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

3
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Key Points

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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

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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

66 -0.1%)) and MACE (-0.5% (-0.7% to -0.3%)). The number needed to treat (NNT) was 250 to
67 avoid one death or MI, 500 to avoid one death, 333 to avoid one MI and 200 to avoid one MACE
68 within 30 days. Subgroup analysis revealed NNT of 14 to avoid one death or MI in the subset of
69 patients with elevated troponin.

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

73

INTRODUCTION

74
75 Acute coronary syndrome (ACS) is high-risk manifestation of coronary atherosclerosis, which
76 includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation
77 myocardial infarction (NSTEMI) and unstable angina (UA). ACS is the leading cause of
78 worldwide mortality and morbidity.^{1,2} The majority of ACS patients present with chest pain to
79 emergency departments (ED), and chest pain is the second most frequent reason for all U.S. ED
80 visits accounting for over seven million annual encounters.³ However, only the minority (1-13%)
81 of these visits are related to ACS. Accurate diagnosis is challenging and fraught with high
82 medical and legal risks.^{4,5} The missed ACS rate after an ED evaluation has been reported as high
83 as 2%-4% and is associated with doubled mortality.⁶⁻⁹ Additionally, missed ACS is the top
84 reason for medical malpractice claims against ED physicians which encourages increased
85 testing.^{10,11}

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

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

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

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

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METHODS

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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 \approx 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

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

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139 We excluded patients if they (1) had MI identified during the ED encounter, (2) had an initial
140 troponin level greater than 0.5 ng/ml, (3) had coronary revascularization procedure performed
141 before NIT, (4) were transferred from another hospital, (5) died in the ED, (6) were in hospice
142 status, (7) had documented “do not resuscitate” order in the EMR.

143 Outcomes, Exposure and Covariates Measurement

144 Outcomes

145 *Primary*

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

150 *Secondary*

151 As our secondary outcome, we measured 30-day incidence of revascularization by percutaneous
152 coronary intervention (PCI) or coronary artery bypass grafting (CABG). Lastly, we also
153 measured 30-day incidence of MI and death independently as secondary outcomes.
154 The 30-day time frame is consistent with ED ACS research guidelines as longer time frames are
155 unlikely to affect ED decision making.²⁶ Lastly, we defined major adverse cardiac event
156 (MACE) as the composite outcome of all-cause death, MI, or revascularization within 30 days.

157 Exposure

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

162 Covariates

163 Covariates included patient demographic information and clinical history (Table 1). Age, sex and
164 race were obtained from the health plan's administrative records. Clinical data were obtained
165 from the EMR. Comorbidities and cardiac risk factors were defined using laboratory values,
166 diagnostic or procedure codes along with the Elixhauser comorbidity index. The details on the
167 procedure and diagnostic codes have been described elsewhere.^{5,27,28} Body mass index (BMI)
168 was measured from ED intake documentation or the most recently available visit, while smoking
169 and family history of CAD/stroke were self-reported EMR fields. Those with a history of PCI or
170 CABG were considered to have had prior coronary vascularization. Initial troponin level was
171 dichotomized with a value below 0.04 ng/ml indicating a normal result and results between 0.04-
172 0.5 ng/ml representing an elevated ACS risk. Lastly, using pharmacy prescription records, we
173 identified patients on active antidiabetic, anticoagulants, anti-hyperlipidemia and anti-
174 hypertension treatment, in the 90-days prior to their ED encounter.

175 Statistical Analysis

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

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

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

203 We report the Number Need to Treat (NNT) as the inverse of the adjusted Absolute Risk
204 Reduction (ARR).
205 In sensitivity analysis, we analyze the data using doubly robust inverse probability of treatment
206 weighted and regression adjusted (IPWRA) models assuming the un-confoundedness
207 requirement was not violated (Table 3). Lastly, we report the treatment effect of early NIT in
208 high cardiac risk sub-groups of patients (Table 4). All hypothesis tests were two sided with an
209 *apriori* type I error set at 5%. Stata/MP[®] version 15 software was used for data analysis (Stata
210 Corp LLC, College Station TX).

211

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RESULTS

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214 The total cohort included 79,040 adults (Figure 1), of whom 16,164 (21%) completed a non-
215 invasive stress test within 72 hours of admission (Table 1). Among the 16,164 tested, 17.3%
216 (n=2796) completed the test as an outpatient while 82.7% (n=13,368) completed it either prior to
217 or on the day of discharge. The distribution of the type of NIT included 47.5% stress
218 electrocardiogram, 17% stress echocardiogram, 35% stress myocardial perfusion, and 0.5%
219 coronary computed tomography angiogram. The mean age of the cohort was 57 (SD ±16) years
220 and the majority were female (58%) and white race (52%). The combined risk of death/MI was
221 0.5% in the control cohort, while in the NIT cohort it was 0.3% (Table 1). The independent risk
222 of death was 0.2% vs 0.1%; of MI was 0.3% vs 0.2%; of coronary revascularization was 0.2%
223 vs 0.4% and of MACE was 0.5% vs. 0.3% in the control vs. early NIT cohorts respectively
224 (Table 1).

225 Specification testing of the IV models suggested that day of the week and medical center's NIT
226 practice pattern, were strong instruments. Independently, one percent increase in a medical
227 center's past practice pattern for NIT was associated with a 6.4% (95% CI 6.0% to 6.9%) higher
228 odds of ordering early NIT. Similarly, as compared to an ED encounter during any weekday
229 (Monday-Friday), the odds of ordering early NIT were lower by 18% (95% CI 14% to 21%)
230 during weekend (eTable 1). All assumptions necessary for consistent parameter estimates from
231 IV analysis were satisfied (eTable 2).

232 The average adjusted risk reduction for death or MI was 0.4% (0.3% to 0.6%) while that for
233 death was 0.18% (0.1% to 0.2%) (Table 2). Similarly, the adjusted risk reduction for secondary
234 aims of MI was 0.3% (0.1% to 0.5%) and MACE was 0.5% (0.3% to 0.7%) (Table 2). The
235 difference in coronary revascularization rate was not statistically significant. The NNT was 250

236 for the death/MI composite outcome while for death, MI and MACE the NNT was 500, 333 and
237 200 respectively (Table 2).

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

241 In the traditional subgroups associated with high cardiac risk, the absolute risk of death and MI
242 composite outcome ranged between 0·4% (female sex and BMI \geq 30) to a maximum of 7%
243 (elevated troponin) in the controls (Table 4). Early NIT reduced the absolute risk of death/MI by
244 0·3% to 7%. Consequently, the NNT ranged between a low of 14 to a high of 333.

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DISCUSSION

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

266 In this cohort, the absolute risks of death/MI, death, MI, revascularization and MACE within 30
267 days of ED discharge were low (<1%) and early NIT had minor benefit in reducing these risks.
268 We find that to benefit from AHA/ACC NIT guidelines, the NNT to avoid one death or MI was
269 250 while 500 suspected ACS patients need to be tested to avoid one death. While we do not find
270 a benefit of NIT at reducing coronary revascularization, however it is interesting to note that
271 revascularization procedures were not increased with early NIT. The lack of increased
272 revascularization rates among NIT patients suggests that other factors are likely driving the
273 reduced event rate. For instance, better medical optimization may play a role, as we noted the
274 early NIT arm had higher utilization of antihyperlipidemics (16.1% vs 9.7%; p<0.001);

275 antihypertensives (13.8% vs 10.2%; $p<0.001$); anti-anticoagulants (4.7% vs 3.6% ; $p<0.001$); and
276 antidiabetic medication (4.4% vs. 3.3% ; $p<0.001$) as compared to the no early NIT arm, in the
277 90-day post discharge period. Thus, NIT may identify patients who could benefit from additional
278 contact with outpatient providers where lifestyle interventions and medication adherence may be
279 emphasized. Hence, if used appropriately, NIT could serve a role in downstream risk
280 stratification to identify CAD and hence may improve outcomes beyond 30 days.

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

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

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

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

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

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

326 **Limitations**

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

341

342 **Conclusion**

343 In suspected ACS patients with MI ruled out, early NIT results in minor reductions (0.4%) in
344 death/MI outcome, but the large number needed to treat required to benefit one patient calls into
345 question this clinical strategy for most patients. Our findings support selective use of NIT by
346 avoiding such testing for most patients evaluated in the ED and reserving NIT for patients at
347 substantial risk of 30-day adverse cardiovascular outcomes.

348

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353
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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 <i>Mean (SD)</i>	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) <i>Mean (SD)</i>	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 <i>Mean (SD)</i>	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 $\alpha=0.05$ 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

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510 **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 $\alpha=0.05$ 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

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

Subgroups	Adjusted Risk No Early NIT (Control)	Adjusted Risk Early NIT (Treatment)	Risk Reduction (RR) Early NIT Adjusted Risk – Control Adjusted Risk	Number Needed to Treat (NNT) = 1/Absolute Risk Reduction
	Mean (Std Error)	Mean (Std Error)	Mean*# (95% CI) p-value	
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
<p>#Bold Font indicate statistically significant differences</p> <p>^Difference in event rates are not statistically significant at $\alpha=0.05$ and the 95% CI contains zero</p> <p>*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</p>				

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516 **Figure Titles and Legends**

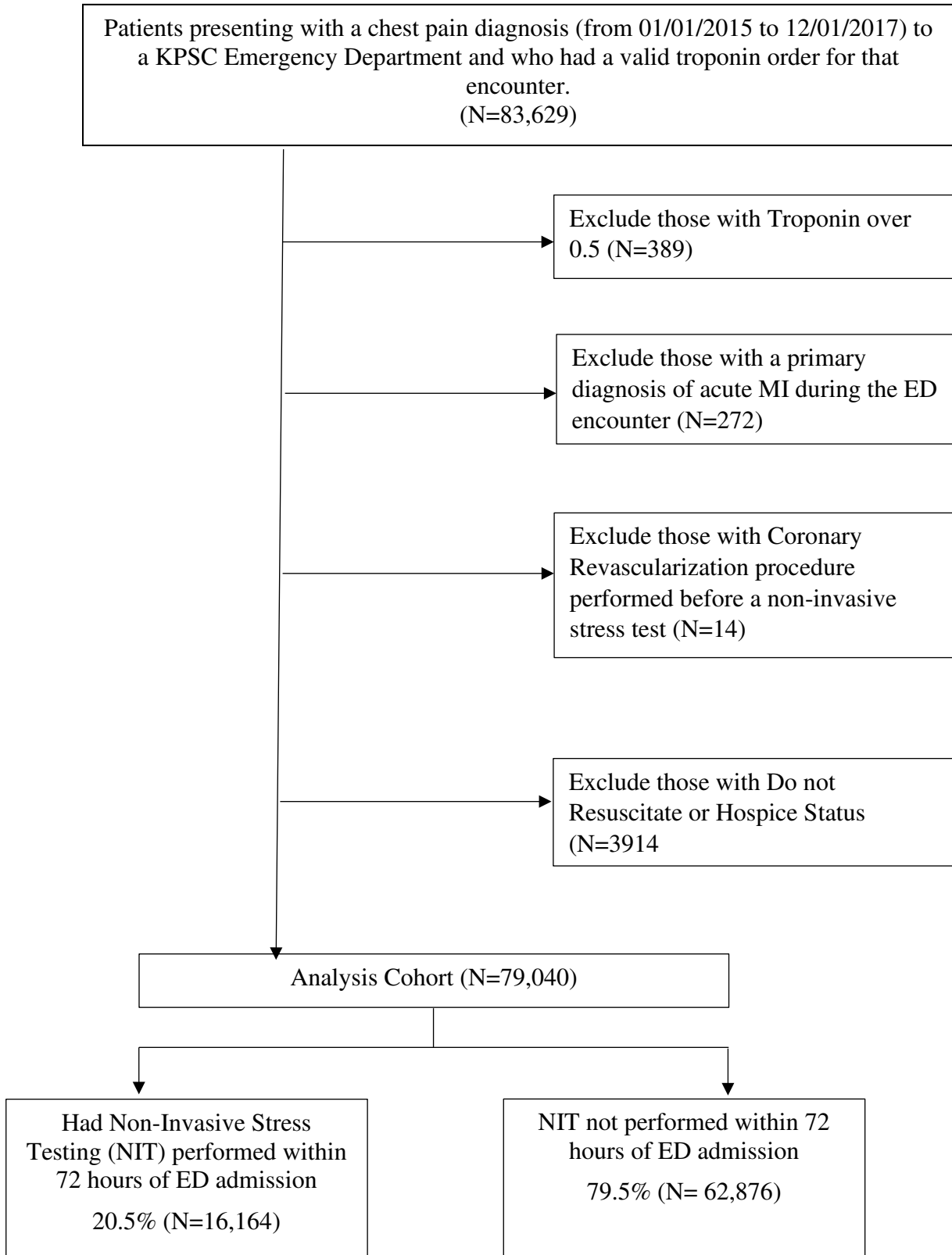
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518 Figure 1. Patients Presenting with Chest Pain to an Emergency Department and Patients Included

519 in the Analysis

520 Figure Legend: Study Patient Flowchart

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



ONLINE SUPPLEMENTAL FILES

Content

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

eTable 2: Overall Diagnostic test for the IV model Assumptions

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
<p>Bold Font Indicates Statistically Significant Estimates <i>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.</i></p>			

eTable 2. Overall Diagnostic test for the IV model Assumptions

Model Assumption	Diagnostic test type	Death/Acute MI Test statistic (<i>P value</i>) or Stock-Yogo (2005) Critical Value*	Death Test statistic (<i>P value</i>) or Stock-Yogo (2005) Critical Value*	Acute MI Test statistic (<i>P value</i>) or Stock-Yogo (2005) Critical Value*	Coronary Revascularization Test statistic (<i>P value</i>) or Stock-Yogo (2005) Critical Value*	MACE Test statistic (<i>P value</i>) 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 <i>J</i> -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)
<i>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</i>						

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 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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