# Rationale, Development, and Implementation of the Electrocardiographic Methods for the Prehospital Identification of Non-ST Elevation Myocardial Infarction Events (EMPIRE)

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**ABSTRACT**

**Background:** The serum rise of cardiac troponin remains the gold standard for diagnosing non-ST elevation (NSTE) myocardial infarction (MI) despite its delayed response. Novel methods for real-time detection of NSTEMI would result in more immediate initiation of definitive medical therapy and faster transport to facilities that can provide specialized cardiac care.

**Methods:** EMPIRE is an ongoing prospective, observational cohort study designed to quantify the magnitude of ischemia-induced repolarization dispersion for the early detection of NSTEMI. In this study, prehospital ECG data is gathered from patients who call 9-1-1 with a chief complaint of non-traumatic chest pain. This data is then analyzed using the principal component analysis (PCA) technique of 12-lead ECGs to fully characterize the spatial and temporal qualities of STT waveforms.

**Results:** Between May and December of 2013, Pittsburgh EMS obtained and transmitted 351 prehospital ECGs of the 1,149 patients with chest pain-related emergency dispatches transported to participating hospitals. After excluding those with poor ECG signal (n = 40, 11%) and those with pacing or LBBB (n = 50, 14%), there were 261 eligible patients (age 57 ± 16 years, 45% female, 45% Black). In this preliminary sample, there were 19 STEMI (7%) and 33 NSTEMI (12%). More than 50% of those with infarction (STEMI or NSTEMI) had initially negative troponin values upon presentation. We present ECG data of such NSTEMI case that was identified correctly using our methods.

**Conclusions:** Concrete ECG algorithms that can quantify NSTE ischemia and allow differential treatment based on such ECG changes could have an immediate clinical impact on patient outcomes. We describe the rationale, development, design, and potential usefulness of the EMPIRE study. The findings may provide insights that can influence guidelines revisions and improve public health.

## INTRODUCTION

Current guidelines recommend the use of serum biomarkers of myocardial necrosis (i.e., troponin) as the gold standard to confirm acute myocardial infarction (MI).[1, 2] However, serum cardiac biomarkers are not elevated until a few hours after ischemic injury,[3] which limits the clinical utility of using these serum enzymes in the prehospital medical care of acute MI patients. In contrast, findings from the standard, 10-second, 12-lead ECG are readily available during prehospital care, which allows immediate intervention to reduce the size of infarction. It is now well-documented that immediate percutaneous intervention (PCI) for those with ST elevation (STE) on the initial ECG (i.e., STEMI) significantly reduces mortality,[4] and, as a result, the prehospital ECG is now incorporated in nearly 90% of systems of care in major metropolitan U.S. cities.[5] Unfortunately, the real clinical need remains unmet for the majority (> 70%) of acute MI events that have little, if any, ischemic ECG changes (i.e., NSTEMI or Unstable Angina [UA]) and constitute more diffuse, multi-vessel coronary disease, for which immediate PCI has not been shown to improve outcomes.[6] Furthermore, STE may be transient and lack of diagnostic criteria for STEMI upon hospital arrival does not exclude presence of critical lesions for which immediate PCI is indicated.[7] Recent clinical trial data supports the early use of innovative treatment strategies (e.g., P2Y12 antagonists[8, 9] and statins[10-12]) to improve outcomes in NSTEMI.[13, 14] To date, we lack the ability to identify NSTEMI very early during care. Concrete ECG algorithms to quantify ischemic burden—and allow us to act on ECG changes—would have an immediate clinical impact by expediting definitive medical care of NSTEMI.

Several ECG patterns associated with particular coronary anatomy and high-risk prognosis in NSTEMI have been identified, including tall positive T waves (with or without ST depression).[15] However, current guidelines do not consider the configuration of the T wave for urgent PCI, and the significance of such changes—in the absence of STE—is considered more contentious. However, given that ongoing ischemia does not necessarily result in STE, quantitative assessment of the T wave would provide a great opportunity for improving

diagnostics. In a recent retrospective analysis, we found that repolarization complexity was significantly correlated with peak troponin level (r = 0.41) during acute coronary events; moreover, this complexity could differentiate NSTEMI patients from others with similar symptoms but no ongoing myocardial injury.[16] Our findings—and the findings of others—have led to the development of the EMPIRE (**E**lectrocardiographic **M**ethods for the **P**rehospital **I**dentification of non-ST Elevation of Co**R**onary **E**vents) study. EMPIRE is designed to quantify the magnitude of ischemia-induced repolarization dispersion for the early detection of NSTEMI. The purpose of this report is to describe the rationale, design, methods, and feasibility data of this ongoing, prospective, observational cohort study.

## METHODS

We are creating a database of patients in the Pittsburgh, PA area who call 9-1-1 to report chest pain. The database includes the digital 12-lead ECGs obtained by onsite Emergency Medical Services (EMS) and data from prehospital and inhospital medical records. Cases are recruited following treatment and transport to the hospital by the City of Pittsburgh Bureau of EMS (Pittsburgh EMS), which staffs 15 ambulances that are distributed in 12 dispatch stations around Pittsburgh. All ambulances are equipped with Philips MRX machines that have 12-lead ECG transmission capacity, and obtaining 12-lead ECGs for non-traumatic chest pain patients is mandated by Pennsylvania statewide protocols. Patients with chest pain are recruited if they are transported by ambulance to one of three main UPMC affiliated hospitals in Pittsburgh (UPMC Presbyterian, Mercy, and Shadyside hospitals). This observational study does not change patient care and possesses minimal risk. There is no direct interaction with study participants—data are collected after 30 days of medical care completion. As such, our preliminary cohort was recruited under waiver of informed consent; this systematic approach is more likely to generate a representative epidemiologic database of all eligible cases because more critically ill patients (i.e., most of those with acute MI) may not be able to be recruited

prospectively, or otherwise choose to withdraw from the study, resulting in a biased sample. This study is approved by the Institutional Review Board of the University of Pittsburgh.

***Inclusion and Exclusion Criteria***

Consecutively enrolled patients meet the following inclusion criteria: (1) 21 years of age or older; (2) chief complaint of non-traumatic chest pain or other atypical, suspicious symptoms requiring ECG evaluation (i.e. shortness of breath); (3) mode of arrival is by EMS transport; and (4) 12-lead ECG obtained prior to ED arrival. There are no restrictions to sex or race. Children and teens (i.e., ≤ 21 years of age) are less likely to have ischemic etiology of chest pain and are not included. Although acute MI is also not prevalent in patients who are 22 to 40 years old, including a representative sample for which true negative values can be tested is equally necessary for our methods and these patients are included. The following patients are excluded: (1) those with traumatic chest pain (e.g., car accident); (2) those arriving at the ED with no prehospital ECG (i.e. either not performed by EMS or if arrival is by private vehicle); and (3) those with un-interpretable 12-lead ECG due to excessive noise or known interpretation confounders (e.g., pacing or left bundle branch block [LBBB]).

***Data Collection Protocol***

After completion of patient care and medical documentation by the EMS providers, the following protocol is followed: (1) Subjects meeting the study criteria are identified using custom reporting software in the prehospital electronic patient care record program (emsCharts, Inc., Warrendale, PA). Data regarding age, sex, date/time of dispatch, and responding EMS agency is documented for each case as a linkage-list to be kept separate from the data. (2) The raw XML files of digital ECGs obtained and transmitted by monitors used on the scene are stored and accessed through a hospital-based server. These XML files are stamped for age/sex, date/time, and EMS agency and, therefore, can be matched with the prehospital records in emsCharts. Linked records are assigned a study ID and stored in a research spreadsheet. (4) Patient identifiers are then used to link prehospital data with inhospital data to abstract

necessary medical records for that hospital admission (including the initial ECG in the emergency department). (5) Data are collected in the de-identified spreadsheet with only a linkage number for identification of patient cases.

***Outcome Data***

The primary outcome of the study is the presence of acute MI, documented by elevation of cardiac troponin and (1) subsequent development of labile, ischemic ECG changes (e.g., STE) during hospitalization; (2) coronary angiography demonstrating greater than 70% stenosis, with or without treatment; and/or (3) functional cardiac evaluation (stress testing) that demonstrates ECG, echocardiographic, or radionuclide evidence of focal cardiac ischemia.[17] Other cardiac conditions (e.g., myocarditis) that result in the rise of troponin levels without evidence of ischemia are identified as negative for the primary outcome. Once acute MI cases are identified, NSTEMI cases can be differentiated based on the presence/absence of STE.

The secondary outcome of the study is the incidence of Major Adverse Cardiac Events (MACE). MACE includes cardiac death (ICD-9 codes 390 to 459[18]) or re-infarction (as defined earlier) within 30 days of initial presentation. The University of Pittsburgh Medical Center's 20-hopsital network enables tracking of patient records, even if a patient is readmitted to a different hospital within the network. Medical records of patients meeting any of the MACE criteria will be retrieved and evaluated by an adjudication committee of study collaborators.

***Electrocardiographic Analysis***

The digital ECG files obtained at the scene are binary XML signals. We will first decompress the signal into common data format (i.e., xls) in which the ECG leads are decoded and stored in columnar matrices (12 [leads] x 5,000 [samples]). To control for baseline noise and artifacts, we will then compute a median beat for each ECG lead, which yields a high signal-to-noise ratio and, hence, stable, artifact-free averages. Using a simple dimension reduction technique (i.e., principal component analysis [PCA]), the main principal components of the 12-lead ECG can be computed. By filtering the STT waveforms of PCA components, we can

obtain the component coefficients of eigenvalues that can be used to project the spatial R and T loops. Accordingly, novel markers of ventricular repolarization dispersion can be computed from the main PCA components and corresponding T loops as previously described by Priori and Mortara.[19] Under pathologic derangements (i.e., ongoing ischemia), there are regional repolarization dispersion currents between endo-mid, endo-epi, apex-base, epi-mid, or endocardial walls, which result in increased differences between STT waveforms of the 12-lead ECG. Isolating the principal repolarization components will identify the orthogonal vectors that contain the most significant information in the data, and would, therefore, provide means for evaluating ischemia-induced repolarization dispersion in the context of chest pain. In this paper, we present data on three spatial and temporal T loop morphology descriptors that could correctly help differentiate an ischemic patient from a non-ischemic one:

1. T wave complexity (TWC): defined as the average ratio of the second to first eigenvalues of repolarization. Larger values suggest more dispersed repolarization energy, which we hypothesize is attributed to localized ischemic injury currents seen during myocardial infarction.
2. T loop morphology dispersion (TMD): defined as a measure of the spatial T-wave morphology variation. Larger values mean that the reconstructed vectors of different ECG leads are grossly different, which we hypothesize is attributed to regional repolarization dispersion between ischemic and non-ischemic fibers.
3. Total cosine R-to-T (TCRT): defined as the average of the cosines of the angles between T and R loops. Larger values mean greater vector deviation between depolarization and repolarization wavefront directions, which we hypothesize is attributed to ischemia-induced repolarization dispersion.

***Statistical Analysis***

In this preliminary analysis, we report the baseline characteristics of our pilot sample. Values are reported as mean ± standard deviation or count (%). Simple comparisons between groups were made using chi-square and ANOVA. All analyses were conducted using SPSS, and a value of $p < 0.05$ determined statistical significance.

**RESULTS**

Between May and December of 2013, Pittsburgh EMS obtained and transmitted prehospital ECGs for 351 of 1,149 patients with chest pain-related emergency complaints (Figure 1). After excluding those with poor ECG signal (n = 40, 11%) and those with pacing or LBBB (n = 50, 14%), there were 261 eligible patients (age 58 ± 16 years, 45% female, 45% Black). Approximately, 20% of the sample had acute MI (19 STEMI and 33 NSTEMI), and nearly 40% had non-cardiac related etiologies (Figure 2). The baseline demographic and clinical characteristics between groups are presented in Table 1. Those with NSTEMI were older and more likely to have a history of infarction or prior revascularization. NSTEMI patients composed a moderate risk group, with nearly 20% experiencing hemodynamic instability requiring intensive care admission and approximately 6% experiencing death or re-infarction within 30 days of initial presentation. More importantly, more than 50% of those with NSTEMI had initial negative troponin levels, necessitating prolonged observations and repeated assays to diagnose MI. Figure 3 compares the prehospital 12-lead ECG of a non-infarction related case (i.e., pleurisy) with that of a NSTEMI case who had initially negative troponin value. Both patients had no STT changes suggestive of ischemic injury (e.g., ST elevation/depression). However, the PCA technique clearly revealed greater ventricular repolarization dispersion in the NSTEMI case, manifested by fatter T loop and greater deviation between depolarization and repolarization wavefront directions. These preliminary findings support the feasibility of performing more comprehensive repolarization analysis of the entire cohort.

Finally, to evaluate whether or not poor ECG recordings are associated with a specific subset of patients or with clinically important events, we compared the clinical data of eligible patients with those of poor ECG recordings (Table 2). Those with noisy ECG recordings were more likely to be either older or with past medical history of congestive heart failure (CHF). The rate of acute CHF exacerbation during the EMS encounter did not differ between groups though (2.5% vs 1.5%, p=0.41). Importantly, poor ECG recordings seem to happen randomly with respect to important clinical outcomes, including STEMI, NSTEMI, ICU admission, and 30-day readmission or MACE.

**DISCUSSION**

There is growing evidence that myocardial ischemia alters the temporal and spatial distribution of ventricular repolarization signal,[16, 20] and ECG methods to quantify such repolarization heterogeneity of the STT waveforms are promising tools to detect myocardial ischemia in the absence of ST segment changes. EMPIRE is an ongoing, prospective, observational study of chest pain patients transported by Pittsburgh EMS to three UPMC-affiliated hospitals in the City of Pittsburgh. This study collects not only prehospital 12-lead ECGs, but also out-of-hospital and inhospital patient data profiles. Our preliminary data demonstrates that the rate of myocardial infarction in this cohort is approximately 20%, with nearly two thirds attributed to NSTEMI. Of those, nearly 50% do not show elevated serum troponin levels, necessitating prolonged observation at emergency departments with repeated cardiac enzyme assays. The adequacy of ECG recordings is nearly 90%, and noisy ECGs seem to happen randomly with regard to important clinical outcomes. The EMPIRE dataset will, therefore, provide necessary data to validate the diagnostic potential of ischemia-induced repolarization heterogeneity to detect NSTEMI events. However, the relatively low number of MACE events (< 10%) suggests that a very large sample size is needed to properly risk-stratify these patients. We anticipate the EMPIRE study to enroll between 600 and 700 cases annually.

**Clinical Perspectives**

Acute myocardial ischemia alters gap junction channel protein expression and, hence, leads to slow conduction and refractory action potential dispersion at ischemic fibers. The result is regional repolarization dispersion between various myocardial segments (endo-mid, endo-epi, apex-base, epi-mid, or endocardial walls), which suggests that early ischemic gradients that alter action potential amplitude, repolarization time, excitability, and conduction would contribute to various repolarization changes—other than STE—on the surface 12-lead ECG very early during MI evolution. Such ischemic injury is most likely to alter local gradients of repolarization manifested in the T waves (i.e., phase 3 of the action potentials) prior to distorting the ST segment (i.e., phase 2 of the action potentials) of the ECG, which leads to our hypothesis that examining the heterogeneity of STT waveforms across different ECG leads is a promising approach in evaluating NSTE myocardial ischemia. In fact, we previously found that (1) there is a direct linear relationship between repolarization dispersion and cardiac troponin levels, and (2) compared to Unstable Angina, NSTEMI patients have greater repolarization dispersion on their baseline ECG, both of which suggest that regional repolarization dispersion is more specific to myocardial necrosis rather than ischemia per se. Here, we report the preliminary ECG results of two patients admitted to the same UPMC hospital on the same day: a 48 year-old male with pleurisy and a 68 year-old male with NSTEMI (Figure 3). Both patients: (1) presented with non-traumatic, substernal chest pain; (2) had no prior history of hypertension, diabetes, CAD, or smoking; and (3) had non-specific T wave changes but negative cardiac troponin values upon admission. Accordingly, both patients were triaged and managed the same. However, the latter became hemodynamically unstable with a sudden rise in serum troponin and was consequently sent for angiography, which revealed 90% occlusion of the left anterior descending artery requiring stent placement. Interestingly, as demonstrated in Figure 3, the PCA technique on the prehospital ECG can differentiate the two patients revealing greater ventricular repolarization dispersion in the NSTEMI patient prior to any ST segment deviation or rise in cardiac troponin. It

is worth saying that, however, inverted T waves alone (due to post injury reperfusion or other non-specific etiology) does not necessary result in greater ventricular repolarization dispersion quantifiable using the PCA method. It is the ongoing ischemia injury currents that result in regional repolarization dispersion and subsequently STT waveform morphology dissimilarities across different leads, which can be subsequently quantified using the PCA method. Further analysis of the entire cohort is warranted to examine the clinical usefulness of this method on the early identification of NSTE ischemic injury and its impact on patient outcomes.

**CONCLUSIONS**

During prehospital care, treatment and destination decisions for patients with chest pain are made instantly, and a majority of patients with MI do not have ST-elevations on the prehospital ECG. Concrete ECG algorithms that can quantify non-STE ischemia and allow us to act on such ECG changes could have an immediate clinical impact on patient outcomes. The ultimate aim of the EMPIRE study is to develop computer algorithms in ECG machines for real-time clinical decision support in the clinical presentation of acute MI. We have described the rationale, development, design, and potential usefulness of the EMPIRE study, which has the potential to serve as the reference for subsequent ECG analyses to validate and refine the clinical utility of ventricular repolarization dispersion for the early detection and risk stratification of ischemic vs non-ischemic chest pain. Findings from EMPIRE study may provide insights that can influence treatment guidelines of NSTEMI, avoid emergency department overload, unnecessary hospital admissions, and, hence, improve public health.

## Figure Legends

### Figure 1: Flowchart of Subject Recruitment with Breakdown of Chest Pain Etiology

(A) We are creating a database of all Emergency Medical Services (EMS)-attended 9-1-1 calls for patients with chest pain in Pittsburgh PA area who have a readable, interpretable prehospital 12-lead ECG. The enrollment started in May of 2013 and this figure shows the findings from our initial pilot sample recruited prior to the end of 2013.

(B) This pie chart shows the percentage distribution of the reported etiology of chest pain based on final discharge diagnosis.

### Figure 2: Principal Component Analysis of the 12-Lead ECG on Selected Patients

Despite the non-specific T wave changes seen in both patients, the PCA technique reveals greater STT morphology deviation between main PCA components and subsequently fatter T loop in the ischemic (panel B) vs the non-ischemic patient (panel A). TWC: T wave complexity (2nd to 1st PCA ratio), TMD: T loop morphology dispersion, and TCRT: total cosine R-to-T.

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**Table 1: Clinical Characteristics of Subjects upon Enrollment**

| Characteristic | All (n = 261) | STEMI (n = 19) | NSTEMI (n = 33) | Others (n= 209) | p value |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 57 ± 16 | 54 ± 12 | **67 ± 18*** | 56 ± 16 | **< 0.01** |
| Sex (female) | 117 (45%) | 6 (32%) | 18 (55%) | 93 (44%) | 0.27 |
| Race (Black) | 118 (45%) | 6 (32%) | 11 (33%) | 101 (48%) | 0.69 |
| **Past Medical History** | | | | | |
| Known CAD | 81 (31%) | 3 (16%) | 13 (39%) | 65 (31%) | 0.21 |
| Prior MI | 65 (25%) | 2 (11%) | **14 (42%)*** | 49 (23%) | **0.02** |
| Prior PCI | 52 (20%) | 3 (16%) | **15 (45%)*** | 34 (16%) | **< 0.01** |
| Prior CABG | 22 (8%) | 1 (5%) | **7 (21%)*** | 14 (7%) | **0.02** |
| Hypertension | 181 (69%) | 10 (53%) | 25 (76%) | 146 (70%) | 0.21 |
| Diabetes Mellitus | 73 (28%) | 4 (21%) | 8 (24%) | 61 (29%) | 0.66 |
| Dyslipidemia | 81 (31%) | 4 (21%) | 13 (39%) | 64 (31%) | 0.37 |
| Ever Smoked | 169 (65%) | 10 (53%) | 21 (64%) | 138 (66%) | 0.81 |
| Known CHF | 28 (11%) | 1 (5%) | 5 (15%) | 22 (11%) | 0.53 |
| **Clinical Presentation** | | | | | |
| Chest Pain | 230 (88%) | 19 (100%) | 30 (91%) | 181 (87%) | 0.20 |
| Shortness of Breathing | 71 (27%) | 3 (16%) | 9 (27%) | 59 (28%) | 0.50 |
| Peak Troponin (ng/dl) | 0.08 ± 0.70 | **36 ± 65*** | **6 ± 21*** | 0.1 ± 0.3 | **< 0.01** |
| Initial Troponin Positive | 23 (9%) | **7 (37%)*** | **16 (48%)*** | 0 (0%) | **< 0.01** |
| Repeated Troponin Positive | 52 (20%) | **19 (100%)*** | **33 (100%)*** | 0 (0%) | **< 0.01** |
| Treated with PCI† | 24 (9%) | **13 (68%)*** | **7 (21%)*** | 4 (2%) | **0.02** |
| Treated with CABG | 22 (8%) | **6 (32%)*** | **8 (24%)*** | 8 (4%) | **0.02** |
| ICU Admission | 29 (11%) | **14 (74%)*** | **6 (18%)*** | 9 (4%) | **< 0.01** |
| 30-Day Readmission | 65 (25%) | 3 (16%) | 9 (27%) | 53 (25%) | 0.06 |
| 30-Day Death/MI | 5 (2%) | **2 (11%)*** | **2 (6%)*** | 1 (0.5%) | **< 0.01** |

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHF: congestive heart failure; MACE: major adverse cardiac events. (*) indicates significance against “others”, (†) PCI anytime during the hospital stay

**Table 2: Comparison between Groups Based on Readability of Prehospital 12-lead ECG**

| Characteristic | Readable ECG (n = 261) | Poor and Noisy ECG (n = 40) | p value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | **57 ± 16** | **64 ± 18** | **0.02** |
| Sex (female) | 117 (45%) | 15 (38%) | 0.38 |
| Race (Black) | 118 (45%) | 9 (23%) | 0.06 |
| **Past Medical History** | | | |
| Known CAD | 81 (31%) | 18 (45%) | 0.10 |
| Prior MI | 65 (25%) | 14 (35%) | 0.17 |
| Prior PCI | 52 (20%) | 12 (30%) | 0.15 |
| Prior CABG | 22 (8%) | 7 (18%) | 0.07 |
| Hypertension | 181 (69%) | 25 (63%) | 0.39 |
| Diabetes Mellitus | 73 (28%) | 9 (23%) | 0.47 |
| Dyslipidemia | 81 (31%) | 13 (33%) | 0.85 |
| Ever Smoked | 169 (65%) | 24 (60%) | 0.64 |
| Known CHF | **28 (11%)** | **12 (30%)** | **< 0.01** |
| **Clinical Presentation** | | | |
| Chest Pain | 230 (88%) | 35 (88%) | 0.91 |
| Shortness of Breathing | 71 (27%) | 14 (35%) | 0.32 |
| Peak Troponin (ng/dl) | 0.08 ± 0.70 | 0.17 ± 0.87 | 0.54 |
| Initial Troponin Positive | 23 (9%) | 3 (8%) | 0.78 |
| Repeated Troponin Positive | 52 (20%) | 7 (18%) | 0.80 |
| STEMI | 19 (7%) | 3 (8%) | 0.96 |
| NSTEMI | 33 (13%) | 4 (10%) | 0.64 |
| Treated with PCI† | 24 (9%) | 5 (12%) | 0.51 |
| ICU Admission | 29 (11%) | 5 (12%) | 0.80 |
| 30-Day Readmission | 65 (25%) | 9 (23%) | 0.74 |
| 30-Day Death/MI | 5 (2%) | 0 (0%) | 0.38 |

Refer to Table 1 for abbreviations

Bold indicates significance between groups

† PCI anytime during the hospital stay

**Figure 1: Flowchart of Subject Recruitment with Breakdown of Chest Pain Etiology**

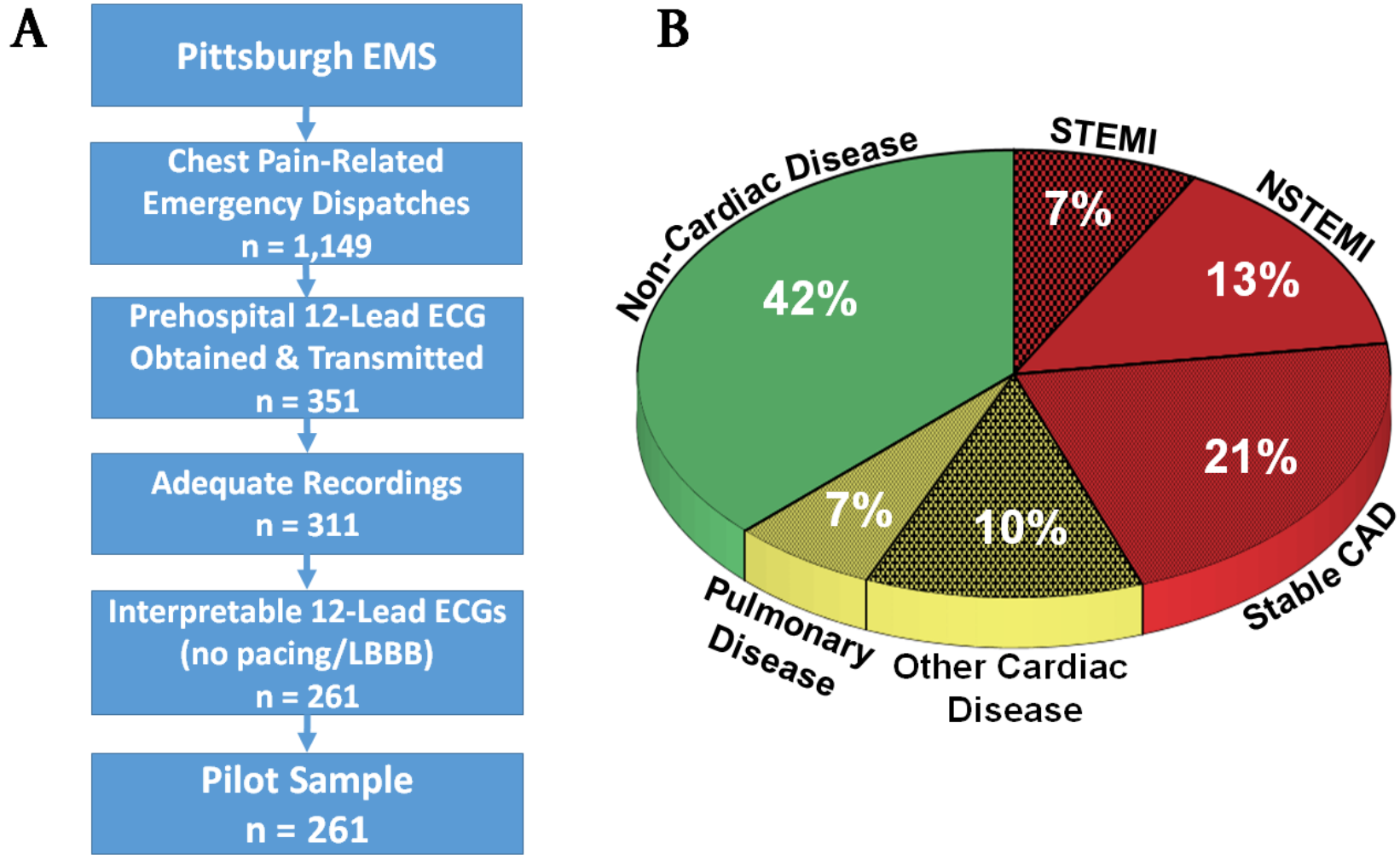

**Figure 2: Principal Component Analysis of the 12-Lead ECG on Selected Patients**