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Re: Mechanisms by Which Metformin Improves Mortality and Hospital Readmission in Diabetic Patients with Heart Failure – A Short Review

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From the UKPDS it was concluded that metformin decreased cardiac events. However, this only occurred in a small group of obese subjects while in a larger group failing sulfonylurea therapy the addition of metformin resulted in an increase in cardiac events [1]. Indeed, a meta-analysis of metformin studies has shown that overall metformin does not decrease cardiac events. However, if in this meta-analysis the group utilizing metformin and sulfonylurea combinations were removed from the analysis then there was a significant decrease in cardiac events with metformin monotherapy[2]. The major decrease in cardiac events, cardiac mortality and total mortality with metformin is likely due to a decreased susceptibility to develop heart failure. From Medicare billing records of 16,417 diabetic patients with heart failure discharged from hospital on metformin were compared to those with heart failure discharged on a sulfonylurea or insulin, mortality was reduced by 13% and readmission by 8% [3].

In a retrospective case-control study of type 2 diabetic patients with heart failure enrolled in a large data base, there was a 35% reduction in mortality with the utilization of metformin which compared favorably with the proven heart failure therapies: blockers of the renin-angiotensin system and beta-blockers which reduced mortality by 45% and 24% respectively [4]. In addition, a retrospective study of diabetic patients with a low ejection fraction heart failure showed that being treated with metformin improved one year survival by 63% [5]. More recently an examination of the National Veterans Health Administration database showed a 32% decrease in heart failure admissions in those subjects utilizing metformin compared with subjects utilizing a sulfonylurea [6]. Therefore, the major cardio protection afforded by metformin is likely due to its effect on heart failure.

Why does metformin improve development of and survival from heart failure? It is likely this occurs through activation of 5-AMP-activated protein kinase (5AMPK) 5AMPK increases intracellular adenosine triphosphate (ATP) levels by increasing the generation of ATP while at the same time decreasing unnecessary ATP utilization [7]. For example, after myocardial ischemia and reperfusion 5-AMPK has been shown to increase glucose uptake, accelerate glycolysis and limit cellular apoptosis in the cardiomyocyte [7, 9].

In this way, through its "fuel-gauge" effect. 5-AMPK preserves myocardial mass and function leading to improved outcomes in diabetic patients with heart failure.

Increased myocardial ATP levels due to activation of 5-AMPK explains why metformin has been shown to reduce mortality and hospital readmissions in diabetic patients with heart failure [9]. Previously, metformin utilization was not recommended in these patients due to the perceived risk of lactic acidosis. Experience with metformin this risk has not been shown to be true [3].

In conclusion, the major cardio protection provided by metformin is due to its effect on heart failure. This protective effect is likely mediated through activation of 5AMPK. Metformin use in heart failure is not contraindicated and may favorably affect survival [9].

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