Clinical research
Coronary heart disease

Failure of investigator adherence to electrocardiographic entry criteria is frequent and influences clinical outcomes: lessons from APEX-AMI

Michael C. Tjandrawidjaja1, Yuling Fu1, Hussein Al-Khalidi2, Thomas G. Todaro2, Peter Adams3, Frans Van de Werf4, Christopher B. Granger5, and Paul W. Armstrong1* on behalf of the APEX-AMI Investigators

1Division of Cardiology, Department of Medicine, University of Alberta, 2-51 Medical Sciences Building, Edmonton, Alberta T6G 2H7, Canada; 2Procter & Gamble Pharmaceuticals, Mason, OH, USA; 3Alexion Pharmaceuticals, Cheshire, CT, USA; 4University Hospital Gasthuisberg, Leuven, Belgium; and 5Duke Clinical Research Institute, Durham, NC, USA

Received 12 March 2007; revised 17 July 2007; accepted 12 September 2007; online publish-ahead-of-print 29 October 2007

This paper was guest edited by Prof. Elliott Marshall Antman, Brigham and Women’s Hospital, Boston, USA.

Aims To examine the extent and impact on clinical outcomes of adherence to electrocardiogram (ECG) entry criteria in ST-elevation myocardial infarction patients in the assessment of pexelizumab in acute myocardial infarction (APEX-AMI) trial.

Methods and results We examined the frequency, characteristics, and outcomes of patients enrolled in APEX-AMI trial who did not meet the trial ECG entry criteria. Among 5615 patients analysed, 28.8% did not meet ECG entry criteria: this occurred more than twice as frequently amongst those with high-risk inferior vs. those with other MI (42.3 vs. 19.3%, P < 0.001).

Regardless of infarct location, patients who failed to meet ECG entry criteria had significantly lower mortality (2.5 vs. 4.5% at 30 days and 3.1 vs. 5.3% at 90 days; both P < 0.001) and the composite rate of death, cardiogenic shock, or CHF (5.8 vs. 10.3% at 30 days and 6.9 vs. 11.4% at 90 days; both P < 0.001) as compared to those who met criteria.

Conclusion In APEX-AMI over one-quarter of enrolled patients did not meet ECG entry criteria and had better outcomes than eligible patients. Although the trial’s primary result was unaffected by alignment with the baseline ECG criteria, our findings may have important implications in designing future trials.

KEYWORDS
Clinical trials;
Myocardial infarction;
ECG

Introduction
The success of a clinical trial is significantly influenced by adherence to pre-specified eligibility criteria. In clinical trials of acute coronary syndromes (ACS), a key and common determinant of patient eligibility is the presence and extent of myocardial territory at risk defined from the admission electrocardiogram (ECG).

Previous studies have highlighted the value of systematic core laboratory ECG analysis in the clinical trial setting by demonstrating frequent misinterpretation of the ECG by individual site investigators and the potential impact on prognosis.1,2 After completion of the GUSTO-IIb trial, Goodman et al.2 found that among patients categorized as non-ST elevation by the site investigators, 1-year mortality rates were almost 30% higher in the 18% of patients with core-laboratory determined ST-elevation. Such findings suggest that if patients enrolled in clinical trials failed to meet ECG entry criteria it may significantly modulate outcomes.

The assessment of pexelizumab in acute myocardial infarction (APEX-AMI) trial of 5745 patients is the largest to date of patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary PCI.3 A unique feature of this trial was that it employed specific ECG criteria to enrol a high-risk population and a central core laboratory (working closely with sponsors) that monitored ECG entry criteria and provided feedback to site investigators during the trial with the intent of enhancing adherence to these criteria. We undertook the current study to systematically evaluate the frequency, characteristics and outcomes of patients who were enrolled in the APEX-AMI trial but did not meet the ECG entry criteria. We also examined whether geographic regional variations existed and if the degree of failure to meet ECG criteria over the time course of the trial changed particularly in relation to core laboratory monitoring and feedback.

Methods
The APEX-AMI trial was a multicentre, randomized, double-blind, placebo-controlled trial of IV pexelizumab (a novel humanized
monoclonal antibody to C5 complement) in conjunction with primary PCI for patients presenting with acute STEMI. The specific entry criteria have been described previously. Briefly patients were ≥18 years old, with symptom onset < 6 h, and had an ECG indicative of acute STEMI that fulfilled any of the following three criteria:

(i) ≥2 mm ST elevation in two anterior or lateral leads; or
(ii) ≥2 mm ST elevation in two inferior leads coupled with ST depression in two contiguous anterior leads for a total ST deviation of > 8 mm; or
(iii) New left bundle branch block (LBBB) with at least 1 mm concordant ST elevation.

The primary endpoint was all-cause mortality at 30 days. Other prospectively identified endpoints included 90-day mortality and the composite of death, cardiogenic shock, or CHF at 30 and 90 days. Enrolment began on July 13, 2004 and ended May 11, 2006, resulting in a final population of 5745 patients from 296 participating hospitals in 17 countries (Table 1).

All admission ECGs were evaluated centrally at the ECG core laboratories (Canadian VIGOUR Centre, Edmonton, Canada; Duke Clinical Research Institute, Durham, NC, USA) without knowledge of treatment assignment and outcomes. Failure to meet pre-specified ECG criteria was ascertained based on ST-segment measurements at the J-point to the closest 0.05 mV (0.5 mm). Infarct size was assessed according to the Selvester QRS score at hospital discharge as well as peak CK/CKMB measurements.

The APEX-AMI trial study management team employed specific measures to encourage patient enrolment in accordance with ECG entry criteria. Multiple newsletters reiterating the correct application of these criteria were routinely distributed to participating sites. In addition, a formalized process was established for the surveillance and site follow-up of adherence to ECG entry criteria. Specifically, the cumulative spreadsheet of ST-segment measurements and met/failed to meet indicators was sent to the sponsors from the ECG core laboratory biweekly beginning April 25, 2005. Sponsor physicians then reviewed the measurements and identified sites to receive follow up action based upon the number or percentage (10% for sites that enrolled >10 patients) of ECGs not meeting entry criteria. Sites identified for follow-up were provided an individualized feedback slide set that included ST-segment measurements of patients not meeting criteria and selected ECG tracings to be reviewed by the site primary investigator. This process was undertaken on a monthly basis beginning April 25, 2005.

We compared patients enrolled before and after July 1, 2005 to examine the impact of core laboratory monitoring and feedback on adherence to ECG entry criteria, allowing for an approximate 2 months grace period (May–June 2005) for feedback transmission and implementation. Furthermore, we compared adherence to ECG entry criteria across geographic regions as described previously in the context of this trial (North America, Australia/New Zealand, Western and Eastern Europe).

Descriptive statistics were reported as percentages for categorical variables and medians with 25th and 75th percentiles for continuous variables. Comparisons between patient groups were made using the chi-square test for categorical variables and Mann–Whitney U test for continuous variables. The Bonferroni correction was applied for multiple comparisons where appropriate. Trend comparisons across geographic patient groups were made using the linear-by-linear association test. Kaplan–Meier survival estimates and the Cox proportional-hazards regression model were used to compare time to the first occurrence of the end points between the groups at 90 days and curve comparisons were made using the log-rank test. Multivariable logistic regression models, by backward and stepwise variable selection procedures, were used to examine the impact of adherence to ECG entry criteria on 90-day clinical outcomes. Variables adjusted in the models are listed in Table 2. The linearity assumption for baseline continuous variables was satisfied using the methodology described by Lee et al. All tests were two-sided, with a 5% level of significance. All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

### Results

#### Study population

Figure 1 shows the derivation of our study population. Patients excluded were 32 patients (0.6%) with baseline ECGs that were not interpretable or unavailable and 98 patients with LBBB (1.7%) that we examined separately. The remaining 5615 patients comprised our study population and were stratified according to infarct location as defined by the entry criteria, i.e. high-risk inferior MI (41.3%) and other MI (58.7%). The proportion of patients who failed to meet ECG entry criteria was 28.8% overall and more than double among those with high-risk inferior vs. other MI (42.3% vs. 19.3%; P < 0.001). Among the 981 patients who failed to meet criteria for high-risk inferior MI, we identified 417 (43%) who had insufficient precordial ST-depression despite having ≥2 mm ST-elevation in at least two inferior leads.
Table 2  Baseline clinical characteristics and ECG variables

<table>
<thead>
<tr>
<th></th>
<th>High-risk inferior MI</th>
<th>Other MI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Failed to meet (n = 981)</td>
<td>Met (n = 1338)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (year)</td>
<td>61 (52–70)</td>
<td>61 (53–70)</td>
<td>0.523</td>
</tr>
<tr>
<td>Female (%)</td>
<td>24.6 (241)</td>
<td>22.7 (304)</td>
<td>0.332</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16.3 (160)</td>
<td>11.9 (159)</td>
<td>0.003</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>51.5 (505)</td>
<td>48.7 (652)</td>
<td>0.193</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>18.9 (185)</td>
<td>13.5 (180)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior CHF (%)</td>
<td>3.2 (31)</td>
<td>3.2 (43)</td>
<td>1.000</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>25.0 (245)</td>
<td>21.5 (288)</td>
<td>0.052</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>14.5 (142)</td>
<td>9.5 (127)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>3.9 (38)</td>
<td>2.2 (30)</td>
<td>0.025</td>
</tr>
<tr>
<td>Prior PCI (%)</td>
<td>11.4 (112)</td>
<td>7.5 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>4.2 (41)</td>
<td>4.6 (61)</td>
<td>0.683</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>44.1 (431)</td>
<td>48.2 (644)</td>
<td>0.047</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 (115–150)</td>
<td>130 (115–150)</td>
<td>0.951</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>71 (60–81)</td>
<td>74 (61–86)</td>
<td>0.001</td>
</tr>
<tr>
<td>Killip class&gt;1 (%)</td>
<td>6.7 (66)</td>
<td>8.7 (117)</td>
<td>0.086</td>
</tr>
<tr>
<td>Σ ST-elevation at baseline (mm)</td>
<td>6 (4–8)</td>
<td>10 (8–14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Σ ST-deviation at baseline (mm)</td>
<td>9 (7–11)</td>
<td>17 (14–22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to treatment (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom to hospital</td>
<td>2.1 (1.3–3.3)</td>
<td>2.1 (1.3–3.3)</td>
<td>0.628</td>
</tr>
<tr>
<td>Door to balloon</td>
<td>1.1 (0.8–1.6)</td>
<td>1.0 (0.7–1.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptom to PCI</td>
<td>3.4 (2.5–4.5)</td>
<td>3.3 (2.5–4.4)</td>
<td>0.122</td>
</tr>
</tbody>
</table>
Patient characteristics and outcomes

Baseline demographic and clinical characteristics are shown in Table 2. Among patients with high-risk inferior MI, those who failed to meet ECG entry criteria more often had a history of diabetes, coronary artery disease, angina, prior MI, and prior coronary revascularization procedures. Comparatively among patients with other MI, differences in baseline comorbidities were not as pronounced although those who did not meet criteria more often were female and had previous CABG. Regardless of infarct location, those who failed to meet ECG criteria had lower risk admission characteristics as defined by slower heart rates. Patients who failed to meet ECG entry criteria had approximately one-half the ∑ ST-deviation of their adherent counterparts. The greater discordance between ∑ ST-deviation and ∑ ST-elevation among high-risk inferior MI patients likely reflects the more complex definition of high-risk inferior MI, which necessitates the presence of anterior ST-depression. Although door to balloon times were slightly longer in those who failed to meet ECG criteria, overall time from symptom onset to PCI was comparable.

Compared to those who met ECG criteria, the 1616 patients who failed to meet ECG entry criteria had significantly lower mortality (2.5 vs. 4.5% at 30 days and 3.1 vs. 5.3% at 90 days; both P < 0.001) and composite of death, cardiogenic shock, or CHF (5.8 vs. 10.3% at 30 days and 6.9 vs. 11.4% at 90 days; both P < 0.001). The frequency of patients with >75% stenosis in the infarct-related artery was identical (97.4%) between patients who met vs. failed to meet ECG criteria. However, patients who failed to meet criteria more often had TIMI 3 flow in the culprit vessel prior to PCI (13.1 vs. 11.3%; P = 0.062) and were more likely to avoid major myocardial necrosis as defined by peak CK < 2x upper limit of normal (13.2 vs. 8.0%; P < 0.001).

Regardless of infarct location, patients who failed to meet criteria had smaller infarct sizes according to peak CK data (U/L) [high-risk inferior MI failed to meet vs. met: 1275 (676–2187) vs. 1990 (1116–3172); other MI failed to meet vs. met: 1340 (551–2799) vs. 2240 (949–4060)] and QRS scores at discharge [high-risk inferior MI failed to meet vs. met: 5 (2–7) vs. 6 (4–8)] (all P < 0.0125 Bonferroni-corrected for multiple comparisons). The impact of failure to meet ECG entry criteria on clinical outcomes according to infarct location is depicted in Figures 2A and B. These figures show that the better outcomes in those who failed to meet criteria were preserved within each category of infarct location. The adjusted hazard ratio for 90-day mortality was 1.59 (95% CI: 0.93–2.69, P = 0.089) for high-risk inferior met vs. those who failed to meet and 1.62 (95% CI: 1.01–2.60, P = 0.045) for other MI met vs. other MI who failed to meet ECG criteria. The adjusted hazard ratio for the 90-day composite endpoint was 1.60 (95% CI: 1.10–2.30, P = 0.013) for high-risk inferior met vs. those who failed to meet and 1.47 (95% CI: 1.09–1.98, P = 0.011) for other MI met vs. other MI who failed to meet ECG criteria. It is noteworthy that patients with core laboratory-confirmed high-risk inferior MI have outcomes that closely approximate those of other MI patients who failed to meet criteria.

As shown in Figures 2A and B, high-risk inferior MI patients who failed to meet criteria had the best outcomes through 90 days as compared to the rest of the study population. Among these patients, we identified 417 with insufficient anterior ST-depression despite having ≥2 mm ST-elevation in at least two inferior leads. These 417 patients constituted an even lower risk sub-population. Their 90-day mortality and composite endpoint were 1.0 and 2.4%, respectively.

In multivariable logistic regression models adjusting for baseline characteristics (Table 2), adherence to ECG entry criteria was an independent predictor of 90-day mortality (OR 1.62, 95% CI: 1.11–2.35, P = 0.012) and composite of death, cardiogenic shock, or CHF (OR 1.53, 95% CI: 1.18–1.98, P = 0.001). Other independent predictors of 90-day mortality included non-inferior MI location, age, diabetes, history of coronary artery disease, heart rate, systolic BP, Killip class > I, and time to treatment.

The APEX-AMI trial found no differences in mortality or composite outcomes between the pexelizumab and placebo treatment groups. The absence of a treatment effect was also true regardless of adherence to ECG entry criteria confirming the primary result was unaffected by baseline ECG risk (Figure 3).
Patients with LBBB

The 98 patients with LBBB comprised 1.7% of the trial population. Almost one in two patients (46.9%) did not meet criteria for at least 1-mm concordant ST-elevation. No statistically significant differences in mortality or composite outcomes were observed between patients who met vs. those who failed to meet criteria (90-day death: 1.9 vs. 8.7%; 90-day composite: 13.5 vs. 15.2%).

Temporal trends and geographic variations in adherence to ECG entry criteria

The degree of adherence to ECG entry criteria during sequential time windows of patient enrolment according to infarct location and geographic region are depicted in **Table 3**. In the overall population, modest improvement in adherence occurred early within 6 months of core laboratory feedback and did not improve further (adherence before vs.
After July 1, 2005: 68.6% vs. 72.7%, \(P = 0.001\). Adherence to criteria defining high-risk inferior MI was consistently worse than that of other MI. The relative improvement in adherence post-core laboratory feedback did not differ significantly between other MI (5.0%) and high-risk inferior MI (6.3%). When adherence to ECG entry criteria amongst enrolling sites was examined based on geographic region it was highest in Australia/New Zealand (79.5%) followed by Eastern Europe (78.0%), Western Europe (72.2%), and North America (63.8%). Modest improvements in adherence to ECG entry criteria were observed over the time course of the trial in North America and Eastern Europe (both \(P < 0.02\)). The improvement in North America was attributed to better adherence of high-risk inferior MI criteria (from 48.0 to 56.3%), and the improvement in Eastern Europe occurred mainly for other MI criteria (from 72.7 to 87.3%).

Discussion

Our study is the first to systematically evaluate the extent of adherence to ECG entry criteria in a large clinical trial of acute STEMI and its impact on clinical outcomes. 28.8% of patients enrolled in the APEX-AMI trial had less than the requisite amount of jeopardized myocardium on the admission ECG: the majority of these patients were in the high-risk inferior MI category unique to APEX-AMI. Patients who failed to meet ECG entry criteria experienced significantly better outcomes than those who met criteria and accordingly this compromised the trial’s aim to enrol a high-risk population. Despite the absence of a treatment effect of pexelizumab in both patients who met vs. those who failed to meet ECG entry criteria, our findings have relevance for future clinical trials of therapies which are driven by acquisition of a target number of endpoints and in whom the anticipated treatment benefit is likely amplified in those with increased risk as assessed from their baseline characteristics.

The value of systematic blinded core laboratory ECG analysis in clinical trials of ACS is well established with previous studies highlighting frequent ECG misinterpretation by site investigators and its impact on outcomes.\(^1,2\) In the GUSTO-IIb trial, Goodman et al. found that one in five patients with core laboratory-determined STEMI was categorized erroneously by site investigators as having no ST-elevation and had predictably worse outcomes. These results indicate the challenge of enrolling patients into clinical trials with different ECG findings than specified by protocol. Importantly these patients may have discordant outcomes from the rest of the study population.

Given the declining mortality associated with STEMI, the sample sizes in clinical trials required to show meaningful differences in outcomes rises accordingly. Hence, enriching the sample with a high-risk cohort defined on the admission ECG is both a legitimate and customary approach to recent contemporary trials. Prior to APEX-AMI, three recent trials (DANAMI-2, WEST, ASSENT-4) have employed ECG criteria unlike those in the majority of STEMI trials since GUSTO-I in attempting to enrol patients at increased risk particularly among inferior MI patients.\(^6,8\) APEX-AMI further raised the ECG ischemia threshold in inferior MI patients by requiring concomitant anterior ST-depression and a minimum total ST-deviation of 8 mm. These novel criteria defining high-risk inferior MI are based upon the recognized association between concomitant anterior ST-depression and larger infarct sizes, worse left ventricular function, and more complications including death.\(^9–12\)

Our data showed that failure to meet ECG entry criteria defining high-risk inferior MI occurred in two out of five patients and was twice as frequent compared to the more conventional criteria employed for other MI location. Furthermore 43% of those that failed to meet criteria for high-risk inferior MI did so because of insufficient anterior ST-depression. These findings suggest that the new criteria coupled with their complexity may have contributed to difficulties in adherence. High-risk inferior MI patients who failed to meet criteria due to insufficient anterior ST-depression exhibited strikingly low mortality through 90 days (1.0%) highlighting the prognostic utility of concomitant anterior ST-depression. Of note was that if conventional guideline-based ECG criteria for STEMI, i.e ST-elevation in \(\geq 2\) contiguous leads with cut-offs \(\geq 2\) mm in leads V1–V3 and \(\geq 1\) mm in other leads were applied to the APEX-AMI population then only 5.5% [inferior MI (2.6%) vs. other MI location (7.6%)] of patients failed to meet them.\(^13\)

Failure to adhere to ECG entry criteria contributed to the low event rate in the APEX-AMI trial and compromised the trial’s aim to enrol a high-risk population based on admission ECG findings. The low mortality rate in placebo arm of APEX-AMI (4.5% at 90 days) was unforeseen and substantially lower than the anticipated rate of 6.5%.\(^3\) Efforts to enrich the study cohort after the first planned interim blinded review by the Data Safety and Monitoring Board (i.e. after accumulation of 26% of the anticipated total number of events showing only 4.1% overall mortality) included restricting those with high risk inferior MI to patients >60 years. Other factors that likely contributed to the lower than expected event rates in APEX-AMI include the promptness of coronary intervention (average door-to-PCI time 1.6 h) and the high degree to which evidence-based concomitant medications were used.

Despite a concerted attempt to improve adherence to ECG entry criteria through contemporaneous core laboratory monitoring and feedback to enrolling sites, the gain was modest and almost one in four patients enrolled towards the end of the trial still did not meet criteria. Had we
continued to enrol patients with the same adherence rates we estimate an approximately 41% longer period would have been required to recruit the sample size herein if all met the ECG entry criteria. The worse adherence in North America compared to other regions is notable and the basis for it is unclear. The poor adherence in North America could relate to lower patient enrolment per site as compared to other regions (Table 1). It follows that sites enrolling fewer patients were less likely to both receive core laboratory feedback and apply it to subsequent patients.

What are potential causes for failure to comply with ECG entry criteria other than criteria complexity? These may include time constraints associated with the imperative for prompt delivery of care, pressure to live up to enrolment expectations, financial incentives afforded by patient enrolment; and perceived clinical benefit for the patient by participating in the trial. In light of our results, it is unclear whether more intense dialogue between core laboratory and site investigators will further improve adherence. Future potential solutions might involve the use of on line computer-based interpretation of the ECG at the point of entry as a requirement for enrolment or economic penalties for failure to comply with protocol inclusion criteria.

Our study has some limitations. As our review and feedback timing lagged and was not performed in real time it is difficult to definitively quantify improvement relative to enrolment timelines. Additionally the dichotomization of the definition of adherence to ECG entry criteria based on ST-measurements to the nearest 0.5 mm might be considered too strict. Counterbalancing this however was that the approximately 50% less \( \Sigma \) ST-deviation in patients who failed vs. those who met criteria had clinically relevant outcome differences.

Conclusions

Patients who failed to meet the ECG entry criteria of the APEX-AMI trial were frequent and had more favourable outcomes compromising the trial’s aim to enrol a high-risk population. Our findings should prove useful for the design, conduct, and interpretation of future STEMI trials.

Table 3 Temporal trends in adherence to ECG entry criteria

<table>
<thead>
<tr>
<th>By region of enrolment</th>
<th>By infarct location</th>
<th>Overall patients met (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients met (%)</td>
<td>Before July 1, 2005</td>
<td>July 1, 2005 to September 30, 2005</td>
</tr>
<tr>
<td>North America</td>
<td>1376/2007 (68.6)</td>
<td>761/1063 (71.6)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>201/280 (71.8)</td>
<td>238/292 (81.5)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>357/491 (72.7)</td>
<td>245/335 (73.1)</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>205/257 (79.8)</td>
<td>90/109 (82.6)</td>
</tr>
</tbody>
</table>

Funding

The APEX-AMI study from which this work was derived was supported by a jointly funded research grant from Procter & Gamble Pharmaceuticals and Alexion Pharmaceuticals.

Conflict of interest: M.C.T., Y.F., H.A., T.G.T., and P.A. have no conflict to declare and F.W.W., C.B.G., and P.W.A. received research grants from the above named sponsors.

References


