Is Liraglutide Associated With Myocardial Protection in ST-Elevation Myocardial Infarction?

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The most effective treatment for ST-elevation myocardial infarction (MI) is primary percutaneous coronary intervention to achieve early coronary reperfusion. Antithrombotic therapy, statins, angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), and β-blockers have all been shown to favorably modify early and late outcomes after ST-elevation MI and are incorporated into routine practice. During prolonged ischemia, lactic acidosis and elevated ATP disrupt key transport mechanisms, leading to intracellular calcium overload, autophagy and apoptosis. Primary percutaneous coronary intervention restores coronary reperfusion but is also paradoxically associated with reperfusion injury with the generation of oxygen free radicals and proinflammatory neutrophil infiltrates that can exacerbate apoptosis and cell death. Myocardial protection is a concept in which the potential adverse effects of reperfusion injury can be attenuated. The main strategy has been to favorably modify target pathways either through specific agents or by general measures such as remote preconditioning in which cells are exposed to moderate levels of ischemia and enhance their protective pathways. In spite of clear biological plausibility and favorable experimental results for numerous putative pathways and therapies, there is no routine specific treatment for myocardial protection after reperfusion for ST-elevation MI.

See Article by WR Chen et al

Renewed interest in myocardial protection from reperfusion injury has come from the glucagon-like peptides 1 (GLP-1) that are gut incretin hormones that stimulate insulin secretion and activate antiapoptotic signaling pathways such as phosphoinositide 3-kinase and mitogen-activated protein kinase in pancreatic and insulinoma cells. GLP-1 analogues improve glycemic control and reduce weight with a low risk of hypoglycemia and are indicated for the management of type 2 diabetes mellitus. Interest in GLP-1 analogues has been heightened by the publication of the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), a randomized comparison of liraglutide with placebo in 9340 higher risk patients with type 2 diabetes mellitus treated for 4 years, showing significant reductions in all-cause mortality and cardiovascular complications with good tolerability. These findings are likely to increase the use of liraglutide for type 2 diabetes mellitus. In the context of myocardial protection from reperfusion injury, GLP-1 may act by increasing intracellular cAMP levels and activating protein kinase-A. Pretreatment with similarly acting agents such as the dipeptidyl peptidase-4 inhibitor sitagliptin has been shown to reduce infarct size in experimental models presumably via the GLP-1 protein kinase-A pathway, and this may represent a glucose-sensitive cardioprotection mechanism.

In this issue of Circulation: Cardiovascular Imaging, WR Chen et al evaluate myocardial protection properties of the GLP-1 analogue liraglutide after primary percutaneous coronary intervention for ST-elevation MI. They randomized 96 patients with ST-elevation MI to subcutaneous liraglutide or placebo starting 30 minutes before primary percutaneous coronary intervention and continuing for 7 days. Myocardial salvage index, estimated from myocardial area at risk during the index admission and final infarct size at 3 months using cardiac magnetic resonance, was 0.66±0.14 in the liraglutide group versus 0.55±0.15 in placebo (P=0.001). Final infarct size, troponin levels at 5 days, and high-sensitivity C-reactive protein levels were also lower in the liraglutide group, and there were favorable effects on nitric oxide levels and left ventricular ejection fraction over time. Adverse events possibly related to liraglutide, including hypoglycemia and gastrointestinal disturbance, were low with no differences between groups, and blood glucose levels showed similar moderate declines in both groups during the first few days. The overall study design, conduct, and outcome measures of this study seem appropriate, and favorable data from troponin, high-sensitivity C-reactive protein, and nitric oxide help to support the hypothesis that liraglutide could reduce the impact of reperfusion injury in ST-elevation MI. The group has also published other reports of liraglutide in acute MI.

In the current report, 22 of the 96 patients randomized did not contribute to the cardiac magnetic resonance data. This dropout rate may introduce a potential selection bias that could skew the study findings. The findings of this study contrast with those of a similar study evaluating a different GLP-1 analogue, exenatide, with no apparent difference in final infarct size. The study with exenatide randomized 191 patients of whom just 91 completed the cardiac magnetic resonance, protocol and issues of selection bias adversely influencing results in this case are possible. In addition, duration of treatment was shorter with exenatide at 72 hours compared with 7 days for liraglutide in this study by WR Chen et al.

The exact mechanism of potential benefit of liraglutide in acute MI is unknown, but there is plausible support for the...
myocardial protection hypothesis based on available information. The findings of the current report by WR Chen et al\textsuperscript{11} need to put in context of the important benefits of liraglutide on clinical outcomes in the large randomized LEADER trial in high-risk type 2 diabetes mellitus.\textsuperscript{7} These studies, along with excellent tolerability data, provide a firm basis for further investigations of liraglutide in ST-elevation MI to evaluate effects on clinical outcomes.

**Disclosures**

None.

**References**


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