Metformin in Patients with Chronic Heart Failure

Henrik Wiggers1*, Anders Hostrup Larsen1, Lars Køber2, Gunnar Gislason3, Morten Schou4, Mikael Kjær Poulsen5, Søren Vraa6, Olav Wendelbo Nielsen7, Niels Eske Bruun8, Morten Bøttcher9, Kirsten Vilain Mikkelsen10, Jens Lomholdt11, Søren Lund Kristensen2, Christian Torp-Petersen12, Hans Eiskjær13, Jacob Møller2, Bo Martin Bibby14, Christian Hassager2, Flemming Hald Steffensen15, Jens Refsgaard16, Dan Eik Hofsten2, Søren Mellemkjær13, Finn Gustafsson2, Helene Nørrelund17

1Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
2Department of Cardiology, Rigshospitalet, Copenhagen, Denmark
3The Danish Heart Foundation, Denmark
4Department of Cardiology, Herlev Hospital, Denmark
5Department of Cardiology, Odense University Hospital, Denmark
6Department of Cardiology, Aalborg University Hospital, Denmark
7Department of Cardiology, Bispebjerg Hospital, Denmark
8Department of Cardiology, Roskilde Hospital, Denmark
9Department of Cardiology, Herning Hospital, Denmark
10Department of Cardiology, Sydvestjysk Sygehus, Esbjerg, Denmark
11Department of Cardiology, Slagelse Hospital, Denmark
12Department of Cardiology, Hillerød Hospital, Denmark
13Department of Cardiology, Aarhus University Hospital, Denmark
14Department of Biostatistics, Aarhus University, Aarhus, Denmark
15Department of Cardiology, Lillebaelt Hospital, Vejle, Denmark
16Department of Cardiology, Viborg Hospital, Denmark
17Clinical Trial Unit, Aarhus University Hospital, Denmark

*Correspondence should be addressed to Henrik Wiggers; henrikwiggers@dadlnet.dk

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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

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### Possible beneficial effects of metformin in heart failure

<table>
<thead>
<tr>
<th>Direct cardiac effects</th>
<th>Indirect cardiac effects</th>
</tr>
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<tbody>
<tr>
<td>↑ AMPK activation</td>
<td>↓ Body weight</td>
</tr>
<tr>
<td>↑ Mitochondrial function</td>
<td>Altered gut microbiota / gut hormones</td>
</tr>
<tr>
<td>↑ Contractility</td>
<td>↓ Inflammation</td>
</tr>
<tr>
<td>↑ Cell survival</td>
<td>↓ Thrombosis</td>
</tr>
<tr>
<td>↓ Fibrosis</td>
<td>↓ Free fatty acids / lipids</td>
</tr>
<tr>
<td>↑ Endothelial function</td>
<td>(↓ Glucose levels)*</td>
</tr>
</tbody>
</table>

*Not strongly believed to be involved in beneficial macrovascular/heart failure effects*

**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 mid-90s. 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](image-url): 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 MVO2 (myocardial oxygen consumption) vs. placebo without changing cardiac work. MVO2 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 ≤ 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. NNFI50C0017450 and no. NNFI8OC0052509), the Danish Health Regions Research Fund (0.33 million euro, grant no. 15/1716), the Independent Research Fund Denmark (0.34 million euro, grant no. DFF 6110-00263) and Aase and Ejnar Danielsens Foundation (0.027 million euro).

Henrik Wiggers has received speaker fees from Merck and Astra Zeneca. He has been principal or sub investigator in clinical trials run by Merck, Pfizer Ltd., Bayer Healthcare AG, Astra Zeneca A/S, Sanofi Aventis, MSD Denmark, Novartis Healthcare A/S, Amgen, Merck Sharp & Dohme Ltd., Bayer A/S, Merck A/S, Novo Nordisk. He has received unrestricted research grants from Novo Nordisk.

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Appendix 1: The DANHEART investigators

Henrik Wiggers, Department of Cardiology, Aarhus University Hospital, Aarhus

Lars Køber, Department of Cardiology, Rigshospitalet, Copenhagen

Gunnar Gislason, The Danish Heart Foundation

Morten Schou, Department of Cardiology, Herlev Hospital

Mikael Kjær Poulsen, Department of Cardiology, Odense University Hospital

Søren Vraa, Department of Cardiology, Aalborg University Hospital

Olav Wendelbo Nielsen, Department of Cardiology, Bispebjerg Hospital

Niels Eske Bruun, Department of Cardiology, Roskilde Hospital

Helene Norrelund, Clinical Trial Unit, Aarhus University Hospital

Malene Hollingdal, Department of Cardiology, Viborg Hospital

Anders Barasa, Department of Cardiology, Hvidovre Hospital

Morten Bottcher, Department of Cardiology, Herning Hospital

Karen Dødt, Department of Cardiology, Horsens Hospital

Vibeke Brogaard Hansen, Department of Cardiology, Lillebaelt Hospital, Vejle Hospital

Gitte Nielsen, Department of Cardiology, Hjørring Hospital

Anne Sejr Knudsen, Department of Cardiology, Silkeborg Hospital

Jens Lomholdt, Department of Cardiology, Slagelse Hospital

Kirsten Vilain Mikkelsen, Department of Cardiology, Sydvestjysk Sygehus, Esbjerg

Bartlomiej Jonczy, Department of Cardiology, Sygehus Sonderjylland, Abenraa

Jens Brunnum-Schou, Amager Hospital

Monica Petronela Poenaru, Department of Cardiology, Lillebaelt Hospital, Kolding

Jawdat Abdullah, Department of Medicine, Cardiology section, Glostrup Hospital