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Metformin in heart failure patients

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SUMMARY

The use of metformin was considered a contraindication in heart failure patients because of the potential risk of lactic acidosis; however, more recent evidence has shown that this should no longer be the case. We reviewed the current literature and the recent guideline to correct the misconception.

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In patients with diabetes mellitus, the incidence of cardiovascular disease is increased, and the outcome following cardiovascular events is worse.

Both diabetes and heart failure have a poorer prognosis, including a 1.5–2-fold higher risk of mortality. The recommendations for the treatment of symptomatic heart failure in patients with diabetes have been largely derived from post hoc analyses or preplanned subgroup analyses in landmark clinical trials.1

Several observational and retrospective studies have shown increased mortality and worsening heart failure with the use of metformin (MET).

Traditionally, heart failure (HF) was considered a contraindication to its use. Until recently, MET was contraindicated in patients with HF because of the potential risk of lactic acidosis; however, more recent evidence has shown that this should no longer be the case.

Data from the literature have demonstrated that in this patient population, which accounts for one third of all cases of HF, MET reduces mortality by 14–35%.2

In patients with a glomerular filtration rate >30 ml/min who do not show dehydration, shock, sepsis, severe liver disease or hypoxemia, the administration of MET doses <2 g/day was associated with a null risk of lactic acidosis.3–6

The change in our understanding was built on several mechanisms that had been implicated in HF. Insulin resistance had been identified as a mechanism in the pathophysiology of chronic HF. Prospective studies, including the TAYSIDE study, were conducted to determine if reversing Insulin resistance with MET will have beneficial effects in patients with CHF.7

MET was associated with a reduced risk of CHF (HR 0.76, 95% CI 0.64–0.91) and mortality (HR 0.54, 95% CI 0.46–0.64) when compared to sulfonylurea.8

MET has demonstrated that metformin may even reduce the risk and incidence of HF and mortality in diabetic patients, while improving survival rates up to 2 years in those with HF.9 Nevertheless, MET was not associated with an improved prognosis of HF patients with a mean HbA1c = <7.0%.10,11

MET use in Rat reduced LV volumes, wall stress, perivascular fibrosis, and cardiac lipid accumulation resulting in attenuation of LV remodeling. It had also been observed that MET improved both systolic, diastolic indices, myocardial mechanical efficiency, Increases in LV systolic pressure and LV ejection fraction and decreases in LV end-diastolic diameter and LV end-systolic diameter.12 Animal studies had postulated that these beneficial effects of MET were associated with increased AMPK and eNOS phosphorylation, as well as reduction in insulin, TGF-β1, basic fibroblast growth factor and tumour necrosis factor-α levels in the circulation and/or myocardium.13 Other possible mechanism is the marked induced activation of AMP-activated protein kinase,

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endothelial nitric oxide synthase, vascular endothelial growth factor, reduced tumour necrosis factor-α expression and myocyte apoptosis.12–14

MET-induced enhancement of myocardial fatty acid oxidation had a neutral effect on cardiac function and survival. Recently reported cardioprotective effects of MET may not be universal to all forms of HF and may require AMPK (AMP-activated protein kinase) activation or ATP depletion.13

Results from 3 trials suggest that MET may be safe to use in heart failure.14 Hence the ESC 2016 HF guidelines stated that MET is safe to use in patients with HFrEF, and it should be the treatment of choice in patients with HF, but is contraindicated in patients with severe renal or hepatic impairment, because of the risk of lactic acidosis, Class IIa, level C.

Use caution in patients with congestive HF with hypoperfusion and discontinue metformin in patients with conditions associated with dehydration, sepsis, or hypoxemia.15

Similarly, ADA 2016 Standards of Care conducted A systematic review of 34,000 patients which showed that MET is as safe as other glucose-lowering treatments in patients with diabetes and congestive HF, even in those with reduced LV ejection fraction or concomitant chronic kidney disease; however, MET should be avoided in unstable or hospitalized patients, level B.16

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