

Providing High Value Care to Patients with Acute Chest Pain

University of Texas Southwestern Medical Center

Internal Medicine Grand Rounds

Dr. Rebecca Vigen

June 14, 2019

This is to acknowledge that Rebecca Vigen has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to the program. Dr. Vigen will not be discussing off-label uses in her presentation.

Rebecca Vigen, MD, MSCS

Assistant Professor of Internal Medicine

Division of Cardiology

Rebecca Vigen, MD, MSCS is an Assistant Professor of Internal Medicine in the Division of Cardiology. She is a general cardiologist and health services researcher focused on high value care for patients with cardiovascular disease. Dr. Vigen received her MD from Louisiana State University and completed her internal medicine training at UT Southwestern. She then completed a research fellowship in cardiovascular outcomes research at the University of Colorado where she earned her MSCS. She then completed her clinical cardiology fellowship at UTSW in 2015 and since then has continued on faculty with a practice in general cardiology, echocardiography, as well as remaining active in health services research and quality improvement.

Purpose and Overview:

The purpose of this presentation is to educate our department about the use of protocols for suspected acute coronary syndrome among patients presenting with chest pain. We will review the potential that new protocols have in improving the efficiency of care delivery.

Educational Objectives:

1. Understand the importance of differentiating cardiac from non-cardiac chest pain among patients presenting to the emergency department.
2. To differentiate the high-sensitivity troponin from the conventional 4<sup>th</sup> generation troponin.
3. To describe different rule out myocardial infarction protocols that incorporate the use of high-sensitivity troponin.
4. To understand the rationale for the creation of the PHHS/UTSW hs-cTnT Protocol.
5. Gain an awareness of how this protocol has affected resource utilization in the health care system.

## Chest pain in the emergency department and ED Overcrowding:

Chest pain is the second most common complaint among patients presenting to the emergency department (ED) in the United States and in 2013 there were over 6 million ED visits for chest pain.[1] The large majority of patients who present with chest pain do not have myocardial infarction, with a prevalence of MI rate that varies based on the population studied. The high volume of chest pain is a contributor to emergency department overcrowding. There is a need to increase the efficiency in the evaluation of patients presenting with chest pain.

Emergency department overcrowding is a major public health problem in the US and has been associated with poor outcomes, increased resource utilization, and restricted access to care. In a study of two large Canadian hospitals of patients presenting with chest pain or shortness of breath, investigators found that during periods of ED crowding, the mean time to physician assessment was 107.3 minutes as compared to 76 minutes during periods in which the ED was not crowded.[2] In a study of 187 hospitals in California in 2007, ED crowding as defined by top quartile of diversion hours per facility was associated with higher odds of inpatient death, longer length of stay, and increased costs per admission.[3] Finally, overcrowding has been associated with delays in care among patients with STEMI.[4]

Despite the low prevalence of ACS among patients presenting with chest pain and new discoveries in the diagnosis and management of acute chest pain, missing myocardial infarctions still occur and are a frequent cause of litigation.[5] In a prospective trial of 10,689 patients presenting to 10 US hospitals in 1993, 17% of patients had either AMI or unstable angina. Of the patients with AMI, 2.1% were discharged from the ED and of those with unstable angina, 2.3% were discharged from the ED. Failure to hospitalize these patients was associated with higher risk-adjusted mortality.[6] In a more contemporary study of ED patients in North Texas between 2009 and 2015, the rates of missed ACS (patient diagnosed with ACS 7 days after an index ER visit) was 3.2%. Additionally, the rates of missed ACS did not change throughout the study period.[7]

The annual ED volume at PHHS is high. For the fiscal year of 2017 – 2018, there were 244,209 arrivals to the PHHS ED. The monthly proportion of patients who undergo cardiac evaluation is also high and from 2017 to September 2019, there were on average 2,604 monthly encounters in which patients underwent ECG and troponin testing. Given the high volume of patients with chest pain evaluated in the ED and the overcrowding that can ensue without rapid triage of patients, it is important to establish efficient and effective ED protocols for the safe rule-out of low risk chest pain. The ideal protocol for chest pain rule out would be fast, highly sensitive and have the ability to identify patients at very low risk for 30 day adverse cardiac events such that these patients can be discharged home instead of being admitted for observation or additional inpatient testing.

## Chest pain work-up and role of hs-cTnT in the diagnosis of AMI:

The fourth universal definition of myocardial infarction emphasizes the difference between myocardial injury and infarction. Injury is defined by an elevation in troponin with at least one level above the 99<sup>th</sup> percentile upper reference limit (URL). This can be either acute, if there is a rise/fall in troponin, or chronic, if the elevation does not change significantly over serial measurement. Myocardial infarction is diagnosed when there is acute myocardial injury with evidence of ischemia.[8] There is a broad differential diagnosis for myocardial injury. Acute myocardial injury can occur in the setting of acute heart failure or myocarditis. Chronic myocardial injury can occur in the setting of structural heart disease or chronic kidney disease. Finally, there are several different types of acute myocardial infarction. Type I occurs secondary to plaque rupture or plaque erosion. Type 2 can occur secondary to oxygen supply mismatch states such as hypertension or arrhythmias. Type 3 is defined by patients who suffer cardiac death before biomarker elevation occurs or when MI is detected on autopsy. Type 4 and 5 are related to PCI and CABG.

### Potential algorithms for chest pain rule out:

After the history, physical, and ECG, cardiac biomarkers are needed to evaluate for myocardial injury. The ACC/AHA NSTEMI guidelines recommend that they be obtained at baseline and 3-6 hours after symptom onset to evaluate for rise/falling pattern.[9] The disadvantage of this protocol is that patients typically have to wait in the ER for prolonged monitoring to rule out MI.

Newer, high-sensitivity assays have been developed and tested in many different rule out algorithms outside the U.S., and the U.S. FDA first approved the use of the hs-cTnT assay in 2017. This assay is both highly sensitive and precise. Because of the sensitivity, small increases can be detected and in some patients, a single blood draw can exclude ACS. Because of the precision of the assay, small changes over time can be monitored such that MI can be ruled out by sequential blood draws in which there are no significant dynamic changes. By definition, a high-sensitivity assay is one in which the coefficient of variance (CV) is <10% at the 99<sup>th</sup> percentile upper reference limit in the population. Additionally, concentrations below the 99<sup>th</sup> percentile should be above the assay's minimum limit of detection for >50% of healthy individuals in the population.[10, 11]

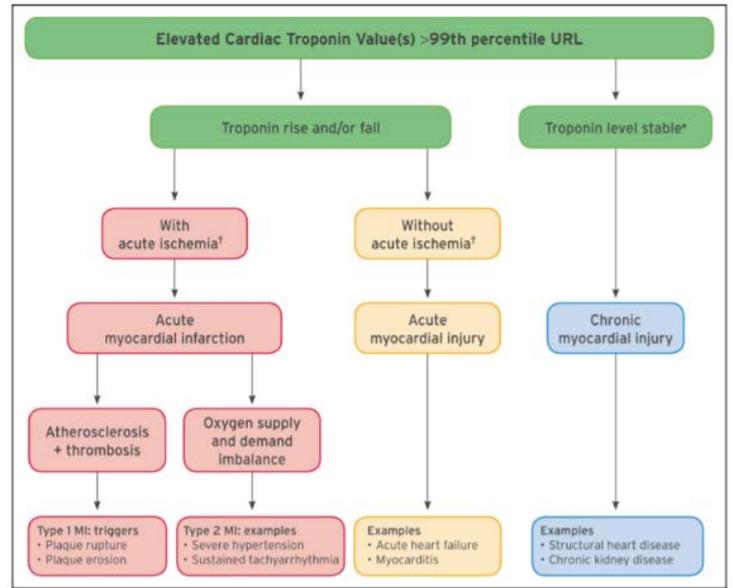


Figure 1: Interpreting Myocardial Injury, Fourth Universal Definition of Myocardial Infarction. Thygesen, K., et al., Circulation, 2018.

Despite the widespread use of the hs-cTnT in Europe, there is no standardized protocol that has been endorsed by the ESC for the evaluation of chest pain. The following are an overview of several different options for implementation.

I. Replace the 4<sup>th</sup> generation cTnT with the hs-cTnT assay and use 99<sup>th</sup> percentile ULN:

One strategy is to simply replace the current troponin test with the 99<sup>th</sup> percentile ULN of the hs-cTnT. The diagnostic accuracy of several hs-cTnT assays and the 4<sup>th</sup> generation assay were compared in a multicenter observational study. The APACE (The Advantageous Predictors of Acute Coronary Syndrome Evaluation) study is a prospective, international multicenter study that evaluated 786 patients who presented to EDs with symptoms concerning for AMI. In the study, investigators measured different troponin assays and adjudicated the final diagnosis in all patients. The sensitivity of the standard 4<sup>th</sup> generation cTnT assay was 83%, the negative predictive value was 97%, and the positive predictive value was 72%. In comparison, the Roche hs-cTnT had a sensitivity of 95%, negative predictive value of 99%, and positive predictive value of 50%. Additionally, this figure demonstrates the higher accuracy of the high-sensitivity assays in the diagnosis of MI which is more pronounced earlier in the presentation of chest pain.[12]

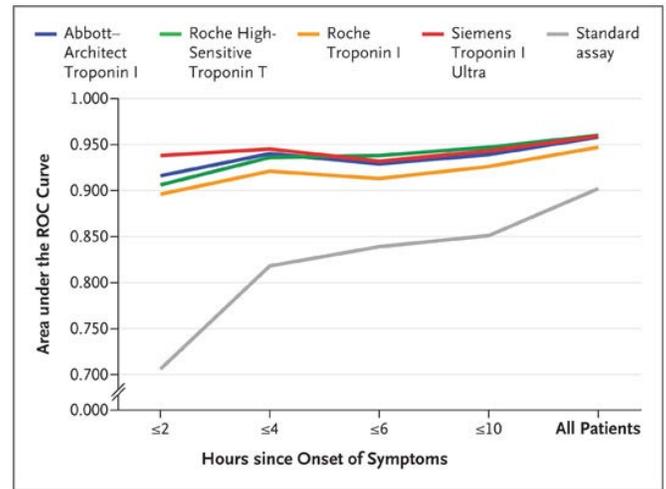


Figure 2: Diagnostic Accuracy of Cardiac Troponin Assays at Presentation According to Time since Onset of Chest Pain, Reichlin, T., et al, N Engl J Med, 2009.

As demonstrated by this study by Reichlin, the higher sensitivity and negative predictive value of the hs-cTnT assays also comes with the expense of a lower positive predictive value. This problem is likely to be magnified in populations in which the prevalence of myocardial infarction is lower. This table demonstrates this problem. As the MI probability goes down, the additional positive test results with the hs-cTnT assay vs. the standard assay increases (false positives). Therefore, the proportion of positive tests with the high-sensitivity assay who do not have myocardial infarction will increase.[13]

MI probability	Positive tests with standard assay (per 1000 patients)	Positive tests with hs assay	Additional positive tests meeting MI definition	Additional positive tests not meeting MI definition
17%	199	328	21	108
10%	146	275	12	117
5%	108	237	8	121
3%	93	222	3	126

Table 1: Estimated Proportion of False Positive MI Diagnoses with hs-cTnT assay, De Lemos, JA, Clin Chem 2011.

## II. 0/3 hour Rule Out Strategy:

The European Society of Cardiology 2011 guidelines recommend a 0/3 hour algorithm using the 99<sup>th</sup> percentile ULN at 0 and 3 hours as seen in this figure. The disadvantages of this protocol are that it requires many patients to remain in the ED for the 3 hour blood draw, relies on the 99<sup>th</sup> percentile ULN which will lead to higher rates of false positives in some populations, and does not specify the change values that are to be considered abnormal.[14]

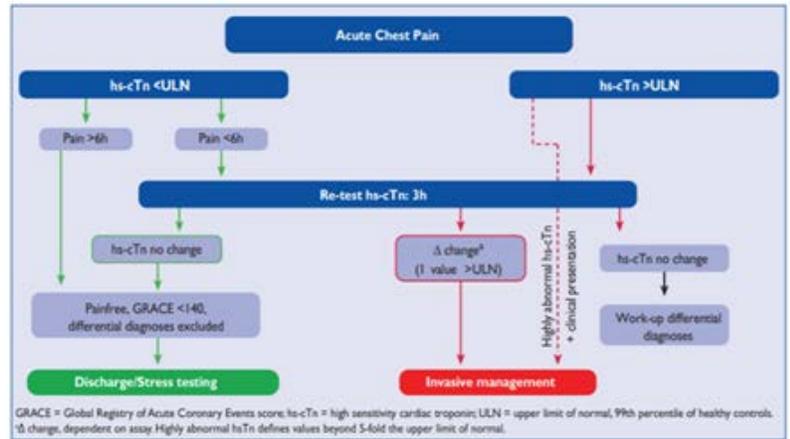


Figure 3: 0/3 Rule Out Strategy, Roffi M., et al., Eur Heart J, 2016.

## III. 0/1 hour rule out strategy:

Investigators developed a 0/1 hour rule out strategy from a prospective cohort study of patients presenting with chest pain to an ED in Basel, Switzerland. In this study, a 0/1 rule out algorithm was derived with optimal thresholds for rule-in and rule-out of myocardial infarction in a derivation subset of the study and then validated in the other half of the cohort. The investigators found that the a rule-out in which the initial troponin was <12 ng/L and the delta between the 0 and 1 hour values was < 3, had a sensitivity and negative predictive value of 100%. A rule-in was considered when the 0 hour value was  $\geq 52$  ng/L and the delta between the 0 and 1 hour value was  $\geq 52$  ng/L.[15] The advantages of using a 0/1 hour algorithm are that it takes advantage of the assay precision, is rapid, and well validated. Disadvantages include the complex timing of the blood draws and that the algorithm cannot be applied to early presenters. Finally, it leaves a proportion of patients in an indeterminate zone in which further evaluation is required.

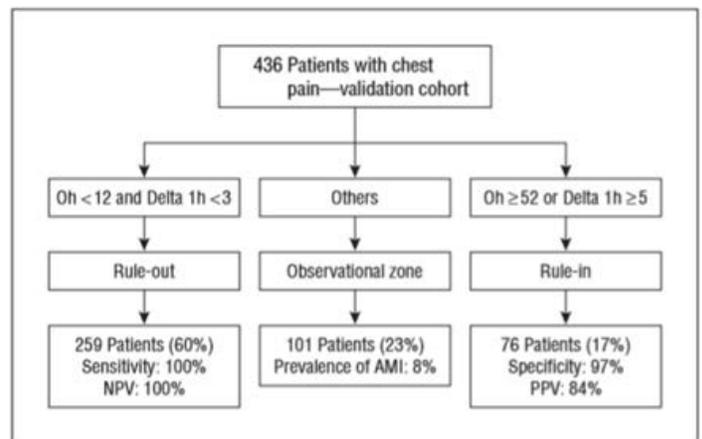


Figure 4: 0/1 hour rule out strategy, Reichlin, T., et al., Arch Intern Med, 2012

## IV. 0 Hour rule out strategy:

Several studies have evaluated a 0 hour rule out strategy in which MI is ruled out on a single blood draw. First, in a prospective cohort study of 703 patients from the UK with chest

pain who were evaluated with both the standard and hs-cTnT, investigators adjudicated final diagnosis of myocardial infarction and calculated the diagnostic performance of both tests. The investigators found that the sensitivity of a hs-cTnT < 3ng/l which was the limit of detection of the assay was 100% (95% CI 97.2 – 100.0) and negative predictive value was 100% (95% CI 98.1 – 100.0).[16] In a second retrospective study in which 7, 130 patients underwent testing with the hs-cTnT, a initial hs-cTnT < 6ng/L had a sensitivity of 99.8% for AMI (95% CI 98.7 – 100) and a negative predictive value of 99.9 (95% CI 99.8 – 100).[17] Therefore, the 0 hour rule out strategy is safe, but it only applies to a small proportion of patients presenting with chest pain (in the study by McRae, et al, only 42% had a initial value of <6 ng/L). Therefore many patients will require subsequent testing. The European society of cardiology NSTEMI guidelines endorse a 0 hour rule out strategy that can be applied to patients who have had chest pain for > 3 hours prior to presentation.[18]

### V. Use of Risk Scores/Accelerated Diagnostic Pathways:

Numerous risk stratification protocols have been developed to identify patients at low risk for adverse outcomes who may be safely discharged from the ED after presenting with chest pain. The HEART score is an algorithm that was previously used in the PHHS ED for patients presenting with chest pain, but not ACS and is predictive of MACE at 6 weeks (ACS, PCI/CABG, death). This score was originally developed in a cohort of 122 chest pain patients and categorizes individuals into low, intermediate, and high risk. The score takes into account history, ECG, age, risk factors, and troponin levels.[19] A score of 0-3 confers a risk of 2.5%, score of 4-6 points, 20.3%, and  $\geq 7$  points, risk of 72.7%.

HEART score for chest pain patients			Score
History	Highly suspicious		2
	Moderately suspicious		1
	Slightly suspicious		0
ECG	Significant ST depression		2
	Nonspecific repolarisation disturbance		1
	Normal		0
Age	<65 year		2
	45-65 year		1
	<45 year		0
Risk factors	$\geq 3$ risk factors or history of atherosclerotic disease		2
	1 or 2 risk factors		1
	No risk factors known		0
Troponin	>2x normal limit		2
	1-2x normal limit		1
	$\leq$ normal limit		0
			Total

Figure 5: HEART Score Components, Six, AJ, et al., Neth Heart J, 2008.

Further studies have evaluated the modified HEART score which combines the history, ECG, age, risk factors elements of the traditional heart score with the hs-cTnT early rule out algorithms. The TRAPID-AMI study, was an international, prospective study designed to evaluate the performance of a same 1-hour algorithm we described earlier with the modified HEART score in patients presenting with chest pain. The investigators found that 30 day MACE rates were 0.2% among patients who ruled out by the 1-hour algorithm and had a modified heart score  $\leq 3$ . Among patients who ruled out by the 1-hour algorithm, but had a heart score of  $\geq 4$ , 30 day MACE rates were 2.3%.[20]

The PHHS/UTSW Protocol:

Parkland was among the first US hospitals to implement the hs-cTnT in routine clinical care. The protocol was developed by a multidisciplinary team from laboratory medicine, emergency medicine, hospitalist medicine, cardiology and the administration. Prior to implementing the hs-cTnT protocol, this multidisciplinary team met on a regular basis to discuss development and roll-out of the protocol.[21]

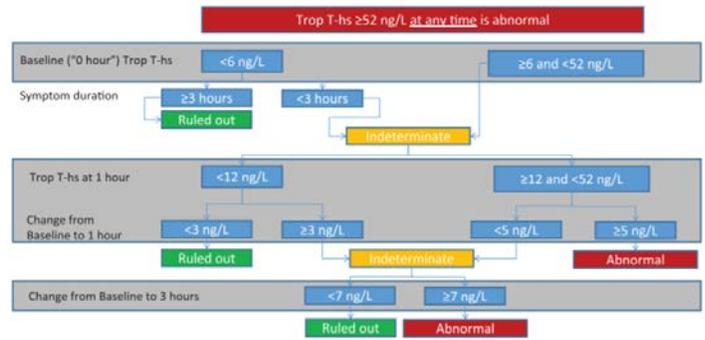


Figure 6: PHHS/UTSW High-sensitivity Troponin T Protocol

There are several unique characteristics of the protocol that differentiate it from previous protocols. First, the protocol capitalizes on the 0 hour and 0/1 hour approaches, but allows for the addition of a 3-hour hs-cTnT measurement for patients who are indeterminate after the 0/1 hour lab collections, and thus a decision is possible on all patients by 3 hours. Second, the protocol categorizes patients as either ruled-out vs. abnormal instead of “ruled-in” given that that large majority of patients with abnormal values do not have acute MI. Finally, the protocol is merged with the HEART score, to provide further guidance regarding the need for subsequent testing and disposition.

Prior to implementation of this protocol, we conducted a pilot study of unselected patients who underwent troponin testing at PHHS from August to October of 2017. Both cTnT and hs-cTnT biomarkers were obtained at 0, 1, and 3 hours after presentation in the ED among 536 patients with symptoms warranting myocardial infarction rule-out. We categorized patients as either abnormal or ruled out based on the hs-cTnT levels and change values per the protocol. We adjudicated the final diagnosis based on the Third Universal Definition of myocardial infarction. We also compared the PHHS/UTSW protocol to the 0/1 hour ESC algorithm.

The final adjudicated diagnosis was MI in 2.1%, unstable angina in 0.4%, and nonischemic myocardial injury in 17%. We found that 55% of patients would have been eligible for discharge at 1 hour and the sensitivity and negative predictive value of the protocol were 100%. However, the positive predictive value of the protocol was only 13%, reflecting the low prevalence of disease in this population. When compared with the ESC 0/1 hour algorithm, a higher proportion ruled out with our new algorithm (83.8 vs 55.4%,  $p < 0.0001$ ), resulting from movement of 152/154

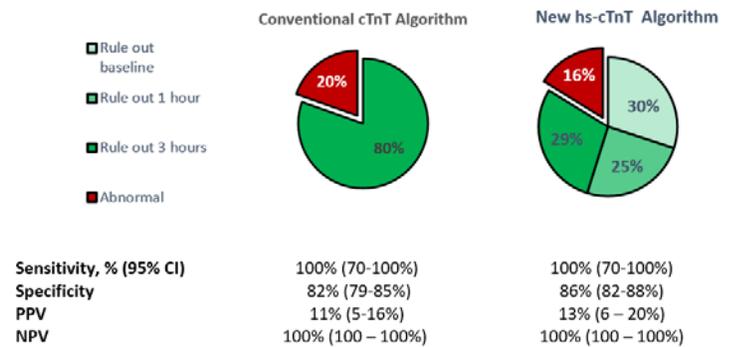


Figure 7: Proportion of patients ruled out for acute myocardial infarction based on the conventional cTnT algorithm and the new hs-cTnT algorithm, Vigen, et al, Circulation, 2018.

patients assigned to observation status with the ESC 0/1 hour algorithm to the rule out group with the new protocol.[22]

### The PHHS Experience with Hs-cTnT Protocol:

Since implementation of the PHHS hs-cTnT algorithm on 12/2017, we have begun a retrospective study of patient encounters seen at PHHS ED. We evaluated changes in temporal trends in ED dwell times, troponin to disposition decision time, and disposition category (discharge from emergency department vs admission to observation vs inpatient admission) before and after the intervention. ED dwell time was abstracted from the electronic medical record and defined as the difference between ED arrival time and ED departure time. Troponin to disposition decision time was the time difference between the time the first troponin test was drawn and the time a disposition order was placed. Disposition category included discharge from the emergency department, inpatient admission, or admission to observation.

For this study, we identified 33,231 encounters from 1/1/2017 to 9/30/2018 in which patients had ECG and troponin testing within 3 hours of ED arrival and in which emergent hemodialysis was not performed in the ED. For this analysis, we excluded 91 outpatients, 470 patients with missing values for troponin to disposition time, 1,118 patients in whom a disposition decision was made prior to troponin draw time and 9 redundant ED encounters. This left us 31,543 unique ED encounters for analysis. The proportion of patients discharged from the ED was 48.2% prior to the intervention and 53.8% after the intervention. The proportion of patients admitted to observation was 22.0% prior to the intervention and 18.9% after the intervention.

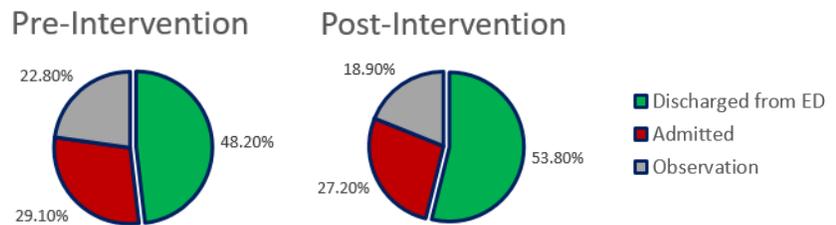


Figure 8: Proportion of encounters in which patients were discharged from ED, admitted, vs. admitted to observation pre and post-intervention, Vigen, et al. unpublished data

Prior to the intervention, ED dwell times were decreasing by -0.7 minutes/month and this change increased to -10.2 min/month post-intervention. Prior to the intervention, troponin draw to disposition times were increasing by 1.78 minutes/month and after intervention, this downtrended to -0.39 minutes per month (analyses adjusted for age, rule out class, sex, race, ethnicity, and financial class). A random effect term was used at the patient level to control for intra-patient effects. For both metrics, the interaction term was significant, supporting that the intervention favorably modified temporal trends in dwell times.

We evaluated safety by linking this data to the Dallas Fort Worth Hospital Council network which includes data from 86 hospitals in North Texas. We were able to match 89.7% of the encounters among patients who ruled out and were discharged in our cohort to this dataset. We evaluated rates of 30 day MACE after discharge using ICD-10 codes for MI and death flag in DFWHC data. MACE rates were <1% throughout the entire study period. These data support that the implementation of the protocol, which increased discharge rates from the ED and shortened dwell times, did not increase rates of complications among those ruled out.

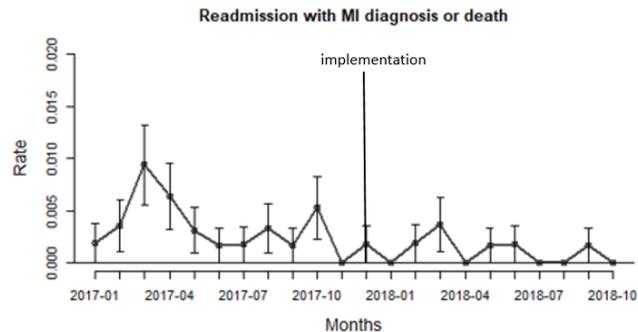


Figure 9: Monthly rates of 30 day readmission for myocardial infarction or death, Vigen et al, unpublished data

### Conclusions:

The use of innovative protocols for ruling out myocardial infarction in the ED using the high-sensitivity troponin and risk stratification pathways such as the HEART score have the potential to improve the quality of and costs associated with the evaluation of patients with chest pain. Studies in the Parkland population have demonstrated that using this novel rule out protocol rules out a larger proportion of the population, and does so more rapidly than the previous protocol. Additionally, our data shows that there are improvements in ED efficiency and disposition. Finally, we have not detected any increase in rates of adverse events after instituting the protocol. This or similar rapid rule out MI protocols have the potential to improve health care quality and reduce ED overcrowding by improving the efficiency of the triage of chest pain patients while maintaining safety. Further investigation is needed to determine the effects on downstream cardiac testing, costs, and protocol adherence.

## REFERENCES

1. *National Hospital Ambulatory Medical Care Survey: 2013 Emergency Department Summary Tables.*
2. O'Connor, E., et al., *Evaluating the effect of emergency department crowding on triage destination.* Int J Emerg Med, 2014. **7**: p. 16.
3. Sun, B.C., et al., *Effect of emergency department crowding on outcomes of admitted patients.* Ann Emerg Med, 2013. **61**(6): p. 605-611 e6.
4. Kulstad, E.B. and K.M. Kelley, *Overcrowding is associated with delays in percutaneous coronary intervention for acute myocardial infarction.* Int J Emerg Med, 2009. **2**(3): p. 149-54.
5. Ferguson, B., et al., *Malpractice in Emergency Medicine-A Review of Risk and Mitigation Practices for the Emergency Medicine Provider.* J Emerg Med, 2018. **55**(5): p. 659-665.
6. Pope, J.H., et al., *Missed diagnoses of acute cardiac ischemia in the emergency department.* N Engl J Med, 2000. **342**(16): p. 1163-70.
7. Chang, M.P., Vigen, Rebecca, Sharma, Sushma, Diercks, Deborah B, *Possible Missed Acute Coronary Syndrome Rate in North Texas: Is There Room to Improve? .* Critical Pathways in Cardiology 2019. **In press.** .
8. Thygesen, K., et al., *Fourth Universal Definition of Myocardial Infarction (2018).* Circulation, 2018. **138**(20): p. e618-e651.
9. Amsterdam, E.A., et al., *2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol, 2014. **64**(24): p. e139-e228.
10. Apple, F.S., P.O. Collinson, and I.T.F.o.C.A.o.C. Biomarkers, *Analytical characteristics of high-sensitivity cardiac troponin assays.* Clin Chem, 2012. **58**(1): p. 54-61.
11. Brush, J.E., Jr., S. Kaul, and H.M. Krumholz, *Troponin Testing for Clinicians.* J Am Coll Cardiol, 2016. **68**(21): p. 2365-2375.
12. Reichlin, T., et al., *Early diagnosis of myocardial infarction with sensitive cardiac troponin assays.* N Engl J Med, 2009. **361**(9): p. 858-67.
13. de Lemos, J.A., D.A. Morrow, and C.R. deFilippi, *Highly sensitive troponin assays and the cardiology community: a love/hate relationship?* Clin Chem, 2011. **57**(6): p. 826-9.
14. Roffi, M., et al., *2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC).* Eur Heart J, 2016. **37**(3): p. 267-315.
15. Reichlin, T., et al., *One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T.* Arch Intern Med, 2012. **172**(16): p. 1211-8.
16. Body, R., et al., *Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay.* J Am Coll Cardiol, 2011. **58**(13): p. 1332-9.
17. McRae, A.D., et al., *Undetectable Concentrations of a Food and Drug Administration-approved High-sensitivity Cardiac Troponin T Assay to Rule Out Acute Myocardial Infarction at Emergency Department Arrival.* Acad Emerg Med, 2017. **24**(10): p. 1267-1277.

18. Roffi, M., et al., [2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation]. *Kardiol Pol*, 2015. **73**(12): p. 1207-94.
19. Six, A.J., B.E. Backus, and J.C. Kelder, *Chest pain in the emergency room: value of the HEART score*. *Neth Heart J*, 2008. **16**(6): p. 191-6.
20. McCord, J., et al., *Prognostic Utility of a Modified HEART Score in Chest Pain Patients in the Emergency Department*. *Circ Cardiovasc Qual Outcomes*, 2017. **10**(2).
21. Hashim, I.A., et al., *Validation and implementation of the fifth-generation high sensitivity Troponin T (hs-TnT) assay at a large teaching county hospital. A laboratory-driven multi-speciality effort*. *Clin Chim Acta*, 2019. **495**: p. 85-87.
22. Vigen, R., et al., *Evaluation of a Novel Rule-Out Myocardial Infarction Protocol Incorporating High-Sensitivity Troponin T in a US Hospital*. *Circulation*, 2018. **138**(18): p. 2061-2063.