Letter To Editor

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Antidiabetics and Heart Failure - Large Trials but Little Mechanistic Insight

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Glucose lowering efficacy was the basis for the approval of antihyperglycaemic drug in the past. However, increasing concerns emerged about potential cardiovascular side effects of these drugs following the metaanalysis of Nissen and Wolski published in 2007 describing a relative 43% increase in myocardial infarction with the thiazolidinedione rosiglitazone. Therefore, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are mandating cardiovascular outcome trials for all new antidiabetic drugs. As consequence more than 160 thousand subjects have been enrolled in cardiovascular outcome trials since 2008. Lowering the risk for macro vascular complications is one of the major tasks in current diabetes management. Thus, augmenting data on potential positive or negative cardiovascular side effects of antidiabetic drugs is of high value since many patients with diabetes have additional cardiovascular risk factors. Lately, beneficial effects have been proven for Liraglutide as well as Empagliflozin in these trials, whereas Saxagliptin tended to increase heart failure hospitalization. However, it has to be kept in mind that patients randomized in clinical outcome trials are commonly of increased cardiovascular risk to sufficiently power these trials whereas a relevant proportion of patients with diabetes do not have additional cardiovascular risk factors. This facilitates misinterpretations of the data, especially in those patients with lower cardiovascular risk.

The results of the latest clinical outcome trials were rather unexpected and shed a light on the limited mechanistic insight of intracellular and molecular effects of these drugs in myocardial tissue. Moreover, available bench data is mainly from animal models or cell cultures indicating a large gap towards the outcome trials already published. The term “diabetic cardiomyopathy” for fibrotic myocardium based on histological findings without coronary heart disease or arterial hypertension as underlying disease was already introduced in the early 70s. Obviously, advanced glycation end products (AGE) and increased content of crosslinking collagen underlie this phenotype. Apart of histological findings, impaired calcium homeostasis seems to play a central role including reduced levels of SERCA2a in diabetic hearts which is of importance as SERCA is not only directly affecting contractility but also regulates of glucose transport in the healthy and diabetic heart via calcium mediated GLUT4 translocation linking contractility with metabolic abnormalities. This is of major importance since robust evidence exists metabolic abnormalities underlie the impaired myocardial function in heart failure. Metabolic parameter such as ATP/PCr have been shown to predict outcome even better than echocardiography or clinical judgement and changes in myocardial metabolism do show direct and acute effects on mechanical performance and this effect seems to be of particular importance in human myocardium.

Thus, more basic research data on cell and tissue level is required to close the large gap between limited knowledge on direct or indirect myocardial effects of antidiabetic drugs and the huge data from clinical outcome trials already available. This is necessary to understand beneficial effects and to avoid patients harm and potential negative outcome of upcoming large clinical outcome trials.