kidney dysfunction (creatinine>200mmol/L).

Overall, the occurrence of T2MI appears to be a marker of risk for mortality, much as myocardial injury is in the perioperative literature.[41]

2.5 Limitations

This study does have limitations. The absence of objective criteria to definitively differentiate between T1MI and T2MI means that our retrospective chart review relied on available data and the impression of the attending team at the time the troponin elevation was noted. Our cohort consisted of patients with positive troponin results. We do not have data for those patients in whom troponin measures were not felt to be indicated. Lastly, our study was performed prior to the use of high-sensitivity troponin. However, this does not significantly impact the results of our study, as the diagnosis of T2MI is a clinical diagnosis and absolute troponin value does not aid in the differentiation of type 1 and 2 MI. The use of high sensitivity troponin could result in the identification of more T2MI patients, potentially identifying another group of patients at risk. Additionally, the management of T2MI has not changed in the interval, with no consensus or guidelines as to the investigation or treatment of T2MI.

2.6 Conclusions

In conclusion, we have described the clinical characteristics and outcomes of a large population of T2MI patients, with long-term follow-up. In this large unselected cohort of patients with elevated cardiac troponin T, one-fifth of patients had type 2 MI. These patients had infrequent, non-specific symptoms and ECG changes, and were rarely investigated further, raising the possibility of both misdiagnosis and potential under

treatment. Most striking, the outcome associated with T2MI was worse than that of T1MI, even after adjustment for comorbidities, emphasizing the importance of further research to identify appropriate investigation and effective treatment strategies for this vulnerable group of patients.

TABLES AND FIGURE

Table 1. Baseline characteristics for age and sex matched type 1 and 2 MI cohorts

Characteristic	Type 1 MI N=756	Type 2 MI N=756	p-value
Mean Age (SD)	70.1 (13.8)	70.2 (14.4)	0.839
Male	421 (55.7%)	421 (55.7%)	1.00
Stroke	9 (1.2%)	75 (9.9%)	<0.0001
Cerebrovascular disease	12 (1.6%)	86 (11.4%)	<0.0001
Diabetes	161 (21.3%)	226 (29.9%)	0.0001
Hypertension	445 (58.9%)	316 (41.8%)	<0.0001
Hyperlipidemia	122 (16.1%)	12 (1.6%)	<0.0001
Peripheral vascular disease	19 (2.5%)	50 (6.6%)	0.0001
Heart Failure	97 (12.8%)	204 (27.0%)	<0.0001
Prior MI	28 (3.7%)	12 (1.6%)	0.010
Prior PCI	39 (5.2%)	3 (0.4%)	<0.0001
Prior CABG	23 (3.0%)	8 (1.1%)	0.007
Dialysis	1 (0.1%)	22 (2.9%)	<0.0001
Pulmonary Disease	45 (6.0%)	158 (20.9%)	<0.0001
Malignancy	13 (1.7%)	103 (13.6%)	<0.0001
Liver/GI Disease	8 (1.1%)	59 (7.8%)	<0.0001
Renal disease	57 (7.5%)	324 (42.9%)	<0.0001
Current Smoker	79 (10.5%)	33 (4.4%)	<0.0001
Dementia	22 (2.9%)	67 (8.9%)	<0.0001
Sepsis/Shock	12 (1.6%)	20 (2.7%)	0.153
Bleed (GI, Intracranial, urological, pulmonary)	22 (2.9%)	114 (15.1%)	<0.0001
Transfusion	0	2 (0.3%)	0.157

MI, myocardial infarction; SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GI, gastrointestinal

Table 2. Characteristics of those with Type 2 MI

Characteristics		N=756
Attending Service		
	Cardiology	41 (5.4%)
	Critical Care	111 (14.7%)
	Family Medicine	193 (25.5%)
	Internal Medicine	272 (36.0%)
	Surgery	112 (14.8%)
Consultation		
	Cardiology consultation (no transfer)	6 (0.8%)
	Cardiology consultation & Transfer	9 (1.2%)
Symptoms		
	Chest pain	64 (8.4%)
	Jaw/neck/arm pain	17 (2.2%)
	Shortness of breath	129 (16.9%)
	Nausea/vomiting	44 (5.8%)
	Diaphoresis	14 (1.8%)
	Weakness/dizziness	95 (12.4%)

MI, myocardial infarction

Table 3. Investigations in those with Type 1 and Type 2 MI

Investigation			Type 1 MI N=756	Type 2 MI N=756	p-value
Laboratory Tests					
	Mean Troponin (SD)		1.46 (3.3)	0.40 (0.98)	<0.0001
	Minimum Troponin		0.10	0.10	NS
	Maximum Troponin		39.40	18.68	<0.0001
Tests					
	Echocardiogram		23 (3.0%)	179 (23.7%)	<0.0001
	MIBI		33 (4.4%)	5 (0.7%)	<0.0001
	CT scan		0	52 (6.9%)	<0.0001
	Coronary Angiogram during index stay		608 (80.4%)	0	<0.0001
ECG Interpretation					
	No ECG		19 (2.5%)	49 (6.5%)	0.0002
	Dynamic ECG change compared to baseline		64 (8.5%)	152 (20.1%)	<0.0001
	Findings on Worst ECG				
		ST Elevation	289 (38.3%)	41 (5.4%)	<0.0001
		ST depression	201 (26.6%)	97 (12.8%)	<0.0001
		T wave changes	269 (25.6%)	176 (23.3%)	<0.0001
		Bundle branch block	77 (10.2%)	81 (10.7%)	0.737
		Paced Ventricular Rhythm	10 (1.3%)	4 (0.5%)	0.107
	No Follow-up ECG Performed		39 (5.2%)	219 (29.0%)	<0.0001

MI, myocardial infarction; SD, standard deviation; WBC, white blood cell; Hgb, hemoglobin; MIBI, technetium 99 sestamibi myocardial perfusion scan; CT, computed tomography; ECG, electrocardiogram; ST, ST segment

Table 4. Relevant Use of Medications prescribed in Type 1 and 2 MI

Medications	Type 1 MI N = 756	Type 2 MI N = 756	p-value
ASA	692 (91.5%)	184 (24.3%)	<0.0001
Clopidogrel	609 (80.6%)	38 (5.0%)	<0.0001
IV-Heparin	158 (20.9%)	70 (9.3%)	<0.0001
Low Molecular Weight Heparin	43 (5.7%)	24 (3.2%)	0.018
Beta Blocker	626 (82.8%)	173 (22.9%)	<0.0001
ACE Inhibitor	547 (72.4%)	126 (16.7%)	<0.0001
Statin	594 (78.6%)	133 (17.6%)	<0.0001

MI, myocardial infarction; ASA, Acetylsalicylic acid; IV, intravenous; ACE, angiotensin-converting enzyme

Table 5. Mortality of Type 1 verses Type 2 MI and Crude & Adjusted Proportional

Outcome	Mortality in Type 1 vs Type 2 MI			Crude and Adjusted HR for Mortality with Type 2 MI	
	Type 1 MI N=756	Type 2 MI N=756	p-value	Crude HR (95% CI)	Adjusted HR† (95% CI)
30-day mortality	14 (1.9%)	122 (16.1%)	<0.0001	8.99 (5.17, 15.64)	6.17 (3.16, 12.02)
1-year mortality	52 (6.9%)	180 (23.8%)	<0.0001	3.80 (2.79. 5.17)	2.02 (1.35, 3.02)
2-year mortality	75 (9.9%)	220 (29.1%)	<0.0001	3.31 (2.55, 4.30)	1.72 (1.21, 2.43)
3-year mortality	112 (14.8%)	253 (33.5%)	<0.0001	2.61 (2.09, 3.26)	1.40 (1.04, 1.90)
4-year mortality	144 (19.1%)	282 (37.3%)	<0.0001	2.30 (1.88, 2.81)	1.33 (1.02, 1.75)
30-day readmission	81 (10.7%)	96 (12.7%)	0.230	1.19 (0.88, 1.59)	0.91 (0.61, 1.37)
1-year readmission	251 (33.2%)	237 (31.4%)	0.441	0.96 (0.80, 1.15)	0.72 (0.56, 0.92)

Hazards Models for Mortality with Type 2 MI

**Reference group=Type 1 MI; †adjusted for comorbidities*

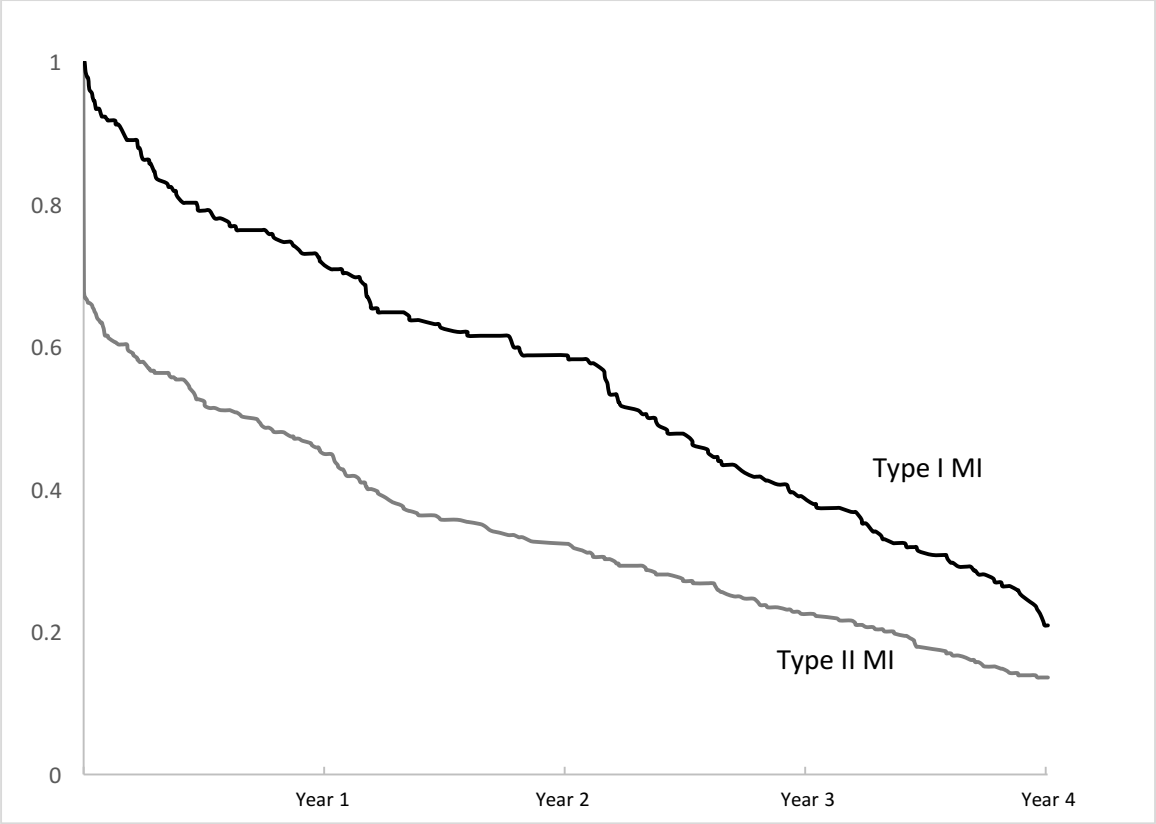
MI, myocardial infarction; HR, Hazards ratio; CI, confidence interval

Table 6. Independent Predictors of 30-day Mortality in the Type 2 MI group (N=756)

Odds Ratio Estimates		
Effect	**Point Estimate**	**95% Wald Confidence Limits**
Stroke	1.97	1.08-3.59
Malignancy	1.76	1.05-2.96
Creatinine >200mmol/L	1.74	1.17-2.59

MI, myocardial infarction; c-statistic=0.601; H-L=1.73 (p=0.422)

Figure 1. Kaplan Meier Survival Curve for Type 1 vs Type 2 Myocardial Infarction



CHAPTER 3 CONCLUSION

Type 2 myocardial infarction is myocardial necrosis as a result of an imbalance in oxygen supply and/or demand.[1] In our large cohort of patients with elevated troponin, we found T2MI to be prevalent, with roughly 20% of patients having T2MI. These patients were older, with more numerous comorbidities. After age-and sex-matching to patients with T1MI, we found patients with T2MI had infrequent, non-specific symptoms and ECG changes, and were seldom investigated further. Patients with T2MI were most often admitted to non-cardiology wards and rarely received cardiology consultation. The investigation and treatment of T2MI was variable, but no patient underwent coronary angiogram and cardiac medications were used infrequently, with aspirin only being prescribed in a quarter of patients. Lastly, the prognosis associated with T2MI was poor, worse than that of T1MI, even after adjustment for comorbidities.

3.1 Limitations

There are limitations of our work, the most significant being the accuracy of diagnosis of T2MI. Our T2MI cohort was assembled was made after performing retrospective chart review on each patient with a positive troponin result and basing the diagnosis on the available data and the clinical impression of the attending team caring for the patient. This is currently a limitation of all research on T2MI and until a biomarker or specific diagnostic criteria are validated for T2MI, we feel some degree of misclassification is inevitable.

Secondly, we did not collect a troponin on all patients admitted to the Calgary Health Region. Instead, we relied on the treating physician's discretion on whether serum troponin should be done. We therefore do not have any information for any patient with a type II MI who was missed because a troponin was not performed.

Lastly, this study was performed prior to the use of high-sensitivity troponin. It has been suggested that with the use of high sensitivity troponin, which is able to detect troponin concentrations 10-100-fold lower than conventional assays, that the diagnosis of T2MI may become more frequent.[8,10] However, this has not be corroborated to date.[42,43] Furthermore, T2MI is a clinical diagnosis and absolute troponin value does not aid in the differentiation of type 1 from type 2 MI. Additionally, the management of T2MI has not changed over this time interval. This is supported by Shah et al, who showed that with the introduction of high sensitivity troponin, outcome of T1MI improved and healthcare utilization increased, however treatment and outcome of T2MI was unchanged.[10]

3.2 Strengths

There are several strengths of our study. The current literature on T2MI is limited by small population numbers and short duration of follow-up. We have included a large population of T2MI patients and we have age- and sex-matched to T1MI patients to attempt to account for confounders. As well, we have follow-up through to 4-years

included in our study. Lastly all electrocardiograms were reviewed by a cardiologist, blind to both patient outcome and diagnosis.

3.3 Future Research Directions

T2MI is a common diagnosis, associated with much diagnostic and therapeutic confusion. More importantly, it is associated with considerable risk for subsequent morbidity, as well as short and long term mortality. In fact, current estimates show that T2MI is associated with a mortality risk that is as great, if not greater than that associated with T1MI, a diagnosis for which we have a robust understanding of the pathophysiology, diagnosis and evidence-based treatments.[10,11,13,14,17] However, the research on T2MI is still in its infancy.

Firstly, research into potential biomarkers to diagnose T2MI would be of great importance as the diagnostic dilemma and adjudication of T2MI contributes greatly to current discrepancies in the literature. Zahran and colleagues have identified troponin proteolytic degradation products are more pronounced in ST elevation MI as opposed to type 2 MI, as cell death activated intracellular proteases and a greater degree of cell death occurs in STEMI, as opposed to T2MI.[21] Future work aimed at validating this research more broadly for potential use in differentiating type 1 and 2 MI holds great potential.

Alternatively, the development of a specific diagnostic criteria for T2MI, like that of Saaby et al, and subsequent validation in a wide variety of patients and patient settings,

could also be beneficial clinically as well as in making future research more reproducible.[16,23] However, due to the wide variety of comorbidities and ages of individuals with T2MI, as well as the vast number of disease states that can cause the supply/demand imbalance causing T2MI, this validation may be difficult.

Currently the majority of the literature, including our own study, reports short and long term mortality as all-cause mortality. With the higher average age of the T2MI patient and numerous comorbidities, it would be interesting to investigate whether deaths in these patients are occurring as a result of future cardiovascular events, or if in fact their mortality may result from other causes.[23] This would entail endpoint adjudication as is done in a clinical trial, as vital statistics recording of cause of death is known to be unreliable.[44-46]

Lastly research into therapies, interventions and risk reduction strategies, to see whether this can mitigate the poor outcome associated with T2MI is necessary. This is an area that could tremendously impact outcomes in a large number of patients, just as the current medical and interventional therapies used in T1MI have significantly improved outcome after acute coronary syndrome.

3.4 Conclusion

In conclusion, T2MI is myocardial necrosis resulting from myocardial oxygen supply demand mismatch. The largely retrospective studies on T2MI are inconsistent, as a result of discrepancies in definitions, sample size and endpoint adjudication, leading to clinical

confusion.[28] However, the literature supports T2MI being highly prevalent and associated with significant morbidity and mortality. Additionally, with the more widespread use of high sensitivity troponins, which are on average ten times more sensitive than conventional troponin assays, there is question of whether the diagnosis of T2MI may increase. With the current estimates of mortality associated with T2MI being as poor as that of acute coronary syndrome, a disease for which we have a large body of high level evidence on diagnosis, investigation, treatment and prognosis, we believe further research in this area is of extreme importance.

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APPENDIX

Retrospective Chart Review Abstraction Form*

Hospital Number: _____ ULI: _____
Date of Birth: _____ Age: ____ Sex: __Male __Female
Date of cTnT elevation _____

Chart notation of symptoms/signs (physician or nursing notes, check if positive):

Retrosternal Chest Pain	□
Jaw pain, neck pain, arm pain	□
Prolonged pain >20 minutes at rest	□
Associated SOB	□
Associated nausea/vomiting	□
Associated diaphoresis	□
Weakness, dizziness, loss of consciousness	□

Lab Data around time of cTnT elevation (within 48 hours):

Peak cTnT	_____	Peak WBC	_____
Lowest Hgb	_____	Peak Creatinine	_____

Treatment – did the patient receive (or continue to receive):

ASA	□	new? □	continued?	□
Clopidogrel	□	new? □	continued?	□
IV heparin	□	new? □	continued?	□
LMWH	□	new? □	continued?	□
Beta blockers	□	new? □	continued?	□
Calcium channel blockers	□	new? □	continued?	□
ACE inhibitors/ARB	□	new? □	continued?	□
Statin	□	new? □	continued?	□
Long acting nitrate	□	new? □	continued?	□

Blood transfusion □ total units ____

Was Cardiology consulted? □ Was the patient transferred to cardiology? □

What tests were done?

Echocardiogram	□	EF _____
MIBI/stress test	□	positive? □
V/Q Scan	□	positive? □
CT PE	□	positive? □

Diagnosis attributable to cTnT rise (if documented in chart)

	By admitting service	**By Cardiology**	**By other _____**
Acute coronary syndrome/MI	□	□	□
Type II MI	□	□	□
Severe valvular disease	□	□	□
AS □ AI □ MR □ other □ ___			
CHF	□	□	□
Sepsis	□	□	□
Pulmonary embolism	□	□	□
Hemorrhage	□	□	□

Stroke	□	□	□
Renal insufficiency	□	□	□
Other Diagnosis	_____	_____	_____
Nothing specified	□	□	□

What happened to the patient?

Discharged home	□
Discharged to other facility/rehab	□
Deceased in hospital	□

**Chart review performed by an International Medical Graduate, previously trained as a cardiologist.*

ULI, Unique Lifetime Identifier; cTnT, cardiac Troponin T; SOB, Shortness of breath; Hgb, hemoglobin; WBC, white blood cells; ASA, Aspirin; IV, intraveneous; LMWH, Low molecular weight heparin; ACE, Angiotensin converting enzyme; ARB, Angiotensin receptor blocker; MIBI, myocardial perfusion scan using methoxy-isobutyl-isonitrile; V/Q scan, ventilation perfusion scan of lungs; CT PE, computerized tomography performed using pulmonary embolism protocol;EF, ejection fraction; MI, myocardial infarction; AS, aortic stenosis; AI, aortic insufficiency; MR, mitral regurgitation; CHF, congestive heart failure