Positive impact of sitagliptin on cardiac function and survival after acute myocardial infarction
L. Krieg¹, H.D. Theiss¹, G. Assmann², J. Mueller-Hoecker², W.-M. Franz¹

Abstract

**Background:**
This study analyzes the effects of sitagliptin +/- G-CSF treatment on survival and myocardial regeneration after myocardial infarction in a mouse model. The SDF-1-CXCR4 axis is a key mechanism of cardiac homing of stem cells. G-CSF is known to mobilize bone-marrow-derived stem cells into peripheral blood, whereas sitagliptin is a DPP-IV (dipeptidylpeptidase IV)-inhibitor. Sitagliptin therefore prevents the essential stem cell homing factor SDF-1 from being cleaved.

**Methods:**
Acute myocardial infarction was induced by surgical occlusion of the left descending artery in 10-11 weeks old male C57BL/6 mice. Sitagliptin was administered per os in a titrated dose regimen with blood levels measured by LC-M/M. DPP-IV activity was analyzed by enzyme activity assays. Saline and G-CSF were injected intraperitoneally for 6 days following myocardial infarction. The effects of the dual therapy as well as the effects of sole sitagliptin treatment on cardiac stem cell mobilization and homing was measured by flow cytometry. The impact on neovascularization and cell proliferation was analyzed by immunohistochemistry and the treatment benefits on infarct size was assessed by histology. The treatment impact on cardiac function and survival was analyzed by millar tip catheterization and the Kaplan-Maier-method.

**Results:**
Enzyme activity assays revealed a significant decrease in DPP-IV enzyme activity after sitagliptin application. Sitagliptin+G-CSF as well as sole sitagliptin therapy Enzyme activity assays revealed a significant decrease in DPP-IV enzyme activity after sitagliptin application. Sitagliptin+G-CSF as well as sole sitagliptin therapy enhanced both mobilisation and cardiac homing of BMCs. Cell proliferation (Ki67+) and neovascularization were increased in both treatment groups, resident cardiac stem cells were stimulated and cardiac remodelling was significantly decreased. Dual therapy consisting of sitagliptin and G-CSF as well as sole sitagliptin application significantly reduced infarct size, had a positive impact on myocardial function and improved survival compared to sole G-CSF or saline application. The beneficial effects seen were most remarkable for the dual therapy group, but also significant for sole sitagliptin administration. Additional application of the CXCR4-antagonist AMD3100 reversed the beneficial treatment effects of both treatment regimens back to baseline. This suggests specificity of the treatment effects to the CXCR4-axis.

**Conclusions:**
This is the first study showing that combined application of G-CSF and Sitagliptin and yet sole sitagliptin administration increases cardiac homing of stem cells, induces neovascularization, reduces cardiac remodelling, enhances cell proliferation, has a positive impact on cardiac function and improves survival after acute myocardial infarction. Combined administration of sitagliptin and G-CSF and even sole sitagliptin application has beneficial effects on cardiac regeneration beyond its known anti-diabetic potential and may be a new therapeutic regimen after myocardial infarction.