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The Appropriate Management of Rural Patients with ST-Segment Elevation Myocardial Infarction When Delays are Expected Due to Long-Distance Transfers

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The Appropriate Management of Rural Patients with ST-Segment Elevation Myocardial Infarction When Delays are Expected Due to Long-Distance Transfers

Abstract

Background: Current guidelines recommend primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) as long as it can be performed quickly by an experienced provider. Unfortunately as time from the onset of symptoms increases, so does the incidence of adverse cardiac events. For patients in rural areas who face inevitable delays due to long-distance transfers, primary PCI is a less than perfect option. Other options include full-dose fibrinolytic therapy with routine transfer to a PCI capable hospital and a relatively new reperfusion strategy called pharmaco-invasive PCI. With multiple treatment options available, what is the most appropriate management of rural patients with STEMIs when delays are expected due to long-distance transfers?

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: myocardial infarction, fibrinolytic agents, myocardial reperfusion, and patient transfer. Articles evaluating the efficacy and safety of treatment options for STEMI patients in rural locations were included. Relevant articles were assessed for quality using GRADE.

Results: Two studies met inclusion criteria and were included in this systematic review. A retrospective observational study with 259 rural STEMI patients found that in-hospital mortality was higher in patients with primary PCI (9.3%) compared with fibrinolysis patients (1.9%; \( P = 0.03 \)). A prospective observational study with 2634 patients found that there was no significant difference in 30-day mortality (5.5 vs 5.6%; \( P = 0.94 \)), stroke (1.1 vs 1.3%; \( P = 0.66 \)) or major bleeding (1.5 vs 1.8%; \( P = 0.65 \)), or re-infarction/ischemia (1.2 vs 2.5%; \( P = 0.088 \)) in rural patients receiving a pharmaco-invasive therapy compared with patients presenting directly to the PCI center.

Conclusion: In rural patients with STEMIs, as delays in transfer time increase due to long-distance travel, the use of fibrinolytic or pharmaco-invasive therapy may be more effective and beneficial than primary PCI reperfusion therapy.

Keywords: Myocardial infarction, myocardial reperfusion, fibrinolytic agents, transfer time, rural healthcare
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The Appropriate Management of Rural Patients with ST-Segment Elevation Myocardial Infarction When Delays are Expected Due to Long-Distance Transfers

Kelsi Coltom

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
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Faculty Advisor: Duc Vo, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

Background: Current guidelines recommend primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) as long as it can be performed quickly by an experienced provider. Unfortunately as time from the onset of symptoms increases, so does the incidence of adverse cardiac events. For patients in rural areas who face inevitable delays due to long-distance transfers, primary PCI is a less than perfect option. Other options include full-dose fibrinolytic therapy with routine transfer to a PCI capable hospital and a relatively new reperfusion strategy called pharmaco-invasive PCI. With multiple treatment options available, what is the most appropriate management of rural patients with STEMIs when delays are expected due to long-distance transfers?

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: myocardial infarction, fibrinolytic agents, myocardial reperfusion, and patient transfer. Articles evaluating the efficacy and safety of treatment options for STEMI patients in rural locations were included. Relevant articles were assessed for quality using GRADE.

Results: Two studies met inclusion criteria and were included in this systematic review. A retrospective observational study with 259 rural STEMI patients found that in-hospital mortality was higher in patients with primary PCI (9.3%) compared with fibrinolysis patients (1.9%; P=0.03). A prospective observational study with 2634 patients found that there was no significant difference in 30-day mortality (5.5 vs 5.6%; P= 0.94), stroke (1.1 vs 1.3%; P = 0.66) or major bleeding (1.5 vs 1.8%; P = 0.65), or re-infarction/ischemia (1.2 vs 2.5%; P = 0.088) in rural patients receiving a pharmaco-invasive therapy compared with patients presenting directly to the PCI center.

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Keywords: Myocardial infarction, myocardial reperfusion, fibrinolytic agents, transfer time, rural healthcare
Acknowledgements

[Redacted for privacy]
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List of Abbreviations

AMI……………………………………………………………………………..Acute Myocardial Infarction
GRADE……..Grading of Recommendations, Assessment, Development and Evaluation
MHI-ANW…………………………..Minneapolis Heart Institute at Abbott Northwestern
PCI…………………………………………………...Percutaneous Coronary Intervention
PCMH………………………………………………...….. Pitt County Memorial Hospital
STEMI………………………………………ST-segment Elevation Myocardial Infarction
TNK…………………………………………………………………………. Tenecteplase
The Appropriate Management of Rural Patients with ST-Segment Elevation Myocardial Infarction When Delays are Expected Due to Long-Distance Transfers

BACKGROUND

Almost 1 million acute myocardial infarctions (AMI) occur in the United States annually. The gold standard of treatment for patients that are diagnosed with a ST-segment elevation myocardial infarction (STEMI) is primary percutaneous coronary intervention (PCI) as long as it can be performed quickly by an experienced provider. Rapid initiation of reperfusion with primary PCI for patients with a STEMI limits the infarct size and improves the survival rates. Unfortunately, for patients requiring primary PCI, as time from the onset of symptoms increases, so does the incidence of death, re-infarction, and stroke. The American College of Cardiology and American Heart Association guidelines currently recommend that primary PCI be performed within 90 minutes from the patient presentation to the emergency room. However, only 25% of hospitals in the United States have the capability to perform primary PCI, and most of these are located in urban settings, making primary PCI a less than perfect option for rural patients with long-distance transfer times.

Other treatment options include full-dose fibrinolytic therapy with routine transfer to a PCI capable hospital for ischemia-guided rescue PCI. Concerns over the safety and efficacy of this treatment when compared to primary PCI have overall made it a second-line reperfusion strategy for the average STEMI patient. However, fibrinolytic therapy
might allow for the advantage of early reperfusion over primary PCI in rural patients that are facing long transfer times. Recently, a hybrid method called pharmaco-invasive PCI that aims to combine the benefits of both strategies (fibrinolytic therapy followed by transfer for early PCI) has shown promise as a new management strategy. With multiple treatment options available, what is the most appropriate management of rural patients with STEMI when delays are expected due to long-distance transfers?

METHODS

An exhaustive literature search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the following search terms: myocardial infarction, fibrinolytic agents, myocardial reperfusion, and patient transfer. Articles with primary data evaluating the efficacy and safety of treatment options for STEMI patients in rural locations were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

RESULTS

The initial search of medical literature generated 40 articles for review. Further evaluation of relevant data from the generated search yielded a total of two articles that met inclusion criteria. Both of these articles were observational studies analyzing the treatment of rural patients diagnosed with STEMI. One evaluated the use of fibrinlytics, while the other the use of a pharmaco-invasive reperfusion strategy. These studies are summarized in Table I and their findings are summarized in Tables II and III.
This retrospective observational study\textsuperscript{8} assessed whether or not the administration of fibrinolytics in rural STEMI patients prior to a long-distance hospital transfer resulted in transfer delays or worse outcomes when compared with direct transfers for primary PCI. Data was collected using information from the National Registry of Myocardial Infarction 5 as well as the Acute Coronary Treatment and Intervention Outcomes Network. All patients included in this study were transferred from 14 non-PCI capable referral hospitals to Pitt County Memorial Hospital (PCMH), a 24 hour PCI-capable hospital in eastern North Carolina. The median distance from the non-PCI hospital to the PCI-capable center was 52 miles (interquartile range [IQR], 38-69), with an average travel time of 72 minutes (IQR, 50-86) by ground.\textsuperscript{8}

Patients with STEMI or new left bundle branch block within 12 hours of symptom onset were included in the study. The administration of intravenous fibrinolytics to STEMI patients was left to the discretion of the admitting ED physician. Standard protocols for administration of fibrinolytics, as well as contraindications were applied, including uncontrolled hypertension, malignant disease, recent major surgery or bleeding, prolonged cardiopulmonary resuscitation, and severe heart failure. Patients that qualified for fibrinolysis were given either full-dose tenecteplase (64.4\%) or reteplase (35.6\%) and were eligible for transfer immediately after completion of fibrinolysis. Patients who did not meet criteria for fibrinolysis, or had transfer times less than 30 minutes, were referred for primary PCI.\textsuperscript{8}

The authors reviewed 259 patients presenting with a STEMI diagnosis to participating non-PCI capable hospitals and were then transferred to PCMH between
December 2006 and June 2008. Of these patients, 43 (16.6%) were transferred for primary PCI, while the remaining 216 (83.4%) were transferred after administration of fibrinolysis for further management. The mean age of patients transferred for primary PCI was 65.2 ± 13.5 years, while the mean age for patients transferred after fibrinolysis was 58.7 ± 12.5 years. There was a higher rate of congestive heart failure in the primary PCI group (20.9%) as compared to the fibrinolytic group (3.7%; P < 0.001). Cardiogenic shock was also higher in the primary PCI group (14.0% vs 0.5%; P < 0.001).8

The incidence of in-hospital mortality was 9.3% in patients with primary PCI compared with 1.9% in patients treated with fibrinolysis (P = 0.03). This results in a risk ratio reduction of 80%. Stroke occurred in 3 patients (1 was hemorrhagic) that received fibrinolysis as compared with 0 patients that underwent primary PCI. The number of major bleeding events that justified transfusion was 4.6% in both the primary PCI and fibrinolytic groups.8 A summary of these findings can be found in Table II.

The median door to door time was 135 minutes for the primary PCI patients, compared with 128 minutes in patients transferred following fibrinolysis (P = 0.71). Door to door to balloon time in the primary PCI group was 182 minutes and the door to balloon time was 49 minutes from the time of arrival at PCMH. Median door to needle time in the fibrinolysis group was 30 minutes, with 51.4% being performed in less than 30 minutes. Rescue PCI has to be performed in 81 (37.5%) of the fibrinolytic patients, and coronary stents were placed in 75 (92.6%) of these patients.8

Larson et al

In this prospective observational study,9 the authors compared the safety and efficacy of pharmaco-invasive PCI with immediate transfer for primary PCI in rural
patients with STEMI. In 2003, a regional system called the “Level 1 MI programme” was established to help with the management of STEMI patients transferred to the Minneapolis Heart Institute at Abbott Northwestern (MHI-ANW) Hospital in Minneapolis, Minnesota, a tertiary cardiovascular center, from community hospitals up to 210 miles away. At the time of study, 11 referral hospitals were < 60 miles from MHI-ANW (designated as Zone 1 hospitals) and 20 referral hospitals were 60-120 miles from MHI-ANW (designated as Zone 2 hospitals). Data was prospectively entered into a registry and clinical outcomes were extracted from the electronic medical record at 30 days and 1 year. A propensity-score method was used to identify comparable patients treated with pharmaco-invasive reperfusion and those receiving primary PCI, in groups A and D. A nearest-neighbor 1:1 matching algorithm was used to match subjects on the basis of the logit of the propensity score.9

A standardized protocol with pre-printed standing orders was implemented at each hospital. Patients who presented to the PCI hospital (MHI-ANW) or were transferred from Zone 1 hospitals (< 60 miles), received primary PCI reperfusion therapy. Patients transferred from Zone 2 hospitals (> 60 miles) received half-dose fibrinolytic followed by emergent transfer for primary PCI (pharmaco-invasive PCI). The decision of type of fibrinolytic to administer was left up to individual hospital protocol, but tenecteplase (TNK) was the most frequently used (97% TNK, 3% reteplase). Contraindications to fibrinolysis included: active bleeding, significant closed head injury within 3 months, suspected aortic dissection, ischemic stroke within 3 months, known intracranial neoplasm or prior intracranial hemorrhage, and out of hospital cardiac arrest with prolonged CPR.9
From April 2003 to December 2009, 2634 consecutive STEMI patients in the Level 1 MI database were enrolled. This study established five patients groups to help with comparison. Group A (n=600) – primary PCI patients who presented directly to the PCI hospital (MHI-ANW). Group B (n=1163) – primary PCI patients transferred from Zone 1 (< 60 miles) hospitals. Group C (n=32) – pharmaco-invasive PCI patients transferred from Zone 1 (< 60 miles) hospitals with anticipated delays due to weather. Group D (n=660) – pharmaco-invasive PCI patients transferred from Zone 2 (> 60 miles) hospitals. Group E (n=179) – primary PCI patients transferred from Zone 2 (> 60 miles).9

Pharmaco-invasive PCI with half-dose fibrinolysis was used in 692 (26.3%) patients including 660 from Zone 2 hospitals and 32 from Zone 1 hospitals with weather related transfer delays. For the most part groups were prognostically balanced. The pharmaco-invasive treated patients (Group C and D) were slightly older than Group A and B, while the patients from Zone 2 that were transferred for primary fibrinolysis (Group D) were older and had more risk factors.9

A pre-specified prospective comparison of patients treated with primary PCI that presented directly to the PCI hospital (Group A) with patients treated with pharmaco-invasive PCI transferred from Zone 2 hospitals (Group D) showed no significant differences with respect to 30-day mortality (5.5 vs 5.6%; P=0.94), recurrent ischemia/AMI (2.5 vs 1.2%; P=0.088), stroke (1.3 vs 1.1%; P=0.66), or major bleeding (1.8 vs 1.5%; P=0.65). Also, when comparing the total number of patients that were treated with primary PCI from the PCI hospital and Zone 2 (Group A and B) with the total number of patients treated with pharmaco-invasive PCI (Group C and D) again showed no significant difference in 30-day mortality (5.6 vs 5.8%; P=0.87), stroke (0.9
vs 1.2%; P=0.48), recurrent ischemia/myocardial infarction (1.5 vs 1.3%; P=0.67) or major bleeding (1.4 vs 1.6%; P=0.76). After adjustment using the propensity-score method, these results were confirmed with similar outcomes when comparing Group A and D. A summary of these findings can be found in Table III.

Of the original group of patients that presented to Zone 2 hospitals, 21.3% did not receive fibrinolytic therapy and were transferred for primary PCI. Contraindications for fibrinolysis were the most common reason. These patients had higher 30-day mortality (10.6 vs 5.6%; P=0.17) compared with patients transferred from Zone 2 with pharmaco-invasive PCI. These patients were higher risk as they were older, had more risk factors, and more likely to have had an out-of-hospital cardiac arrest (11.7 vs 7.0%; P=0.037).

Median door to balloon times were 62 minutes for patients presenting directly to a PCI capable hospital (Group A), 92 minutes for primary PCI patients transferred from Zone 1 hospitals (Group B), and 122 minutes for pharmaco-invasive treated patients from Zone 2 hospitals (Group D). The median door to needle time was 29 minutes for patients receiving fibrinolytic therapy prior to transfer.

**DISCUSSION**

For all patients with STEMIs, both urban and rural, the recommended standard of treatment of primary PCI within 90 minutes of presenting to the hospital remains the gold standard for reperfusion therapy. However, of the thousands of patients that are diagnosed with STEMI every year in the United States, almost 75% of them present to hospitals lacking the staff and resources to perform primary PCI. Furthermore, with approximately 20% of the general population and more than 52% of the rural
population living more than 60 minutes from a primary PCI facility, achieving door to balloon times within 90 minutes remains a significant challenge.

Treatment of STEMI patients with fibrinolytic reperfusion therapy is a second-line strategy due to its increase risk for bleeding and overall efficacy when compared to primary PCI. However, most would agree that the benefits of primary PCI decrease when there is a significant delay due to transfer. A recent study showed that patients who are transferred for primary PCI with delays to reperfusion greater than 90 minutes have significantly greater 30-day mortality. The study Beri et al found that rural STEMI patients who received fibrinolysis as an initial reperfusion strategy did not have overall worse outcomes like majoring bleeding, stroke, or death when compared to patients transferred directly for primary PCI. However, due to the overall very low quality, results from this article should be interpreted cautiously and a strong recommendation cannot be made on this article alone. Findings similar to Beri et al were reported in the DANAMI-2 trial, while the PRAGUE-2 and CAPTIM trials showed that thrombolysis might be an equally effective or better strategy than primary PCI in patients who could be reperfused within 2 to 3 hours of symptom onset. Other studies showed that as delays in transfers increased so did the benefit of fibrinolysis over primary PCI. Although these trials did not specifically study rural populations, transfer delay was the issue being addressed, which is the important problem at hand for rural patients. Multiple articles with similar findings help to strengthen the overall recommendation. In rural patients with STEMIIs facing delays greater than 90 minutes, fibrinolytics appears to have no adverse effect in patients and may lead to better outcomes.
An alternative strategy to these traditional methods of reperfusion is a treatment that combines the advantages of the availability of fibrinolysis with the effectiveness of primary PCI. The study Larson et al.\textsuperscript{9} found that STEMI patients that presented to rural hospitals greater than 60 miles from PCI capable facilities routinely had delays in transfer times greater than 120 minutes. The results from this study for these patients indicate pharmaco-invasive PCI treatment being equally effective and safe with outcomes similar to patients presenting directly to a PCI-capable hospital.\textsuperscript{9} A recent meta-analysis\textsuperscript{20} revealed that “routine early PCI, following fibrinolysis, in patients presenting to non-PCI hospitals, leads to significant reduction in re-infarction, recurrent ischemia, and the combined endpoint of death and re-infarction at 30 days with no significant increase in bleeding complications” compared with standard reperfusion therapy. The results found in the meta-analysis lead to a class 1a recommendation by the 2010 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization for transfer of all post-fibrinolysis STEMI patients to a PCI-capable hospital for immediate rescue PCI if fibrinolysis is unsuccessful or coronary angiography within 3-24 hours and delayed PCI as needed.\textsuperscript{20} Despite these promising results, more research needs to be conducted on the exact pharmacologic regimen, dosing, and timing of PCI following fibrinolysis before any firm recommendations can be made.

While both studies\textsuperscript{8,9} demonstrated the safety and efficacy of alternative reperfusion strategies for rural STEMI patients, they are not without limitations. The Beri et al study\textsuperscript{8} was a retrospective observational study, automatically making it a low quality. The study was further downgraded to a very low due to the fact that the study
group was prognostically different then the control group and no statistical adjustment was done to make the groups equivalent. There may also been a selection bias due to the fact that there was a higher percentage of patients with heart failure and related cardiogenic shock in the primary PCI group compared to the fibrinolysis group. This may have led to sicker patients being designated for primary PCI rather than thrombolytics, resulting in delays in transfer and worse outcome. However, older patients with severe heart failure are more likely to have contraindications for fibrinolysis. This study was also limited to hospitals in the eastern part of North Carolina, and similar results may not be attained in other regions of the country.8

The Larson et al study9 was a registry investigational study and was therefore automatically a low quality to begin with. However, registry data does have the advantage of including a higher risk patient population not included in randomized trials,22 and recent research shows that it is difficult to enroll STEMI patients in a randomized control trial because of the lack of research support in rural hospitals.22,23 Also results were obtained through an “organized STEMI system of care” that required significant physician and nurse training, and similar results may not be applicable to other areas that do not have similar systems.9

CONCLUSION

When managing rural STEMI patients, direct transfer for primary PCI remains the strategy of choice for patients with contraindications to fibrinolysis or short transfer times. The benefit of primary PCI over fibrinolysis is reduced when there is a significant delay related to transfer,13-15 making on-site fibrinolytic therapy a more practical option for reperfusion as transfer times increase. The relatively new method of pharmaco-
invasive therapy may be a safe and effective reperfusion strategy for rural STEMI patients when delays are expected due to long-distance travel. Further studies reinforcing the safety and efficacy, as well as establishing a standardized protocol will help to strengthen this recommendation.


References


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<th>No. of Studies</th>
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<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
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<td>Observational</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
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<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very Low</td>
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<sup>a</sup> Study group is prognostically different then control group in Beri et al.<sup>8</sup> with no statistical adjustment done

<sup>b</sup>Only one study evaluated this outcome
Table II. Summary of Findings Beri et al$^8$

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>pPCI (total)</th>
<th>Mortality (%)</th>
<th>Effect</th>
<th>Stroke</th>
<th>Major Bleed</th>
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<tbody>
<tr>
<td>Fibrinolytic</td>
<td>216</td>
<td>4 (1.9)</td>
<td></td>
<td>Relative Risk Reduction: 0.80</td>
<td>3 (1.4)</td>
<td>10 (4.6)</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>43</td>
<td>4 (9.3)</td>
<td>Number Needed to Treat: 14</td>
<td>0 (0.0)</td>
<td>2 (4.7)</td>
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</tr>
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pPCI, primary percutaneous coronary intervention.
Table III. Summary of Findings Larson et al\textsuperscript{9}

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Outcomes</th>
<th></th>
<th>Major Bleed Relative Risk</th>
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<tr>
<td></td>
<td>Treatment (total)</td>
<td>Mortality</td>
<td>Re-infarction</td>
<td>Stroke</td>
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<td>Larson et al\textsuperscript{9}</td>
<td></td>
<td></td>
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<tr>
<td>Group A</td>
<td>600</td>
<td>33 (5.5)</td>
<td>15 (2.5)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Group B</td>
<td>1163</td>
<td>66 (5.7)</td>
<td>12 (1.0)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>Total pPCI</td>
<td>(A + B) 1763</td>
<td>99 (5.6)</td>
<td>27 (1.5)</td>
<td>15 (0.9)</td>
</tr>
<tr>
<td>Group C</td>
<td>(PI, Zone 1) 32</td>
<td>3 (9.6)</td>
<td>1 (3.1)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Group D</td>
<td>(PI, Zone 2) 660</td>
<td>37 (5.6)</td>
<td>8 (1.2)</td>
<td>7 (1.1)</td>
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<tr>
<td>Total PI</td>
<td>(C + D) 692</td>
<td>40 (5.8)</td>
<td>9 (1.3)</td>
<td>8 (1.2)</td>
</tr>
<tr>
<td>Group E</td>
<td>(pPCI, Zone 2) 179</td>
<td>19 (10.6)</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
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pPCI, primary percutaneous coronary intervention; PCI, percutaneous coronary intervention; PI, pharmaco-invasive.

Mortality Relative Risk when comparing Group A to Group D is 1.02.