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Early Non-Invasive Cardiac Testing after Emergency Department Evaluation for Suspected Acute Coronary Syndrome

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Key Points

Question: Is early non-invasive cardiac testing (NIT) after an emergency department (ED) evaluation for acute coronary syndrome more effective than not testing, to reduce the risk of death or acute myocardial infarction (MI) within 30 days?

Findings: In a retrospective cohort of 79,040 adults presenting to the ED with chest pain and had MI ruled out, early NIT was associated with a small (0.4%) but significant decrease in the absolute composite risk of death/MI. The number needed to treat was 250.

Meaning: Early NIT may reduce the risk of death/MI, but its value is questionable for most ED patients.

ABSTRACT

Importance: Professional guidelines recommend non-invasive cardiac testing within 72 hours of an emergency department evaluation for suspected acute coronary syndrome. However, there is inexact evidence that this strategy reduces the risk of future death or acute myocardial infarction.

Objective: The objective of this study was to evaluate the effectiveness of early non-invasive cardiac testing in reducing the risk of death or acute myocardial infarction within 30 days.

Design: Retrospective cohort study. We compared the effectiveness of early non-invasive cardiac testing vs. no testing, in patients presenting to an emergency department from 01/2015 to 12/2017. Patient were followed up for up to 30 days post emergency department discharge.

Setting: Multicenter study within the Kaiser Permanente Southern California integrated health care delivery system.

Participants: Adult patients presenting to an emergency department with chest pain and in whom acute myocardial infarction was ruled out.

Exposure: Non-invasive cardiac testing performed within 3 days of an emergency department evaluation for suspected acute coronary syndrome.

Main Outcome(s) and Measure(s): The primary outcome was composite risk of death or acute myocardial infarction, within 30 days of an emergency department discharge.

Results: The mean age of the cohort (N=79,040) was 57 (±16) years, and 16,164 (21%) patients had completed early NIT. The absolute risk of death or MI within 30 days was low (<1%). Early NIT had minor benefit in reducing the absolute composite risk of death or MI (0·4% (95% CI -0·6% to -0·3%), and separately of death (0·2% (95% CI -0·2% to -0·1%)); MI (-0·3% (-0·5% to

-0·1%)) and MACE (-0·5% (-0·7% to -0·3%)). The number needed to treat (NNT) was 250 to avoid one death or MI, 500 to avoid one death, 333 to avoid one MI and 200 to avoid one MACE within 30 days. Subgroup analysis revealed NNT of 14 to avoid one death or MI in the subset of patients with elevated troponin.

Conclusions and Relevance: Early NIT was associated with a small decrease in the risk of death or MI in ED patients with suspected ACS, but this clinical strategy may not be optimal for most patients given the large NNT.

INTRODUCTION

Acute coronary syndrome (ACS) is high-risk manifestation of coronary atherosclerosis, which includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). ACS is the leading cause of worldwide mortality and morbidity.[1,2] The majority of ACS patients present with chest pain to emergency departments (ED), and chest pain is the second most frequent reason for all U.S. ED visits accounting for over seven million annual encounters.[3] However, only the minority (1-13%) of these visits are related to ACS. Accurate diagnosis is challenging and fraught with high medical and legal risks.[4,5] The missed ACS rate after an ED evaluation has been reported as high as 2%-4% and is associated with doubled mortality.[6-9] Additionally, missed ACS is the top reason for medical malpractice claims against ED physicians which encourages increased testing.[10,11]

The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend non-invasive cardiac stress testing (NIT) before discharge or within 72 hours of discharge, after serial electrocardiogram (ECG) and troponin biomarkers have excluded acute myocardial infarction (MI) in patients with suspected ACS (Class IIA recommendation).[12-14] This approach is recommended for even low-risk patients and is the ED standard of care in the US.[12,14] The European Society of Cardiology (ESC) guidelines (2015) recommend a non-invasive stress test (preferably with imaging) for inducible ischemia, during admission or shortly after discharge, in patients with no recurrence of chest pain, normal ECG and normal cardiac troponin levels, but suspected ACS.[15] The National Institute for Health and Care Excellence (NICE) has questioned ESC guidelines since stress testing has relatively low sensitivity and

specificity for diagnosing coronary artery disease (CAD) in suspected troponin-negative ACS patients.[16]

Patients with suspected ACS are often hospitalized to facilitate early NIT. Evaluation of suspected ACS is the top reason for U.S. short-stay (<48 hours) inpatient and observation admissions and accounts for over $3 billion in hospital costs per year.[17-20] However, there is no evidence that early NIT benefits patients.[2,21-23] Recent data suggest that current use of early NIT increases rates of invasive coronary angiography and revascularization without reducing risk of MI.[2,24] However, these studies used administrative data and are limited by lack of mortality data, clinically relevant information such as cardiac biomarkers, and potential for unmeasured confounding.[2,24,25]

We evaluated the effect of early NIT in a large representative cohort of people presenting to the ED with suspected ACS, in one of the largest integrated healthcare delivery systems in the U.S. The objective of this study was to evaluate the effectiveness of early NIT in reducing the primary outcome of all-cause death or MI within 30 days of ED encounter.

METHODS

Study Design, Population, and Settings

A retrospective cohort study was conducted in the member population of Kaiser Permanente Southern California (KPSC), an integrated healthcare organization with over 7,500 physicians, 15 medical centers and 231 medical offices. KPSC provides comprehensive health care to over 4·6 million racially and socio-economically diverse members residing within seven counties of Southern California. Health care at KPSC is coordinated through region wide electronic medical records (EMR) that capture detailed information on care provided to members at outpatient visits and during inpatient stays, as well as pharmacy, immunizations, imaging and laboratory services received at KPSC-owned and contracting facilities. Research database also includes administrative claims for our members that capture any out of network clinical care and patient outcomes.

KPSC hospitals provide care to over 1 million ED patients per year (study sites ranging from ≈25,000 to 95,000 ED visits per year). Of these ED visits, approximately 80% are health plan members. All sites use the same troponin lab assay (Beckman Coulter Access AccuTnI+3) as well as a uniform >0·5 ng/ml MI threshold and a 0·04-0·5 ng/ml elevated risk cutoff. ED physicians can order NIT as part of the evaluation and discharge plan of patients with suspected ACS.

The study was approved by the Institutional Review Board (IRB) of KPSC. The IRB granted a waiver/exemption from the requirement of obtaining informed consent from study participants.

Inclusion/Exclusion

We included all KPSC members aged 18 years or older with a visit for chest pain between 01/01/2015 to 12/01/2017 at 13 EDs operated by KPSC. To ensure complete co-morbidity and

outcomes capture, all included patients were required to have continuous health plan enrollment in the 12 months prior to and for at least 30 days post discharge from their ED visit. ED encounters were included in the study if a valid troponin biomarker assay result was available for that encounter.

We excluded patients if they (1) had MI identified during the ED encounter, (2) had an initial troponin level greater than 0·5 ng/ml, (3) had coronary revascularization procedure performed before NIT, (4) were transferred from another hospital, (5) died in the ED, (6) were in hospice status, (7) had documented "do not resuscitate" order in the EMR.

Outcomes, Exposure and Covariates Measurement

Outcomes

Primary

The primary outcome was the composite risk of 30-day MI or all-cause death. Death data was obtained from KPSC administrative records, EMR as well as claims for out of network deaths. These data were supplemented with California state death files and Social Security Administration (SSA) records for out-of-state deaths.

Secondary

As our secondary outcome, we measured 30-day incidence of revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Lastly, we also measured 30-day incidence of MI and death independently as secondary outcomes.

The 30-day time frame is consistent with ED ACS research guidelines as longer time frames are unlikely to affect ED decision making.[26] Lastly, we defined major adverse cardiac event (MACE) as the composite outcome of all-cause death, MI, or revascularization within 30 days.

Exposure

The exposure was performance of non-invasive stress testing within 3 days of the ED visit. NIT included any of the following: stress electrocardiogram, stress echocardiogram, stress myocardial perfusion, or coronary computed tomography angiogram that were identified by Current Procedural Terminology (CPT)® codes or EMR order entry.

Covariates

Covariates included patient demographic information and clinical history (Table 1). Age, sex and race were obtained from the health plan's administrative records. Clinical data were obtained from the EMR. Comorbidities and cardiac risk factors were defined using laboratory values, diagnostic or procedure codes along with the Elixhauser comorbidity index. The details on the procedure and diagnostic codes have been described elsewhere.[5,27,28] Body mass index (BMI) was measured from ED intake documentation or the most recently available visit, while smoking and family history of CAD/stroke were self-reported EMR fields. Those with a history of PCI or CABG were considered to have had prior coronary vascularization. Initial troponin level was dichotomized with a value below 0·04 ng/ml indicating a normal result and results between 0·04-0·5 ng/ml representing an elevated ACS risk. Lastly, using pharmacy prescription records, we identified patients on active antidiabetic, anticoagulants, anti-hyperlipidemia and anti-hypertension treatment, in the 90-days prior to their ED encounter.

Statistical Analysis

Evaluation of the effect of early NIT on primary and secondary outcomes using an observational study design is challenging due to the non-randomized assignment (selection-bias) to treatment (i.e. early NIT) as well as heterogeneity of the effect of NIT on outcomes observed in the diverse sample of ED patients.[29] We used Rubin's potential outcomes framework to evaluate the

treatment effect of early NIT on primary and secondary outcomes.[30] The treatment effect was estimated relaxing the restrictive assumption of un-confoundedness, by using generalized method of moments based residual inclusion instrumental variables (IV) techniques.[31,32] Models adjusted for socio-demographic and clinical covariates. To intuitively understand IV analysis, we can consider the variation in the receipt of treatment (i.e. early NIT) to have two parts; the part that is not confounded and the part that is correlated with the error ("bad" variation or confounding by indication).[33,34] IV analysis isolates and retains only the unconfounded variation in the treatment and disregards the "bad" variation. IV models generate this quasi-experimental variation through excluded (from the outcome model) instruments that predict receipt of the treatment but are not related to prognosis.[33,34] We used (a) each KPSC medical center's practice pattern for NIT within 72 hours and (b) day of the week of the ED encounter, as two excluded instruments to isolate the "good" variation.[27] We postulated that weekend related scheduling delays make it less likely that stress testing can be completed within 72 hours if the order was placed on a weekend.[23] Each medical center's practice pattern was calculated as the percent of suspected ACS patients receiving NIT, in the one year prior to the ED date of each included cohort case with suspected ACS. The medical center's practice pattern synthesizes consensus, experience and training of the ED professional staff, medical center's protocol/policies and available infrastructure to support early NIT. The calculation of the medical center's practice pattern based on presenting patient's ED encounter date, made it dynamic and allowed capturing changes over time at the same medical center based on changes to any system or human capital factors.

We provide estimates of the first stage IV treatment selection model (eTable 1) as well as statistical tests to evaluate the validity of our IV modelling assumptions (eTable 2).

We report the Number Need to Treat (NNT) as the inverse of the adjusted Absolute Risk Reduction (ARR).

In sensitivity analysis, we analyze the data using doubly robust inverse probability of treatment weighted and regression adjusted (IPWRA) models assuming the un-confoundedness requirement was not violated (Table 3). Lastly, we report the treatment effect of early NIT in high cardiac risk sub-groups of patients (Table 4). All hypothesis tests were two sided with an *apriori* type I error set at 5%. Stata/MP® version 15 software was used for data analysis (Stata Corp LLC, College Station TX).

RESULTS

The total cohort included 79,040 adults (Figure 1), of whom 16,164 (21%) completed a non-invasive stress test within 72 hours of admission (Table 1). Among the 16,164 tested, 17.3% (n=2796) completed the test as an outpatient while 82.7% (n=13,368) completed it either prior to or on the day of discharge. The distribution of the type of NIT included 47·5% stress electrocardiogram, 17% stress echocardiogram, 35% stress myocardial perfusion, and 0·5% coronary computed tomography angiogram. The mean age of the cohort was 57 (SD ±16) years and the majority were female (58%) and white race (52%). The combined risk of death/MI was 0·5% in the control cohort, while in the NIT cohort it was 0·3% (Table 1). The independent risk of death was 0·2% vs 0·1%; of MI was 0·3% vs 0·2%; of coronary revascularization was 0·2% vs 0·4% and of MACE was 0·5% vs. 0·3% in the control vs. early NIT cohorts respectively (Table 1).

Specification testing of the IV models suggested that day of the week and medical center's NIT practice pattern, were strong instruments. Independently, one percent increase in a medical center's past practice pattern for NIT was associated with a 6·4% (95% CI 6·0% to 6·9%) higher odds of ordering early NIT. Similarly, as compared to an ED encounter during any weekday (Monday-Friday), the odds of ordering early NIT were lower by 18% (95% CI 14% to 21%) during weekend (eTable 1). All assumptions necessary for consistent parameter estimates from IV analysis were satisfied (eTable 2).

The average adjusted risk reduction for death or MI was 0·4% (0·3% to 0·6%) while that for death was 0·18% (0·1% to 0·2%) (Table 2). Similarly, the adjusted risk reduction for secondary aims of MI was 0·3% (0·1% to 0·5%) and MACE was 0·5% (0·3% to 0·7%) (Table 2). The difference in coronary revascularization rate was not statistically significant. The NNT was 250

for the death/MI composite outcome while for death, MI and MACE the NNT was 500, 333 and 200 respectively (Table 2).

Sensitivity analysis using inverse probability weighted models showed similar results with slightly smaller treatment effect (hence higher NNT) but the MI outcome was not found to be significantly different (Table 3).

In the traditional subgroups associated with high cardiac risk, the absolute risk of death and MI composite outcome ranged between 0·4% (female sex and BMI ≥ 30) to a maximum of 7% (elevated troponin) in the controls (Table 4). Early NIT reduced the absolute risk of death/MI by 0·3% to 7%. Consequently, the NNT ranged between a low of 14 to a high of 333.

DISCUSSION

We evaluated the effect of early NIT in a large cohort of ED patients presenting with suspected ACS, on the risk of death, MI, coronary revascularization and MACE within 30-days post discharge. Few prior studies have evaluated the impact of NIT on cardiovascular outcomes and only one study has evaluated the effect of NIT performed within 30 days, on cardiovascular death.[2,23-25,35] We focus on evaluating outcomes in the 30-day follow-up period since it allows disentangling the immediate impact of early NIT on outcomes as opposed to that observed from the cascade of events leading to improved downstream processes of care that ultimately may have led to the lower outcomes which have been reported in prior studies. The 30-day follow-up is also more closely related to ED decision making and any benefit of early NIT should be identified within this timeframe. By combining the comprehensive EMRs with California State level death data and national death data obtained from the SSA, we believe this is one of the first studies to report on the impact of early (within 72 hours) NIT on the risk of death, at the population level.

In this cohort, the absolute risks of death/MI, death, MI, revascularization and MACE within 30 days of ED discharge were low (<1%) and early NIT had minor benefit in reducing these risks. We find that to benefit from AHA/ACC NIT guidelines, the NNT to avoid one death or MI was 250 while 500 suspected ACS patients need to be tested to avoid one death. While we do not find a benefit of NIT at reducing coronary revascularization, however it is interesting to note that revascularization procedures were not increased with early NIT. The lack of increased revascularization rates among NIT patients suggests that other factors are likely driving the reduced event rate. For instance, better medical optimization may play a role, as we noted the early NIT arm had higher utilization of antihyperlipidemics (16.1% vs 9.7%; p<0.001);

antihypertensives (13.8% vs 10.2%; p<0.001); anti-anticoagulants (4.7% vs 3.6% ; p<0.001); and antidiabetic medication (4.4% vs. 3.3% ; p<0.001) as compared to the no early NIT arm, in the 90-day post discharge period. Thus, NIT may identify patients who could benefit from additional contact with outpatient providers where lifestyle interventions and medication adherence may be emphasized. Hence, if used appropriately, NIT could serve a role in downstream risk stratification to identify CAD and hence may improve outcomes beyond 30 days.

The absolute risk of death/MI was highest in patients with elevated troponin who also experienced the most risk reduction (7%) related to early NIT. With a NNT of 14 observed in traditional troponin assays, there appears promise in adoption of high sensitivity troponin assays for future ACS evaluation. High-sensitivity cardiac troponin (Hs-cTn) assays increase diagnostic accuracy for MI at the time of presentation and allow for a more rapid 'rule-in' and 'rule-out' of MI.[15] In most other high cardiac risk subgroups, the NNT was above 100. Our findings suggest a need for implementation of risk stratification models in the ED to better identify those more likely to benefit from NIT and avoid unhelpful tests. For example, in addition to biomarkers and ECG, a low HEART score has been associated with low 30-day MACE outcome.[36,37] Along with increased adoption of HEART score for ED evaluation of ACS, refinement of existing HEART score with Hs-cTn assays could significantly reduce unhelpful NIT.

Our results on MI and coronary revascularization are similar to published reports.[2,23,25,35] Using IV analysis in a retrospective cohort of privately insured patients, Sandhu et al. report that cardiac testing was associated with increased revascularization without a significant change in MI.[23] Foy et al. report that ED patients with chest pain who do not have an MI are at very low risk of experiencing an MI during short- and longer-term follow-up and this low risk does not appear to be affected by the initial testing strategy.[2] These two studies do not include patients

over the age of 65, Medicare/Medicaid enrollees, and have not adjusted race/ethnicity related differences. Roifman et al. have reported on the effect of NIT performed within 30 days of chest pain visit on composite MI or death in 90 days and 1 year follow-up in population of Ontario, Canada. Their propensity score matched analysis estimated a NNT of 974 to prevent one event of MI or cardiovascular death in a 1-year follow-up. In the short term 90-day follow-up, the NIT arm had marginally higher composite outcome which could be due to unmeasured confounding that was not addressed in their analysis.[25,38] The majority of these prior studies have lacked information on clinically important variables such as initial troponin value and hence may have not identified type 2 MI which is based on the level of troponin. Reinhardt et al. preformed a secondary analysis of the ROMICAT-II trial and report that stress testing leads to longer length of stay, more downstream testing, more radiation exposure, and greater cost without an improvement in clinical outcomes.[35]

Cumulatively, these consistent results observed across geographically diverse populations question the current ACC/AHA recommendations of early NIT in ED patients with suspected ACS.[39] The PROMISE and SCOT-HEART trials, as well as several population-based studies including this study have found low rates of MI and death and it's difficult to further reduce what are already low rates, by NIT.[25,40,41] Hence, future guideline revisions on NIT could recommend increased role for risk stratification to identify high risk patients and soften NIT recommendation for low-risk patients. Additionally, in low risk patients, once ACS is ruled out, they could be managed according to guidance for the management of suspected CAD, which is aimed at primary care and/or their cardiologist.

We also foresee benefits of developing new risk stratification models using high sensitivity troponin assays or modifying existing models to incorporate high sensitivity troponin assays

instead of traditional troponin assays. Additionally, increased adoption and documentation of shared decision-based treatment where patients understand their options and the trade-offs involved with NIT may reduce overutilization of NIT and allow patients to protect themselves financially from the inevitable gaming involved in the complex US healthcare reimbursement system.[42]

Limitations

There are several potential limitations to our study. This study provides data on the short-term safety of early NIT in a low-risk population, which is typical of most suspected ACS ED encounters. Our findings may not apply beyond the 30-day post ED discharge period. However, other studies have failed to show significant benefit of NIT for longer term outcomes.[2,23] Additionally, results do not apply to MI cases presenting without chest pain, which can be seen in older patients, women, diabetics and heart failure patients. Also, the patient population is geographically limited to Southern California and belongs to a single integrated healthcare system which may limit practice pattern variation observed across the U.S. and in fee-for-service systems. The lack of Hs-cTn assay is a limitation that impacts the generalizability of our results. Hs-cTn assay can theoretically better risk stratify patients on presentation and hence adoption of high-sensitivity assays will likely further drive down rates of NIT from the ED. We also do not have patient level social risk data which may contribute to the receipt of early NIT because those who lack transportation, don't speak English well, or have lower education levels may not be able to navigate the health system as well.

Conclusion

In suspected ACS patients with MI ruled out, early NIT results in minor reductions (0·4%) in death/MI outcome, but the large number needed to treat required to benefit one patient calls into question this clinical strategy for most patients. Our findings support selective use of NIT by avoiding such testing for most patients evaluated in the ED and reserving NIT for patients at substantial risk of 30-day adverse cardiovascular outcomes.

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Table 1. Descriptive Statistics of the Cohort's Demographics and Clinical Characteristics

	Total Cohort **N= 79,040 (100%)**	**No Early NIT** **N= 62,876 (79·5%)**	**Early NIT** **N= 16,164 (20·5%)**	**p-value of Mean Differences***
Outcomes				
Acute Myocardial Infarction (MI) or Death within 30 days[#]	344 (0·4%)	296 (0·5%)	48 (0·3%)	p=0.003
Death within 30 days	143 (0·2%)	134 (0·2%)	9 (0·1%)	p<0.001
MI within 30 days	209 (0·3%)	170 (0·3%)	39 (0·2%)	p=0.52
Coronary Revascularization within 30 days	209 (0·3%)	143 (0·2%)	66 (0·4%)	p<0.001
Major adverse cardiovascular events (MACE) within 30 days	355 (0·4%)	306 (0·5%)	49 (0·3%)	p=0.002
Demographics and Clinical Characteristics				
Age *Mean (SD)*	57·1 (16·3)	55·7 (16·8)	62·4 (12·6)	p<0.001
Age 65 and Above	27441 (34·7%)	20221 (32·2%)	7220 (44·7%)	p<0.001
Female	45586 (57·7%)	36782 (58·5%)	8804 (54·5%)	p<0.001
White	40787 (51·6%)	31822 (50·6%)	8965 (55·5%)	p<0.001
Active/Passive Smoker	5663 (7·2%)	4562 (7·3%)	1101 (6·8%)	p=0.051
Body Mass Index (BMI) Mean (SD)	30·0 (6·88)	30·0 (6·95)	30·0 (6·60)	p=0.83
Overweight or Obese	60191 (76·2%)	47595 (75·7%)	12596 (77·9%)	p<0.001
Elevated Troponin (0·04 to 0·5)	2854 (3·6%)	2085 (3·3%)	769 (4·8%)	p<0.001
Coronary Artery Disease (CAD)	13987 (17·7%)	10877 (17·3%)	3110 (19·2%)	p<0.001
Stroke	2006 (2·5%)	1595 (2·5%)	411 (2·5%)	p=0.97
Percutaneous transluminal coronary angioplasty (PTCA) or Coronary artery bypass graft (CABG) in prior year	1008 (1·3%)	859 (1·4%)	149 (0·9%)	p<0.001
Family history: CAD	26337 (33·3%)	20526 (32·6%)	5811 (36%)	p<0.001
Family history: Stroke	14472 (18·3%)	11507 (18·3%)	2965 (18·3%)	p=0.90
Anti-diabetic Medications	12493 (15·8%)	9423 (15%)	3070 (19%)	p<0.001
Anti-hyperlipidemia Medications	23947 (30·3%)	17880 (28·4%)	6067 (37·5%)	p<0.001
Anti-hypertension Medications	33673 (42·6%)	25580 (40·7%)	8093 (50·1%)	p<0.001
Anti-coagulant Medications	7459 (9·4%)	5902 (9·4%)	1557 (9·6%)	p=0.49
Elixhauser Comorbidity Index *Mean (SD)*	3·6 (2·98)	3·5 (3·04)	3·7 (2·73)	p<0.001

8 patients had MI and died subsequently. They have not been counted twice in the composite outcome.

**chi-square or ANOVA

508 **Table 2. Absolute Risk, Risk Reduction and NNT**

Outcome	Adjusted Risk		Risk Reduction (RR)	Number Needed to Treat (NNT)
	No Early NIT (Control) (N= 62,876) Mean (Std Error)	**Early NIT (Treated)** (N= 16,164) Mean (Std Error)	**Early NIT Adjusted Risk – Control Adjusted Risk** Mean*# (95% CI) p-value	**1/Absolute Risk Reduction**
Death/MI	0·005 (0·0008)	0·0008 (0·0004)	**-0·004** **(-0·006 to -0·003)** p<0.001	1/0·004 = **250**
Death	0·0019 (0·0003)	0·00013 (0·00005)	**-0·002** **(-0·002 to -0·001)** p<0.001	1/0·002 = **500**
Acute MI	0·003 (0·0009)	0·0007 (0·0003)	**-0·003** **(-0·005 to -0·001)** p=0.004	1/0·003 = **333**
Coronary Revascularization	0·004 (0·002)	0·002 (0·002)	-0·002 (-0·006 to 0·003) p=0.45	N/A^
MACE	0·006 (0·001)	0·0008 (0·0003)	**-0·005** **(-0·007 to -0·003)** p<0.001	1/0·005 = **200**

#Bold Font indicate statistically significant differences

^ Difference in event rates are not statistically significant at α=0·05 and the 95% CI contains zero

*All models adjusted for age, sex, race, smoking, BMI, self and family history of CAD, initial troponin, antidiabetic medication, anticoagulant medication, anti-hyperlipidemia medication, anti-hypertension medication and Elixhauser comorbidities

509

Table 3. Sensitivity Analysis Inverse Probability Weighted Models

Outcome	Adjusted Risk		Risk Reduction (RR)	Number Needed to Treat (NNT)
	No Early NIT (Control) (N= 62,876) Mean (Std Error)	**Early NIT (Treated)** (N= 16,164) Mean (Std Error)	**Early NIT Adjusted Risk – Control Adjusted Risk** Mean[#] (95% CI) p-value	**1/Absolute Risk Reduction**
Death/MI[*]	0·005 (0·0003)	0·003 (0·0005)	**-0·002 (-0·003 to -0·001)** p=0.001	1/0·002 = **500**
Death[$]	0·005 (0·0003)	0·003 (0·0004)	**-0·002 (-0·003 to -0·001)** p<0.001	1/0·002 = **500**
Acute MI[*]	0·003 (0·0002)	0·002 (0·0004)	-0·001 (-0·002 to 0·0003) p=0.22	N/A^
Coronary Revascularization[*]	0·003 (0·0002)	0·003 (0·0004)	0·001 (-0·0002 to 0·002) p=0.13	N/A^
MACE[*]	0·005 (0·0003)	0·003 (0·0005)	**-0·002 (-0·003 to -0·001)** p=0.001	1/0·002 = **500**

#Bold Font indicate statistically significant differences

^ Difference in event rates are not statistically significant at α=0·05 and the 95% CI contains zero

$ Estimate based on inverse probability weighting model without regression adjustment since one or more covariates perfectly predicted death.

*Doubly robust inverse probability weighting model models with regression adjustment for age, sex, race, smoking, BMI, self and family history of CAD, initial troponin, antidiabetic medication, anticoagulant medication, anti-hyperlipidemia medication, anti-hypertension medication and Elixhauser comorbidities

513 **Table 4. Effect of Early NIT on Death/Acute MI in High Cardiac Risk Subgroup**

Subgroups	**Adjusted Risk No Early NIT (Control)** Mean (Std Error)	**Adjusted Risk Early NIT (Treatment)** Mean (Std Error)	**Risk Reduction (RR)** **Early NIT Adjusted Risk – Control Adjusted Risk** Mean*# (95% CI) p-value	**Number Needed to Treat (NNT) = 1/Absolute Risk Reduction**
Age above 65 (N=27,169)	0·01 (0·002)	0·005 (0·006)	-0·005 (-0·016 to 0·007) p=0.43	N/A^
Female Sex (N=44,612)	0·004 (0·001)	0·001 (0·001)	**-0·004 (-0·007 to -0·0006)** p=0.018	1/0·004 = **250**
Male Sex (N=31,605)	0·007 (0·001)	0·001 (0·001)	**-0·005 (-0·007 to -0·003)** p<0.001	1/0·005 = **200**
Quit Smoking (N=22,711)	0·01 (0·004)	0·002 (0·002)	**-0·008 (-0·016 to -0·0004)** p=0.04	1/0·008 = **125**
Active/Passive Smoker (N=5,596)	0·005 (0·001)	0·001 (0·0004)	**-0·004 (-0·006 to -0·002)** p=0.001	1/0·004 = **250**
Obese (n=32,728)	0·004 (0·001)	0·0005 (0·0001)	**-0·003 (-0·006 to -0·0013)** p=0.002	1/0·003 = **333**
Coronary Artery Disease (N=13,883)	0·015 (0·002)	0·007 (0·009)	-0·008 (-0·03 to 0·01) p=0.42	N/A^
Elevated Troponin (N=2,828)	0·07 (0·03)	0·006 (0·002)	**-0·07 (-0·12 to -0·013)** p=0.015	1/0·07 = **14**
Family History of CAD (N=25,695)	0·007 (0·002)	0·001 (0·0002)	**-0·006 (-0·01 to -0·0004)** p=0.033	1/0·006 = **167**
Anti-Diabetes Medication (N=12,413)	0·009 (0·002)	0·0012 (0·0009)	**-0·008 (-0·011 to -0·004)** p<0.001	1/0·008 = **125**
Anti-Hypertension Medication (N=33,367)	0·009 (0·002)	0·001 (0·0004)	**-0·008 (-0·012 to -0·004)** p<0.001	1/0·008 = **125**
Anti-Hyperlipidemia Medication (N=23,758)	0·009 (0·002)	0·002 (0·002)	**-0·007 (-0·013 to -0·001)** p=0.027	1/0·007 = **143**

Anti-Coagulation Medication (N=7,431)	0·01 (0·002)	0·003 (0·002)	**-0·009 (-0·015 to -0·002)** p=0.007	1/0·009 = **111**

#Bold Font indicate statistically significant differences

^Difference in event rates are not statistically significant at α=0·05 and the 95% CI contains zero

*Except for each sub-group stratification variable, models adjusted for age, sex, race, smoking, BMI, self and family history of CAD, initial troponin, antidiabetic medication, anticoagulant medication, anti-hyperlipidemia medication, anti-hypertension medication and Elixhauser comorbidities

514

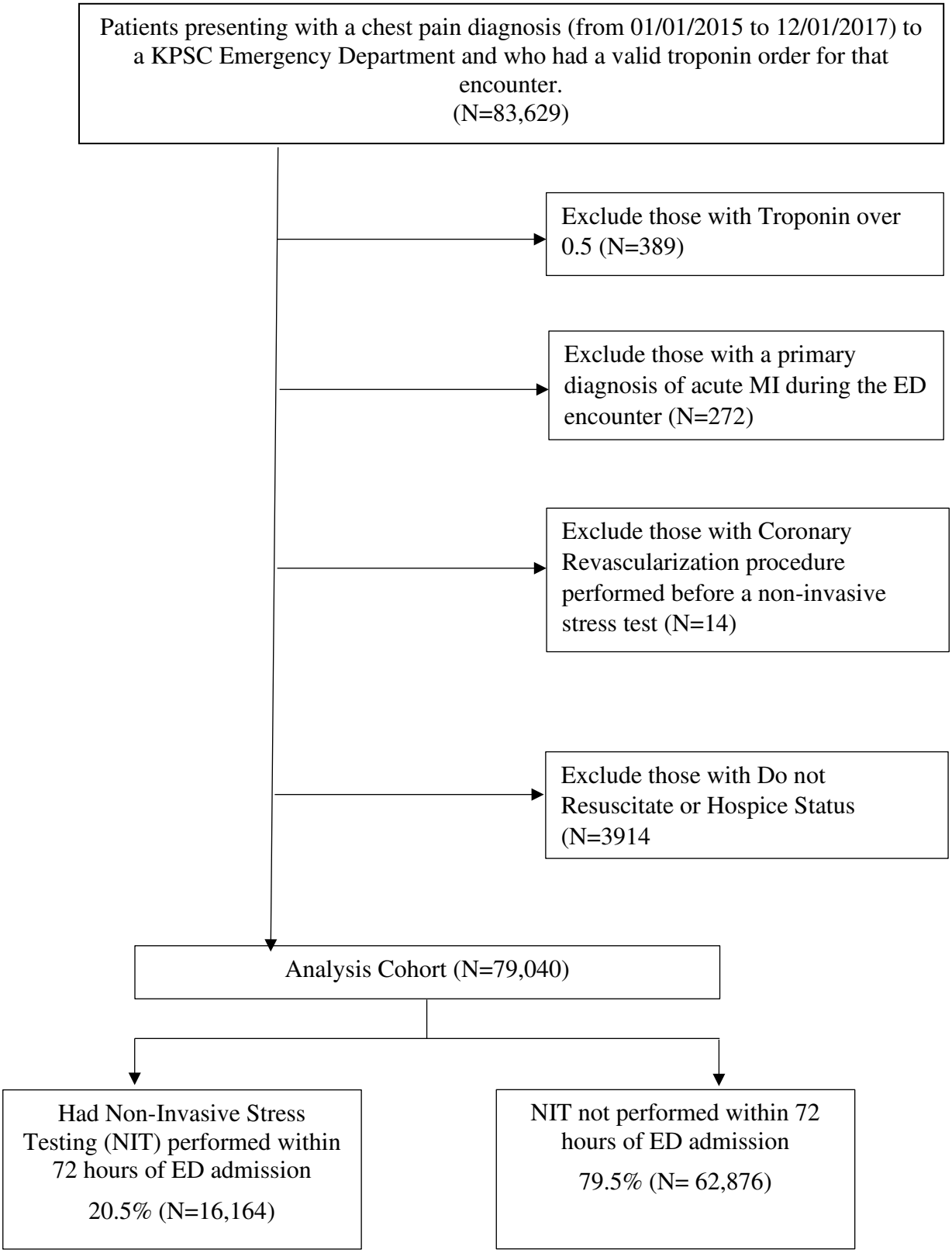
515

Figure Titles and Legends

Figure 1. Patients Presenting with Chest Pain to an Emergency Department and Patients Included in the Analysis

Figure Legend: Study Patient Flowchart

Figure 1. Patients Presenting with Chest Pain to an Emergency Department and Patients included in the analysis.



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Content

eTable 1. Logistic Regression of First Stage IV Model Predicting Early NIT

	Odds Ratio	**Lower 95% CI**	**Upper 95% CI**
Medical Center Practice Pattern	**1·06**	**1·06**	**1·07**
Day of the Week IV			
Weekday	Reference		
Weekend	**0·82**	**0·78**	**0·88**
Age Categories			
18-49	Reference		
50-69	**3·0**	**2·84**	**3·16**
70 and Above	**3·34**	**3·12**	**3·56**
Sex Female	Reference		
Male	**1·19**	**1·15**	**1·24**
Race Categories			
White	Reference		
Black	**0·90**	**0·85**	**0·95**
Asian	**1·66**	**1·0003**	**1·13**
All Other Race	0·96	0·91	1·005
Smoking Status			
Never Smoked	Reference		
Quit Smoking	0·98	0·94	1·02
Active/Passive Smoker	1·02	0·95	1·10
Body Mass Index (BMI)			
Normal BMI	Reference		
Under Weight	**0·76**	**0·62**	**0·93**
Overweight	**1·15**	**1·10**	**1·20**
Obese	**1·30**	**1·23**	**1·36**
Elevated Troponin (0·04-0·5)	**1·37**	**1·25**	**1·50**
Coronary Artery Disease (CAD)	**0·84**	**0·80**	**0·89**
Stroke	0·93	0·83	1·05
Percutaneous transluminal coronary angioplasty (PTCA) or Coronary artery bypass graft (CABG) in prior year	**0·64**	**0·53**	**0·77**
Family history of CAD	**1·13**	**1·08**	**1·17**

Family history of Stroke	0·98	0·93	1·03
Antidiabetic medications in past 90 days	**1·24**	**1·17**	**1·31**
Anticoagulant medications in past 90 days	**0·89**	**0·84**	**0·95**
Anti-hyperlipidemic medications in past 90 days	**1·13**	**1·08**	**1·18**
Anti- hypertension medications in past 90 days	**1·17**	**1·12**	**1·23**
Elixhauser Comorbidity Index	**0·93**	**0·92**	**0·94**

Bold Font Indicates Statistically Significant Estimates
Logit model estimates are only presented for ease of interpretability of the odds ratio. Actual estimation used a probit model specification instead of logit model.

eTable 2. Overall Diagnostic test for the IV model Assumptions

Model Assumption	Diagnostic test type	**Death/Acute MI** Test statistic (*P value*) or Stock-Yogo (2005) Critical Value*	**Death** Test statistic (*P value*) or Stock-Yogo (2005) Critical Value*	**Acute MI** Test statistic (*P value*) or Stock-Yogo (2005) Critical Value*	**Coronary Revascularization** Test statistic (*P value*) or Stock-Yogo (2005) Critical Value*	**MACE** Test statistic (*P value*) or Stock-Yogo (2005) Critical Value*
Instrument Strength	First Stage F	1531 (p<0·0001)	1531 (p<0·0001)	1531 (p<0·0001)	1531 (p<0·0001)	1531 (p<0·0001)
Weak Instrument	Cragg-Donald Wald F statistic	1475 (8·7)*	1475 (8·7)*	1475 (8·7)*	1475 (8·7)*	1475 (8·7)*
Rank Test/Under-identification test	Kleibergen-Paap rk LM statistic	2816 (p<0·0001)	2816 (p<0·0001)	2816 (p<0·0001)	2816 (p<0·0001)	2816 (p<0·0001)
Overidentification	Sargan–Hansen test *J*-statistic	0·902 (p=0·34)	0·144 (p=0·70)	0·42 (p= 0·52)	0.05 (p=0.82)	0·76 (p=0·38)
Instrument redundancy	LM test of redundancy	2747 (p<0·0001)	2747 (p<0·0001)	2747 (p<0·0001)	2747 (p<0·0001)	2747 (p<0·0001)
Testing is based on linear additive specification. Actual estimation used a probit model for the treatment choice (early NIT vs not) as well as probit model for the binary outcomes associated with death, acute myocardial infarction, coronary revascularization and major adverse cardiovascular events						

The order condition for identification of an IV model is a necessary condition and generally easy to check. The order condition however is not a sufficient condition. To ensure that the necessary and sufficient rank condition was satisfied, we checked the Kleibergen–Paap Lagrange multiplier (LM) statistic.[1,2] The precision of IVs parameters is generally lower and in the presence of weak instruments, the loss of precision will be severe.[2,3] The problem with weak instruments arises when the strength of the correlation between the endogenous regressors and the excluded instruments is statistically significant but small in magnitude.[4,5] We evaluated the validity of our IV approach to the weak instruments problem on the basis of the individual first-stage F-statistic and also the Angrist–Pischke first-stage F-statistic.[6]

To check is if the excluded instruments are uncorrelated to the error we performed overidentification test. This orthogonality condition is generally not confirmed statistically. However, in the overidentified case, if we maintain the hypothesis that the model is identified, a rejection of the hypothesis implies rejecting the orthogonality conditions. Given these assumptions, an overidentification test was performed for all excluded instruments on the basis of the Hansen J-statistic to ensure that the excluded instruments are uncorrelated to the error.[2,3,7-9] Lastly, because our model was overidentified, it is important to ensure that the excluded instruments are not redundant and that each adds to the efficiency of the estimator. On the basis of the LM test, we checked the redundancy of the IV medical center practice pattern conditional on the weekend IV as the excluded instrument.[10-12] Most of the test statistics were made robust to arbitrary heteroskedasticity.[13]

The IV specification testing presented in supplemental table 2 indicated that the two excluded instruments: 1. Medical Center Practice Pattern and 2. Day of the Week were a) strongly correlated to the treatment (i.e. NIT within 3 days); b) were not weak instruments; c) satisfy the order as well as rank condition; d) were not redundant and lastly were orthogonal to the outcome error and appropriately excluded from the outcome model since they only acted through the exposure of early NIT. The IV models satisfied all assumption necessary for consistent estimate of the parameters.

The average treatment effect parameter identified by our IV models maybe sensitive to our covariate or functional form specification.[6] Additionally, it could be the case that medical centers with higher NIT preference may have increased adoption of other ACC/AHA guidelines and/or protocols that may improve outcomes. To mitigate these concerns, we estimated the local average treatment effect (LATE) as the ratio of the expected death/MI risk reduction to the probit model estimate of day of the week IV.[6] This LATE estimate was a 3.7% reduction in risk of the primary outcome. Though LATE is based on weaker assumption compared to the IV models, it only applies to compliers i.e. those patients who are influenced to undertake treatment only by change in value of the IV and not otherwise.[14] Some non-compliers could be unusually sick and/or maybe persistent in obtaining NIT even on weekends or at medical centers with low preferences due to being unusually organized and aware. Non-compliers also include a portion that could really benefit from NIT and are strongly advised to have these tests performed, yet they leave without testing, against medical advice. LATE filters out some of these non-compliers and hence it's estimate is higher compared to the estimated average treatment effect.

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