

## Metformin in Patients with Chronic Heart Failure

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### Heart Failure is a Common and Deadly Disease

Heart failure affects 1-2% of the adult population in developed countries and the lifetime risk of a heart failure diagnosis is 20% [1]. Patients with heart failure have markedly reduced life expectancy, physical capacity and

quality of life. One-year all-cause mortality rates for heart failure patients range between 7 and 17% and the yearly hospitalization rate can be as high as 44% [2]. Morbidity of these patients pose a challenge to the health system due to a high number of contacts. Health care costs are presently higher for heart failure than for any other diagnosis in the American health system [3]. Therefore, in spite of improvement in patient management, there is a definite need for new treatment modalities to improve prognosis, quality of life and health economy for this group of patients.

## Insulin Resistance and Diabetes in Patients with Heart Failure

The majority of heart failure patients display whole-body and myocardial metabolic abnormalities [4]. Type 2 diabetes (T2D) and insulin resistance is observed in more than 50% of patients [5,6] and among heart failure patients without diabetes 3%-10% develop new-onset diabetes every year [6,7]. Diabetes and insulin resistance are associated with reduced physical capacity [8] and a 50% increase in yearly mortality [5,6,9,10]. It has been hypothesized that insulin resistance and deranged glucose-, lipid- and protein-metabolism has independent causal effects and promote progression of heart failure and loss of lean body mass [4]. Thus, treatments that counteract these metabolic abnormalities could have beneficial effects [4]. However, at present no major clinical randomized trials have addressed this hypothesis.

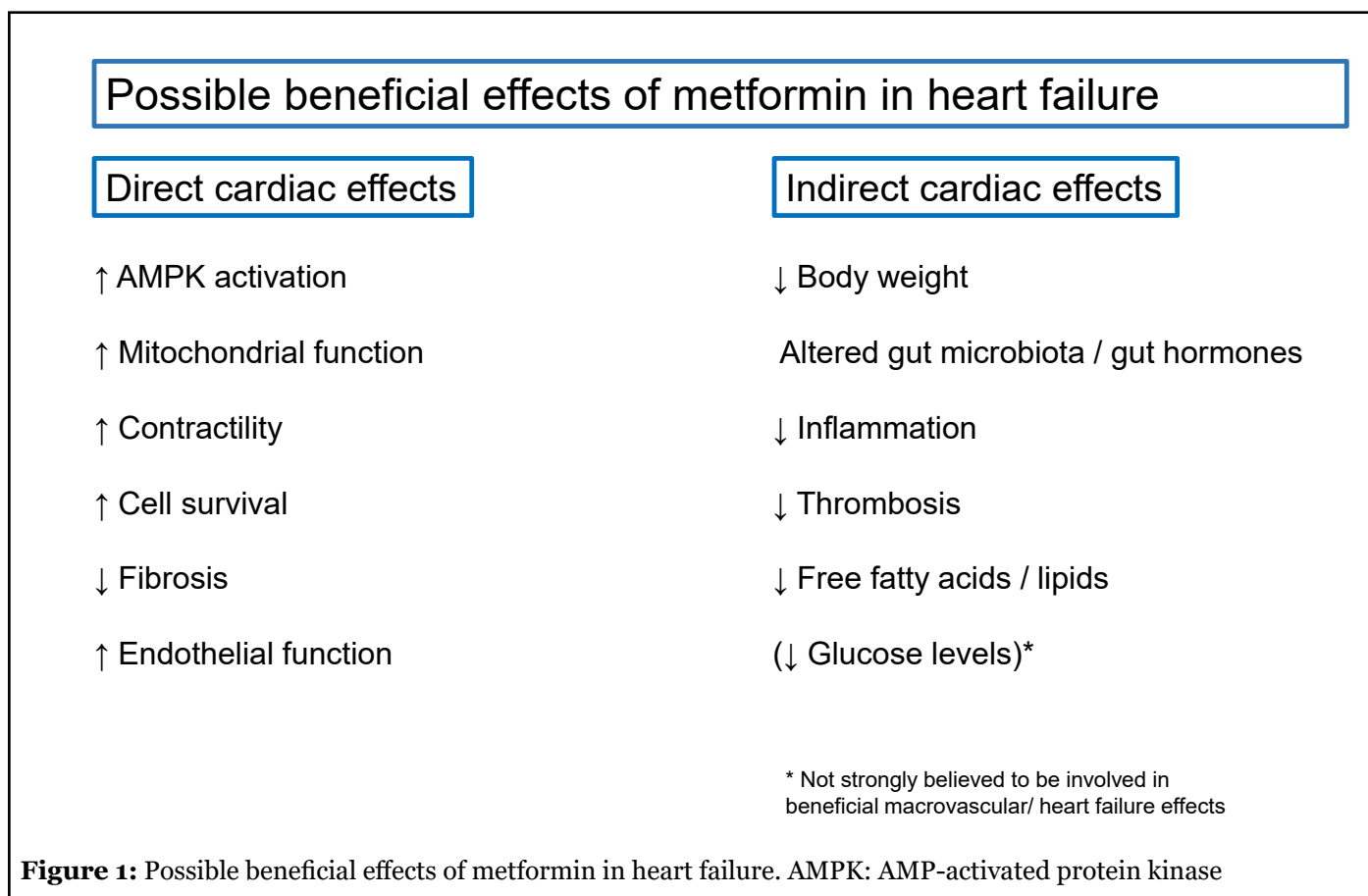
## Metformin in the Treatment of Diabetes

Metformin has been used for decades as a glucose-lowering drug. It acts through several mechanisms including reduced hepatic gluconeogenesis and increased insulin sensitivity. In the UKPDS study of patients with T2D, the drug reduced diabetes related death [11] and in patients with insulin resistance, metformin reduced the

occurrence of diabetes with 31% [12]. The ORIGIN study showed that reduction in blood glucose levels itself does not reduce cardiovascular event in the population studied [13]. Since the treatment effect of metformin in the UKPDS occurred in spite of similar blood glucose levels, the effects of metformin is believed to be mediated through pleiotropic effects beyond blood glucose control. This could involve both direct and indirect cardiac effects as summarized in Figure 1. Some of the possible direct cardiac effects include AMPK-activation, mitochondrial effects and activation of intracellular cell survival pathways. Whole body effects may also contribute to improved outcome in heart failure patients through weight loss, altered gut hormones, reduced circulating lipids and free fatty acids and suppressed inflammation responses [14-16].

## Metformin is Challenged as the Cornerstone in Glucose Lowering Treatment in Type 2 Diabetes

Metformin is used as glucose-lowering treatment in patients with T2D and is taken daily by millions of patients worldwide. As mentioned previously, the UKPDS study of patients with T2D, showed that metformin reduced diabetes-related death with 30%, acute myocardial infarction by 39%, coronary death by 50%, and stroke by 41% over a 10-year period [11]. For that reason, metformin



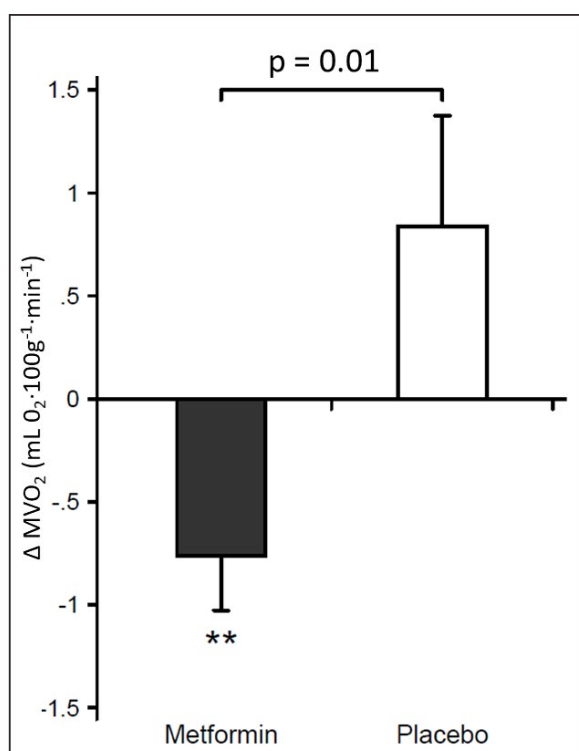
**Figure 1:** Possible beneficial effects of metformin in heart failure. AMPK: AMP-activated protein kinase

has been the recommended first-line glucose-lowering therapy in the treatment of T2D in Europe for decades and in the USA since the mid90s. However, recent guidelines have downscaled the recommendation for treatment with metformin in T2D [17]. The first reason for this is criticism of the design of the UKPDS trial [18]. It compared conventional therapy with metformin in 753 patients in a study design that was not purely double blind and randomized. Second, few patients in the UKPDS were on randomized therapy after 5 years. Third, there has been no contemporary randomized outcome trials to assess the effect of metformin on cardiovascular events. Finally, and most importantly, the recent large randomized clinical trials of sodium glucose co-transporter 2 (SGLT2)-inhibitors [19,20] and glucagon like peptide 1 (GLP1)-analogues [21] have provided strong evidence of a beneficial clinical effect of these newer drug classes in patients with T2D.

### Metformin Treatment in Patients with Heart Failure

Heart failure patients treated with metformin can develop lactate acidosis and the drug was previously not recommended in these patients. However, during the last decade registry studies reported that Metformin treatment

was associated with a 28-35% reduction in mortality [22-24] and that the risk of lactate acidosis was similar in patients treated with and without metformin [25]. For that reason, the ESC, EASD and FDA now approve the use of metformin in heart failure patients. Experimental studies have shown that metformin has pleiotropic cardiac effects beyond the effects on whole body metabolism and insulin resistance and that early treatment with the drug protects against development of heart failure [26,27]. The randomized data on metformin in heart failure patients are scarce. The lack of patent and product protection explain why no private companies will sponsor a large trial with metformin. The largest clinical randomized metformin study in chronic heart failure patients randomized only 60 insulin resistant subjects to treatment for 4 months [28] but failed to reach any firm clinical conclusion due to surrogate endpoints and a short treatment period. The only other randomized study included 36 heart failure patients with prediabetes. In that study, metformin treatment for 3 months reduced myocardial oxygen consumption by 17% as compared with placebo [29] suggesting a beneficial effect on the coupling between energy- and force-generation in the failing heart (Figure 2). This is compatible with a direct mitochondrial effect of metformin [30].



**Figure 2:** In a double-blind randomized design, 36 non-diabetic heart failure patients received either metformin 1000 mg x 2 or placebo x 2 daily for 3 months. Metformin reduced MVO<sub>2</sub> (myocardial oxygen consumption) vs. placebo without changing cardiac work. MVO<sub>2</sub> was determined by 11 C-acetate positron emission tomography (adapted from Larsen et al. [29]).

## The Metformin in Patients with Chronic Heart Failure and Diabetes or Insulin Resistance Trial (Met-HeFT)

The Met-HeFT is a part of the nationwide, randomized DANHEART trial in chronic heart failure patients at 22 heart failure clinics in Denmark. The study design has been described in more detail previously [31]. The Met-HeFT study arm of DANHEART will include 1,100 patients, who will be followed for an average of 4 years. It will be the largest randomized study to date of the efficacy and safety of metformin versus placebo in patients with prediabetes or diabetes and established heart disease. It will also be the first study in heart failure patients powered to address the effect of metformin on clinical outcomes. The main inclusion criteria in Met-HeFT is symptomatic chronic heart failure (New York Heart Association class II-IV), left ventricular ejection fraction  $\leq 40\%$  and known type 2 diabetes, insulin resistance or obesity. The target dose is metformin or placebo 1000 mg x 2 daily. In patients with reduced renal function the target dose is reduced. The primary composite endpoint includes death, hospitalization with worsening heart failure, acute myocardial infarction, and stroke. Secondary endpoints include reduction in new-onset diabetes and patient safety (lactic acidosis). Thus, the Met-HeFT study has the potential to yield new knowledge about the causality between insulin resistance, diabetes, abnormal whole body metabolism and the progression of heart failure. As of end of the year 2020, 360 patients have been included.

## Conclusion

Registry data suggest a beneficial effect of metformin in heart failure patients. The randomized data on metformin in heart failure patients are scarce although millions of patients take the drug every day. The Met-HeFT study will be the largest randomized study to date of metformin in patients with established heart disease and the first study in heart failure patients powered to address clinical outcomes.

## Conflicts of Interest

This investigator driven study is financed through support from various foundations with The Danish Heart Foundation as the main contributor. The Danish Heart Foundation has guaranteed financial support up to an amount of 3.2 million Euro (grant no. 15-R100-A6113-93104). In addition to the direct study costs, the Danish Heart Foundation finances the cost of project managing during the study which is 0.44 million Euro. The DANHEART study has also received funding from the Novo Nordisk Foundation (0.48 million euro, grants no. NNF15OC0017450 and no. NNF18OC0052509), the Danish Health Regions Research Fund (0.33 million

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## Appendix 1: The DANHEART investigators

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