GLP-1 Infusions in the setting of Acute Myocardial Infarction Improve Myocardial Function and Reduce Morbidity and Mortality

Gavin J. Bush
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Abstract

Background: Type II diabetes mellitus (DM II) and coronary artery disease (CAD) are widely understood to be intimately intertwined disease processes. Today, coronary artery disease is the leading cause of morbidity and mortality worldwide, and the prevalence of diabetes is reaching epidemic proportions. New therapies for the management type II DM utilizing incretin mimetics including Glucagon like peptide (GLP-1) receptor agonists are revolutionizing the current management of DM II. The purpose of this study was to attempt to elucidate whether GLP-1 infusions improve cardiac markers in setting of acute myocardial infarction (AMI) in humans.

Methods: An exhaustive search of Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the keywords: GLP-1, exenatide, liraglutide, myocardial infarction, myocardial ischemia, cardioprotection, angioplasty, percutaneous coronary intervention (PCI), ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI). All bibliographies were screened for relevant articles. All relevant articles were assessed for quality using GRADE.

Results: Three studies met inclusion criteria and included in this systematic review. A randomized, double-blinded, placebo-controlled trial of 172 ST-elevation myocardial infarction (STEMI) patients revealed a 15% larger myocardial salvage index and a 23% smaller final infarct size in the treatment group. A post-hoc analysis of this data investigating system delay demonstrated no difference between groups with delay >132 minutes. The final study was a non-randomized pilot study of 21 AMI patients demonstrated improved left ventricular ejection fraction (LVEF) in the GLP-1–treated group.

Conclusion: Longer duration GLP-1 infusions have been shown to improve LVEF in AMI, a finding that is more pronounced in patients with clinically severe disease or patients under cardiovascular stress. GLP-1 infusions also increase myocardial salvage and decrease final infarct size. The data is suggestive that GLP-1 infusions have a more profound effect on larger infarcts. There is an upper limit to the timing of GLP-1 administration, which appears to be Finally, GLP-1 infusions also appear to decrease morbidity and mortality themselves, as evidenced by the reduction of in-hospital mortality and length of hospital stay in AMI patients undergoing PCI.

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First Advisor
Mark Pedemonte, MD

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Clinical Graduate Project Submitted to the Faculty
School of Physician Assistant Studies
Pacific University
Hillsboro, OR

For the Degree MPAS

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Abstract

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Conclusion: Longer duration GLP-1 infusions have been shown to improve LVEF in AMI, a finding that is more pronounced in patients with clinically severe disease or patients under cardiovascular stress. GLP-1 infusions also increase myocardial salvage and decrease final infarct size. The data is suggestive that GLP-1 infusions have a more profound effect on larger infarcts. There is an upper limit to the timing of GLP-1 administration, which appears to be <132 minutes. Finally, GLP-1 infusions also appear to decrease morbidity and mortality themselves, as evidenced by the reduction of in-hospital mortality and length of hospital stay in AMI patients undergoing PCI.

Keywords: GLP-1, exenatide, liraglutide, myocardial infarction, myocardial ischemia, cardioprotection, angioplasty, PCI, STEMI, NSTEMI
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<td>Acute Myocardial Infarction</td>
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<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<td>DM II</td>
<td>Diabetes Mellitus Type II</td>
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<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>GLP-1</td>
<td>Glucagon-Like-Peptide-1</td>
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<tr>
<td>rGLP-1</td>
<td>Recombinant Glucagon-like-Peptide-1</td>
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<tr>
<td>DPP-4</td>
<td>Dipeptidyl Peptidase-4</td>
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<tr>
<td>ACCORD</td>
<td>Action to Control Cardiovascular Risk in Diabetes</td>
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<tr>
<td>VADT</td>
<td>Veterans Affairs Diabetes Trial</td>
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<tr>
<td>FDA</td>
<td>Federal Drug Administration</td>
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<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<tr>
<td>cAMP</td>
<td>Cyclic Adenosine Phosphate</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>bid</td>
<td>twice daily</td>
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<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
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<td>STEMI</td>
<td>ST Elevation Myocardial Infarction</td>
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<tr>
<td>NSTEMI</td>
<td>Non ST Elevation Myocardial Infarction</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
</tr>
<tr>
<td>HD</td>
<td>Hemodialysis</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>DKA</td>
<td>Diabetic Ketoacidosis</td>
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<tr>
<td>CPR</td>
<td>Cardiopulmonary Resuscitation</td>
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<tr>
<td>WMSI</td>
<td>Wall Motion Score Index</td>
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<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>AAR</td>
<td>Area At Risk</td>
</tr>
<tr>
<td>CMR</td>
<td>Cardiac Magnetic Resonance imaging</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicyclic Acid (aspirin)</td>
</tr>
<tr>
<td>po</td>
<td>by mouth</td>
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<tr>
<td>LAD</td>
<td>Left Anterior Descending Artery</td>
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<tr>
<td>HgbA1c</td>
<td>Hemoglobin A1c</td>
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<tr>
<td>LVEDV</td>
<td>Left Ventricular End Diastolic Volume</td>
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<tr>
<td>LVESV</td>
<td>Left Ventricular End Systolic Volume</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke Volume</td>
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<tr>
<td>MACE</td>
<td>Major Adverse Cardiac Events</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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GLP-1 Infusions in the setting of Acute Myocardial Infarction Improve Myocardial Function and Reduce Morbidity and Mortality

BACKGROUND

Type II diabetes (DM II) and coronary artery disease (CAD) are widely understood to be intimately intertwined disease processes. Today, CAD is the leading cause of morbidity and mortality worldwide, and the prevalence of diabetes is reaching epidemic proportions. The community-based Framingham Heart Study\(^1\) reports the incidence of DM II has doubled over the last 30 years, and the worldwide prevalence of diabetes is projected to increase from 135 million in 1995 to 300 million in 2025.\(^2\) A retrospective study by Hu et al,\(^3\) found that female patients who were diagnosed with DM II over the course of a 20-year study were 3.71 times more likely to suffer an adverse cardiac event, and those women who already carried the diagnosis prior to entering the study were 5 times more likely to have an adverse cardiac event. Norhammar et al,\(^4\) investigated the glucose metabolism in patients with acute myocardial infarction (AMI) and found that of those patients who suffer an AMI without a current diagnosis of DM II, 31% will be discharged with the diagnosis of DM II, and 35% will be discharged with impaired glucose tolerance. This indicates that 2/3 of patients who suffer an AMI have some aberration of their glucose metabolism. Additionally, those patients with hyperglycemia have increased mortality post-myocardial infarction (MI). Bolk et al,\(^5\) found that the 1-year mortality rate following AMI is 22% in patients with glucose levels $>$200mg/dL upon admission, and just 6% for patients with a blood glucose level of $<$101mg/dL. These studies\(^1-5\) all point to a strong and very clinically relevant relationship
between CAD and diabetes, and the need to improve management and reduce risk of adverse cardiac events.

New therapies for the management DM II utilizing incretin mimetics including glucagon-like-peptide-1 (GLP-1) receptor agonists (liraglutide and exenatide) and dipeptidyl-peptidase-4 (DPP-4) inhibitors (the ‘gliptins) are revolutionizing the current management of DM II and have shown great promise of cardioprotective effects. GLP-1 is a gut-derived hormone that is secreted in response to oral ingestion of glucose. Endogenous GLP-1 has a half-life of 1-2 minutes before being broken down quickly by the enzyme DPP-4. In contrast, GLP-1 receptor agonists are resistant to degradation by DPP-4 and therefore have a much longer half-life providing a much larger therapeutic window. GLP-1 and GLP-1 receptor agonists inhibit glucagon release and have an insulinotropic and insulinomimetic effects that are dependent on plasma glucose levels, thus GLP-1 receptor agonists control plasma glucose levels with minimal risk of inducing hypoglycemia. This is important to note because multiple studies have shown hyperglycemia to be an independent risk factor associated with poor outcomes in the setting of AMI.6,7 While, paradoxically the large sample ACCORD8 and VADT9 studies reported that hypoglycemia additionally increases the risk of cardiovascular events.

Taken together, these characteristics suggest GLP-1 receptor agonists are ideal for the pharmacological management of DM II by helping to maintain euglycemia and consequently reducing cardiovascular risk. In addition to a very favorable glycemic profile, GLP-1 receptor agonists have also been found to have multiple extra-glycemic effects including: promotion beta cell proliferation and prevention beta cell apoptosis, slowing gastric emptying, increasing satiety centrally, promoting weight loss, improving
endothelial function, decreasing systolic BP, and improving lipid profile. Many of these effects portend an additional reduction in cardiovascular morbidity and mortality. Best et al\textsuperscript{10} concluded in retrospective epidemiological study of 21 754 DM II patients that patients treated with the GLP-1 receptor agonist exenatide twice daily were 19\% less likely to have a cardiovascular event than 361 771 DM II patients treated with other glucose lowering agents.

In addition to cardiovascular risk reduction, GLP-1 and GLP-1 receptor agonists have shown direct cardioprotective effects in the reduction of final infarct size and protection from oxidative stress and reperfusion injury in AMI animal models.\textsuperscript{11,12} Bose et al\textsuperscript{11} was able to reproduce these cardioprotective effects in both in-vivo and in-vitro studies of GLP-1. In both arms of the study GLP-1 was shown to reduce the final infarct size in rat hearts. The in-vivo model, showed a 20\% reduction in the final infarct size compared to the control group. The in-vitro study was suggestive that GLP-1 has a direct cardioprotective effect that is independent of improved glycemic control via insulin, as the study was performed in the absence of circulating insulin. Additionally, Bose et al\textsuperscript{11} may have provided the potential anti-apoptotic cellular pathway of GLP-1 via cAMP and G-protein activation of the PI3k enzyme to abolish the effects of BAD peptide. BAD is the cardiac myocytes pro-apoptotic member of the Bcl-2 family.

In study conducted in the porcine model, Timmers et al\textsuperscript{12} reported a 40\% reduction in final infarct size following 75 minute total occlusion of the Left circumflex artery in pigs treated with exenatide versus placebo. The authors also noted that the left ventricular ejection fraction (LVEF) was significantly higher in the exenatide group as well.\textsuperscript{12}
As previously discussed, GLP-1 receptor agonists are being utilized with increasing frequency to improve the management of DM II, and a new role of cardioprotection for GLP-1 receptor agonists has shown great promise in animal models of AMI. The purpose of this review was to attempt to elucidate whether GLP-1/GLP-1 receptor agonist infusions improve cardiac markers in setting of AMI in the human model.

METHODS

An exhaustive search was conducted using Medline-OVID, CINAHL, EBMR Multifile, Web of Science, and NIH clinical trials website using the keywords: GLP-1, incretins, exenatide, liraglutide, myocardial infarction, myocardial ischemia, myocardial stunning, reperfusion injury, diabetes, cardioprotection, angioplasty, percutaneous coronary intervention (PCI), ST-elevation myocardial infarction (STEMI), Non-ST-elevation myocardial infarction (NSTEMI), and troponin. All bibliographies of papers obtained through this search were screened for additional relevant articles. The inclusion criteria was comprised of studies investigating the cardioprotective effects of GLP-1 in diabetic and non-diabetic patients undergoing cardiac revascularization in the setting of AMI using cardiac markers such as LVEF, myocardial salvage index, infarct size, and wall motion. Excluded were animal studies, studies whose primary endpoints were other than those outlined above, studies conducted on elective procedures, studies utilizing other cardioprotective measures (including ischemic post-conditioning, cyclosporine A, and remote conditioning). All relevant articles were assessed for quality using GRADE.13
RESULTS

The initial result of the search yielded 13 articles for review from this search 2 articles met inclusion criteria. Subsequent searches using combinations of the key terms outlined previously yielded 3 more articles that met inclusion criteria. Another article was found through review of pertinent bibliographies. This resulted in a total of 6 relevant randomized controlled trials. A more detailed screening of these articles revealed only 3 met criteria of GLP-1 receptor agonists in the setting of AMI (see Table 1). Lastly, a search of the NIH clinical trials website revealed there are 3 current or on-going clinical trials involving GLP-1 receptor agonist and cardiac markers.

Nikolaidis, et al

This paper described the results of a small (n=21), single center, non-randomized, pilot study\(^1\) designed to evaluate the safety and clinical efficacy of recombinant GLP-1 (7-36) amide (rGLP-1) in high-risk patients with an AMI and physical exam evidence of left ventricle (LV) dysfunction. This study investigated whether a continuous 72-hour infusion of rGLP-1 improved ventricular function in the early post-myocardial infarction period in patients with Killip class II-IV after successful reperfusion. The Killip classification is a system used for risk stratification in AMI using physical exam signs of left ventricular dysfunction or heart failure (see Table 2). Patients were excluded from the study if they had coronary anatomy warranting coronary artery bypass graft (CABG), required hemodialysis (HD), had malignancy, HIV, or CNS disorders, had CPR >30 min,
had diabetic ketoacidosis (DKA), or symptomatic hypoglycemia of <60mg/dL.\textsuperscript{14}

The treatment and control groups were not strictly equivalent. The authors\textsuperscript{14} reported the rGLP-1 group tended to be younger, with fewer women, had higher peaks of CPK, and a higher prevalence of multivessel disease. However, both treatment and control groups had a mean Killip class of III, 3.0±0.1 and 3.1±0.2 respectively. Additionally, LV volumes, global and regional indexes, and blood pressures were similar between the groups. The authors\textsuperscript{14} also reported that time of symptom onset, and time to reperfusion was also comparable between groups. In terms of treatment, both groups received standard post-MI therapy after primary angioplasty, including aspirin, plavix, heparin, glycoprotein IIb/IIIa, beta-blockade, ACE inhibitor, and statin.\textsuperscript{14}

Evaluation of LV function was performed by echocardiography within 2 hours of successful angioplasty. After the baseline echocardiography, 72-hour infusion of rGLP-1 at 1.5pmol/kg/min was initiated. Plasma GLP-1 levels throughout the 72-hour infusion were 168±21pmol/L versus 62±11pmol/L, in the treatment and control groups respectively. Assessment of LV function by echocardiograph and was repeated within 6-12 hours after completion of rGLP-1 infusion. The echocardiograph reader was blinded to the treatment.\textsuperscript{14}

Global LVEF post-infusion improved from 29±2% to 39±2% (p<0.01) in the rGLP-1–treated patients. This effect was not seen in the control group as Global LVEF post-infusion did not improve substantially from 28±2% to 29±2% (no p value reported). Regional wall motion score index (WMSI) was reported to be significantly decreased by -21±2% (p<0.001) in the rGLP-1–treated group. Again, the change -4±4% reported in the control group was not significant. Global WMSI also improved -15±3%, (p<0.001) in
rGLP-1–treated patients, but not in the control group 0±3%.14

The authors14 reported that rGLP-1 infusion had no effect on left ventricular end diastolic volume (LVEDV) 91±9 mL to 90±6. However, improvement was noted left ventricular end systolic volume (LVESV) which changed from 64±7 mL to 55±5, (p<0.01), and therefore stroke volume (SV) was also improved from 26±2 mL to 35±2, (p<0.02). There was no evidence of significant change in the control group. Benefits of rGLP-1 on global and regional contractile functions were evident in both diabetic and non-diabetic patients, as well as patients with anterior and non-anterior infarcts. What’s more, follow-up echocardiograms within 120 days after the AMI were available in 4 of the rGLP-1–treated patients, all of whom demonstrated sustained benefit (LVEF, 36±3%), whereas 4 control patients showed LVEF remained at baseline (27±3%).14

In-hospital mortality rate was 10% (1 of 10) in the rGLP-1–treated group and 27% (3 of 11) in the control group. There were no cardiovascular deaths in the rGLP-1 treated group, and 2 in the control group (18%): 1 from ventricular fibrillation and 1 from cardiogenic shock. Hospital length of stay was additionally significantly reduced in the rGLP-1 treated group compared with control subjects 6.1±1.3 versus 9.8±1.5 days, (p=0.02).14

Taken together, the authors14 concluded that the results show that the GLP-1 treated group showed significant improvement of global LVEF, as well as regional functional recovery in the “peri-infarct” zone as expressed by decreased ventricular wall motion in the 72-hour post-operative period. Additionally, there was a trend toward decreased in-hospital mortality and decrease length of hospital stay.14

Lonborg et al “Parent study”
This paper described the results of a randomized, double-blinded, placebo-controlled study performed at Copenhagen University Hospital in Rigshospitalet, Denmark and Aarhus University Hospital in Skejby, Denmark. This research investigated the cardioprotective effects of intravenous (IV) exenatide administered prior to reperfusion and continued after restoration of coronary blood flow in STEMI patients undergoing PCI. 172 patients met inclusion criteria and were eligible for the intention-to-treat analysis. Patients were then randomized to either placebo or exenatide groups using a 1:1 computer generated sequence and numbered sealed envelopes with group assignment prior to angiography. Both operator and patient were blinded to the treatment before, during, and after the infusion. The placebo group received a saline infusion at the same rate as the treatment group infusion. Both treatment and placebo infusion contained human serum albumin. A 3-month cardiac magnetic resonance (CMR) was performed on 117 patients. Of the total sample, 105 patients were available for the per-protocol study analysis of the primary endpoint: 85 patients in the treatment group and 87 the placebo group. This indicates that there was 39% loss to follow up for the per-protocol analysis of the primary endpoints due to contraindication, refusal, incapability, death, reinfarction, stent thrombosis, or temporary pacemaker.

Exenatide infusion was commenced 15 minutes before the intervention and maintained for 6 hours after the procedure at 72mL/h (0.12ug/min) with a plasma goal of 30-300 pmol/L. Mean plasma concentration of exenatide was 177±69 pmol/L. CMR was utilized to assess the myocardial area at risk (AAR) and final infarct size. The primary endpoint of this study was the myocardial salvage index measured by CMR after 3 months. Secondary endpoints included final infarct size as assessed after 3 months, final
infarct size ratio (final infarct size (g)/AAR(g)), peak plasma level of troponin, LVEF by CMR at 3 months, and 30 day clinical events.

Patients eligible for PCI were treated with ASA 300mg po (or 500mg IV), clopidogrel 600mg po, and 10,000u heparin IV. After randomization, angiography was performed to identify the location of the lesion. Direct stenting, thrombolectomy, and choice of stent were left to the discretion of the operator. Ischemic post conditioning, defined as 30 sec cycles of interruption of myocardial reperfusion with re-occlusion of vessel was not allowed. Balloon angioplasty alone was limited to cases in which stent could not be deployed or was considered harmful.15

The authors15 reported a significantly larger myocardial salvage index of 15% and a 23% smaller final infarct size ratio in the exenatide group (p=0.003). The AAR was not statistically different between treatment groups and peak troponin T levels were comparable between groups (6.4±4.9; 6.5±5.4ug/L). The authors15 reported the treatment effect was more pronounced with infarcts occurring in the distribution of the left anterior descending artery (LAD): 19% salvage index and 30% infarct size/AAR ratio. Finally, the authors15 reported no difference between groups at 90 days LVEF by CMR.15

Lonborg et al “Post-hoc analysis”

This paper described the results of a post-hoc analysis16 of the above “parent study” that investigated system delay defined as time of first medical contact to balloon treatment on the effect of infarct size and myocardial salvage index in the setting of AMI for the exenatide group compared to the saline infusion group. This four-arm analysis allocated patients into exenatide or saline infusion groups, and divided the population by system delay of greater than or less than 132 minutes. In this study, 132 minutes was
defined by the authors\textsuperscript{16} as the median system delay for the patients. The inclusion and exclusion criteria differed from the “parent” study only in that patients with multivessel disease were not excluded from this study. There was significant loss to follow up consistent with the Lonborg et al “parent” study.\textsuperscript{15} However, inclusion of patients with multivessel disease yielded slightly different percentages of loss to follow up, 27\% versus 30\% in treatment and control groups respectively due to the same reasons as outlined in the “parent” study.\textsuperscript{16}

The authors\textsuperscript{16} concluded in this post-hoc analysis that exenatide treatment decreased final infarct size 30\% and increased myocardial salvage index 14\% in STEMI patients with short system delay (<132 minutes). These findings were consistent with the previous study. Of interest, however, no effect of exenatide was observed in patients with long system delays (>132) minutes, and the authors\textsuperscript{16} concluded that this likely indicated an upper limit of ischemia duration for the cardioprotective effect of exenatide in AMI. Importantly, the inclusion or exclusion of patients with multivessel disease in a multi-variable analysis did not affect the overall results.\textsuperscript{16}

**DISCUSSION**

This review reveals a growing body of data supporting that GLP-1 or GLP-1 receptor agonists have cardioprotective effects in the setting of AMI. These cardiac effects include improved LVEF, decreased infarct sizes, and increased myocardial salvage index. However, as of today, the cardioprotective capabilities of GLP-1 receptor agonists in the human model have not shown the same magnitude of outcomes as animal
models, and have yet to impact clinical practice in the management and treatment of AMI patients.

**Final Infarct Size, Myocardial Salvage Index, and Wall Motion**

One mechanism that may explain the cardioprotective effects of GLP-1 receptor agonists in AMI is the stimulation of glucose metabolism over fatty acid metabolism, which is a more efficient utilization of oxygen for ATP production in the ischemic myocardium. The shift from fatty acid metabolism to glucose metabolism by the cardiac myocytes is consistent with the insulinotropic effect of GLP-1 and the subsequent rise in plasma insulin following the administration of GLP-1 in both human and animal models. Additionally, GLP-1 appears to have an anti-apoptotic effect independent of insulin on cardiac myocytes via cellular signaling and reduces the oxidative stress following reperfusion. Lonborg et al was able to show that infusion of exenatide in the setting of AMI increases myocardial salvage and decreases final infarct size. Interestingly, this effect was more pronounced with occlusions that occurred in the LAD. This is important to note because Stone et al found that patients with anterior infarcts (i.e. infarcts involving the LAD) had a disproportionate reduction in LVEF when compared to inferior infarcts. As a result, these patients had a higher incidence of heart failure, larger infarction sizes, and higher cardiac mortality over a 30-month period. Combining the data from these two studies leads to speculation that an anterior MI involving the LAD is statistically more severe and therefore GLP-1 has a more profound effect on infarct size and cardiac myocyte salvage. If this speculation is correct it would indicate a greater treatment effect in patients with more clinically significant disease.
Distracting from the possibility of a greater treatment effect of GLP-1 infusions with larger infarcts is the post-hoc analysis by Lonborg et al.\textsuperscript{16} This data is suggests a temporal upper limit to the efficacy of GLP-1 infusions in setting of AMI. Lonborg et al\textsuperscript{16} reported an abolishment of benefit from GLP-1 infusions when time of first medical contact to reperfusion exceeds 132 minutes. The loss of cardioprotection in the extended system delay group is consistent with the findings of Gersh et al\textsuperscript{22} in that there is a “striking benefit” to interventions that occur in the first 2-3 hours after onset of ischemic symptoms. Therefore, it seems likely that the loss of cardioprotective benefit in the extended delay group is related more to the duration of time from symptom onset to definitive treatment, and less to do with the efficacy of the GLP-1 infusion itself. Both of these studies\textsuperscript{16,22} add to the large body of literature noting AMI patients with longer ischemic times will likely have larger infarction areas, which results in fewer viable cardiac myocytes for salvage by reperfusion, thus patients will have increased morbidity and mortality post-MI. The absolute upper time limit of GLP-1 infusion has yet to be defined, but according to the Lonborg et al\textsuperscript{16} data appears to be less than 132 minutes.

Another cardiac marker used to assess ventricular dysfunction in post-MI patients is ventricular wall motion. Nikolaidis et al\textsuperscript{14} reported that the regional wall motion score index (WMSI) over the area of ischemia was significantly decreased in the GLP-1 treated group, whereas no change was noted in the control group. This finding was replicated by Read et al\textsuperscript{19} in patients during dobutamine stress tests performed prior to elective PCI or CABG. Read et al\textsuperscript{19} reported that following a 30-minute GLP-1 infusion, patients demonstrated improved regional wall function, and the area of greatest benefit was seen in the region of the ischemic ventricular wall. Additionally, Nikolaidis et al\textsuperscript{14} reported
Global WMSI was also improved in GLP-1 treated patients, an effect that again was not observed the control group. Although Nikolaidis et al\textsuperscript{14} did not directly measure final infarct size or salvage index, one can postulate that decreased ventricular wall motion post-MI correlates with smaller infarct sizes and thus greater cardiac myocyte salvage, especially considering that the area of greatest benefit was observed in the distribution of the ischemic myocardium.

**Left Ventricular Ejection Fraction (LVEF)**

In the setting of AMI, GLP-1 infusions have been shown to improve LVEF in rat, porcine, and dog models,\textsuperscript{11, 12, 23} research in the human model has been less conclusive. Improvement in LVEF with GLP-1 infusion was noted in the Nikolaidis et al\textsuperscript{14} study. This study\textsuperscript{14} was able to show significant improvement of LVEF in Killip class II-IV patients, whereas no improvement was seen in the control group. Additionally, at 120 days follow-up echocardiography exhibited sustained LVEF benefit in the treatment group.\textsuperscript{14} The Lonborg et al “parent” study\textsuperscript{15} was unable to show any benefit in LVEF in the treatment group at 90 days by CMR; however, the patient populations are not comparable between these studies.\textsuperscript{14, 15} The Nikolaidis et al\textsuperscript{14} patients had a baseline mean LVEF of 29%, while the Lonborg et al\textsuperscript{15} patients LVEF was assessed only at 90 days and were clinically normal with a mean of 55%. Considering this, evaluation of LVEF at 90 days in post-MI patients with normal LVEF is not likely to exhibit a statistically significant improvement between treatment and control groups. Additionally, LVEF was a secondary endpoint of the Lonborg et al\textsuperscript{15} study, and the study was not powered to evaluate LVEF. In a study that was powered to evaluate LVEF, Read et al\textsuperscript{19} reported GLP-1 infusion improved myocardial function by increasing LVEF during peak stress
and that effect was still evident 30 minutes into recovery. Interestingly, all patients in the Read et al study had clinically normal ejection fractions at rest. Based on these data sets, GLP-1 appears to have a more pronounced effect on LVEF in patients with clinically significant ejection fractions, or if LVEF is assessed while patients are under cardiovascular stress.

**CMR versus Echocardiography**

Echocardiography and CMR are the two most common and noninvasive modalities in use today to assess cardiac function. Although similar clinical endpoints are measured (i.e. LVEF and ventricular wall motion) there are some discrepancies between the two modalities. In a moderately large prospective study comparing CMR versus echocardiography of post-MI patients in which patients served as their own control, Gardner et al reported that when compared to CMR, echocardiography underestimates left ventricular end diastolic volume (LVEDV) by an average of 69 ml, left ventricular end systolic volume (LVESV) by 35 ml, and stroke volume (SV) by 34 ml. Global LVEF correlated moderately well across the 2 modalities. However, echocardiography underestimated LVEF compared to CMR by 4% (CMR 51%, Echo 47%). Additionally, echocardiography underestimated wall motion scores (WMS) compared to CMR. In this study wall motion was completely normal in 32% of patients assessed by echo, compared to only 4% assessed by CMR, suggesting that CMR is more sensitive in distinguishing diseased from normal subjects. Another study reported an intra-observer variability in LVEF by echocardiography of 6% and an inter-observer variability of 7%, which creates an additional potential for inaccuracy. Applying these to the Nikolaidis et al and Lonborg et al data, suggests that the LVEF findings of the Nikolaidis et al
data may be more robust than originally reported, while improved wall motion is potentially over-reported. Conversely, the Lonborg et al\textsuperscript{15} findings by CMR are likely very accurate due to the reproducibility and accuracy of CMR.

**Infusion Times and Plasma Concentration**

The optimal duration of infusion and plasma concentration of GLP-1 infusions has yet to quantified and with studies reporting conflicting data in regards to specific outcomes such as LVEF further research will be necessary. In this review, GLP-1 infusion times were vastly different between the Nikolaidis et al\textsuperscript{14} and Lonborg et al studies\textsuperscript{15,16} (72 hours versus 6 hours respectively). These discrepancies of infusion duration may additionally help account for the lack of LVEF improvement at 90 days seen by Lonborg et al.\textsuperscript{15} A similar discrepancy of GLP-1 dose, duration, and conflicting findings regarding LVEF occurred in the setting of heart failure. Sokos et al\textsuperscript{25} was able to demonstrate improvement in LVEF in patients with New York Heart Association class II/IV heart failure after a 5-week infusion of GLP-1. Conversely, Halbirk et al,\textsuperscript{26} reported that a 48-hour infusion in non-diabetic patients with New York Heart Association class II/III heart failure had no effect on LVEF. What remains unclear at this time is whether there is a duration of GLP-1 infusion associated with sustained improvement in LVEF, and the Halbirk et al\textsuperscript{26} and Lonborg et al\textsuperscript{15,16} studies failed to achieve this threshold.

Plasma concentrations were comparable between studies during infusion, Nikolaidis et al\textsuperscript{14} 168\textpm21 pmol/L and Lonborg et al\textsuperscript{15,16} 177\textpm69 pmol/L. If one looks at clinically dosed GLP-1 receptor agonists in DM II, Byetta (exenatide) IR 10ug dosed twice daily achieves a mean plasma concentration of 50.4 pmol/L\textdagger with each dose,\textsuperscript{27} and Bydureon (exenatide) ER 2mg dosed once weekly achieves a similar mean plasma
concentration of 55.4 pmol/L,† but Bydureon achieves steady state plasma levels after just 2 weeks instead of 6 weeks as seen with Byetta.27,28 The minimum effective plasma concentration of exenatide is known to be 11.94 pmol/L† to effectively reduce fasting plasma glucose.28 However, minimum plasma concentration that still provides cardioprotection has yet to be explored. If the exenatide minimum effective plasma concentration for cardioprotection is near 50pmol/L, then exenatide and perhaps other GLP-1 receptor agonists could have great additional indications for use in the DM II population that carries a substantial elevated risk of adverse cardiac events. Again, the animal model has shown promise in this area. As an adjunct to intraoperative infusion of exenatide, pigs dosed with the standard human dose of exenatide IR 10ug twice daily for 2 days following reperfusion exhibited a reduction in final infarct size and increased LVEF.12 Therefore, further studies are needed to quantify both the minimum effective cardioprotective plasma concentration, as well as the duration of infusion that will provide maximum benefit for AMI patients.

**In-Hospital Mortality and Hospital Length of Stay**

The reduction of in-hospital mortality and length of hospital stay is of importance for patients and healthcare systems alike in any setting. The ability to reduce morbidity and mortality of AMI patients is the primary goal of intervention in this population. In a broader context, decreasing hospital length of stay additionally decreases the risk of nosocomial infection and other hospital-associated comorbid conditions, as well as the ever pertinent reduction of overall healthcare costs. Nikolaidis et al14 reported a trend toward decreased of in-hospital mortality in the treatment group (10% versus a 27% in the control group). In a study29 investigating the predictive value of the Killip
classification in AMI patients undergoing PCI, DeGeare et al\textsuperscript{29} reported in-hospital mortality rates of 7\% and 19\% for Killip class II and Killip class III, respectively.\textsuperscript{29} This data is of interest because the patients in the Nikolaidis et al\textsuperscript{14} study were on average Killip class III patients and underwent the same procedure as the DeGeare et al\textsuperscript{29} patients. The Nikolaidis et al\textsuperscript{14} study reported a higher mortality of control patients than similar patients in the Degeare et al\textsuperscript{29} study, which may reflect that the Nikolaidis et al\textsuperscript{14} study included some Killip class IV patients, and had a significantly smaller sample size. However, mortality rates were significantly lower amongst comparable groups when treated with a GLP-1 infusion. Therefore, application of the findings of DeGeare et al\textsuperscript{29} to the trend reported by Nikolaidis et al\textsuperscript{14} is very suggestive of a significant reduction of in-hospital mortality with the use of GLP-1 infusions in the treatment of AMI by PCI.

Similarly, Nikolaidis et al\textsuperscript{14} reported a decreased length of hospital stay in the treatment group compared to the control group (6.1 days versus 9.8 days respectively). This data is again comparable to the DeGeare et al\textsuperscript{29} data, which reported mean a hospital length of stay of 8.2 days in Killip class II patients and 10.8 days for Killip class III. The similarity of length of stay between the control group and the DeGeare et al\textsuperscript{29} patients lends credence to the 3 day reduction of hospital stay observed in the treatment group of Nikolaidis et al\textsuperscript{14} study. Taken together, the results of these studies\textsuperscript{14,29} suggest that GLP-1 infusion in the setting of AMI appears to have great potential for the reduction of morbidity and mortality, as well as reducing the duration of hospital stay.
LIMITATIONS OF STUDIES

The Nikolaidis et al study\textsuperscript{14} is limited most severely by design and sample size. The study was a non-randomized pilot study, but pretest analysis reveals that treatment and placebo groups were very similar, which decreases the risk of selection bias. The trial additionally would have been strengthened if it were placebo-controlled and double-blinded. Instead, only echocardiogram readers were blinded. The extremely small sample size (n=21) additionally leads to many issues especially with precision.\textsuperscript{14}

The Lonborg et al “parent study”\textsuperscript{15} is significantly limited by the loss to follow up of 39\% in the per-protocol analysis. There were 31 (36\%) patients lost to follow up treatment group and 36 (41\%) patients in control group. Additionally, the opening of numbered envelopes may have created a potential for selection bias, as the authors were aware of which infusion the patients would receive immediately following informed consent, but there is no discussion as to how the operators and patients remained blinded to the treatment. Finally, there also is no mention of visual characteristics of treatment infusion versus placebo infusion other than the rates of the infusions were the same, and both infusions contained human serum albumin, which leads to potential issues with concealment\textsuperscript{15}

The Lonborg et al post hoc analysis\textsuperscript{16} was inherently limited by significant loss to follow up in the per protocol analysis. However, inclusion of patients with multivessel disease yielded slightly lower percentages of loss to follow up, 27\% versus 30\% in both the treatment and control groups respectively.\textsuperscript{16} Additionally, there is significant potential for selection bias in that the exact system delay cut-off time unknown, however the authors\textsuperscript{16} use of a median minimizes the risk of selection bias when a population is
broken into subgroups.16

RECOMMENDATIONS

More research needs to be conducted on GLP-1 infusions in the setting of AMI. Currently underway are two large FDA mandated trials:30 LEADER31 and EXSCEL.32 Unfortunately, these two trials31,32 are not expected to report data until 2016 or later. The LEADER trial31 is a multi-national, multi-centered, randomized, double-blinded, placebo controlled study of 9341 patients with DM II. The LEADER trial31 is examining the effect of liraglutide 1.8mg on the primary outcomes of cardiovascular death, non-fatal MI, and non-fatal stroke over five years. The EXSCEL trial32 is a randomized, double-blinded, placebo controlled study whose primary outcome is the first confirmed cardiac event of 9500 patients with DM II over 5.5 years. Additionally underway is the EXAMI trial,33 a multicenter, prospective, randomized, placebo controlled trial underway investigating a 72-hour exenatide infusion following AMI and PCI. This study33 will use both MRI and echocardiography to assess regional cardiac function. These three studies will hopefully provide answers to many of the questions raised by previous investigations into the cardioprotective effects of GLP-1 receptor agonists.

CONCLUSION

The studies14-16 reviewed in this paper provide very clinically relevant and encouraging results for a future role of GLP-1/GLP-1 receptor agonists in patients suffering an AMI. Longer duration GLP-1 infusions have been shown to improve LVEF, a finding that was more pronounced in patients with clinically severe disease,14 or in
patients under cardiovascular stress.\textsuperscript{18} Infusions of exenatide in the setting of AMI increases myocardial salvage and decreases final infarct size with more profound findings involving infarcts over the distribution of the LAD.\textsuperscript{15} Anterior MIs involving the LAD have been shown to be clinically more severe,\textsuperscript{21} which gives rise to the potential that GLP-1 infusions have a more profound effect on larger infarcts since there are likely more cardiac myocytes available for salvage. However, there does appear to be an absolute upper limit to the timing of GLP-1 administration, and at this time, this limit is less than 132 minutes from the time of first medical contact.\textsuperscript{16} This finding is consistent with current understanding that the shorter the delay in treatment of AMI yields a greater reduction in morbidity and mortality.\textsuperscript{22} GLP-1 infusions also appear to decrease morbidity and mortality in AMI patients themselves, as evidenced by the reduction of in-hospital mortality and length of hospital stay.\textsuperscript{14} At this time, GLP-1 infusions remain as a potential therapy for cardioprotection and reduction of morbidity and mortality in setting of AMI. We await the results of the ongoing LEADER, EXSCEL, and EXAMI studies with great anticipation for the potential implications on future clinical practice in the management of DM II and AMI.
# TABLE 1

**Characteristics of Studies and Findings**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Infusion Time and Plasma Conc.</th>
<th>Ratio Final Infarct Size (AAR/Infarct Size)</th>
<th>Regional Wall Motion</th>
<th>Myocardial Salvage Index</th>
<th>LVEF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nikolaidis et al</td>
<td>Non-Randomized Pilot Study</td>
<td>72 hour post-op infusion rGLP-1 @1.5pmol/kg/min.</td>
<td>N/A</td>
<td>Decreased -21+-2% (P&lt;0.001)</td>
<td>N/A</td>
<td>GLP-1: (29+-2% to 39+-2%) Control: (28+-2% to 29+-2%) (P&lt;0.01) Post infusion: GLP-1: (36+-3%) Control: (27+-3%) at 120 days.</td>
</tr>
<tr>
<td>Lonborg et al “Parent”</td>
<td>RCT</td>
<td>15 min pre-op and 6 hours post-op @ 72mL/h 0.12ug/kg/min for 15min, then .043ug/kg/min for 6 hours.</td>
<td>Decreased 23%</td>
<td></td>
<td></td>
<td>GLP-1: (55+-9%) Control: (58+-8%) (P=0.13) At 90 days</td>
</tr>
<tr>
<td>Lonborg et al “system delay”</td>
<td>Post hoc Analysis</td>
<td>15 min pre-op and 6 hours post-op @ 72mL/h 0.12ug/kg/min for 15min, then .043ug/kg/min for 6 hours.</td>
<td>&lt;132 min: Decreased 30% &gt;132 min: No Difference</td>
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<td></td>
<td>GLP-1: (53+-6%) Control: (55+-7%) (P=0.41) at 90 days</td>
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</table>
Table 2

1. Killip Classification of Acute Myocardial infarction\textsuperscript{34}

<table>
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<th>Class</th>
<th>Description</th>
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<tr>
<td>Class I</td>
<td>No evidence of heart failure</td>
</tr>
<tr>
<td>Class II</td>
<td>Physical exam findings consistent with mild to moderate heart failure (S3 gallop, Lung rales half way up posterior lung fields, or jugular venous distension)</td>
</tr>
<tr>
<td>Class III</td>
<td>Overt pulmonary edema</td>
</tr>
<tr>
<td>Class IV</td>
<td>Cardiogenic shock</td>
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</table>

\textsuperscript{†} Exenatide plasma concentrations were calculated by the author using molecular weight of extendin-4 (exenatide) = 4186.61.\textsuperscript{35,36}
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34. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit:


Table 3 GRADE Quality Assessment

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
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<tr>
<td></td>
<td>No. of Studies</td>
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<tr>
<td>Myocardial Salvage Index</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>LVEF%</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Final infarct size/Area At Risk (AAR) &amp; Regional wall motion</td>
<td>3</td>
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<tr>
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</table>

*a No Randomization and single center sample in the Nikolaidis et al 12 study creates significant potential for selection bias, however, pretest analysis revealed similarity between groups. Additionally, echocardiogram readers were blinded to reduce risk of detection bias. There was also significant loss to follow up in the Nikolaidis et al study 15 and the Lonborg et al studies 16.*

*b Wide confidence intervals and small sample sizes.

Lonborg studies were funded by Novo Nordisk Foundation, which markets the Victoza (liraglutide) another GLP-1 agonist and competitor to Byetta (exenatide)