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Clinical implications of glycometabolic disturbances in acute coronary

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Summary and Conclusions

Prevalence of glycometabolic disturbances in patients with a suspected acute coronary syndrome is high (**Chapter 2**). One in three patients has signs of disturbed glucose metabolism and this condition is associated with previous or newly diagnosed coronary artery disease.

In **Chapter 3.1**, we found that the prognostic impact of admission hyperglycaemia in 522 patients with a suspected acute coronary syndrome was greater than long-term glucose dysregulation. Patients with higher admission glucose (7.8 - 11.0 or ≥ 11.1 mmol/L) had significantly higher mortality (9% and 21%) as compared to patients with normal glucose levels (6%). Mortality in patients with elevated Hba1C ($\geq 6.2\%$) was not significantly higher (8% vs. 12%). Probably, apart from a sign of glycometabolic dysregulation, admission hyperglycaemia is also a symptom of stress and a more sick patient population. In **Chapter 3.2** the prognostic importance of admission glucose in 356 non-diabetic patients with ST-elevation myocardial infarction (STEMI) was described. Patients with elevated admission glucose (7.8 - 11.0 or ≥ 11.1 mmol/L) had a larger enzymatic infarct size, a lower left ventricular ejection fraction and a higher long-term mortality. In patients with diabetes (**Chapter 3.3**), long-term mortality after STEMI was significantly higher when compared to patients without diabetes, despite the use of reperfusion therapy. The increased mortality in patients with diabetes after STEMI was mainly due to heart failure, whereas the occurrence of sudden death was comparable between patients with and without diabetes. Although there was only a small number of diabetic patients in this study, primary percutaneous coronary intervention (PCI) seemed preferable to thrombolysis. In **Chapter 3.4** the prognosis of patients with diabetes with non-STEMI was assessed. After non-STEMI, patients with diabetes (n=1677) had a higher mortality compared to patients without diabetes (n=6123): one-year mortality was 13.5% in patients with diabetes compared to 6.9% in those without diabetes. Further risk stratification in diabetic patients is possible according to the presence of clinical risk-indicators, ST-depression on admission and the measurement of biomarkers such as troponin, Nt-proBNP and interleukin-6. In **Chapter 4.1** it was demonstrated that STEMI patients (n=460) with admission hyperglycaemia measured before reperfusion therapy, more often had impaired epicardial flow of the infarct related artery compared to patients with normoglycaemia. Antegrade epicardial flow before reperfusion was present in 28% of the patients with normoglycaemia compared to 12% of patients with hyperglycaemia. Furthermore, when epicardial reperfusion had been achieved through primary PCI, myocardial flow was disturbed in patients with diabetes (**Chapter 4.2**). Good myocardial blush (90% vs. 80%) and complete ST-segment resolution (65% vs. 45%) as signs of

restored myocardial perfusion were more often observed in patients without diabetes (n=322) compared to patients with diabetes (n=64). **Chapter 4.3** showed that both elevated erythrocyte sedimentation rate (ESR) and admission glucose were independent predictors of long-term mortality in STEMI patients treated with reperfusion therapy. There was, however, no association or interaction between glucose levels and the inflammatory response as reflected by ESR.

In **Chapter 5.1** results were presented of a meta-analysis of randomised trials comparing thrombolysis with primary PCI. It was shown that the beneficial effects of primary PCI compared to thrombolysis in diabetic patients with STEMI (n=947) were at least equal to the effects in patients without diabetes (n= 5368). Primary PCI resulted in a 50% reduction of 30-day mortality in patients with diabetes (6.1% vs. 11.6%) and a 30% reduction in patients without diabetes (4.9% vs. 7.0%). Although the relative risk reduction of primary PCI in diabetic and non-diabetic patients is comparable, the absolute risk reduction is much greater in diabetic patients. In **Chapter 5.2** it was made clear that intervention in glucose metabolism through administration of glucose - insulin - potassium (GIK) was associated with a small reduction in 3-year mortality (9.7% vs. 11.2%) in STEMI patients (n=940) treated with primary PCI. However, in patients without signs of heart failure on admission, the initial beneficial effect of GIK administration was sustained during long-term follow-up (5.4% vs. 9.5%). The rationale of the GIPS – II study was described in **Chapter 5.3**. The GIPS – II study aimed to confirm the beneficial effects of GIK administration in STEMI patients without heart failure treated with reperfusion therapy. In **Chapter 5.4** however, it was shown that the GIPS – II study did not confirm the beneficial effect of GIK intervention as found in the subgroup analysis of the GIPS – I. Intervention with GIK in STEMI patients (n=858) without signs of heart failure treated with reperfusion therapy, did not result in a reduced 30-day mortality (2.9% vs. 1.8%, OR 1.6; p=0.27) or a reduction in enzymatic infarct size (2008 ± 1930 vs. 1932 ± 1847 U/L, p=0.53) compared to patients not treated with GIK.

Final comments

The prevalence of diabetes has increased dramatically in the past 50 years and it is estimated that approximately one in three persons born in 2000 will develop diabetes at some point in their lifetime [1,2]. As a sharp rise in the number of diabetic patients presenting with cardiovascular disease is expected, it is of the utmost importance to improve outcome of this high-risk patient group. Moreover, one must acknowledge that glycometabolic disease in non-diabetic patients is also associated with a risk for cardiovascular disease and patients presenting with hyperglycaemia on admission should be identified as high-risk patients,

irrespective of their diabetic patients may have unrecognised specific therapeutic performed [5]. Although glucose or a glucose ACS.

To improve prognosis evidence based treatment mainly caused by including beta-blockers encouraged. Results of glucose lowering there is no clinical sulphonylureas, biguanides. Additional randomised however, should be preferred method of mortality in diabetic primary PCI in these epicardial and myocardial glycometabolic disturbances possible causes in or

Earlier studies were patients with STEMI sample sizes, whereas More recent trials, with reperfusion era, failed GIK intervention as a should not be part of explanations for the a generally administered FFA's with increased primarily effective in reperfusion. Furthermore to improved prognosis The lack of beneficial contrast with studies