Aldose Reductase Inhibition by AT-001 Prevents Diabetic Cardiomyopathy via Reducing Myocardial Fatty Acid Oxidation Rates

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Introduction
- The number 1 cause of death in patients with type 2 diabetes (T2D) is cardiovascular disease.
- This includes diabetic cardiomyopathy (DbCM), which is a cardiac dysfunction in the absence of underlying coronary artery disease and/or hypertension in diabetic individuals, and for which there are no approved therapies.1

In T2D patients, compared with control subjects, LV diastolic function and myocardial glucose uptake are shown to be decreased, whereas myocardial non-esterified fatty acid uptake and oxidation are increased.1

The expression of aldose reductase, the rate-limiting enzyme in the polyol pathway that converts glucose to sorbitol, is increased under hyperglycemic conditions.1

Studies have shown that increased aldose reductase activity can modulate myocardial glucose and fatty acid oxidation, while also promoting cardiac dysfunction.1

It has been suggested that optimizing the altered cardiac energetics observed in T2D (i.e., impaired glucose oxidation rates and elevated fatty acid oxidation rates) via aldose reductase inhibition may be a novel strategy to prevent the progression of DbCM.1

Objectives
- Our goal was to determine whether AT-01, a novel generation aldose reductase inhibitor, could mitigate experimental DbCM, and whether the potential mechanisms of benefit involve alterations in myocardial glucose and/or fatty acid oxidation rates and cardiac efficiency.

Methods & experimental design
- Cardiac mice were treated with AT-01, a novel generation aldose reductase inhibitor.
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Results
- AT-001 CORRECTS ABNORMAL ENERGY METABOLISM IN A MOUSE MODEL OF DbCM
- AT-001 PREVENTS DIASTOLIC DYSFUNCTION IN A MOUSE MODEL OF DbCM
- AT-001 PREVENTS CARDIAC HYPERTROPHY IN A MOUSE MODEL OF DbCM

Summary & conclusions
- Aldose reductase inhibition by AT001 in DbCM:
- Improves diastolic function and decreases myocardial palmitate oxidation rates.
- Improves cardiac efficiency evident by increased cardiac work normalized to TCA activity (acetyl-CoA production).
- Prevents cardiac structural and functional abnormalities in a mouse model of DbCM, and normalizes cardiac energetics by shifting cardiac metabolism towards a non-diabetic metabolic state.

Future directions
We will investigate the effect of AT001 treatments on cardiac lipotoxicity and cardiac insulin sensitivity in DbCM.

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References

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