PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Randomised Double Blind Control Study of Early Intra-coronary Autologous Bone Marrow Cell Infusion in Acute Myocardial Infarction (REGENERATE-AMI)
AUTHORS	Hamshere, Stephen; Choudhury, Tawfiq; Jones, Dan; Locca, Didier; Knight, Charles; Mills, Peter; Rothman, Martin; Agrawal, Samir; Martin, John; Mathur, Anthony; Parmar, Mahesh

VERSION 1 - REVIEW

REVIEWER	Jay H Traverse, MD Minneapolis Heart Institute at Abbott Northwestern Hospital Cardiovascular Division, University of Minnesota School of Medicine
REVIEW RETURNED	06-Nov-2013

GENERAL COMMENTS	The time point for cell delivery is novel and the potential to modify ischemia / reperfusion injury is an interesting hypothesis and should be expanded. This randomized (1:1), placebo-controlled trial will administer BMCs within 24 hours following successful reperfusion with PCI and stenting in 100 patients with anterior STEMIs. The chosen time-point of delivery within 24 hours of STEMI is novel and has not been previously explored in a clinical trial. The authors hypothesize that this time-point may be beneficial, due to potential effects in moderating I/R injury that recapitulates several successful studies in murine infarct studies where stem cells are traditionally delivered within hours after infarction (1). The primary endpoint of the study is change in LVEF from baseline (day 3) to 1-year as measured by cardiac MRI. The author's will also utilize other measurement tests such as echocardiography and LV angiography at different time-points throughout the first year of follow-up. The timing of cell delivery within 24 hours of reperfusion of STEMI is highly novel and will compliment other randomized, placebo-controlled BMC trials that specifically examined the timing of cell delivery. Unfortunately the TIME (3 vs 7 days) (2), LateTIME (2-3 weeks) (3) and SWISS-AMI (5-7 days vs 3-4 weeks) (4) trials all failed to show that BMCs enhance the recovery of LV function compared to placebo. Therefore, given the rather modest effects of BMCs on LV function following STEMI, the notion that BMCs could modify reperfusion injury presents an intriguing target for therapy. BMC administration immediately following reperfusion in a rat infarct model activates key myocardial survival pathways such as PI3K / Akt that translated into greater myocardial salvage (5). Perhaps this mechanism contributed to the dramatic effects observed in the paper by Orlic et al. (1). It remains to be determined if BMCs can modify reperfusion injury when administered up to 24 hours following PCI. The authors should consider measuring myocardial salvage at the 3-

	day MRI with T2-weighted imaging of myocardial edema to address this hypothesis. This would make an excellent primary co-endpoint. Greater discussion of these ideas is warranted in the manuscript. Although the LVEF measured at 1-year may be quite stable, it is the measurement of the baseline LVEF that is problematic for determining the true effect of therapy following STEMI. Dramatic changes in LVEF may occur over the first week following STEMI due to resolution of myocardial stunning that may be highly variable in patients. Even at Day-3, as chosen by the authors, there will still be ongoing improvements in LVEF over the next several days that will occur independently of cell therapy. The implications of using Day 3 as your baseline should be well thought out. Enrollment into the trial required the presence of q-waves on the EKG and anterior wall motion abnormality. However, this criteria may still potentially admit a significant number of patients with small infarcts who are unlikely to derive significant benefit. Several studies suggest that cell therapy provides its greatest benefit to those patients with the largest infarctions at baseline. Perhaps the authors should add a peak-CKMB threshold and ischemic duration to the entry criteria and exclude patients pre-infarction angina. Cell processing may have a dramatic effect on efficacy of the delivered cells (6), yet scant discussion of the author's cell processing methods is presented. In fact, more text is utilized describing the stop-flow technique of cell delivery. The presence of heparin and red blood cells in the final product may adversely affect cell function but this is never addressed. The authors propose local cell processing at each of the sites, but no discussion is provided to ensure how an equivalent cell product is delivered across centers. It is unclear why the authors have proposed to perform repeat LV-angiography in patients at 6-months as a secondary endpoint. There is simply no need for this invasive and potentially risky procedure to be performed when MRI measurements are vastly superior for LV volumes and function and will be measured at 3-months. This should be eliminated from the protocol or clear justification provided. Minor Points: 1.) Why refer to bone marrow mononuclear cells (BMCs) as bone marrow derived cells (BMDC) throughout the manuscript? Just call them BMCs as there are many types of BMDCs used in clinical trials. 2.) Would include the placement of ICDs as a secondary endpoint. The reduction in ICD utilization by cell therapy may be an underappreciated benefit. 3.) What testing of the BMCs will be performed at the individual centers to ensure a uniform product? 4.) What are the potential risks to the cells by administering them within 24 hours of reperfusion. This should be discussed (?ROS, etc.) 5.) The primary endpoint for REPAIR-AMI was 4-months and not 2 years 6.) The REPAIR-AMI Investigators have demonstrated that heparin

	impairs the functional status of the BMCs (via SDF-1 pathway). Should you consider giving bivalrudin in lieu of heparin at the time of BMC infusion? 7.) How will you compare those patients that had MRI at baseline and required CT imaging at the one-year endpoint because of ICD placement? 8.) How will incomplete data of your primary endpoint be analyzed? References 1.) Orlic D, et al. Bone marrow cells regenerate infarcted myocardium. Nature 2001;410:701-5. 2.) Traverse JH, et al. Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. JAMA 2012;308:2380-2389. 3.) Traverse JH, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. JAMA 2011;306:2110-9. 4.) Surder d, et al. Intracoronary injection of bone marrow mononuclear cells early or late after acute myocardial infarction: effects on global left ventricular function. Circulation 2013;127:1968-79. 5.) Lovell MJ, et al. Bone marrow mononuclear cells reduce myocardial reperfusion injury by activating the PI3K/Akt survival pathway. Atherosclerosis 2010;213:67-76. 6.) Seeger FH, et al. Heparin disrupts the CXCR4 / SDF-1 axis and impairs the functional capacity of bone marrow-derived mononuclear cells used for cardiovascular repair. Circ Res 2012;111:854-62.

REVIEWER	Alexander Hirsch Academic Medical Center, Amsterdam
REVIEW RETURNED	12-Nov-2013

GENERAL COMMENTS	The manuscript is clear and well written. However I have some comments. Comments 1. Introduction, page 2, line 30: "to date no randomized, controlled trials have tested the outcome of early BMDC injection (within 24 hours ....)'. However, the study by Janssens et all described in their manuscript that they performed bone marrow aspiration within 24 hours after primary PCI and cell infusion was performed within 4 to 6 hours after aspiration (Janssens et al Lancet 2006, Herbots et al. EHJ 2009). Unfortunately the exact timing of the cell infusion is not described. Please change the introduction and also the first bullet in the paragraph ‘strength and limitations’ (page 4). 2. What will be the estimated timing of cell infusion in the REGENERATE-AMI study? How many hours after primary PCI? When is the bone marrow aspiration performed: same day as primary PCI, next day? Also during night time? The cell processing will take 6-8 hours. Will patents be excluded if the planned infusion within 24 hours can not be fulfilled? Should Hep B/C, HIV tests be negative before bone marrow aspiration? If yes what is the expected time delay?

	3. Strength and limitations (page 4), second bullet: '….making the results applicable to the general population..'. There is a clear selection of patients with only anterior myocardial infarction and no previous myocardial infarction (exclusion regional wma in other territory). Therefore the results will not be applicable to the general infarct population. Please change this point. 4. One of the hypothesis of the study is that early infusion of bone marrow cells may limit I-R injury (page 5, line 53). However the primary endpoint is the difference in change of ejection fraction between 3 days and 1 year. Why is this endpoint chosen? Limitation of I-R injury will probably result in smaller infarction/larger myocardial salvage and/or better function at 3 days. The early effect (reducing I-R injury) can be missed by looking at the change of function between late time points. 5. Do the authors expect an increased bleeding risk by performing the bone marrow aspiration very early after primary PCI with all anti-coagulantia (i.e. abciximab in a substantial percentage of patients)? Please comment on this. 6. Power analysis (page 16). The primary endpoint is the difference in change in EF between the cell infusion group and control. In the manuscript the authors describe that an absolute increase in EF of 6% compared to baseline will be considered significant. Is this the change in EF in bone marrow group? What is the expected change in EF in control group and what is the expected difference in change? If 6% is the difference in change between groups this is very optimistic considering the current literature (including the negative study of Janssens et all. with early cell infusion (within 24 hours). 7. Summary, page 20. 'If BMDC improves outcomes following anterior AMI it would pave the way for future development of easily available and cheap treatment…. '. Why 'easily available and cheap' The suggested additional treatment is rather complex (bone marrow aspiration, cell processing, extra catheterisation etc) and to my opinion not cheap. Please comment. Minor comments: 1. Introduction, line 37: ....in cardiac function in pre-clinical studies'. Please include references. 2. Page 7, line 45-50. The results of the Repair-AMI are described. Please cite the original article (NEJM) instead of the article in Future Card as a reference. 3. Methods, CMR: why is T2 imaging for assessing oedema also performed at 3 and 12 months? 4. Methods: page 13, line 23: 'ballon occlusion intends to enhance adhesion and migration of the infused cells'. Is there evidence for this concept? Please include reference(s). 5. Figure 1: echo is performed before bone marrow aspiration, day 3, 3 months, 6 months and 1 year. However in the text (page 16, line 17-19) the echo at 3 months is not mentioned. 7. Figure 1: During primary PCI LV angio is performed. However the patient is not included in the study at this time moment and has not given informed consent yet. Is this routine practice in every patient treated with primary PCI at the participating centres? 8. Reference 25 is not cited correctly (no volume, page). Please correct. 9. Table 1: what is 'significant' regional WMA on LV angio? How is this defined? 10. Table 2: why is previous MI not an exclusion criteria? How are regional WMA abnormalities outside the area involved in the index MI defined?

VERSION 1 – AUTHOR RESPONSE

REVIEWER
Jay H Traverse, MD - Institution and Country Minneapolis Heart Institute at Abbott Northwestern Hospital

COMMENTS
1. The timing of cell delivery within 24 hours of reperfusion of STEMI is highly novel and will compliment other randomized, placebo-controlled BMC trials that specifically examined the timing of cell delivery. Unfortunately the TIME (3 vs 7 days) (2), LateTIME (2-3 weeks) (3) and SWISS-AMI (5-7 days vs 3-4 weeks) (4) trials all failed to show that BMCs enhance the recovery of LV function compared to placebo. Therefore, given the rather modest effects of BMCs on LV function following STEMI, the notion that BMCs could modify reperfusion injury presents an intriguing target for therapy. BMC administration immediately following reperfusion in a rat infarct model activates key myocardial survival pathways such as PI3K / Akt that translated into greater myocardial salvage (5). Perhaps this mechanism contributed to the dramatic effects observed in the paper by Orlic et al. (1). It remains to be determined if BMCs can modify reperfusion injury when administered up to 24 hours following PCI. The authors should consider measuring myocardial salvage at the 3-day MRI with T2-weighted imaging of myocardial edema to address this hypothesis. This would make an excellent primary co-endpoint. Greater discussion of these ideas is warranted in the manuscript.

Thank you for your comments. We agree that MSI would be an interesting endpoint to assess for any reduction in I/R injury. We will be measuring myocardial oedema with T2 imaging as a sub study given the current limitations of this technique. We have amended the text on page 15 to reflect this.

2. Although the LVEF measured at 1-year may be quite stable, it is the measurement of the baseline LVEF that is problematic for determining the true effect of therapy following STEMI. Dramatic changes in LVEF may occur over the first week following STEMI due to resolution of myocardial stunning that may be highly variable in patients. Even at Day-3, as chosen by the authors, there will still be on going improvements in LVEF over the next several days that will occur independently of cell therapy. The implications of using Day 3 as your baseline should be well thought out.

Although myocardial stunning is a factor for all acute infarction studies we feel that we needed an appropriate and consistent time post-infarction to ensure patient stability especially in view of the patient population recruited (anterior infarcts). The majority of infarct studies use this time period and performing analysis much later after therapy may limit any difference seen with cell therapy, especially if this benefit is early. Delaying the baseline MRI scan would result in delayed discharge of the patient. To assess any early differences we will be able to compare echocardiography performed immediately post PPCI to a Day 3 Echo to assess if there is any evidence of change.

3. Enrolment into the trial required the presence of q-waves on the EKG and anterior wall motion abnormality. However, this criteria may still potentially admit a significant number of patients with small infarcts who are unlikely to derive significant benefit. Several studies suggest that cell therapy provides its greatest benefit to those patients with the largest infarctions at baseline. Perhaps the authors should add a peak-CKMB threshold and ischemic duration to the entry criteria and exclude patients pre-infarction angina.

Due to the nature of the patients within the trial we have a very narrow time window for patients to be consented, undergo bone marrow aspiration and infusion (target <6 hours). We are unable to assure a CK-MB result within this timeframe across all centres and hence this has not been included in the main trial.

We do have a maximum ischemia time within the inclusion criteria with only patients who underwent PPCI within 24 hours of chest pain to be recruited. Although pre-infarction angina is not in the exclusion criteria, as previously stated, all patients must have chest pain within 24 hours which will exclude pre-angina or delayed presentation patients.

4. Cell processing may have a dramatic effect on efficacy of the delivered cells (6), yet scant discussion of the author's cell processing methods is presented. In fact, more text is utilized describing the stop-flow technique of cell delivery. The presence of heparin and red blood cells in the final product may adversely affect cell function but this is never addressed. The authors propose local cell processing at each of the sites, but no discussion is provided to ensure how an equivalent cell product is delivered across centres.

Due to the variability of cell numbers collected in bone marrow aspirates between different patients and the ethical considerations of performing this form of intervention and then excluding the patient based on a notional parameter we decided to standardise the cell preparation protocol based on the percentage recovery of mononuclear cells (more than 60% as per Ficoll manufacturers guidance). We will record the characteristics of the cell product and attempt to correlate differences in composition with outcome. We accept that this is a potential shortfall in the study however it allows a pragmatic approach based on the diversity of the patient population bone marrow harvest.
With regards to the issues around heparin and cell mobility, we do not use heparin in the final cell product. We have added a statement to reflect this in the manuscript (page 12)

5. It is unclear why the authors have proposed to perform repeat LV-angiography in patients at 6-months as a secondary endpoint. There is simply no need for this invasive and potentially risky procedure to be performed when MRI measurements are vastly superior for LV volumes and function and will be measured at 3-months. This should be eliminated from the protocol or clear justification provided.

The use of LV angiography as a secondary endpoint is for the purpose of using a comparison to early trials such as REPAIR-AMI that used LV angiography as its primary end point. We have added a statement to reflect this rationale (page 15-16).

MINOR POINTS
1. Why refer to bone marrow mononuclear cells (BMCs) as bone marrow derived cells (BMDC) throughout the manuscript? Just call them BMCs as there are many types of BMDCs used in clinical trials.

We have adjusted our manuscript to reflect this comment. Therefore all abbreviations are now BMCs. Changes are present on: Page 2, 3, 4, 6, 8, 11, 12, 18, 19, 20

2. Would include the placement of ICDs as a secondary endpoint. The reduction in ICD utilization by cell therapy may be an underappreciated benefit.

We will have the data of all patients who go on to have a device within the 1-year follow up and this will be addressed as part of the safety data. This has been added to the manuscript (page 14)

3. What testing of the BMCs will be performed at the individual centres to ensure a uniform product?

All centres will follow the same cell preparation methods and undergo training by our cell processor team. We only require a minimum of 60% recovery of cells from the preparation process. Beyond this all processing must comply to the standardised GMP regulatory process.

4. What are the potential risks to the cells by administering them within 24 hours of reperfusion. This should be discussed (?ROS, etc.).

We have added the following statement to reflect this point: "The literature has not reported any significant harm following early injection of BMC's in animal models, despite the views of some that this may be hazardous either to the subject or the cell products. The aim of Regenerate AMI is to ensure that this lack of evidence is captured in the safety analysis of the trial."(page 8)

5. The primary endpoint for REPAIR-AMI was 4-months and not 2 years

We have adjusted accordingly on page 7

6. The REPAIR-AMI Investigators have demonstrated that heparin impairs the functional status of the BMCs (via SDF-1 pathway). Should you consider giving bivalrudin in lieu of heparin at the time of BMC infusion?

Due to the timing of the infusion many patients may be still anticoagulated with heparin therapy or on GP IIa IIIb from PPCI so the decision was made to maintain concurrent therapy. No heparin is added to the cell therapy product itself, which is in keeping with the views of the REPAIR- AMI investigators.

7. How will you compare those patients that had MRI at baseline and required CT imaging at the one-year endpoint because of ICD placement?

Our primary aim is to compare paired same modality imaging data for all patients - if there is unpaired imaging modality data this will be included in a sub analysis of the primary end point. Attempts will be made to correlate values obtained from different modalities and the data presented separately should a strong positive correlation be seen.

8. How will incomplete data of your primary endpoint be analyzed?

Since the trial is powered for within group changes in cardiac function incomplete data will be excluded from the primary endpoint. These patients will however be in the safety analysis as part of intention to treat.

REVIEWER
Alexander Hirsch - Institution and Country Academic Medical Center, Amsterdam

COMMENTS
1. Introduction, page 2, line 30: "to date no randomized, controlled trials have tested the outcome of early BMDC injection (within 24 hours ....)'. However, the study by Janssens et al. described in their manuscript that they performed bone marrow aspiration within 24 hours after primary PCI and cell infusion was performed within 4 to 6 hours after aspiration (Janssens et al Lancet 2006, Herbots et al. EHJ 2009). Unfortunately the exact timing of the cell infusion is not described. Please change the introduction and also the first bullet in the paragraph ‘strength and limitations’ (page 4)

Thank you for your suggestions, however Janssens et al 2006 paper is for stem cell infusion one day after a PPCI - patients underwent bone marrow aspiration within 24 hours. Timing for reinfusion wasn't stated in the paper so our trial will be the first published where patients will receive stem cells within 24 hours of PPCI.

2. What will be the estimated timing of cell infusion in the REGENERATE-AMI study? How many hours after primary PCI? When is the bone marrow aspiration performed: same day as primary PCI, next day? Also during night time? The cell processing will take 6-8 hours. Will patents be excluded if the planned infusion within 24 hours can not be fulfilled? Should Hep B/C, HIV tests be negative before bone marrow aspiration? If yes what is the expected time delay?

Thank you for this comment, patients will be included in to the trial at any time point between 0 to 20 hours, this is due to the cell preparation time and return for infusion. Bone marrow therefore can occur at any time point between the previous stated times. During the hours of 18:00 to 08:00 patients can be included into the trial but bone marrow aspiration cannot occur due to stem cell processing times unless special dispensation has occurred with the research stem cell technician. If for unforeseeable circumstances planned infusion is greater than 24 hours we will go ahead on an intention to treat basis and be included in the final analysis.
Serology testing takes more than 24 hours in our main centre and therefore only patients with known positive serology at the time of recruitment will be excluded. The cell processing laboratory will handle all material as high risk until the results of the serology tests are received.

3. Strength and limitations (page 4), second bullet: '….making the results applicable to the general population..'. There is a clear selection of patients with only anterior myocardial infarction and no previous myocardial infarction (exclusion regional wma in other territory). Therefore the results will not be applicable to the general infarct population. Please change this point.

Thank you for highlighting this misunderstanding. The point being made was that of the value of multi-centre versus single-centre trials - the manuscript has been adjusted accordingly (page 4)

4. One of the hypothesis of the study is that early infusion of bone marrow cells may limit I-R injury (page 5, line 53). However the primary endpoint is the difference in change of ejection fraction between 3 days and 1 year. Why is this endpoint chosen? Limitation of I-R injury will probably result in smaller infarction/larger myocardial salvage and/or better function at 3 days. The early effect (reducing I-R injury) can be missed by looking at the change of function between late time points.

The current literature does not make it clear at what stage the modification of ischaemia-reperfusion injury leads to a functional benefit in man. We accept that Day 3 is a compromise but the imaging time point has been chosen for logistical reasons and is consistent with previous trials. We will use other imaging modalities (echocardiography and T2 weighted MRI) to assess any early differences between the groups.

5. Do the authors expect an increased bleeding risk by performing the bone marrow aspiration very early after primary PCI with all anti-coagulantia (i.e. abciximab in a substantial percentage of patients)? Please comment on this.

This specific point has been discussed extensively with our haematology colleagues. The feeling is that due to the consistency and biological nature of the bone marrow aspirate we are unlikely to see excess bleeding from the aspiration site. However given the novelty of the study there is little preceding data and therefore this will be monitored closely as part of the safety analysis.

6. Power analysis (page 16). The primary endpoint is the difference in change in EF between the cell infusion group and control. In the manuscript the authors describe that an absolute increase in EF of 6% compared to baseline will be considered significant. Is this the change in EF in bone marrow group? What is the expected change in EF in control group and what is the expected difference in change? If 6% is the difference in change between groups this is very optimistic considering the current literature (including the negative study of Janssens et all. with early cell infusion (within 24

hours).

Our aim is to detect a within group increase in ejection fraction of 6%. Although it was envisaged that there would be no increase in the control group there is some literature to suggest that this is not the case. Given the novelty of trial design it is still unclear as to what changes may be expected in the control arm however PPCI data suggest that this may be as much as 2%. [Petronio, A.S., et al., Effects of abciximab on microvascular integrity and left ventricular functional recovery in patients with acute infarction treated by primary coronary angioplasty. European Heart Journal, 2003. 24(1): p. 67-76]
Using this information we will perform a post hoc analysis to compare the two groups, which will have 80% power to detect the 4% difference. This has been added to the manuscript (page 17)

7. Summary, page 20. 'If BMDC improves outcomes following anterior AMI it would pave the way for future development of easily available and cheap treatment…. '. Why 'easily available and cheap' The suggested additional treatment is rather complex (bone marrow aspiration, cell processing, extra catheterisation etc) and to my opinion not cheap. Please comment.

We agree that this statement is ambitious and have removed it from the manuscript.

MINOR COMMENTS
1. Introduction, line 37: ....in cardiac function in pre-clinical studies'. Please include references.

We have altered the paper accordingly: Page 2 (Reference 4: Orlic, D., et al., Bone marrow cells regenerate infarcted myocardium. Nature, 2001. 410(6829): p. 701-5.)

2. Page 7, line 45-50. The results of the Repair-AMI are described. Please cite the original article (NEJM) instead of the article in Future Card as a reference.

We have altered the paper accordingly: Page 7 (Reference 22: Schachinger, V., et al., Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med, 2006. 355(12): p. 1210-21.)

3. Methods, CMR: why is T2 imaging for assessing oedema also performed at 3 and 12 months?

T2 imaging is performed to assess myocardial oedema, in some acute studies myocardial oedema has been seen up to and including 3 months. To reduce the chance of poor image quality a standardized cardiac MRI sequence was set up to include T2 in every scan.

4. Methods: page 13, line 23: 'balloon occlusion intends to enhance adhesion and migration of the infused cells'. Is there evidence for this concept? Please include reference(s).

As with previous trials that showed positive results of cell therapy e.g. TOPCARE-AMI patients undergo the same infusion procedure to allow for adhesion and potential transmigration of the infused cells through the endothelium. We have adjusted the manuscript accordingly (page 13)

5. Figure 1: echo is performed before bone marrow aspiration, day 3, 3 months, 6 months and 1 year. However in the text (page 16, line 17-19) the echo at 3 months is not mentioned.

The figure has been adjusted to reflect the text

7. Figure 1: During primary PCI LV angio is performed. However the patient is not included in the study at this time moment and has not given informed consent yet. Is this routine practice in every

patient treated with primary PCI at the participating centres?

Yes, it is routine practice at the participating centres for patients with anterior infarction to have PPCI and LV angiogram.

8. Reference 25 is not cited correctly (no volume, page). Please correct.

We have altered the paper accordingly: Page 23 (Reference: Hirsch, A., et al., Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. Eur Heart J, 2011. 32(14): p. 1736-47.)

9. Table 1: what is 'significant' regional WMA on LV angio? How is this defined?

Significant is defined as an anterior regional wall motion abnormality in comparison to a normal LV ventricular gram

10. Table 2: why is previous MI not an exclusion criteria? How are regional WMA abnormalities outside the area involved in the index MI defined?

We accept that this statement is confusing and at variance. We have adjusted the text to reflect the fact that the wall motion abnormality needs to correspond to the angioplasty culprit (page 24).