SERUM TROPONIN I LEVELS AND ALL CAUSE MORTALITY AND INCIDENT MYOCARDIAL INFARCTION: ANALYSIS OF THE PITTSBURGH VETERAN'S HEALTHCARE SYSTEM

by

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in both men and women. Although rates of CVD have declined, the overall number of people who will develop CVD is substantial. Given current demographic trends and the future "silver tsunami", the number of deaths due to CVD and incident CVD events will increase. Circulating levels of cardiac troponin have been shown to predict subsequent cardiac events. In addition, the predictive value of cardiac troponin I (cTnI) may extend beyond death and myocardial infarction. Most of the data come from observational studies of community dwelling subjects with relatively short follow-up period. It is important to systematically evaluate whether serum levels of cTnI predict CVD outcomes over the long term. In this dissertation, we evaluated a policy implemented at the Veteran's Affair (VA) Healthcare System in Pittsburgh. This policy required that serum cTnI levels be drawn on all patients admitted to the hospital with pain between their ears and hips. After excluding patients who had an acute myocardial infarction or who died in the hospital, we identified 2901 patients with a serum cTnI level drawn in fiscal 2010. Follow-up continued for 365 days after their initial admission. Patients with elevated troponin I levels were more likely to die, odds ratio (OR)=2.31;95% confidence interval (CI), 1.52-3.52; to have a myocardial infarction, OR=5.46; 95% CI, 2.70-11.04; to develop heart failure OR=2.15;95% CI, 1.35-3.42; and left ventricular hypertrophy, OR=2.11; 95% CI, 1.18-3.77. The association with one year mortality

was consistent in patients with and without acute coronary syndrome. We found no association with diabetes or hypertension. Serum cTn1 predicted chronic kidney disease in models that did not adjusted for baseline renal function, OR=2.06; 95% CI, 1.54-2.75. Given the public health importance of CVD, our results show the value in a single measure of troponin in predicting future CVD events over one year of follow-up.. Our results suggest that the Pittsburgh VA Health System should continue measuring troponin on these patients. Patients with elevated levels could be targeted for interventions aimed at preventing CVD events.

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1.0 OVERARCHING HYPOTHESIS

To determine if an initial cardiac troponin I level $\geq$0.04ng/mL is associated with acute myocardial infarction (MI), all-cause mortality, and certain chronic medical conditions including diabetes, chronic kidney disease, hypertension, heart failure, left ventricular hypertrophy, cardiomyopathy or heart failure readmissions in a consecutive sample of primarily older adult males admitted to the Veteran's Pittsburgh Healthcare System in fiscal year 2010.

2.0 BACKGROUND AND RATIONALE

The figure below is inserted so that there is an item in the sample List of Figures To improve the early identification of acute coronary syndrome at the Pittsburgh Veteran's Affairs (VA) Healthcare System a process was implemented to obtain troponin I levels on all patients with any complaint of discomfort between their ears and their hips. In addition, all indeterminate troponin I levels (0.10ng/mL-0.60ng/mL) are reviewed daily by a staff cardiologist to determine if the indeterminate troponin I level is consistent with a presentation of acute coronary syndrome, an integral component in the evaluation of acute coronary syndrome.

Biomarkers have been shown to predict short-term and long-term adverse cardiac events in those presenting with symptomatic stable acute coronary syndrome (ACS) [1, 2]. However, the presence of circulating troponins levels may have significant predictive value in the absence of an acute MI, (Figure 1) [3]. Because of this, there has been a change in the interpretation of circulating levels of cardiac troponin to general markers of myocardial damage instead of solely as specific identifiers of MI [3-5].

The prognostic value of an initial level of cardiac troponin I (cTnI) $\geq$0.04ng/mL warrants further investigation to determine the existence of an association with acute coronary syndrome, all-cause mortality and heart failure readmissions. Furthermore, the relationship between the initial cTnI I level of $\geq$0.04ng/mL and chronic disease states such as diabetes, hypertension, chronic kidney disease, heart failure, cardiomyopathy and left ventricular hypertrophy given traditional risk factors including smoking status, age and male gender has not been extensively studied.

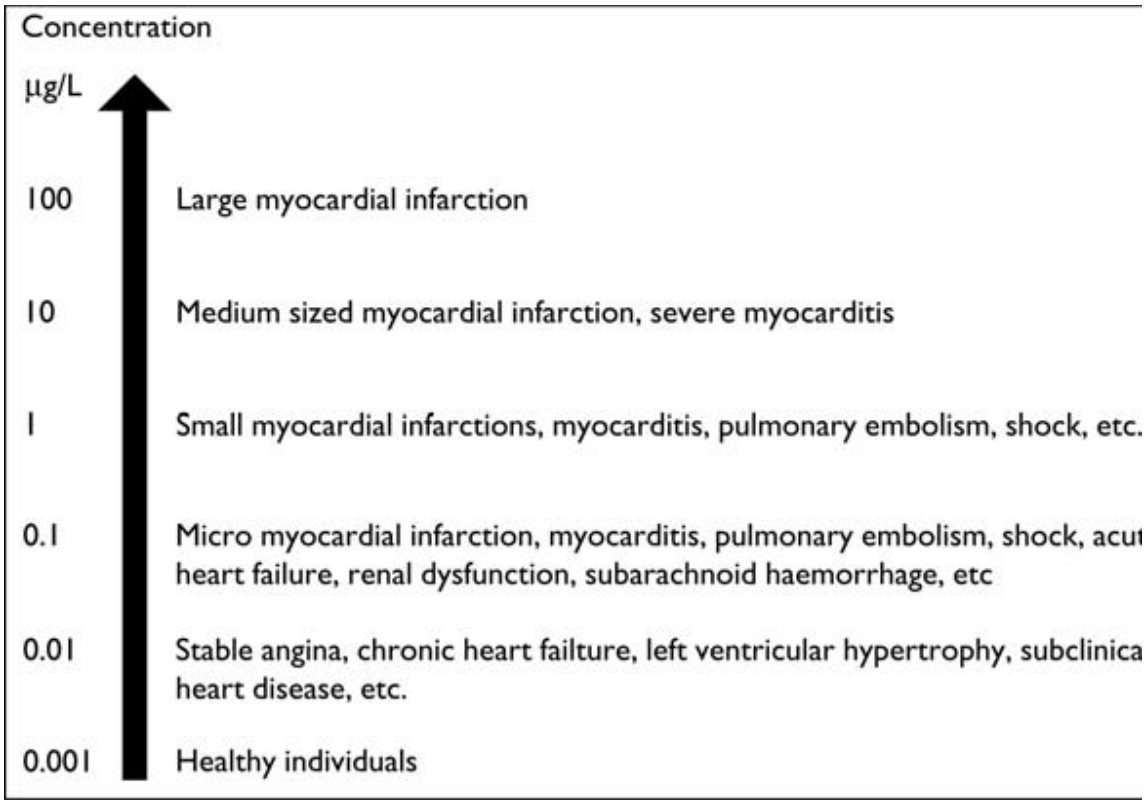

Figure 1. Relation between Troponin Level and Possible Cause

According to the American Heart Association's Heart Disease and Stroke 2013 Statistical Update, an estimated 83.6 million adults in the United States have at least one form of cardiovascular disease (CVD). Total cardiovascular disease includes hypertension, and coronary heart disease (CHD) with CHD further categorized into myocardial infarction (MI), and angina, heart failure (HF) and stroke. Among those with CVD, 42.2 million are estimated to be ≥ 60 years of age [6].

On average, over 2150 Americans die each day from CVD or approximately 1 death every 40 seconds [7, 8]. The total direct medical costs of CVD are projected to increase from $272.5 billion in 2010 to $818 billion by 2030. The indirect costs from lost productivity secondary to morbidity and premature mortality associated with CVD are expected to increase by 61% or from $171.7 billion to $275.8 billion over the same time period [9].

CVD ranked the highest among all disease categories for inpatient hospital discharges, accounting for the first listed diagnosis in 5,802,000 cases in 2010 [6] (NHDS, NHBLI

tabulation). The distribution of aggregate hospital costs in 2011 was highest among diseases of the circulatory system at 18%. Specifically, the cost-per-stay for atherosclerosis increased from 1997 to 2011, however, the aggregate costs decreased by 3% annually [10].

The magnitude of this issue is further described by considering the impact of CHD in the United States. It is projected by 2030 the prevalence of CHD will increase by almost 17%. This is equivalent to an additional 8 million people with CHD when compared to the CHD prevalence rates from 2010 [9].

Improvement in treatment modalities (~47%) and risk factor management (~44%) are attributed to the decrease in age-adjusted mortality rates for CHD since the 1960's [11, 12]. The age-adjusted prevalence of CHD in the United States from 2006 to 2010 declined from 6.7% to 6.0%. In 2010, the prevalence of CHD was highest among people ≥ 65 years of age (19.8%), followed by those 45-64 years of age (7.1%) and then those 18-44 years of age (1.2%) [13].

A dramatic change in the United States demographics will have a substantial impact on the nation's public health system secondary to an aging society. The number of U.S. adults 65 years or older will increase more than 50% by the year 2030 reaching approximately 71 million [13].

Over the past century there has been a substantial shift in the leading cause of death for all age groups from acute illnesses and infectious diseases to chronic diseases. Heart disease poses the greatest risk accounting for 27.7% of deaths among U.S. adults aged 65 or older. Multiple chronic diseases are present in 66% of older Americans and treatment for this population accounts for two thirds of the country's healthcare budget [14].

Cardiovascular risk factors are frequently under-diagnosed and under-treated in older adults possibly secondary to the ambiguity that surrounds the usefulness of risk factor reduction in this population [15, 16].

Although advances have been made, CHD remains a significant contributor to morbidity and mortality in the United States. One of the objectives of Healthy People 2020 is to lower the CHD death rate by 20%, from a baseline in 2007 of 126.0 per 100,000 (age adjusted to the year 2000 standard population) to 100.8 per 100,000 by 2020 [17].

ACS is a major cause of emergency medical care and hospitalizations. The National Center for Health Statistics reported in 2004 that there were 1,565,000 hospitalizations for the primary or secondary diagnosis of acute coronary syndrome, 669,000 for unstable angina and 896,000 for MI [18, 19].

ACS describes clinical symptoms consistent with acute myocardial ischemia. ACS is classified based on the presence or absence of ST-segment elevation and includes non-ST-segment elevation MI (NSTEMI), ST-segment elevation MI (STEMI) and unstable angina (USA). These high-risk features of coronary atherosclerosis are central to the use of emergency medical care services and hospitalization in the United States [20] .

Diseases of the heart are ranked as the leading cause of death in 2010 according to the National Vital Statistic Reports [21]. Annually, an estimated 715,000 Americans will experience a heart attack, of these approximately 525,000 people will have a new heart attack and about 190,000 people will suffer a recurrent event [6].

In the United States, cardiac related inpatient procedures have increased by 28% from 5,939,000 in 2000 to 7,588,000 in 2010 [6]. This includes but is not limited to an estimated one million cardiac catheterizations, 954,000 percutaneous interventions (cardiac stents and/or balloon angioplasties) and 395,000 coronary artery bypass surgeries in 2010 [22].

The Global Registry for Acute Coronary Events (GRACE) is a multinational observational cohort study of ACS that had identified changes in practice relating to the use of pharmacological and interventional modalities for both NSTEMIand STEMI patients. This change in practice led to decreased rates of in-hospital death, cardiogenic shock and new MI among patients with NSTEMI and among patients with STEMI there has been a significant decrease in rates of death, cardiogenic shock, and HF[23]. Although GRACE showed advancements in ACS outcomes, there remains room for improvement.

A National Quality Improvement Initiative entitled, “CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines)” enrolled 64775 patients who presented with chest pain and positive electrocardiographic changes (ECG) or cardiac biomarkers consistent

with NSTEMI. It was determined that 26% of the opportunities to provide the American College of Cardiology / American Heart Association's (ACC/AHA) Guideline-centered care for patients with ACS, were missed [24].

When patients present to the hospital with a suspected acute coronary syndrome a rapid diagnosis is essential. Patients are triaged quickly based on clinical symptoms, electrocardiogram (ECG) findings and myocardial biomarkers such as the troponin level. Decisions that are made on the basis of the initial evaluation have significant clinical and economic impact [25].

2.1 CARDIAC TROPONIN

Cardiac biomarkers are an essential component used to diagnose acute MI [26]. Considerable advances in the early detection of acute MI have been made over the past few decades secondary to the development of cardiac specific biomarkers [27, 28].

After a MI there is a distinct release kinetic pattern that occurs. Initially, troponin is released from a loosely bound protein pool that is followed by a prolonged elevation in levels secondary to degradation of the contractile apparatus, (Figure 2) [3, 29, 30]. There is data indicating that the initial troponin pool may give information on the degree of micro-vascular reperfusion, while the size of the MI is reflected in the troponin level 3 or 4 days after the event [31].

Cardiac troponin consists of three subunits of tissue specific isoforms called troponin I, T and C, that are encoded by different genes. Troponin and tropomyosin are located on the actin filament in myofibrils and are necessary for calcium-mediated contraction of cardiac and skeletal muscle, (Figure 3) [32-35]. Troponin C does not have cardiac specificity as it is shared with skeletal muscle thus, it is not used as a diagnostic tool for the diagnosis of ACS [12, 36]. Troponin I, and troponin T, do possess cardiac specificity and sensitivity making them ideal for detecting myocardial injury [37] .

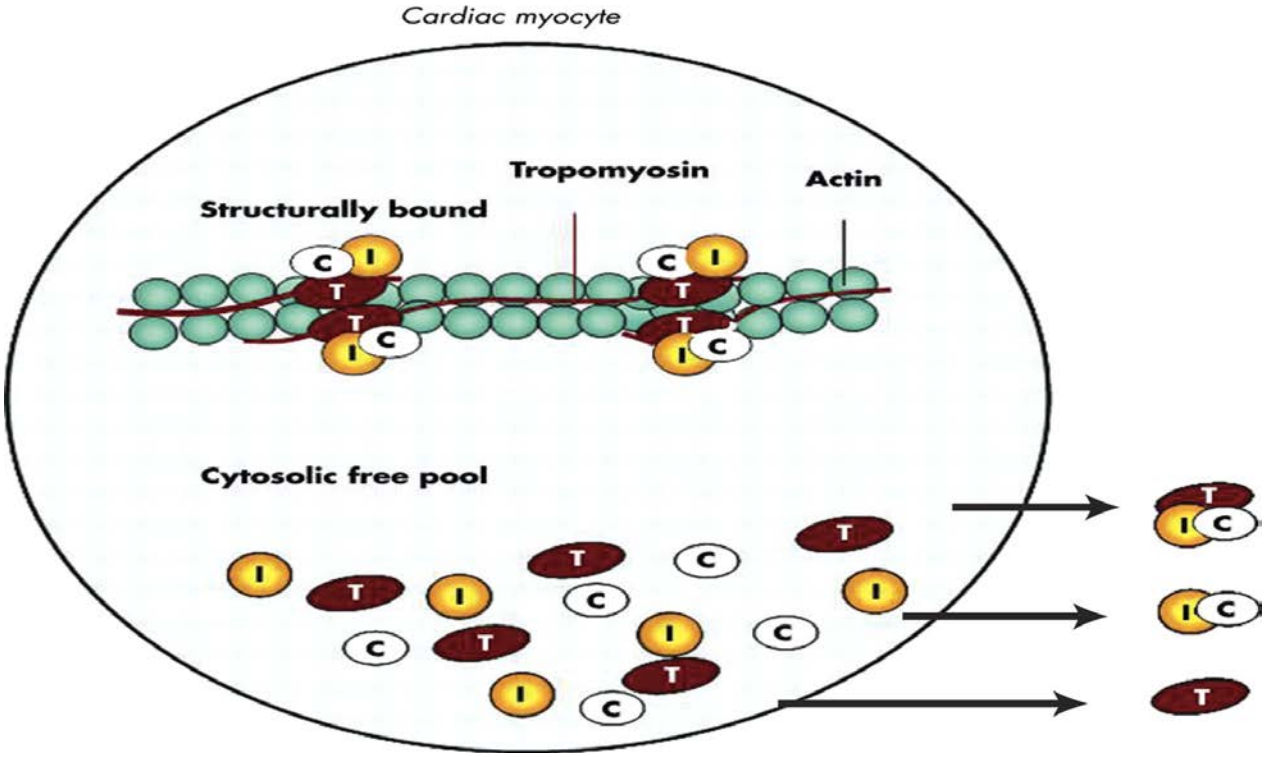

Figure 2. Schematic Representation of the Cardiac Myofibrillar Thin Filament

Cardiac Troponins Exist in a Structural (bound) Form and in a Free Cytosolic Pool. Cardiac Troponins are Released from Monocytes as Complexes or as Free Protein

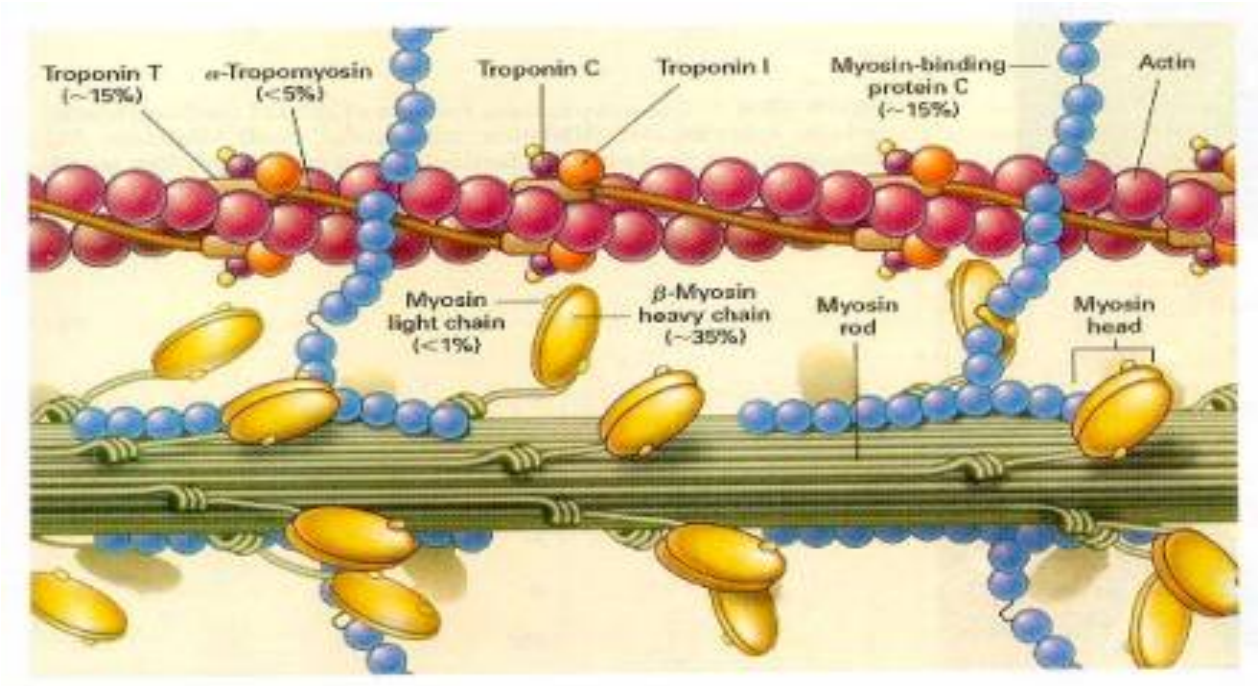

Figure 3. Troponin Complex

2.2 TROPONIN ASSAYS

Immunoassays have been developed to make a distinction between cardiac and skeletal subforms of troponin I and of troponin T [38] and because of this the interpretation and comparison of troponin levels has been challenging. There are several cardiac troponin I assays available for use compared to one troponin T assay. The troponin I assays are not standardized leading to considerable dissimilarities among procedures [39].

The heterogeneity of troponin assays necessitates that clinicians know the limitations and analytical quality of the assay being used. It is recommended that the detection limit for myocardial injury be the concentration that corresponds to the 99th percentile limit of the reference distribution in healthy people, (Figure 4) [35].

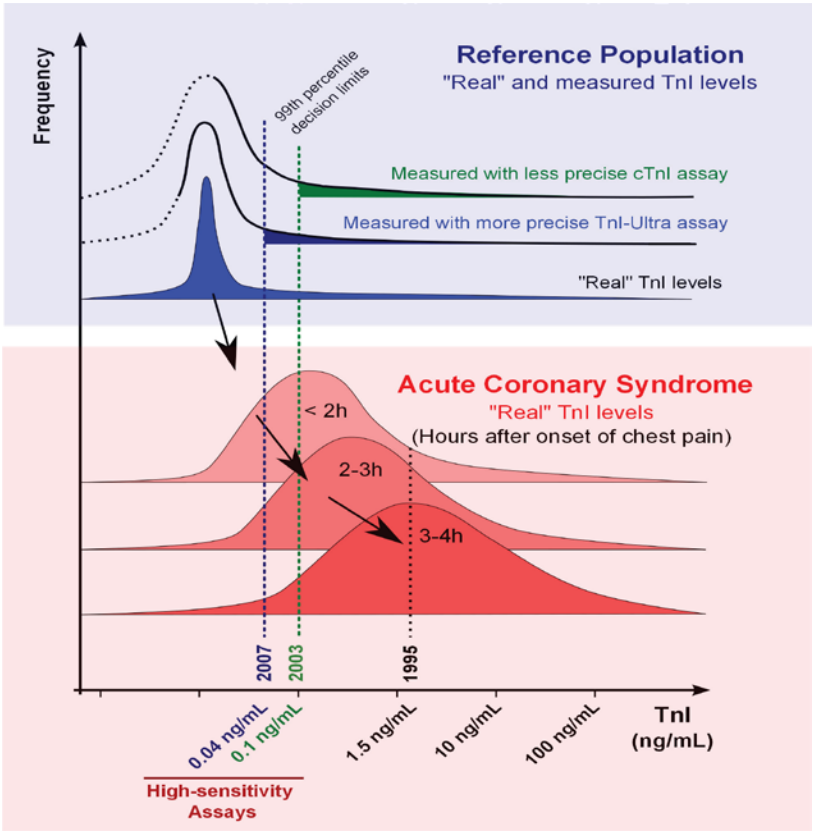

Figure 4. Troponin I in a Health Reference Population and in an Acute Coronary Syndrome Population

Cardiac troponin immunoassays use two reference ranges to report troponin levels, the coefficient of variation and the upper percentile reference limit. The goal is for the coefficient of variation (CV) to be ≤10 % at the 99th percentile or three standard deviations above the mean for the normal range [40]. The CV is the percent variation in assay results that may be expected when the same sample is repeatedly analyzed. The upper percentile reference limit gives the upper limit of what may be expected in a healthy, normal adult population.

Even though the development of cardiac troponin assays with increasing sensitivity lowers the number of potentially missed ACS diagnosis, it presents a diagnostic challenge as the gains in sensitivity have come at the cost of decreasing specificity [41].

The VA Pittsburgh Healthcare System performed Troponin I methodology on the Siemens Xp and instrument using the Troponin-I Flex® reagent cartridge. The CTNI method for the Dimension clinical chemistry system with heterogenous immunoassay module as an in-vitro diagnostic test is intended to quantitatively measure cTnI levels in human serum and heparinized plasma. Lithium heparin plasma is the sample of choice. Specimens are stable for 8 hours when at 20-25 degrees Celsius, 2 days at 2-8 degrees Celsius. For longer storage, specimens may be frozen at -20 degrees Celsius or colder. This is a highly sensitive colorimetric immunoassay that measures cTnI, however, it is not considered a high-sensitivity troponin assay. The manufacturers biometric assay reference range: 0.04-0.99ng/mL (negative); 0.10-0.6ng/mL (indeterminate); and >0.6ng/mL (positive) (Seimens Healthcare Diagnostics Inc, Deerfield IL).

2.3 THIRD UNIVERSAL DEFINITION OF MYCOCARDIAL INFARCTION

In 2012, a Task Force comprised of the European Society of Cardiology (ESC), American College of Cardiology Foundation (ACC), American Heart Association (AHA) and the World Heart Federation (WHF) [35] released its third universal definition of MI. The new universal definition of MI is classified into various types based on clinical, pathological and prognostic differences, as well as treatment options, Table 1 [35].

Table 1. Universal Classification of Myocardial Infarction

Type I: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type II: Myocardial infarction secondary to an ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type III: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type IVa: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or a persistent slow or no flow or embolization, or (IV) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type IVb: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis or detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type V: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤ 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

This definition takes into account the increasing sensitivity of troponin assays that are frequently elevated in conditions other than acute MI allowing for the differentiation between pathologic MI and benign myocardial injury, (Figure 5) [42].

Moreover, in addition to troponin elevation, the detection of MI takes into consideration the clinical symptoms, and EKG findings at the time of presentation [35] .

The clinical features of MI include chest, arm, shoulder, jaw or epigastric discomfort, shortness of breath, nausea, diaphoresis, syncope or fatigue that usually lasts more than 20 minutes and may occur with rest or exertion. The associated ECG changes are usually T wave and ST segment changes. It is prudent to consider troponin elevation, ECG changes, and clinical presentation when diagnosing MI.

Upon hospital admission, the sensitivity of cTnI is less than 45%; however, the sensitivity increases to 100% at 6 to 12 hours after admission [43, 44]. Cardiac troponin I levels can be detected as soon as 2 to 4 hours after symptom onset with peak values occurring between 8 to 16 hours after the onset of symptoms and may be present for up to 4 to 14 days [1].

The use of cardiac troponin I and T levels for the diagnosis of acute MI and the prediction of subsequent cardiac events has been well established (Tables 2 and 3), [45]. While troponin I and T elevation reflects myocardial injury, it does not specify the etiology of the injury [46, 47]. The diagnostic value of troponin I extends beyond identifying myocardial injury, (Figure 6) [42]. Troponin I can provide prognostic information for many other medical conditions such as heart failure [48], hypertension [49], hypertrophic cardiomyopathy [50] and renal failure [51-53]. The predictive value of an initial cTnI in determining all-cause mortality, acute MI, and as a prognostic tool for other medical conditions in the VA Pittsburgh Healthcare System is unknown.

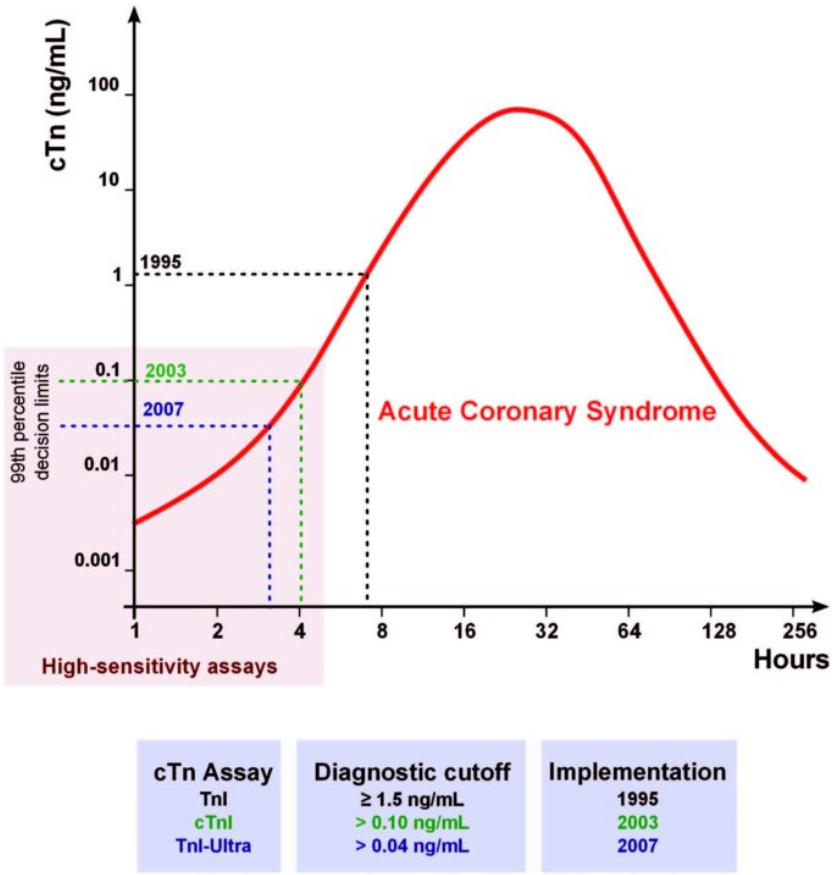

Figure 5. Evolution of the Cardiac Troponin Assays and their Diagnostic Cutoffs

Table 2. Outcomes for Studies of Troponin T

Author	Definition of Positive Troponin	Follow-Up (Weeks)	Death/Total Troponin		Death or MI/Total* Troponin	
			Positive	Negative	Positive	Negative
Antman et al. (24)	Any	2	2/116	7/481	na	na
de Winter et al. (31)†	Any	26	0/24	1/146	1/24	2/146
deFilipp et al. (32)†	Initial	52	4/39	0/132	na	na
Gokhan Cin et al. (33)	Initial or second	1	6/24	2/48	na	na
Hamm et al. (10)†	Any	4	16/123	4/650	na	na
Hamm et al. (34)	Any	1	5/33	1/51	10/33	1/51
Hamm et al. (35)	Any	24	9/275	10/615	46/275	52/615
Lindah et al. (36)†	Any	20	13/399	0/182	51/399	8/182
Luscher et al. (42)†	Any by 6 h	4	8/249	1/267	na	na
Mathew et al. (44)‡	Any	12	1/31	0/183	na	na
Mockel et al. (37)	Any	12	1/11	2/95	na	na
Ohman et al. (13)	Initial	4	13/131	4/189	na	na
Olatidoye et al. (43)	Initial	4	na	na	5/14	3/93
Pettijohn et al. (38)†	Any	24	2/35	3/94	6/35	7/94
Ravkilde et al. (11)†	Any	24	3/44	1/83	6/44	3/83
Ravkilde et al. (12)†	Any	112	3/25	3/99	na	na
Rebuzzi et al. (39)	Initial	12	1/14	0/88	7/14	8/88
Stubbs et al. (40)†	Initial	147	12/62	14/121	na	na
Yang et al. (41)	Any	1	na	na	11/34	1/60
Total or mean		28	99/1,635	53/3,524	136/804	80/1,183

*In unstable angina patients; †deaths limited to those of cardiac cause; ‡data available for serum and whole-blood assays. Whole-blood assay data used for summary calculation.
MI = myocardial infarction; na = not available/applicable.

Table 3. Outcomes for Studies of Troponin I

Table 3. Outcomes for Studies of Troponin I

Author	Definition of Positive Troponin	Follow-up (Weeks)	Death/Total Troponin		Death or MI/Total* Troponin	
			Positive	Negative	Positive	Negative
Antman et al. (9)	Any	6	21/573	8/831	na	na
Brscic et al. (25)	Any	4	2/22	2/70	na	na
Christenson et al. (23)	Initial	4	26/220	24/550	na	na
Fearon et al. (29)	Any	28	na	na	3/16	5/77
Galvani et al. (26)†	Any	4	2/22	0/69	5/22	4/69
Hamm et al. (10)†	Any	4	19/171	1/602	na	na
Heeschen et al. (27)	Any	4	25/629	36/1,593	na	na
Janorkar et al. (28)	Any	38	1/34	1/46	na	na
Luscher et al. (42)†	Any by 6 h	4	7/213	2/303	na	na
Olatidoye et al. (43)	Initial	4	na	na	5/13	3/94
Mathew et al. (44)	Any	12	1/55	0/159	na	na
Meyer et al. (30)	Any	24	4/42	3/199	na	na
Total or mean		10	108/1,981	77/4,422	13/51	12/240

*In unstable angina patients; †deaths limited to those of cardiac cause.
MI = myocardial infarction; na=not available/applicable.

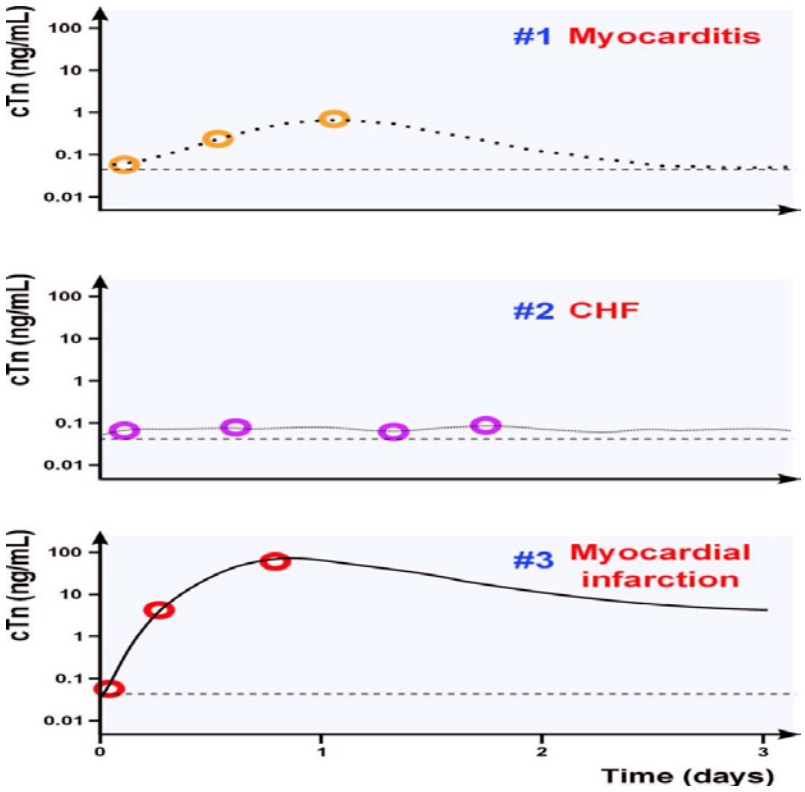

Figure 6. Troponin Kinetics

2.4 CHRONIC KIDNEY DISEASE

There is a significant increase in mortality and morbidity from CVD among patients with chronic kidney disease (CKD) [54] and CKD has been shown to be an independent risk factor for cardiovascular events [55]. Patients with CKD, but not on dialysis, are more likely to die from CVD than to progress to renal failure[56, 57]. Premature coronary atherosclerosis is associated with CKD particularly in the setting of several chronic renal failure induced risk factors including hypertension and lipid disorders [58, 59].

The increased risk of cardiovascular events such as recurrent MI, heart failure, restenosis and death, according to most cardiovascular outcome studies, occurs when the serum creatinine level is approximately >1.5mg/dL which translates to an eGFR <60mL/min/1.73m^2 in the general population [60, 61].

In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) published the first internationally accepted definition and classification of CKD. In 2004, this definition was supported by the workgroup, Kidney Disease: Improving Global Outcomes (KDIGO). This model encouraged deepened awareness of CKD as a public health issue, as well as its importance in research and clinical practice. KDOQI and KDIGO indicated that the definition and classification of CKD should be indicative of the patient's prognosis. This stance prompted debate. In 2009, a collaborative meta-analysis to assess the association of eGFR and albuminuria to mortality and kidney outcomes and a Controversies Conference was initiated by KDIGO. Based on the analysis of 45 cohorts consisting of over 1.5 million subjects that represented the general, high-risk and kidney disease populations, it was agreed to retain the current definition of CKD and to modify the classification of CKD [62] .

CKD is defined as a Glomerular filtration rate (GFR) <60ml/min/1.73m^2 for ≥ 3 months with or without kidney damage or a urinary albumin-to-creatinine ratio >30mg/g. The classification of CKD was modified by the addition of the stage of albuminuria, subdivision of stage 3 and highlighting the clinical diagnosis. The previous GFR 5-stage classification subdivided category 3 (GFR 30-59 mL/min per 1.73m ^{2}) into category 3a (GFR 45-59 mL/min per 1.73m ^{2}) and 3b (GFR 30-44 mL/min per 1.73m ^{2}). This change was the result of various risk profiles and different outcomes that were supported by the data [63]. Based on the clinical diagnosis, stage and other important aspects relevant to the outcome of interest a prognosis can be made.

Kidney damage was defined as structural or functional abnormalities of the kidney ≥ 3 months, with or without a decrease in the GFR with evidence of markers of kidney damage, such as abnormalities of blood, urine or imaging test [64]. Based on the level of GFR, the various stages of CKD, stages I through V, are shown in Table 4 [64] .

Table 4. Stages of Chronic Kidney Disease

Stage	Description	GFR, mL/min per 1.73m^2
I	Kidney damage with normal or increased GFR	≥90
II	Kidney damage with mildly decreased GFR	60 to 89
III	Moderately decreased GFR	30 to 59
IV	Severely decreased GFR	15 to 29
V	Kidney failure	< 15 or dialysis

The persistent presence of albumin in the urine is recognized as an early sign of renal pathology, preceding an actual decline in GFR [65, 66]. An albumin-creatinine ratio (ACR) greater than 30mg/g creatinine in a spot urine sample is usually considered abnormal [67].

In 2012, KDIGO updated the Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, made recommendations regarding the definition and classification of CKD. The group retained the diagnostic cut-offs for an ACR ≥30mg/g creatinine and GFR of <60mL/min per 1.73m^2. The updated definition of CKD was defined as "abnormalities of the kidney structure or function, present for >3 months, with implications for health (not graded)"[56, 68]. It is important to note, debate existed among the work group members regarding making recommendations in the setting of a weak level of evidence. However, the group opted to provide guidance instead of remaining quiet to assist the healthcare provider with making clinical decisions [56].

The guideline evidence was graded based on the Grading of Recommendations Assessment, Development and Evaluation system (GRADE) [69]. To emphasize areas of uncertainty in clinical practice and important concepts, the workgroup made proposals based on consensus even when the quality of the evidence was low. The addition, "with implications for health," takes into consideration that while different anomalies of renal function and structure may be present, not all will have health consequences.

In the setting of CKD the interpretation of cardiac biomarkers, cTnI and cardiac troponin T (cTnT) can prove to be difficult, Table 5, [70]. In studies using first generation troponin assays, up to 71% of cTnT and approximately 7% of cTnI were elevated in the absence of myocardial ischemia. Even with the development of newer assays, cTnT remains more elevated than cTnI in patients with CKD and without evidence of myocardial necrosis with up to 53% of patients with elevated cTnT and 15% cTnI respectively [71-73].

According to the American College of Cardiology Foundation Task Force 2012 Expert Consensus Document on Practical Clinical Considerations in the Interpretation of Troponin Elevations levels of elevated troponin in patients with reduced renal function remains somewhat controversial [74]. Troponin I levels after an MI appear to be similar in patients with end-stage renal disease as well as those with normally functioning kidneys [75], whereas the troponin T levels are broken down into smaller particles that are small enough to be filtered by the kidney thereby detected by the assay which may partially account for the elevations of troponin T seen in patients with renal disease [76].

The National Academy of Clinical Biochemistry practice guidelines recommend the use of troponin in all CKD patients with suspected ACS. The dynamic changes seen in troponin levels among patients with end-stage renal disease should be ≥20% in the 6 to 9 hour window after presentation to meet criteria for MI [77].

No clear mechanism exists to explain this increase but several have been proposed. In addition to CKD as a mechanism for elevated levels of circulating cardiac troponins precursors to heart failure such as left ventricular hypertrophy (LVH), myocarditis [78, 79] and epicardial coronary disease [80] may act as a substrate.

The physiological relations between CKD and HF are multifaceted and causally connected [81] Many people with HF also have CKD, usually marked by a decrease in GFR. The risk of developing HF is significantly increased with declining renal function [82].

Table 5. SOE for Diagnostic Accuracy and Prognostic Value of Elevated Troponin Level in Patients with CKD and Suspected ACS

Table 5. **SOE for Diagnostic Accuracy and Prognostic Value of Elevated Troponin Level in Patients With CKD and Suspected ACS**

Search	String	Hits, *n*
PubMed		
#1	"kidney failure, chronic" [mh]	76 668
#2	Renal[tiab]	450 226
#3	Kidney[tiab]	290 781
#4	Dialysis[tiab]	82 081
#5	Hemodialysis[tiab]	46 266
#6	Haemodialysis[tiab]	11 831
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	707 117
#8	"acute coronary syndrome" [mh]	7168
#9	"acute coronary syndrome"[tiab] OR "acute coronary syndromes"[tiab]	18 355
#10	"angina, unstable" [mh]	9860
#11	"unstable angina"[tiab]	10 960
#12	"myocardial infarction"[tiab]	131 848
#13	"Non-ST-segment elevation"[tiab] OR "non-ST-elevation"[tiab] OR "non-ST elevation"[tiab] OR "ST-segment elevation"[tiab] OR "ST-elevation"[tiab] OR "ST elevation"[tiab] OR (elevation[tiab] AND (ST[tiab] OR "S-T"[tiab] OR "ST-segment"[tiab]))	17 313
#14	Acute[tiab]	851 571
#15	#12 AND (#13 OR #14)	65 756
#16	#8 OR #9 OR #10 OR #11 OR #15	87 657
#17	"Troponin I"[mh] OR "Troponin T"[mh]	8311
#18	Troponin*[tiab]	16 081
#19	#17 OR #18	17 214
#20	(#7 AND #16) OR (#7 AND #19)	4482
#21	(animal[mh] NOT human [mh])	3 885 191
#22	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR "Case Reports"[pt] OR "Classical Article"[pt] OR "Clinical Conference"[pt] OR "Collected Works"[pt] OR Comment[pt] OR Congresses[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR "Legal Cases"[pt] OR Legislation[pt] OR News[pt] OR "Newspaper Article"[pt] OR Portraits[pt]	2 922 900
#23	#20 NOT #21 NOT #22	3857
–	Publication date from 01August, 2013 to present (May 12, 2014)	396
EMBASE		
#1	'chronic kidney failure'/exp	54 230
#2	"Renal":ti,ab	525 969
#3	"Kidney":ti,ab	330 513
#4	"Dialysis":ti,ab	96 520
#5	"Hemodialysis":ti,ab	55 567
#6	"Haemodialysis":ti,ab	14 180
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	822 852
#8	'acute coronary syndrome'/exp	26 253
#9	"acute coronary syndrome":ti,ab OR "acute coronary syndromes":ti,ab	23 742
#10	'unstable angina pectoris'/exp	16 558
#11	"unstable angina":ti,ab	13 871
#12	"myocardial infarction":ti,ab	13 871
#13	"Non-ST-segment elevation":ti,ab OR "non-ST-elevation":ti,ab OR "non-ST elevation":ti,ab OR "ST-segment elevation":ti,ab OR "ST-elevation":ti,ab OR "ST elevation":ti,ab OR ("elevation":ti,ab AND ("ST":ti,ab OR "S-T":ti,ab OR "ST-segment":ti,ab))	22 318
#14	"acute":ti,ab	1 009 558
#15	#12 AND (#13 OR #14)	83 038
#16	#8 OR #9 OR #10 OR #11 OR #15	116 007
#17	'Troponin i'/exp OR 'Troponin T'/exp	18 483
#18	Troponin*:ti,ab	19 501
#19	#17 OR #18	24 191
#20	(#7 AND #16) OR (#7 AND #19)	6618
#21	([animals]/lim NOT [humans]/lim)	4 534 849
#22	'conference abstracts':it OR 'conference paper':it OR 'conference reviews':it OR editorial:it OR erratum:it OR letter:it OR note:it	2 578 437
#23	#20 NOT #21 NOT #22	6172
#24	Publication date from 1990	5831
Cochrane Central Register of Controlled Trials		
#1	"kidney failure, chronic":ti,ab,kw	3704
#2	Renal:ti,ab,kw	22 257
#3	Kidney:ti,ab,kw	17 529
#4	Dialysis:ti,ab,kw	6781
#5	Hemodialysis:ti,ab,kw	3612
#6	Haemodialysis:ti,ab,kw	1015
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	28 862
#8	"acute coronary syndrome":ti,ab,kw	1026
#9	"acute coronary syndrome":ti,ab,kw OR "acute coronary syndromes":ti,ab,kw	1706
#10	"angina, unstable":ti,ab,kw	882
#11	"unstable angina":ti,ab,kw	1797
#12	"myocardial infarction":ti,ab,kw	13 540
#13	"Non-ST-segment elevation":ti,ab,kw OR "non-ST-elevation":ti,ab,kw OR "non-ST elevation":ti,ab,kw OR "ST-segment elevation":ti,ab,kw OR "ST-elevation":ti,ab,kw OR "ST elevation":ti,ab,kw OR (elevation:ti,ab,kw AND (ST:ti,ab,kw OR "S-T":ti,ab,kw OR "ST-segment":ti,ab,kw))	1876
#14	Acute:ti,ab,kw	54 681
#15	#12 AND (#13 OR #14)	7163
#16	#8 OR #9 OR #10 OR #11 OR #15	8958
#17	"Troponin I":ti,ab,kw OR "Troponin T":ti,ab,kw	911
#18	Troponin*:ti,ab,kw	1006
#19	#17 OR #18	1012
#20	(#7 AND #16) OR (#7 AND #19)	274
–	Publication date from 1990/01/01 and only trials	244

2.5 HEART FAILURE

Circulating levels of cardiac troponin have been shown to predict mortality in patients with HF. According to the 2009 Focused Update [83] Incorporated into the American College of Cardiology and American Heart Association's (ACC/AHA) 2005 Guideline Update for the Diagnosis and Management of Chronic HF in Adults [84], HF is defined as a disorder that impairs the ability of the ventricle to fill with or eject blood secondary to a functional or structural cardiac abnormality.

Various hemodyamic and neurohormonal changes lead to progressive myocyte damage via apoptic cell death and necrosis resulting in fibrosis that may contribute to progressive cardiac dysfunction and left ventricular remodeling [85, 86].

HF is a major and growing health problem in the United States [87]. An estimated 5.1 million Americans ≥20 years of age have HF. The prevalence of HF is projected to increase from 2013 estimates by 25% and the cost will increase by approximately 120% to 70 billion by 2030 [6]. It is classified in to 4 stages (Table 6 [88]) that emphasize both the development and progression of the disease.

Table 6. Stages of Heart Failure

Stage A	Stage B	Stage C	Stage D
At high risk for HF but without structural heart disease or symptoms of heart failure.	Structural heart disease but without signs or symptoms of HF.	Structural heart disease with prior or current symptoms of HF.	Refractory heart failure requiring specialized interventions

Stages A and B are used to describe those people who have risk factors for developing HF but do not currently have HF. Risk factors included hypertension, metabolic syndrome, obesity, CHD or diabetes. Stage A describes people with risk factors with preserved ejection fraction, hypertrophy or structural distortion. Stage B describes people who are asymptomatic but have evidence of impaired left ventricular function and/or left ventricular hypertrophy

(LVH). Stage C identifies people with current or past symptoms of HF in the setting of structural heart disease. Lastly, Stage D consists of people with refractory HF who may be eligible for specialized advanced treatments or end-of-life care [89-91].

Circulating levels of cTnI and cTnT are associated with an increased risk of morbidity and mortality in both acute and chronic HF [92]. Elevated cardiac troponin levels are also detectable in patients with HF in the absence of unstable coronary syndromes and may act as a marker for the progression of HF [93] The magnitude of troponin elevations in patients with HF has been associated with disease severity and a worse prognosis [94, 95].

Troponin elevations may be seen in acute and chronic HF [93, 96] and may have broad implications for the treatment, development of new treatment options, prognosis and comprehension of underlying physiology [92]. The levels of cardiac troponins in HF are generally lower than those seen with ACS and lack of the characteristic rise and fall pattern [4].

The Acute Decompensated Heart Failure National Registry (ADHERE) is a large multicenter prospective registry that was designed to collect data on patients hospitalized with acute decompensated heart failure beginning at the point of entry and concluded with the patients' discharge, transfer or in-hospital death thus allowing for evaluation of the management of heart failure patients under "real world" conditions [97, 98]. The ADHERE study showed a significant increase in in-hospital mortality (8.0% vs. 2.7%, $p < 0.0001$), in patients with acute HF, with an elevated cardiac troponin level defined as cardiac troponin I level of 1.0 μg per liter or higher or a cardiac troponin T level of 0.1 μg per liter or higher by any assay during the time of hospitalization [99], Figure 7.

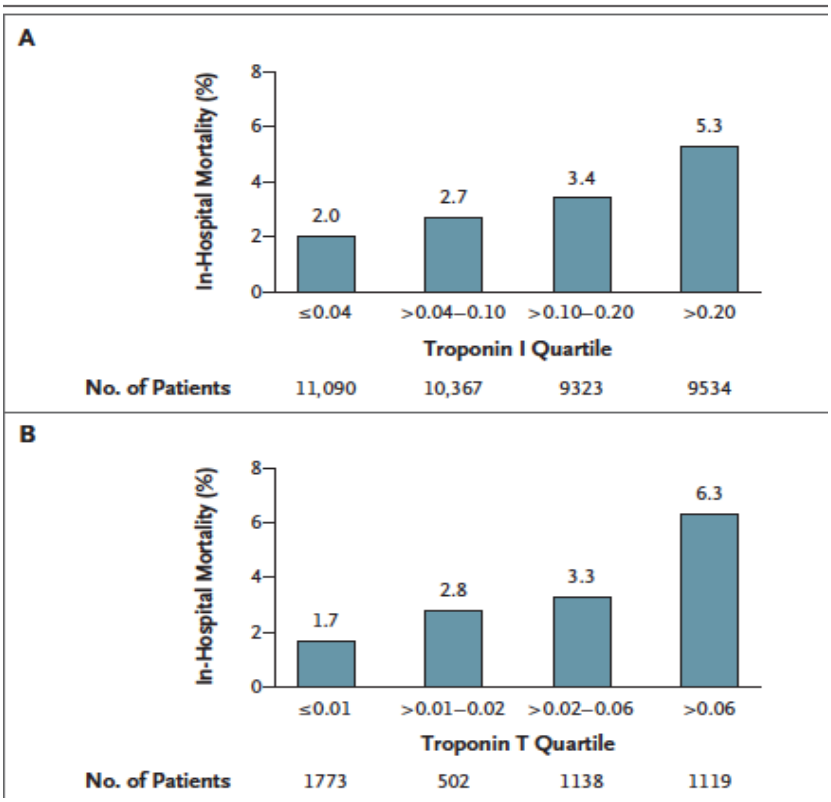

Figure 7. In-Hospital Mortality According to Troponin I or Troponin T Quartile

P<0.001 by the chi-square test for all comparison

The ADHERE investigators reported in an analysis of >105,000 cases, only 6.2% had a troponin level above the upper reference limit corresponding to the 10% imprecision whereas 75% of cases had a detectable troponin level. Troponin levels above the upper reference limit were associated with more severe HF [85-87].

In patients with chronic stable HF measurable or elevated circulating troponin levels are common [100, 101]. The Valsartan Heart Failure Trial (Val-HeFT) was a multicenter, randomized, placebo-controlled, double-blind, parallel-arm trial that examined the effects of valsartan, an angiotensin blocker vs. placebo in 5010 patient with stable symptomatic HF with left ventricular dysfunction [102]. In 4053 chronic heart failure patients, the troponin level using

a conventional troponin assay was reported to be positive in 10.4% compared to 92% using the highly-sensitive troponin assay in the Val-HeFT trial [82].

While cardiac troponin levels in HF lack the characteristic rise and fall pattern seen in patients with ACS and are lower [103], they have been shown to predict adverse outcomes in acute [104] and chronic HF [48, 105]. HF is the final phase of hypertensive heart disease (HHD). The pathophysiology of HHD is a progressive process that begins with hypertension followed by LVH and ultimately to HF [106].

2.6 HYPERTENSION

Hypertension is a major public health concern responsible for considerable morbidity and mortality [107]. One third of adults or approximately 77.9 million people in the United States have high blood pressure and about 6% of Americans have undiagnosed hypertension. The estimated direct and indirect cost for high blood pressure in 2009 $51 billion with projections to increase to $343 billion by 2030 [6, 9, 108] .

The prevalence of hypertension is projected to increase by 7.2% from 2013 estimates by 2030 [6]. African Americans have among the highest prevalence of high blood pressure in the world and it continues to rise increasing from 35.8% in 1988 to 41.4% in 2002 [109].

The death rate from high blood pressure has increased by 17.1% from 1999-2009 [6, 7]. The age-adjusted mortality rate from NHANES I and II compared hypertensive and non-hypertensive people revealed a decrease among people with hypertension of 4.6/1000 person-years compared to 4.2/1000 person-years among people without hypertension [110].

According to the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) published in 2003 there is a continuous relationship between blood pressure and risk of cardiovascular events. This relationship is continuous, consistent, and independent of other risk factors. The risk of experiencing a heart attack, HF, stroke, and kidney disease increases as blood pressure rises[111].

For people 40–70 years of age, each increment of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure doubles the risk of CVD across the entire range of blood pressure from 115/75 to 185/115 mmHg [112] .

Patients with prehypertension are at increased risk for progression to hypertension; those in the 130–139/80–89 mmHg BP range are at twice the risk to develop hypertension as those with lower hypertension as those with lower values, (Table 7) [111].

In 2014, The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-8) was published. However, unlike previous JNC reports, JNC-8 was not supported by any major American or European cardiovascular organization given the prolonged time interval between JNC publications [111, 113, 114]. This time delay led to other hypertensive guidelines being crafted by other key groups, (Table 8), [115].

The classic paradigm of HHD is that the left ventricle thickens as a consequence of elevated blood pressure as an adaptive mechanism to decreased myocardial wall stress ultimately resulting in a transition to failure whereby the left ventricle dilates and the ejection fraction decreases [116].

The ability to predict the development of CVD in patients with hypertension is valuable. Several studies have shown that apoptotic cardiomyocytes are associated with hypertension [117, 118]. Yet few studies have assessed ongoing myocardial damage in vivo and its relationship to the prognosis of hypertensive patients.

A study by Setsuta et al provided the first evidence that hypertensive patients with elevated cTnT have a significantly higher incidence of future cardiovascular or cerebrovascular events [119]. Values for cumulative freedom from cardiovascular or cerebrovascular event rates were significantly lower in patients with than without elevated cTnT, (Table 9) [119].

Hypertension is a precursor to left ventricular dysfunction, a significant antecedent in the development of heart failure with preserved ejection fraction [120, 121], as well as a major risk factor for other cardiovascular diseases [122].

Table 7. JNC 7 Classifications and Management of Blood Pressure for Adults

BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial drug therapy	
				Without Compelling Indication	With Compelling Indications (See Table 8)
Normal	<120	and <80	Encourage	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
Prehypertension	120–139	or 80–89	Yes		
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

* Treatment determined by highest BP category.

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

Table 8. Summary of Major Hypertension Guidance Documents

	JNC-7	JNC-8	ASH/ISH	ESH/ESC	CHEP	ADA
Year Published	2004	2014	2013	2013	2013	2013
BP goals in general population without diabetes or CKD						
Patients <60 years (mm Hg)	<140/90	<140/90	<140/90	<140/90	<140/90	NA
Patients 60 to 79 years (mm Hg)	<140/90	**<150/90**	<140/90	<140/90	<140/90	NA
Patients ≥80 years (mm Hg)	**<140/90**	<150/90	<150/90	<150/90	<150/90	NA
Recommended initial therapy in general population without diabetes or CKD						
All ethnicities except Black	**Thiazide**	Thiazide, ACE inhibitor, ARB, CCB	ACE inhibitor or ARB <60 years; CCB or Thiazide ≥60 years	Thiazide, ACE inhibitor, ARB, CCB, BB	Thiazide, ACE inhibitor, ARB; BB if <60 years	NA
Black (African descent/African American)	**Thiazide**	Thiazide or CCB	Thiazide or CCB	Thiazide, ACE inhibitor, ARB, CCB, BB	Thiazide, ARB; BB if <60y	NA
BP goals in population with diabetes mellitus but without CKD						
Adults (mm Hg)	**<130/80**	<140/90	<140/90	**<140/85**	**<130/80**	**<140/80**
Recommended initial therapy in population with diabetes mellitus but without CKD						
Adults (mm Hg)	ACE inhibitor, ARB, thiazide, CCB, BB	Thiazide, ACE inhibitor, ARB, CCB	ACE inhibitor, ARB (thiazide or CCB acceptable if Black)	ACE inhibitor, ARB	ACE inhibitor, ARB with extra CVD RF; ACE inhibitor, ARB, thiazide, DHP CCB w/o Extra CVD RF	ACE inhibitor, ARB
BP goals in population with chronic kidney disease						
With proteinuria (mm Hg)	**<130/80**	<140/90	<140/90	**<130/90**	<140/90	NA
Without proteinuria (mm Hg)	**<130/80**	<140/90	<140/90	<140/90	<140/90	NA
Recommended initial therapy in population with CKD						
Adults	ACE inhibitor, ARB	ACE inhibitor, ARB	ACE inhibitor, ARB (ACE inhibitor data in Blacks strong)	ACE inhibitor, ARB	ACE inhibitor, ARB	NA

Abbreviations: JNC, Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; ASH/ISH, American Society of Hypertension and International Society of Hypertension; ESH/ESC, European Society of Hypertension and European Society of Cardiology; CHEP, Canadian Hypertension Education Program; ADA, American Diabetes Association; BP, blood pressure; CKD, chronic kidney disease; NA, not applicable; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; BB, β-blocker; CVD, cardiovascular disease; RF, risk factors; DHP, dihydropyridine.
[a]Items in bold denote areas of major disagreements between guidelines.

Table 9. Cardiovascular or Cerebrovascular Events During Follow-up Period in Patients with cTnT and ≥ and 0.02ng/Ml

	cTnT ≥0.02ng/mL (n=15)	cTnT <0.02ng/mL (n=161)
Heart failure, n (%)	5 (33%)	10 (6%)
Cerebral infarction, n (%)	4 (27%)	7 (4%)
Acute coronary syndrome, n (%)	2 (13%)	1 (1%)
Aortic dissection	1 (7%)	2 (1%)
Cerebral hemorrhage, n (%)	0 (0%)	1 (1%)
Transient ischemic attack	0 (0%)	1 (1%)

2.7 LEFT VENTRICULAR HYPERTROPHY

In patients with hypertension, with the exception of age, LVH is the strongest predictor of adverse cardiovascular outcomes and is an independent risk factor for HF, sudden death, CHD and stroke [123, 124].

The natural history of LVH is heterogeneous, while some individuals do not experience difficulty others go on to develop heart failure. The progression from hypertension to concentric left ventricular hypertrophy to heart failure is a vital component in this pathway. Biomarkers may help to identify asymptomatic individuals at high risk of disease progression and to develop treatments that prevent disease transition [90, 125].

Pathophysiologic changes that occur in hypertensive LVH consists of an increase in the cardiomyocyte size, changes in the extracellular matrix [126], buildup of fibrosis and intramyocardial vascular abnormalities such as perivascular fibrosis and medial hypertrophy [127, 128]. Decreases in blood pressure have been shown to reduce LVH [129].

LVH is diagnosed using EKG, echocardiography (ECHO) or cardiac magnetic resonance imaging (MRI). Electrocardiography is the most readily available and also the most economic.

A systematic review of 21 studies [130] revealed that various voltage criteria in addition to several other factors that may be taken into consideration when determining the presence of LVH by EKG such as ST-T wave abnormalities, left atrial abnormalities or the duration of the QRS complex were found to be less sensitive than specific [131, 132].

The issue of decreased sensitivity for the diagnosis of LVH via EKG, which results in an under-diagnosing of LVH, is related to the method of measuring the electrical cardiac activity on the skin surface to predict the left ventricular mass as this is affected by air, fluid, adipose tissue as well as age and race [133]. Although the EKG has decreased sensitivity, it is still used in the diagnosis and management of LVH.

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed regression of LVH in response to Losartan along with improved cardiovascular outcomes, independent of blood pressure, using the Cornell criteria or the Sokolow-Lyon index methods for diagnosing LVH on EKG [134] .

ECHO is more sensitive than electrocardiography in determining the presence of LVH and LVH diagnosed by ECHO, is a precursor to premature mortality across all races, ages and genders [135, 136]. Even after adjustment for possible confounders, there is growing evidence of an association between an increase in left ventricular mass and higher rates of cardiovascular morbidity and mortality [137, 138].

The gold standard for measuring LVH is cardiac MRI as it is more accurate and reproducible [139]. However, the use of cardiac MRI is restricted secondary to the high cost and limited availability [140].

LVH screening programs have been mired by low LVH prevalence rates, decreased sensitivity of electrocardiography and the use of echocardiography as a screening tool is cost prohibited [141]. The Dallas Heart Study suggested by adding validated markers associated with LVH such as highly sensitive troponin T and amino-terminal B-type natriuretic peptide to the 12-lead EKG may be able to function as an inexpensive screening tool for LVH in selected populations [142] .

In the general population, there is a strong correlation between circulating levels of high sensitivity cardiac troponin T and cardiac structure abnormalities such as left ventricular hypertrophy [143]. Identification of biological pathways that provide **INFORMATION** related to the progression from left ventricular hypertrophy to heart failure and the biomarkers that represent these pathways may assist with the identification of individuals considered to be a high risk for adverse events and to develop therapeutic modalities to prevent disease progression [144].

cTnT is one of the cardiac biomarkers released in response to increased LVH and wall stress [78] in the general population and has been strongly associated with incident heart failure [145, 146] and mortality [145]. However the data regarding the impact of minimally elevated troponin T are lacking.

2.8 DIABETES

Diabetes is a major risk factor for CHD and stroke [147]. The prevalence of diabetes for all age groups is projected to be 4.4% in 2030 compared to an estimated 2.8% in 2002 [6]. According to the 2014 National Diabetes Statistics Report, 29.1 million people or 9.3% of the U.S. population have diabetes, this reflects 21 million people who have been diagnosed with diabetes and 8.1 million people undiagnosed [148].

The Framingham Heart Study has shown that diabetes continues to be associated with incremental cardiovascular disease risk, despite improvements in cardiovascular morbidity and mortality. There was a 50% reduction in the rate of incident cardiovascular events among adults with diabetes; however, the absolute risk of cardiovascular disease remained 2-fold greater than among people without diabetes [149].

Patients with type 2 diabetes (T2DM) without prior CVD [150] and an elevated hemoglobin A1C level have been found to have increased hs-cTnT levels [151]. Nevertheless, the clinical interpretations of this are unclear. The Women's Health Study showed that a detectable level of hs-TnT in diabetic women was associated with increased cardiovascular morbidity and mortality [150]. In contrast, a study by Hallen et al. did not predict adverse events in diabetic patients with an elevated hs-TnT over a 2 year follow-up phase [152]. hs-cTnI is a more sensitive assay for subtle myocardial damage given the higher proportions of patients without diabetes have a detectable level of hs-cTnI when compared to hs-TnT [153]. The data are lacking in regards to the predictive value of hs-cTnI in patients with type 2 diabetes.

2.9 SUMMARY

The overall significance of this proposed descriptive study is to provide baseline data to determine whether the initial level of cTnI $\geq$0.04ng/mL provides additional information regarding the identification and management of ACS, all-cause mortality, and HF readmissions within one year of discharge in the time frame of interest, fiscal year 2010. In addition to

determine the value of an initial troponin level in patients without MI on the presence of HF, diabetes, renal disease, hypertension and LVH as data in this area are lacking.

The potential of this study is to identify patients with acute MI in a timelier manner, particularly because previous studies have shown that about 67% of Veterans wait approximately 12 hours prior to presenting to the VA Healthcare System with symptoms consistent with a heart attack, compared to 18% of Medicare recipients.

The ability to identify and intervene early on the natural history of these diseases may indeed decrease the clinical squeal as well as readmissions, length of stay, improve clinical outcomes, decrease mortality/morbidity and improve quality of life and provide cost savings.

3.0 SYNOPSIS AND METHODS

This is a retrospective record review at the VA Pittsburgh Healthcare System to assess the predictive value of the initial cTnI level in determining acute MI, all-cause mortality and the prognostic value of troponin levels in patients without acute MI in determining the presence of several chronic diseases by utilizing the computerized patient records system (CPRS). The data warehouse and the daily automated troponin list will be used to identify patients who had a troponin level drawn during fiscal year 2010, the timeframe of interest in this study. Patients will be followed for 365 days post-discharge to determine if mortality and/or acute MI has occurred. The prognostic value of the initial cTnI level ≥0.04ng/mL in those patients without an acute MI will be evaluated.

The primary analysis will exclude individuals who died during the hospitalization, had a length of stay >30 days, transferred to a different facility or were discharged home with hospice. The study is descriptive so there is no comparison group.

The subjects will be placed into one of two groups according to the instrument's analytical sensitivity. Either ≥0.04ng/mL or <0.04ng/mL based on the initial cTnI result. The group with levels ≥0.04ng/mL will be further categorized by the manufacturers biometric assay reference range: 0.04-0.099ng/mL (negative); 0.10-0.6ng/mL (indeterminate); and >0.6ng/mL (positive).

The data will be stored in an Excel spreadsheet for future import into STATA statistical software package for data analysis.

3.1 DEFINITION OF VARIABLES

The definitions of the outcome variables for this study are described by the Center for Medicare and Medicaid Services ICD-9 codes. The outcome variables will be treated as dichotomous and are as follows: acute MI is defined as the initial episode of care (410.01-410.20) for STEMI and 410.0 -410.72 for NSTEMI; HF codes 428.1-428.32; CKD codes 585.1-585.9; LVH 429.3; hypertension codes 401-405 and diabetes code 250.

Categorical variables during the admission of interest include the following: Sex is defined as male or female; race is defined as Caucasian, African American, Asian, Other or Unknown; Electrocardiogram (EKG) is defined as Other, STEMI or NSTEMI; Ejection fraction (EF) is categorized in increments of 10, starting with an EF >55%, 45-54%, 25-34%, <24% and unknown; smoking status (SMK) is categorized into never smoker, current smoker, previous smoker and unknown; MODE is the testing modality used to obtain the ejection fraction and includes echocardiogram, stress test, cardiac catheterization or multiple gated acquisition scan (MUGA); (TOT) is the date of testing when the ejection fraction was obtained and is defined as before, during, after the admission of interest or unknown.

Continuous variables during the admission of interest include the following: age in years; body mass index (BMI); length of stay (LOS) reported in days; time to presentation (TTP) the time in hours from symptom onset until presentation for medical care; troponin (TRO) is the initial troponin level reported as mg/mL with a manufacturers reference of 0.04- >0.60ng/mL; brain natriuretic peptide (BNP) reported as pg/mL with a reference range as 5-100 pg/mL; serum creatinine (CREAT) reported in mg/dL with a reference range of 0.50-1.20mg/dL; estimated glomerular filtration rate (eGFR) reported as mL/min/1.73^2; serum albumin (ALB) reported as gm/dL with a reference range of 3.2 -5.5 gm/dL.

The goals of this study are to examine all patients admitted with cTnI levels drawn and specifically levels $\geq$0.04 ng/mL to determine if the initial troponin at very low levels is associated with all-cause mortality, acute MI, congestive heart failure readmission at one year post discharge, as well as simultaneous diagnosis of the chronic diseases of interest (HTN, HF, LVH, CKD) at the time of the initial troponin during the admission of interest in fiscal year 2010 or with the potential diagnosis of the chronic disease of interest at 365 days post discharge.

The cardiac troponin-I (cTnI) method used at the VA Pittsburgh Healthcare System is performed on the Siemens Dimension® XPAND machine using the Troponin-I Flex® reagent cartridge. This is a highly sensitive, colorimetric immunoassay that measures cardiac troponin-I, however, it is not considered a high-sensitivity troponin assay.

The initial troponin level will be used as the reference hospitalization. Patients will be followed retrospectively after reference hospital discharge to determine 365-day occurrence of acute MI, HF admission, all-cause mortality and certain chronic diseases (hypertension, LVH, diabetes and CKD) based on ICD-9 codes.

The data will be described using means +/- standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Numbers and percents will be used for categorical variables. The study population demographics will be compared (age, race, gender) between the two troponin groups, troponin $\geq$0.04mg/dL and troponin <0.04mg/mL.

For these comparisons, t-tests (or Mann-Whitney) will be used for continuous variables and Chi-square tests (or Fisher's exact) if the data are categorical. If a statistically significant difference is detected between the two groups for a certain variable, the variable will be included in an adjusted model when assessing the predictive ability of the troponin groups. In addition, known confounders from the literature such as age, race and gender will also be included in adjusted models. Other potential confounders will be investigated as needed.

The first hypothesis will assess whether the initial troponin level is a predictor of all-cause mortality. Logistic regression will be used to calculate the odds ratio (OR) and 95% confidence intervals (CI) of experiencing an event by serum, troponin level. The group with troponin I levels <0.04 will form the referent group.

The second part of the initial hypothesis is to determine of the initial troponin level is a predictor of acute MI. Logistic regression will be used to calculate the OR (95% CI) of AMI by troponin. AMI will be defined by ICD-9 codes from 31 days after hospital discharge from the reference hospitalization.

The second hypothesis will assess whether there is an association between the initial cTnI level $\geq$0.04 ng/mL and HF admission. HF admission will be defined by ICD-9 codes for 31 days

after hospital discharge from the reference hospitalization. Logistic regression will be used to test if there is a difference in heart failure admissions between the two troponin groups. We will also attempt to assess whether a statistically significant interaction exists between troponin and acute MI (yes/no).

The third hypothesis will assess whether there is an association between the initial cTnI level $\geq$0.04 ng/mL and other chronic medical conditions such as diabetes, hypertension, LVH and CKD. All chronic medical conditions considered will be defined by ICD-9 codes, from 31 days after hospital discharge from the reference hospitalization. Logistic regression will be used to test whether there is a difference in the presence of diabetes, hypertension, LVH and CKD between the two troponin groups. We will also attempt to assess whether a statistically significant interaction exists between troponin and acute MI (yes/no).

Sample size computations are not necessary as all patients are included within the time frame of interest, fiscal year 2010. Since effect size is not hypothesized an estimate of power is not indicated given it is a descriptive study.

4.0 SPECIFIC AIMS

I propose to carry out a retrospective cohort study at the VA Pittsburgh Healthcare System University Drive Campus to assess the predictive value of the initial concentrations of cTnI ≥0.04ng/mL in determining all-cause mortality, MI, HF readmission at one post discharge from initial troponin during admission of interest in fiscal year 2010 and whether the initial concentration of cTnI are predictive of other medical conditions such as diabetes, hypertension, left ventricular hypertrophy and kidney disease by utilizing the automated daily troponin list, the data warehouse and the computerized patient records data (CPRS).

4.1 SPECIFIC AIM 1

Determine the association of initial cTnI levels of ≥0.04ng/mL on all-cause mortality and acute MI at one year post-discharge from the admission of interest during fiscal year 2010.

4.1.1 Hypothesis 1

cTnI can be detected as soon as 2 to 4 hours after symptoms and even mild elevations in conventional troponin assays have been associated with an increase in mortality rates. However, 67% of veterans admitted to the VA Healthcare Systems waited more than 12 hours after onset of MI symptoms before presenting to the hospital [37]. The predictive value of the initial cardiac troponin I level ≥0.04ng/mL is not well studied.

4.2 SPECIFIC AIM 2

Determine the association of initial cTnI levels on HF readmission at one year post discharge from the admission of interest.

4.2.1 Hypothesis 2

cTnI levels in acute and chronic HF have been shown to predict adverse outcomes with troponin levels above the upper reference limit associated with more severe HF. The predictive value of the initial cTnI level $\geq$0.04 ng/mL on future HF admissions is unknown.

4.3 SPECIFIC AIM 3

Determine the association of the initial cTnI level $\geq$0.04 ng/mL with other chronic medical conditions such as diabetes, hypertension, LVH and CKD.

4.3.1 Hypothesis 3

The presence of circulating cTnI levels may have significant predictive value in the absence of MI. Troponins provide prognostic information for many medical conditions. The predictive value of an initial cardiac troponin I level $\geq$0.04ng/mL as a predictor for chronic medical conditions in the VA Healthcare System is unknown.

5.0 RESULTS

The analytic flow charts for hypothesis 1 and 2 and hypothesis 3 are shown in Figure 8 and Figure 9. As noted in the methods, we identified all patients with inpatient admissions during 2010 who had cTnI assessed during their initial hospital admission. We excluded those who had an incident AMI during initial hospitalization, died in the hospital, were discharged from the emergency room or had a length of stay >30 days or were transferred to another facility. After exclusions, in total 2,129 patients were admitted to the VA Pittsburgh Healthcare System in 2010 with a serum cTnI level drawn. Of these, 706 (33.3%) patients had an initial troponin level $\geq$0.04ng/mL, (Table 10). Subjects with a higher serum troponin I, were significantly older, had a longer length of stay, were more likely to be male, had higher serum creatinine, lower eGFR and higher BNP. Differences in BNP were especially large with the median BNP among patients with serum troponin I levels $\geq$0.04ng/mL of 589.3 compared to 172 in patients with troponin I < 0.04ng/mL. There was no difference in race or BMI by level of troponin I measured on hospital admission. Patients with elevated serum troponin I were, however, less likely to be a current smoker.

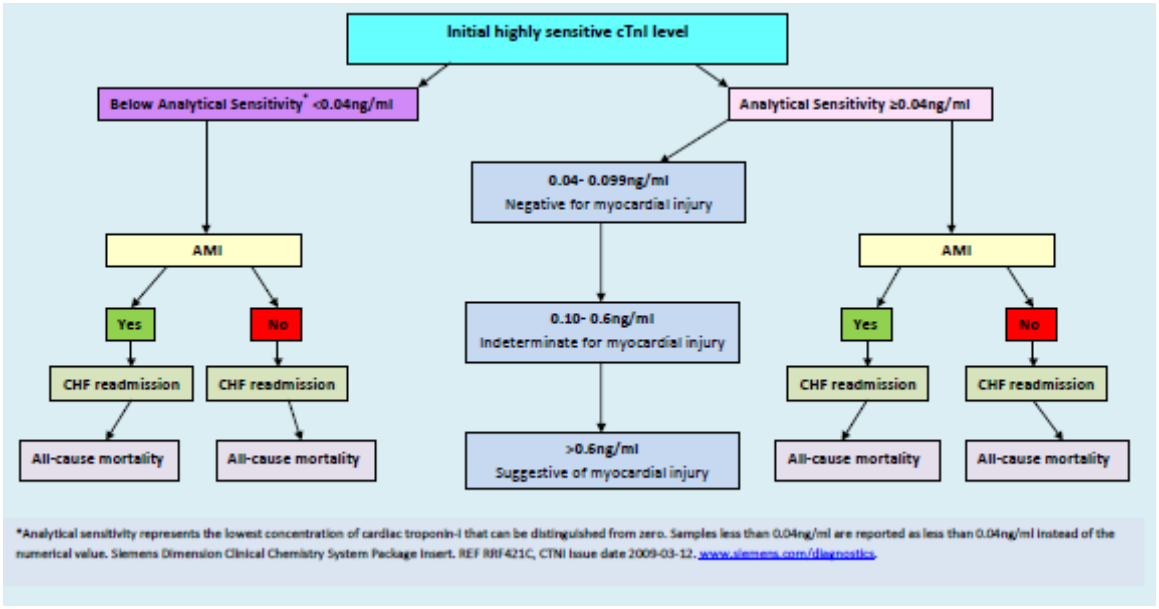

Figure 8. Initial Highly Sensitive cTnI Level as Predictor of Acute Coronary Syndrome and CHF Readmission at one year post-discharge, Hypotheses 1 and 2

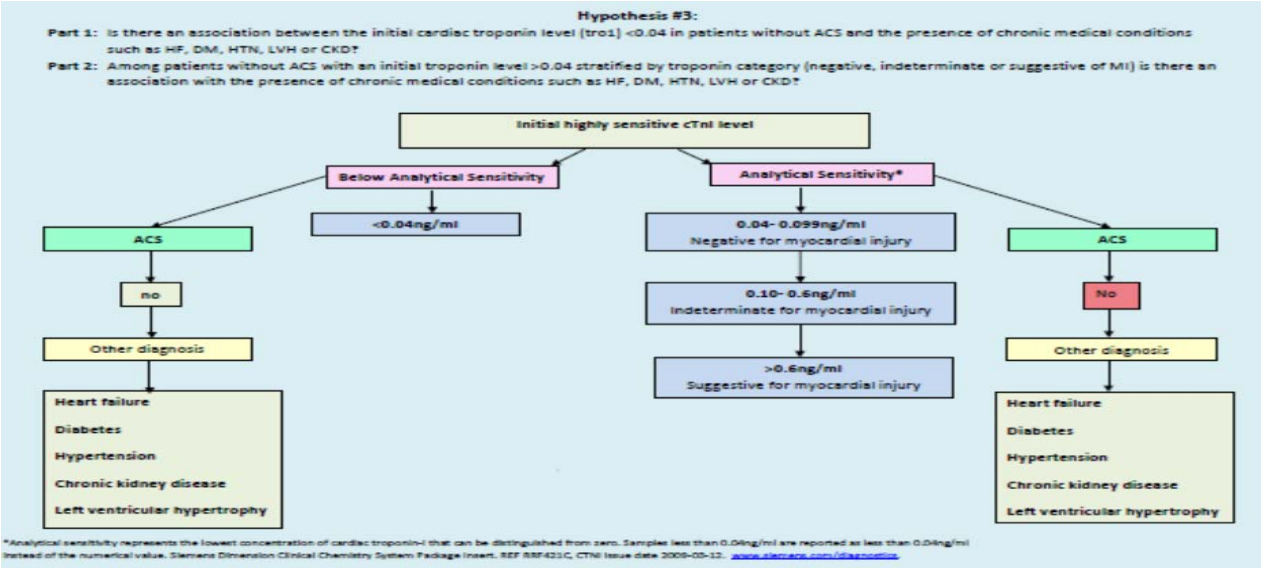

Figure 9. Initial Highly Sensitive cTnI Level as Predictor of Heart Failure, Diabetes, Chronic Kidney Disease and Left Ventricular Hypertrophy - Initial Highly Sensitive cTnI Level as predictor of Acute Coronary Syndrome and CHF Readmission at one year discharge – Hypothesis 3

Table 10. Characteristics of Eligible Subjects by Initial Troponin Category (n=2,129)

Variable	Initial Troponin <0.04 n=1423 n (%)	Initial Troponin >0.04 n=706 n (%)	Total N=2129 n (%)	p-value[$]
Age, mean (SD)	62.33 (13.14)	70.11 (11.82)	64.91 (13.23)	<0.00001
Initial Troponin, mean (SD)	0.01 (0.01)	0.87 (4.40)	0.30 (2.57)	--
Length of Stay, mean (SD)	4.43 (5.07) n=855	5.56 (5.14) n=562	4.91 (5.17) n=1417	<0.0001
Gender n (%)				
Female	98 (6.9)	17 (2.4)	115 (5.4)	<0.0001
Male	1325 (93.1)	689 (97.6)	2014 (94.6)	
Race n (%)				
White	971 (68.2)	499 (70.7)	1470 (69.0)	
Black	313 (22.0)	144 (20.4)	457 (21.5)	0.502*
Other	15 (1.1)	10 (1.4)	25 (1.2)	
Unknown/Missing	124 (8.7)	53 (7.5)	177 (8.3)	
Smoking (yes) n(%)	711 (50.0)	284 (40.2)	995 (46.7)	<0.0001
Biological Variables				
BMI, mean (SD) kg/m^2	29.95 (8.18) n=895	29.42 (8.88) n=538	29.75 (8.45) n=1433	0 .434
Creatinine, median (IQR) (mg/dl)	1.10 (0.60) n=536	1.49 (1.20) n=358	1.04 (0.43) n=894	<0.00001[#]
eGFR, mean (SD)mL/min/1.73^2	86.56 (29.91) n=536	70.96 (29.47) n=358	80.31 (30.68) n=894	<0.0001
Albumin, mean (SD)(g/dL)	3.22 (0.57) n=197	3.15 (0.68) n=161	3.19 (0.62) n=358	0.267
BNP, median (IQR)(pg/ml)	172.1 (268.5) n=299	589.3 (633.3) n=296	193 (458.0) n=575	<0.00001[#]

SD=standard deviation; IQR=interquartile range; $ - p-values based on t-tests or chi-square tests unless otherwise noted; * Fisher's exact test; # Mann-Whitey test

5.1 HYPOTHESIS 1

Hypothesis 1 tests the research question whether there is an association between initial cTnI level and all-cause mortality at 365 days post discharge and whether this association differs by prevalence of ACS. Over the one year of follow-up 89 (12.6%) with elevated cTnI levels died compared to 58 (4.1%) among those with cTnI <0.04 ng/mL, (Table 11). In the unadjusted model, patients with an initial cTnI level ≥0.04ng/mL were 3.39 (95% CI; 2.40, 4.79) times more

likely to die within one year compared to those with levels <0.04ng/mL, (Table 12). These associations were attenuated slightly in models adjusting for age, race, sex but remained statistically significant. In the final model additionally adjusting for cigarette smoking and renal function, patients with an initial troponin level ≥0.04ng/mL had a two-fold increased risk of dying within one year after their hospitalization.

Of the 2,129 patients, 588 (27.6%) had a diagnosis of ACS, (Table 11). In both patients with or without ACS, patients with initial troponin levels ≥0.04ng/mL were more likely to die, 11.1% versus 3.5% in those with ACS and 13.5% versus 4.3% in those without ACS, (Table 11). Logistic regression results showed increased odds of dying within 365 days among subjects with and without ACS, (Table 13). In the fully adjusted models (age, race, sex, smoking and eGFR), patients with ACS and a serum troponin level ≥0.04ng/mL were 3.81(95% CI; 1.62, 8.96) times more likely to die. Similarly, among patients without ACS, patients with elevated initial troponin level were, 2.05 (95% CI; 1.23, 3.41) times more likely to die within 365 days of initial admission. The interaction between ACS and serum troponin levels was not significant (unadjusted model, p interaction=0.914; fully adjusted model, p interaction=0.21).

5.2 HYPOTHESIS 2

The second hypothesis of this dissertation examines whether there is an association between initial troponin level and MI and HF readmission among patients who were alive 365 days after discharge. A total of 1,982 (93%) of patients were alive 365 days post discharge, (Table 11). Of these 35 patients who experienced a MI, 5.7% had a troponin level ≥0.04ng/mL compared to 1.2% with lower troponin levels. Indeed, patients with troponin levels ≥0.04ng/mL were more than 5.46 times (95% CI; 2.70, 22.0) more likely to experience an incident MI even after adjusting for age, race, sex, smoking status and renal function, (Table 12).

Of those 1,982 patients alive at 365 post discharge only 11 patients were readmitted for heart failure, but there was no difference by initial troponin levels (Tables 11 and 12).

Table 11. Summary of Results for Hypothesis 1. 2 1d 3: Number of Patients with an Event by Serum Troponin Level at Admission. Outcomes within 365 days of Post Discharge

Outcome	Initial Troponin <0.04ng/mL n (%)	Initial Troponin >0.04 ng/mL n (%)	p-value*
Hypothesis 1a: Is there an association between the initial troponin level and all-cause mortality at 365 post discharge			
Mortality			
Dead	58 (4.1)	89 (12.6)	<0.0001
Alive	1365 (95.9)	617 (87.4)	
Hypothesis 1b: Is there an association between the initial troponin level and all-cause mortality at 365 post discharge with and without Acute Coronary Syndrome (ACS)			
With ACS			
Mortality			
Dead	11 (3.5)	30 (11.1)	
Alive	307 (96.5)	240 (88.9)	<0.0001
Without ACS			
Mortality			
Dead	475 (4.3)	59 (13.5)	<0.0001
Alive	1058 (95.8)	277 (86.5)	
Hypothesis 2a: Is there an association between the initial troponin level and myocardial infarction among patients who were alive 365 post discharge			
Myocardial Infarction			
Yes	16 (1.2)	35 (5.7)	<0.0001
No	1349 (98.8)	582 (94.3)	
Hypothesis 2b: Is there an association between the initial troponin level and heart failure readmission among patients who were alive 365 post discharge			
Readmit for Coronary Heart Failure			
Yes	7 (0.5)	4 (0.6)	0.747#
No	1358 (99.5)	613 (99.4)	
Hypothesis 3: Is there an association between the initial troponin level and selected chronic medical conditions among patients without ACS and who were alive 365 post discharge			
Heart Failure			
Yes	222 (21.0)	185 (49.1)	<0.0001
No	836 (79.0)	192 (50.9)	
Diabetes			
Yes	452 (42.7)	195 (51.7)	0.003
No	606 (57.3)	182 (48.3)	
Hypertension			
Yes	871 (82.3)	345 (91.5)	<0.0001
No	187 (17.7)	32 (8.5)	
Left ventricular hypertrophy			
Yes	72 (6.8)	56 (14.9)	<0.0001
No	986 (93.2)	321 (85.2)	
Chronic kidney disease			
Yes	202 (19.1)	146 (38.7)	<0.0001
No	856 (80.9)	231 (61.3)	
Any of the above chronic medical conditions			<0.0001
Yes	904 (85.4)	361 (95.8)	
No	154 (14.6)	16 (4.2)	

* based on Chi-square test

Table 12. Results of Logistic Regression Models for Outcomes Within 365 Days of Post Discharge

Outcome	OR	95% CI	p-value*
Hypothesis 1a: Is there an association between the initial troponin level and all-cause mortality at 365 post discharge			
Unadjusted model			
Initial Troponin			
<0.04			<.0001
0.04+	3.39	2.40-4.79	
Adjusted for age, race, sex			
Initial Troponin			
<0.04			<.0001
0.04+	2.61	1.79-3.81	
Adjusted for age, race, sex, smoking and eGFR			
Initial Troponin			
<0.04			<.0001
0.04+	2.31	1.52-3.52	
Hypothesis 1b: Is there an association between the initial troponin level and all-cause mortality at 365 post discharge with and without Acute Coronary Syndrome (ACS)			
With ACS Unadjusted			
Initial Troponin/ACS			
<0.04			.001
0.04+	3.49	1.71-7.10	
Adjusted for age, race, sex			
Initial Troponin/ACS			
<0.04			.001
0.04+	3.37	1.60-7.11	
Adjusted for age, race, sex, smoking and eGFR			
Initial Troponin/ACS			
<0.04			.002
0.04+	3.81	1.62-8.96	
Without ACS Unadjusted			
Initial Troponin/ACS			
<0.04			<.0001
0.04+	3.52	2.36-5.26	
Adjusted for age, race, sex			
Initial Troponin/ACS			
<0.04			<.0001
0.04+	2.45	1.56-3.86	
Adjusted for age, race, sex, smoking and eGFR			
Initial Troponin/ACS			
<0.04			.006
0.04+	2.05	1.23-3.41	
Hypothesis 2a: Is there an association between the initial troponin level and myocardial infarction among patients who were alive 365 post discharge			
Unadjusted model			
Initial Troponin			
<0.04			<.0001
0.04+	5.07	2.78-9.23	

Table 12 continued

Outcome	OR	95% CI	p-value*
Adjusted for age, race, sex			
Initial Troponin			
<0.04			<.0001
0.04+	5.27	2.73-10.14	
Adjusted for age, race, sex, smoking and eGFR			
Initial Troponin			
<0.04			<.0001
0.04+	5.46	2.70-11.04	
Hypothesis 2a: Is there an association between the initial troponin level and heart failure readmission among patients who were alive 365 post discharge			
Unadjusted model			
Initial Troponin			
<0.04			.708
0.04+	1.27	0.37-4.34	
Adjusted for age, race, sex			
Initial Troponin			
<0.04			.967
0.04+	1.03	0.29-3.65	
Adjusted for age, race, sex, smoking and eGFR			
Initial Troponin			
<0.04			.893
0.04+	1.10	0.29-4.13	
Hypothesis 3: Is there an association between the initial troponin level and selected chronic medical conditions among patients without ACS and who were alive 365 post discharge			
Unadjusted model			
Heart Failure -			
Initial Troponin			<.0001
<0.04			
0.04+	3.63	2.82-4.66	
Diabetes –			
Initial Troponin			.003
<0.04			
0.04+	1.44	1.13-1.82	
Hypertension -			
Initial Troponin			<.0001
<0.04			
0.04+	2.31	1.56-3.44	
Left ventricular hypertrophy -			
Initial Troponin			<.0001
<0.04			
0.04+	2.39	1.65-3.46	
Chronic kidney disease -			
Initial Troponin			
<0.04			<.0001
0.04+	2.68	2.07-3.47	
Any of the above chronic medical conditions -			
Initial Troponin			<.0001
<0.04			
0.04+	3.84	2.26-6.52	
Adjusted for age, race, sex			

Table 12 continued

Outcome	OR	95% CI	p-value*
Heart Failure - Initial Troponin			
<0.04			<.0001
0.04+	2.40	1.81-3.17	
Diabetes – Initial Troponin			
<0.04			.846
0.04+	1.03	0.79-1.34	
Hypertension - Initial Troponin			
<0.04			.407
0.04+	1.22	0.46-1.97	
Left ventricular hypertrophy - Initial Troponin			
<0.04			.002
0.04+	1.86	1.25-2.79	
Chronic kidney disease - Initial Troponin			
<0.04			<.0001
0.04+	2.06	1.54-2.75	
Any of the above chronic medical conditions - Initial Troponin			
<0.04			.092
0.04+	1.68	0.92-3.06	
Adjusted for age, race, sex, smoking and eGFR			
Heart Failure - Initial Troponin			
<0.04			.001
0.04+	2.15	1.35-3.42	
Diabetes – Initial Troponin			
<0.04			.167
0.04+	0.73	0.47-1.14	
Hypertension - Initial Troponin			
<0.04			.520
0.04+	1.46	0.46-4.57	
Left ventricular hypertrophy - Initial Troponin			
<0.04			.012
0.04+	2.11	1.18-3.77	
Chronic kidney disease - Initial Troponin			
<0.04			.688
0.04+	0.88	0.470-1.64	
Any of the above chronic medical conditions - Initial Troponin			
<0.04			.183
0.04+	4.08	0.51-32.32	

5.3 HYPOTHESIS 3

The third hypothesis of this dissertation examines whether there is an association between initial cTnI level and selected medical conditions among patients without ACS who were alive 365 post discharge. Specific medical conditions of interest included HF, diabetes, hypertension, LVH, CKD and any of these medical conditions. Patients with initial cTnI levels $\geq$0.04 ng/mL compared to patients with lower initial cTnI levels were more likely to have HF (49.1% versus 21.09%) diabetes (51.7% versus 42.7%), hypertension (91.5% versus 82.3%), LVH (14.9% versus 6.8%), and CKD (38.7% versus 19.1%), all $p<0.0001$, (Table 11). The prevalence of any of these chronic medical conditions was extremely high in this population but nevertheless, 95.8% of patients with higher initial cTnI levels, compared to 85.4% of patients with lower levels ($p<0.0001$) had at least one of these important medical conditions.

In the unadjusted logistic model, the odds of having these selected medical conditions was significantly higher among patients with initial troponin levels $\geq$0.04ng/mL.: HF, (OR=3.63; 2.82, 466); diabetes, (OR=1.44; 1.13, 1.82); hypertension, (OR=2.3; 1.56, 3.44); LVH, (OR=2.39; 1.65, 3.46); CKD, OR=2.68; 2.07, 3.47); and any of the above medical conditions, (OR=3.84; 2.26, 6.52), Table 12. However, after adjusting for age, race and sex, only the associations with HF, LVH and CKD remained statistically significant. In models further adjusted for smoking and eGFR, only the association with HF, (OR=2.15; 1.35, 3.42) and LVH (OR=2.11; 1.18, 3.77) remained significant.

We additionally categorized troponin by the manufacturer's biometric assay reference range: range 0.04-0.099ng/mL (negative); 0.10-0.60ng/mL (indeterminate) and $\geq$0.60ngml (positive), (Table 13). In general, patients with elevated serum troponin $\geq$0.04ng/mL had an increased risk of heart failure and LVH. However, there was no clear trend likely reflecting the smaller sample sizes in some of these strata. The magnitude of odds ratio ranged from 1.58 (diabetes) to 4.04 (any of the medical conditions), (Table 13). Adjusting models for age, race and sex attenuated associations with diabetes, hypertension, and any condition. Further adjusting for smoking and eGFR, patients with elevated serum cTnI were more than 2-fold more likely to

have HF and LVH but there was no association between troponin and diabetes, hypertension, CKD or any of these conditions, (Table 13).

Table 13. Is there an Association Between the Initial Troponin Level and Selected Chronic Medical Conditions Among Patients Without ACS who were Alive 365 Post Discharge: Stratification of Serum Troponin Levels

Outcome	OR	95% CI	p-value*
Unadjusted model			
Heart Failure - Initial Troponin			
<0.04	1.00		<0.0001
0.04-.099	3.24	2.46-4.28	
.10-.599	6.15	3.81-9.92	
.60+	2.05	0.75-5.61	
Diabetes – Initial Troponin			
<0.04	1.00		0.013
0.04-.099	1.35	1.04-1.76	
.10-.599	1.87	1.18-2.97	
.60+	1.19	0.46-3.11	
Hypertension - Initial Troponin			
<0.04	1.00		0.0005
0.04-.099	2.11	1.36-3.25	
.10-.599	2.61	1.12-6.09	
.60+	--	--	
Left ventricular hypertrophy - Initial Troponin			
<0.04	1.00		<.0001
0.04-.099	2.47	1.65-3.70	
.10-.599	2.70	1.42-5.12	
.60+	--	--	
Chronic kidney disease - Initial Troponin			
<0.04	1.00		<.0001
0.04-.099	2.41	1.81-3.22	
.10-.599	4.13	2.59-6.59	
.60+	1.77	0.62-5.07	
Any of the above chronic medical conditions - Initial Troponin			
<0.04	1.00		<.0001
0.04-.099	3.82	2.09-6.98	
.10-.599	3.19	1.15-8.86	
.60+	--	--	
Adjusted for age, race, sex			

Table 13 continued

Outcome	OR	95% CI	p-value*
Unadjusted model			
Heart Failure - Initial Troponin			
<0.04	1.00		<.0001
0.04-.099	2.04	1.49-2.79	
.10-.599	4.52	2.67-7.66	
.60+	1.65	0.54-5.05	
Diabetes – Initial Troponin			
<0.04	1.00		.727
0.04-.099	0.95	0.71-1.28	
.10-.599	1.29	0.78-2.11	
.60+	1.20	0.41-3.55	
Hypertension - Initial Troponin			
<0.04	1.00		.754
0.04-.099	1.12	0.66-1.89	
.10-.599	1.39	0.53-3.62	
.60+	--	--	
Left ventricular hypertrophy - Initial Troponin			
<0.04	1.00		.005
0.04-.099	1.93	1.25-2.98	
.10-.599	2.06	1.04-4.06	
.60+	--	--	
Chronic kidney disease - Initial Troponin			
<0.04	1.00		<.0001
0.04-.099	1.81	1.32-2.50	
.10-.599	3.30	1.98-5.52	
.60+	1.62	0.51-5.12	
Any of the above chronic medical conditions - Initial Troponin			
<0.04	1.00		.274
0.04-.099	1.75	0.87-3.51	
.10-.599	1.28	0.44-3.69	
.60+	--	--	
Adjusted for age, race, sex, smoking and eGFR			
Heart Failure - Initial Troponin			
<0.04	1.00		.003
0.04-.099	1.73	1.04-2.90	
.10-.599	4.88	1.92-12.44	
.60+	2.48	0.47-13.20	
Diabetes – Initial Troponin			
<0.04	1.00		.463
0.04-.099	0.72	0.44-1.17	
.10-.599	0.66	0.29-1.52	
.60+	1.42	0.25-7.99	

Table 13 continued

Outcome	OR	95% CI	p-value*
	Unadjusted model		
Hypertension - Initial Troponin			
<0.04	1.00		.844
0.04-.099	1.20	0.33-4.43	
.10-.599	1.78	0.21-14.82	
.60+	--	--	
Left ventricular hypertrophy - Initial Troponin			
<0.04	1.00		.025
0.04-.099	2.26	1.21-4.22	
.10-.599	2.19	0.82-5.83	
.60+	--	--	
Chronic kidney disease - Initial Troponin			
<0.04	1.00		.606
0.04-.099	0.75	0.38-1.49	
.10-.599	1.66	0.53-5.18	
.60+	0.68	0.06-7.87	
Any of the above chronic medical conditions - Initial Troponin			
<0.04	1.00		.852
0.04-.099	--	--	
.10-.599	1.23	0.14-10.59	
.60+	--	--	

6.0 DISCUSSION

The Pittsburgh Veteran's Healthcare System implemented a process to obtain cTnI levels on all patients with any complaint of discomfort between their ears and their hips. The purpose of this policy was to improve early identification of patients with ACS. The purpose of this dissertation was to evaluate this policy and test whether patients with elevated cTnI levels ($\geq$0.04ng/mL) have an increased risk of death one year after discharge. Since troponin levels are an established biomarker for AMI, we excluded patients with AMI and patients who died in the hospital. Results showed that patients with elevated serum troponin levels were 2.3 times more likely to die within one year after they were discharged. We also showed that this association was slightly stronger in patients with ACS (almost 3.8-fold increased risk of dying). However, even among patients without ACS, there was a 2.0-fold increased risk of mortality among those with elevated troponin levels. The interaction between ACS and troponin level was, however, not significant.

Patients with serum cTnI levels at initial hospitalization $\geq$0.04ng/mL were also more likely to have an AMI within a year of their initial admission. This association was independent of age, race, sex, smoking and renal function. Patients with elevated cTnI levels also had a >5-fold increased risk of MI. There was, however, no association between cTnI and HF readmissions. However, in the subset of patients without ACS, initial troponin level was associated with a 2-fold increased risk of developing HF and LVH but there was no association between cTnI and diabetes, hypertension, CKD or any of these medical conditions. These results support the use of a broad based recommendation to continue measuring cTnI levels on patients with pain from their ears to their hip at the VA Pittsburgh Healthcare System.

Our results between elevated serum cTnI and increased mortality and MI risk are consistent with previous studies [45]. In addition, the predictive value of cTnI extend beyond

MI. We showed that those with elevated troponin were more likely to be hospitalized for heart failure and left ventricular hypertrophy. This finding is also consistent with previous research [48].

Elevated serum troponin I levels have been shown to provide prognostic information for hypertension [49] and diabetes [150]. However, we found no association between troponin and diabetes or hypertension.

Patients with elevated serum troponin levels were more likely to have CKD in the unadjusted and age, sex, race adjusted models. The association was quite strong showing a 2-fold increased risk. However, this association was attenuated in models adjusting for eGFR. This latter adjustment is likely over adjustment since individual with lower GFR are more likely to have chronic kidney disease. Chronic kidney disease may reflect a mechanism whereby elevated serum troponin predicts heart failure and left ventricular hypertrophy.

In the fully adjusted model, we found no significant association between serum troponin and any of the chronic diseases combined as an aggregate. This may reflect the very high prevalence of any of these diseases in patients both with and without elevated serum troponin. The level of comorbidity was high in these older veterans.

6.1 STRENGTHS AND WEAKNESSES

We carried out a large retrospective study and comprehensively evaluated all patients with a serum troponin I level drawn in fiscal year 2010. We worked with the Veteran's Affairs Medical Data System and programmers at the Veteran's Affairs Healthcare System in Pittsburgh familiar with the data system. Thus, our ascertainment of patients who met our entry criteria was likely very high. We were able to adjust for important demographic and lifestyle factors (e.g, smoking).

There are, however, several weaknesses. We did not have information on medication use which could have influenced subsequent outcomes. The diagnostic sensitivity of troponin varies

by when the troponin is measured after admission. Peak values occur 8 to 16 hours after the onset of symptoms [1]. We had no information on the timing of the troponin blood draw and the onset of symptoms. Finally, our subjects were all US veterans with a high level of comorbidity and, therefore, our results may not be generalizable to patients admitted to general community hospitals.

6.2 PUBLIC HEALTH REVELANCE

CVD is the leading cause of death in both men and women, killing over 600,000 people annually. Diseases of the heart accounted for about 25% of deaths [154]. Troponin levels have been identified as a key biomarker of heart disease. Raised troponin levels indicate cardiac muscle cell death as the enzyme is released into the blood upon injury to the heart. The VA Health System in Pittsburgh instituted a policy to measure troponin I levels on all patients with pain between their ears and hips. It is critical to evaluate whether this policy is effective in identifying patients at risk of death, MI and other diseases. The VA Health System is constrained by current healthcare funding. It is important to evaluate whether the cost of these assays are justified. Indeed, in 2010, over 2000 patients had a troponin level drawn. Our study showed that this practice will identify patients at risk of dying, developing MI, heart failure or left ventricular hypertrophy. These results are important from a public health perspective, given that CVD is the leading cause of death in the United States.

6.3 CONCLUSION

Elevated serum troponin levels ($\geq$0.04ng/mL) are predictive of overall mortality, MI, HF and LVH. Our results suggest that the VA Health System should continue to measure troponin on patients with pain between their hips and ears. Patients admitted with elevated troponin levels should be targeted for interventions to prevent death, MI, HF and LVH.

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