

# Glucose-lowering interventions and risk assessment in patients with coronary heart disease and disturbed glucose metabolism

AKADEMISK AVHANDLING

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# ABSTRACT

## Background

Abnormal glucose regulation (AGR) including impaired glucose tolerance (IGT) and diabetes mellitus type 2 (T2DM) are common in patients with stable and unstable coronary artery disease (CAD) and impair their prognosis. Available glucose lowering interventions have not fully succeeded in improving the detrimental prognosis and accurate screening methods and new treatment strategies are needed.

The aims of this thesis were to

1. decrease the restenosis rate after percutaneous coronary intervention (PCI) in patients with T2DM
2. validate the oral glucose tolerance test (OGTT) for the detection of glucose disturbances in patients with acute coronary syndromes (ACS)
3. evaluate the accuracy of a technique for continuous glucose monitoring in patients in the coronary care unit (CCU)
4. improve beta-cell function in patients with ACS and newly detected AGR

## Restenosis in patients with T2DM (Study I)

The restenosis rate six months after PCI was investigated in 93 patients with T2DM randomised to either intensive glucose control by means of insulin (I group; n=44) or to continue ongoing glucose-lowering treatment (C group; n=49). At the end of the follow-up period restenosis rate was available in 82 patients. The glucose control did not differ between the two groups (change in HbA1c -0.2 vs. -0.1%;  $p=0.3$  and in fasting blood glucose +0.2 vs. -0.3 mmol/L;  $p=0.3$  in the I and C groups). The restenosis rate was 41% in the I and 44% in the C group ( $p=0.8$ ). Independent predictors for restenosis were previous myocardial infarction (OR 8.0, 95% CI 2.5–25.7;  $p<0.001$ ) and fasting blood glucose at baseline (OR 1.4, 95% CI 1.1–1.9;  $p=0.015$ ).

## Screening for glucose abnormalities in ACS (Studies II and III)

The value of an OGTT for screening of unknown AGR in patients with ACS was explored. Infarct size did not influence the result but patients with transmural myocardial infarctions (MI) (n=70) had higher glucose levels at admission and fasting during the next two days (7.0, 5.7, 5.4 mmol/L) compared to those with subendocardial MI (n=102; 6.0, 5.3, 5.0 mmol/L;  $p<0.001$ ,  $p=0.01$ ,  $p=0.004$ ; **Study II**). More patients were classified as T2DM according to OGTT (n=27) compared to fasting plasma glucose (n=10) and HbA1c (n=2; **Study III**).

## Continuous glucose monitoring in the coronary care unit (Study IV)

The accuracy of an intravenously inserted microdialysis catheter intended for continuous glucose monitoring was validated in 14 patients in a CCU setting. Although predominantly delivering correct values, the stability over time was insufficient. Thus the microdialysis technique requires further improvements to be useful in this setting.

## Beta-cell function in ACS (Study V)

The effect of a DPP-IV inhibitor on beta-cell function, expressed as insulinogenic index (IGI) and acute insulin response to glucose (AIRg), in patients with ACS and newly discovered AGR was investigated by randomising 34 such patients to sitagliptin (S) and 37 to placebo (P). After 12 weeks of treatment the IGI improved in the sitagliptin group (S: 69.9 to 85.0 vs. P: 66.4 to 58.1 pmol/mmol;  $p=0.019$ ) as did the AIRg (S:1394 to 1909 vs. P:1106 to 1043 pmol • l-1 • min-1;  $p<0.0001$ ). Insulin resistance remained unaffected.

## Conclusion

It is difficult to achieve glucose normalisation in patients with T2DM and CAD by means of available drugs. Early detection of AGR in patients with ACS is essential and an OGTT is a useful tool. New technology in the form of equipment for continuous glucose monitoring and novel treatment strategies e.g. DPP-IV inhibitors deserves further attention in attempts to improve the management and thereby prognosis in this vulnerable patient category.