#AHA22

UNIVERSITY OF ALBERTA

ALDOSE REDUCTASE INHIBITION BY AT-001 ALLEVIATES FIBROSIS AND ADVERSE REMODELLING IN DIABETIC CARDIOMYOPATHY BY REDUCING MYOCARDIAL FATTY ACID OXIDATION

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American Heart Association.

Disclosure

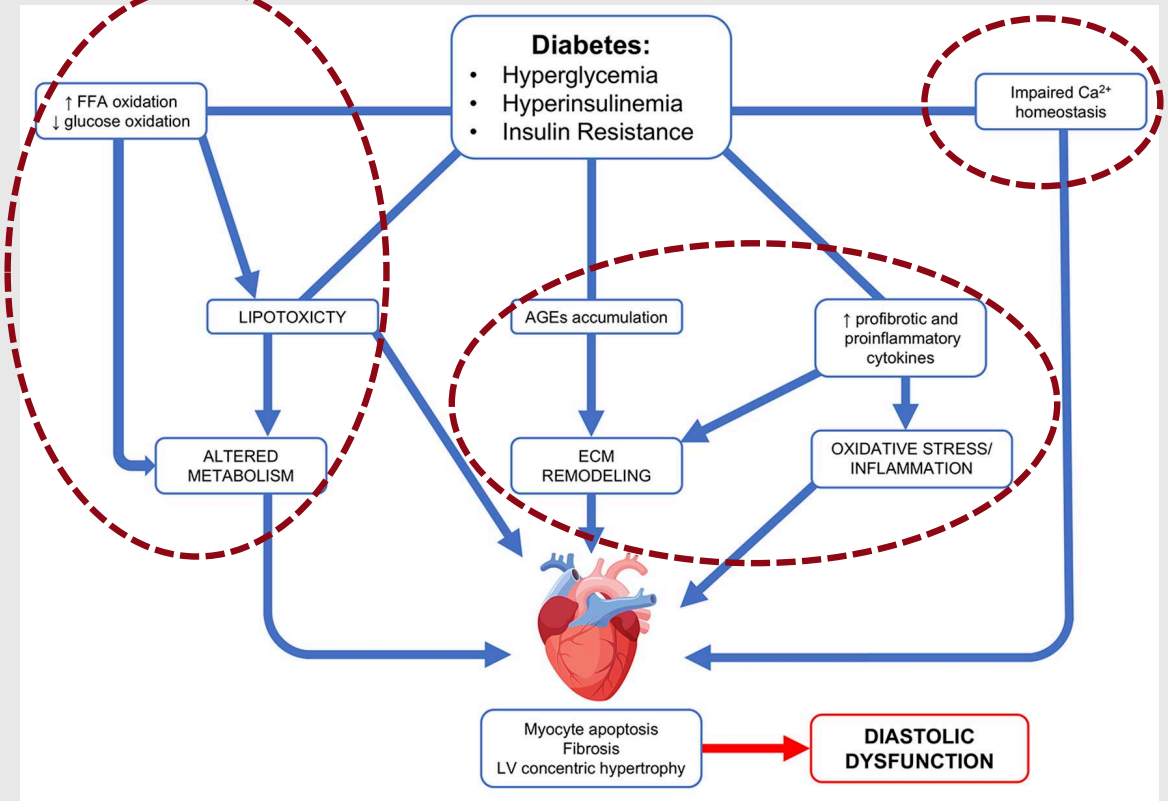
K. Gopal, Q. Karwi, S. Tabatabaei dakhili, C.S. Wagg, L. Zhang, Q. Sun, C. Saed, S. Panidarapu, J.R. Ussher, G.D. Lopaschuk: None

R. Ramasamy: Modest; Applied Therapeutics.

R. Perfetti: Significant; Applied Therapeutics, Stock Shareholder; Modest; Sanofi, Stock Shareholder.

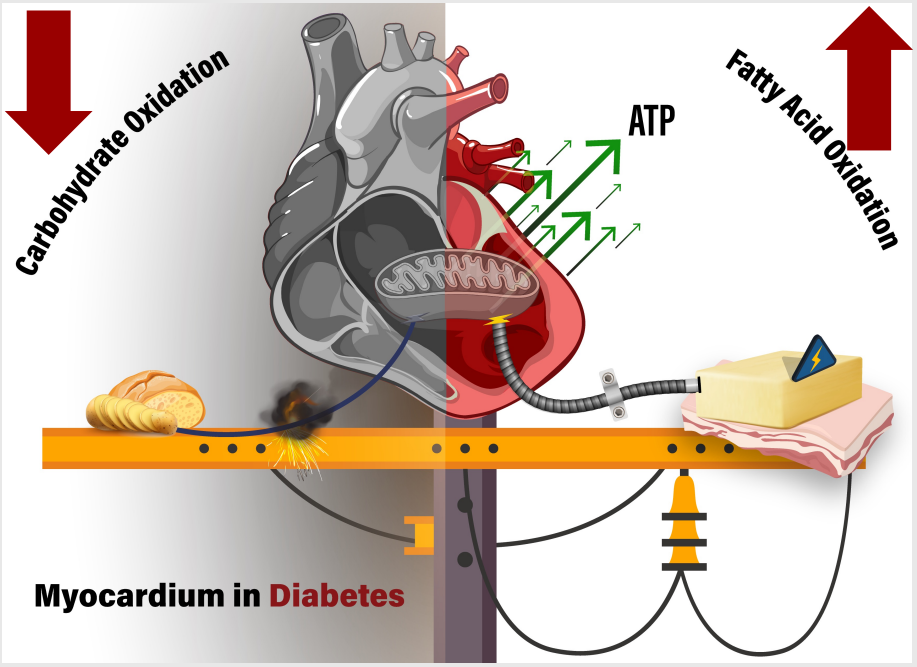
Diabetic Cardiomyopathy

- Diabetic Cardiomyopathy is a cardiac dysfunction independent of coronary heart disease and/or hypertension in patients with diabetes.
- Diastolic dysfunction is an early functional echocardiographic abnormality observed in patients with diabetes.

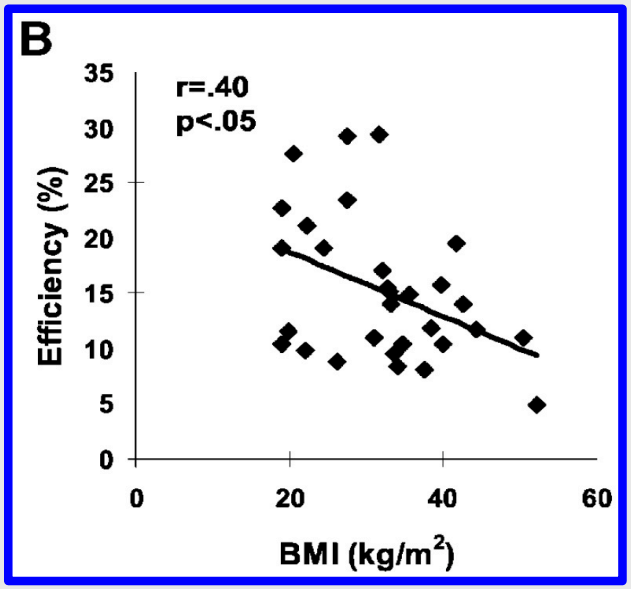


Borghetti G. *et al. Front. Physiol.*, (2018)

Perturbations in Cardiac Energy Metabolism During Type 2 Diabetes



Tabatabaei Dakhili SA *et al. Journal of Lipid and Atherosclerosis.* (2022)

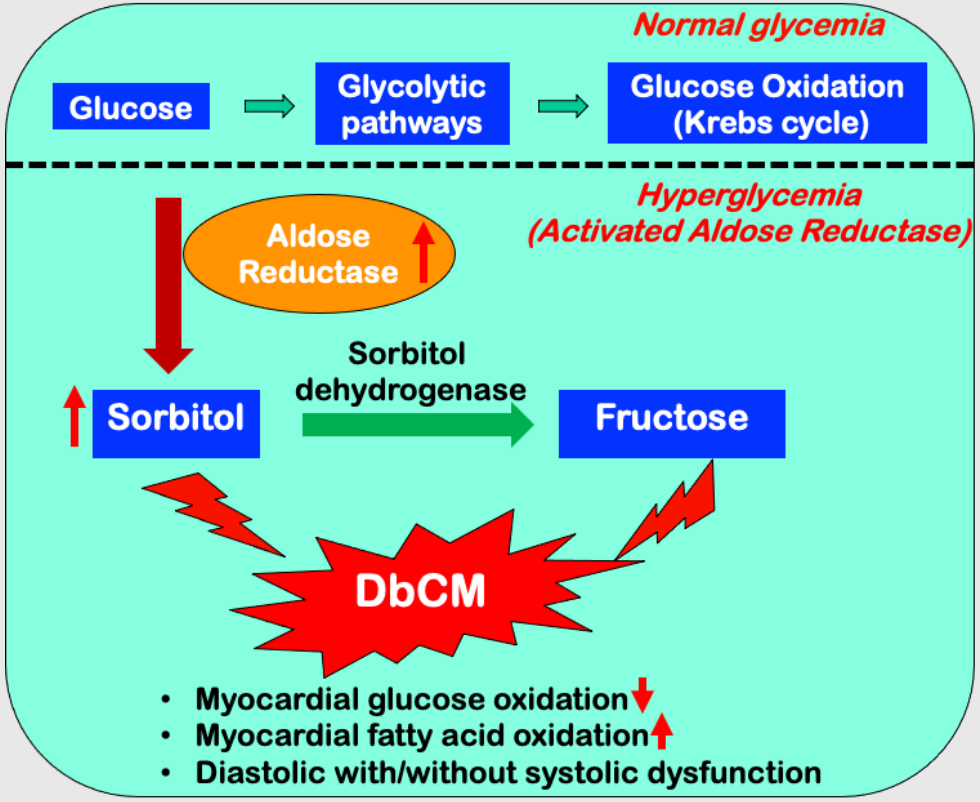


Peterson LR *et al. Circulation.* (2004)

Increased fatty acid oxidation and reduced glucose oxidation in the hearts of patients with type 2 diabetes reduce cardiac efficiency.

Hyperactivated Polyol Pathway Contributes to Pathology of Diabetic Cardiomyopathy

- Increased cardiac aldose reductase activity in type 2 diabetes plays a critical role in the pathogenesis of diabetic cardiomyopathy.
- Increased aldose reductase activity leads to altered cardiac energy metabolism and eventually to fibrosis.



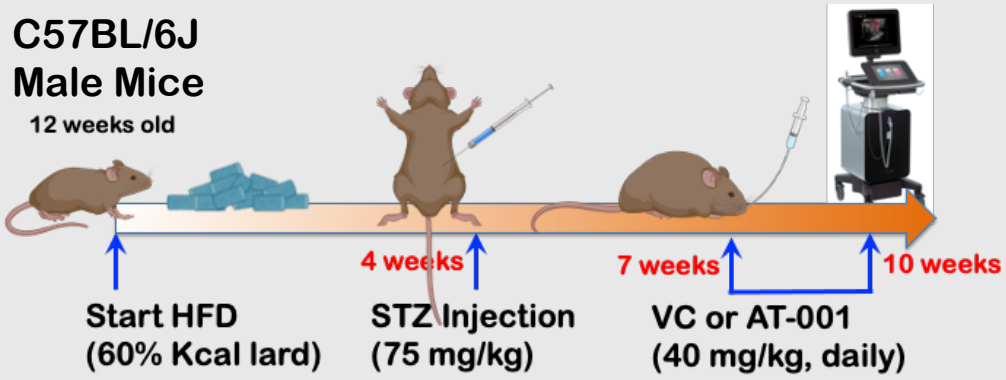
DbCM – Diabetic Cardiomyopathy

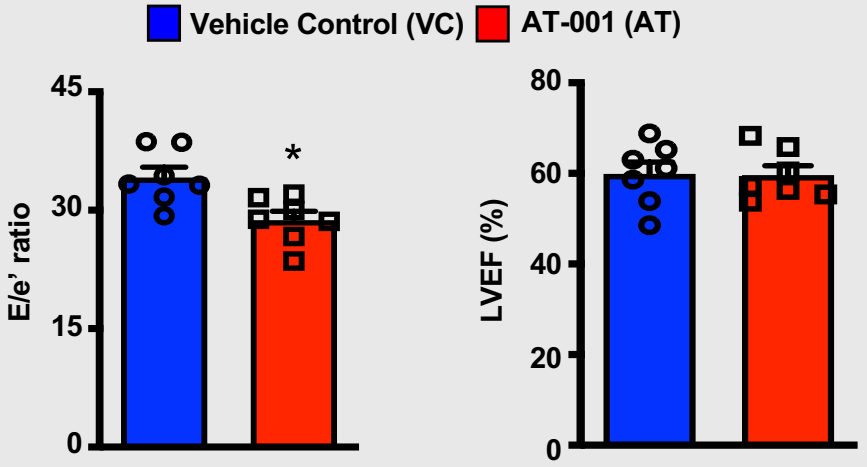
Brownlee M. *Diabetes.* (2005)

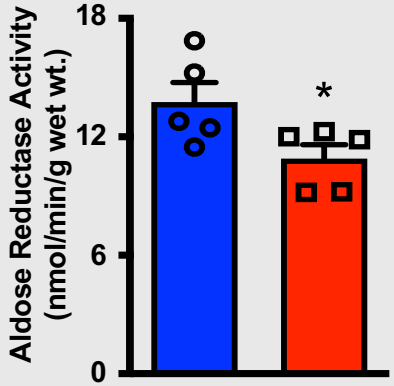
Hypothesis

Pharmacological inhibition of aldose reductase by AT-001, a potent and selective inhibitor could mitigate diabetic cardiomyopathy by correcting altered cardiac energy metabolism and adverse remodeling.

AT-001 Prevents Diastolic Dysfunction in a Mouse Model of Diabetic Cardiomyopathy



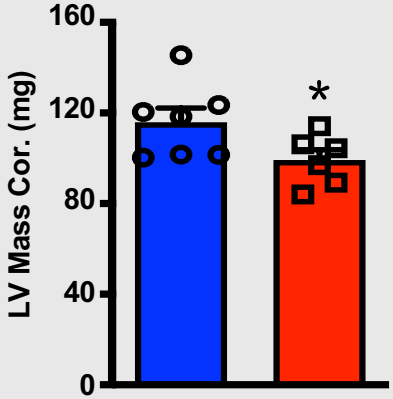




Aldose reductase activity inhibition by AT-001 ameliorates diabetic cardiomyopathy by preventing diastolic dysfunction with no adverse effect on systolic function.

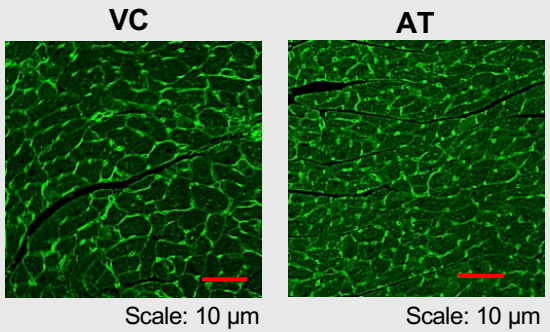
HFD – High fat diet
STZ – Streptozotocin
LVEF – Left ventricular ejection fraction

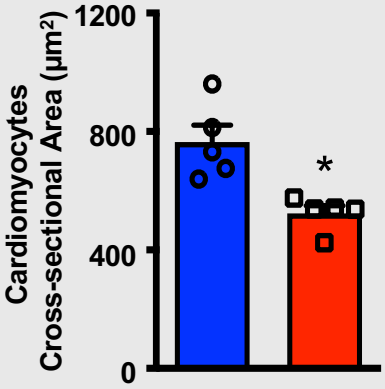
AT-001 Prevents LV Hypertrophy in a Mouse Model of Diabetic Cardiomyopathy



WGA staining of LV cross-section

Vehicle Control (VC) AT-001 (AT)





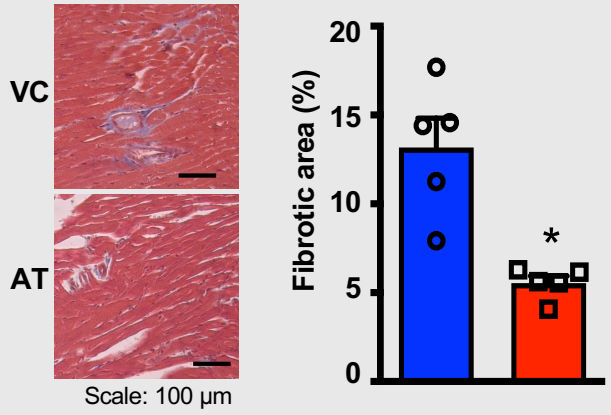
- AT-001 attenuates LV enlargement, shown by a reduction in LV Mass.
- AT-001 attenuates cardiomyocyte hypertrophy, shown by a reduction in cardiomyocytes' cross-sectional area in WGA-stained LV cross-section.

VC – Vehicle control
AT – Aldose reductase inhibitor
LV – Left ventricle
WGA: Wheat germ agglutinin

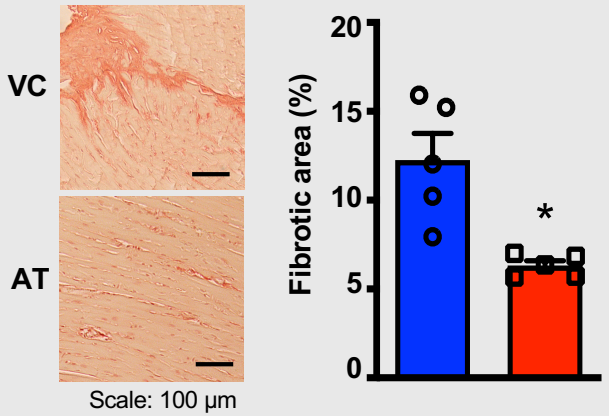
AT-001 Attenuates Cardiac Fibrosis in a Mouse Model of Diabetic Cardiomyopathy

Vehicle Control (VC) AT-001 (AT)

Masson's Trichrome staining of LV cross-section



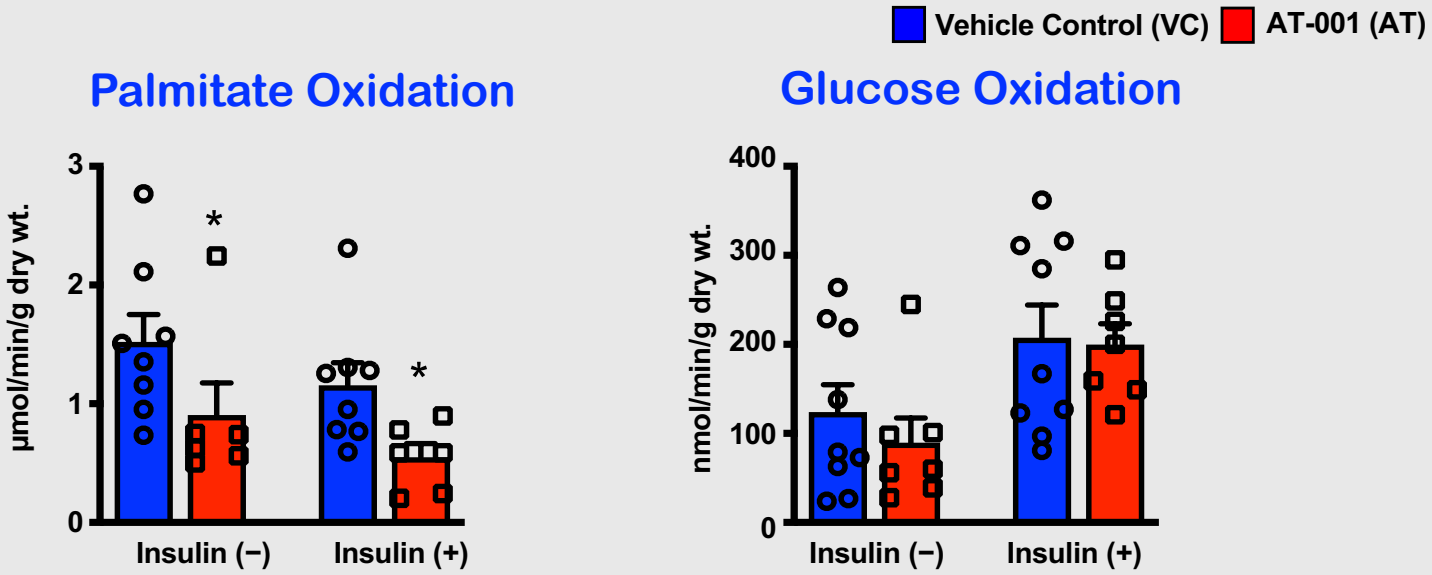
Picro-Sirius Red staining of LV cross-section



AT-001 attenuates adverse cardiac remodeling by preventing cardiac fibrosis in a mouse model of diabetic cardiomyopathy.

VC – Vehicle control
AT – Aldose reductase inhibitor
LV – Left ventricle

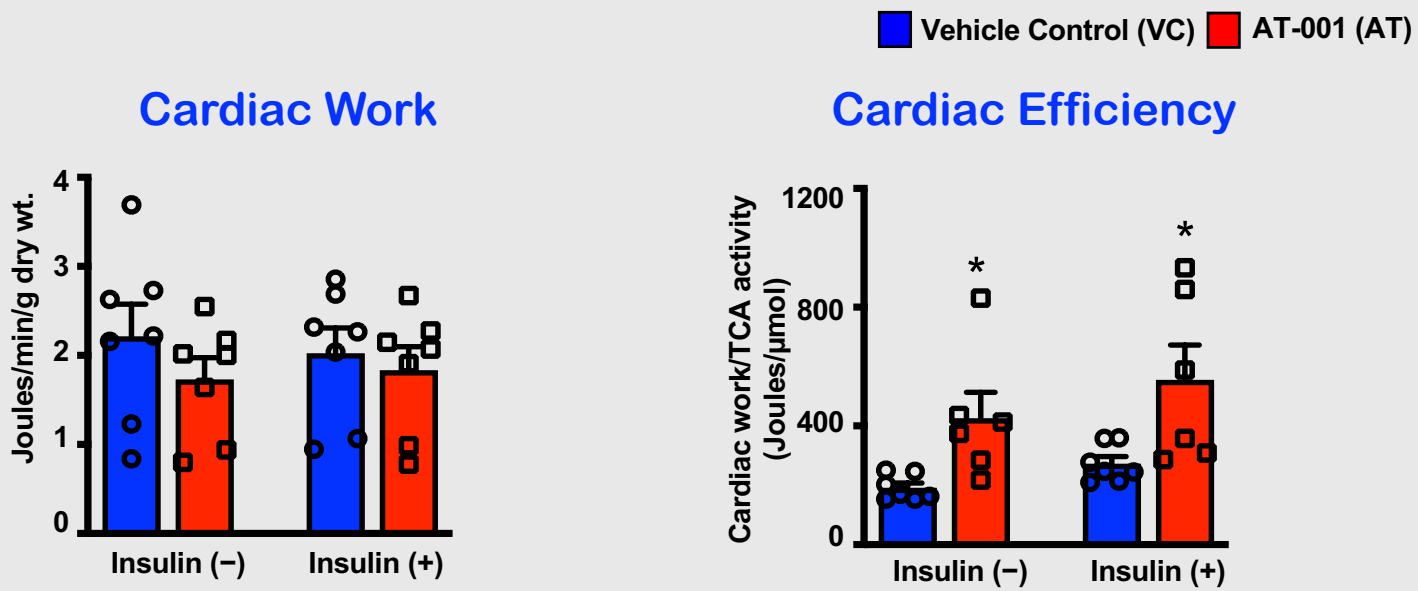
AT-001 Reduces Myocardial Fatty Acid Oxidation in a Mouse Model of Diabetic Cardiomyopathy



AT-001 attenuates altered cardiac energy metabolism by reducing myocardial fatty acid oxidation in a mouse model of diabetic cardiomyopathy.

VC – Vehicle control
AT – Aldose reductase inhibitor

AT-001 Improves Cardiac Efficiency in a Mouse Model of Diabetic Cardiomyopathy



AT-001 improves cardiac efficiency denoted by cardiac work normalized to TCA cycle activity in a mouse model of diabetic cardiomyopathy.

TCA – Tricarboxylic acid cycle

Conclusions

- **Pharmacological inhibition of aldose reductase by AT-001 prevents cardiac structural (e.g., hypertrophy and fibrosis) and functional (e.g., diastolic dysfunction) abnormalities in a mouse model of diabetic cardiomyopathy.**

- **AT-001 improves cardiac efficiency and normalizes cardiac energetics by shifting cardiac metabolism towards a non-diabetic metabolic state.**

THANK YOU

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