Aldose Reductase Inhibitors:

AT-001: a Next Generation Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy (DbCM)

Francesca Lawson, MD, FAHA

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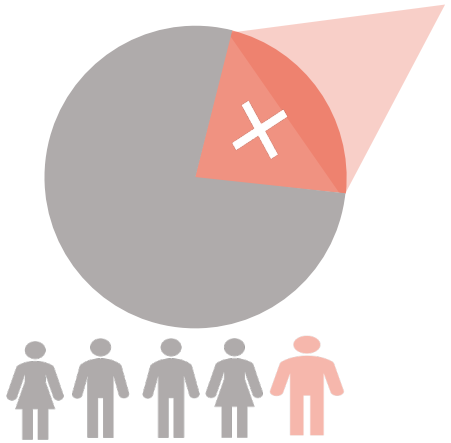
Disclosures

- Employee at Applied Therapeutics
- Shareholder of Applied Therapeutics

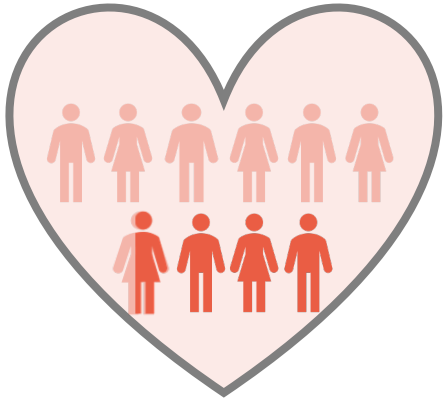
Diabetic Cardiomyopathy: Abnormal Cardiac Structure and Functional Capacity Resulting from Diabetes-Associated Metabolic Alterations



Approximately, **17-24%** of patients with diabetes have DbCM in the absence of other forms of heart disease. [1,2]

~77 M patients worldwide have DbCM[3]

- ~ 8.0M in North America
- ~ 10.0M in Europe



- ~24% of DbCM patients progress to overt heart failure or death within **1.5 years**[4]
- 37% within 5 years[5]

- Patients with diabetes are counseled on HF risk reduction:
  - Lifestyle modification
  - Hypertension
  - Dyslipidemia
  - Hyperglycemia
  - Albuminuria

No Treatment for DbCM

- No therapies target the metabolic derangement responsible for DbCM and subsequent worsening to overt HF
- Heart Failure treatment is only initiated upon onset of clinical symptomatology (stage C heart failure)

1. Dandamudi et al. J Card Fail. 2014;20(5):304-309. 2. Pham et al. Intl J Endocrinology 3. International Diabetes Foundation, 2017,4. Wang et al. JACC: Cardiovasc Imaging 2018; 5. From et al. JACC 2010

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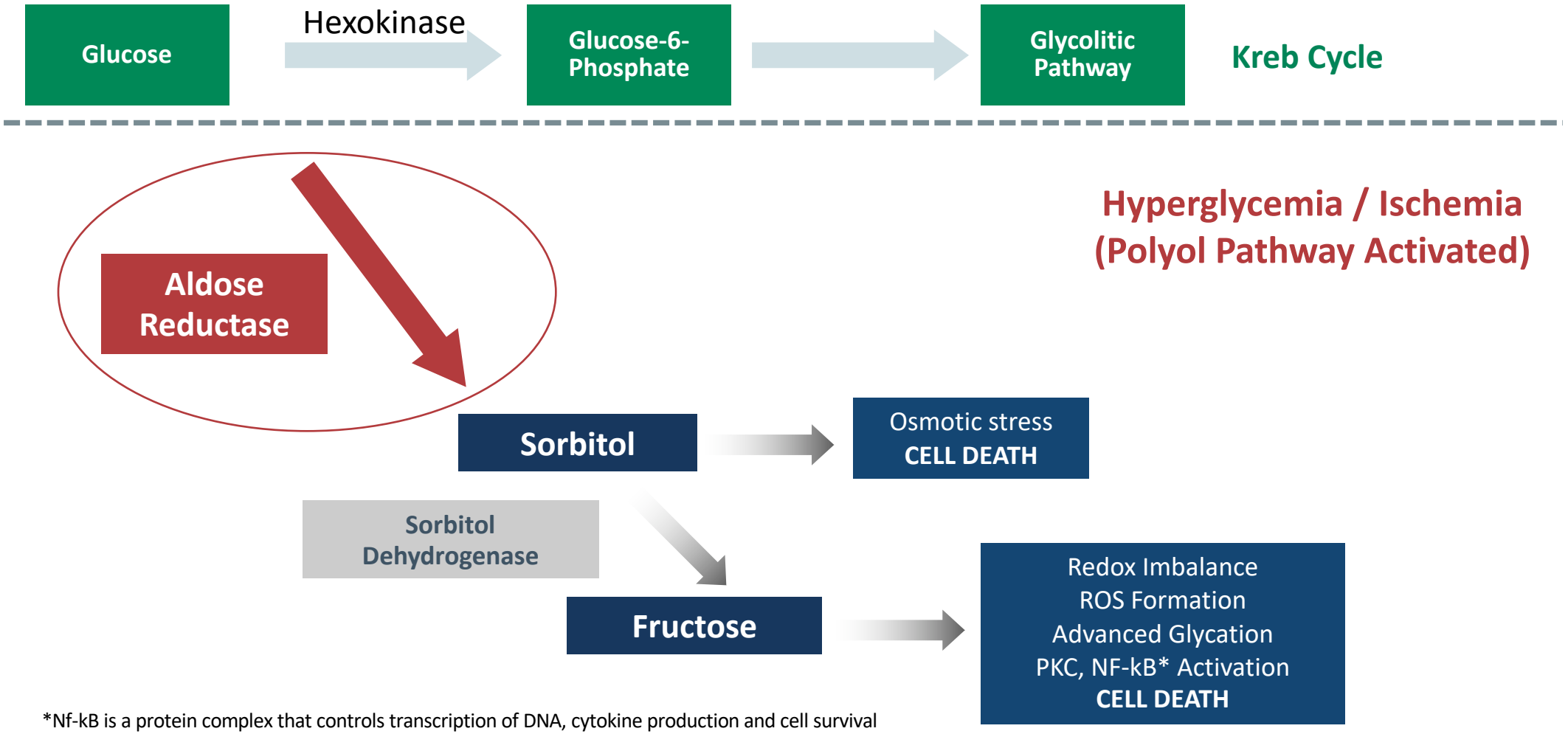
Pathogenesis of DbCM & Hyperactivation of Polyol Pathway[1,2]



*Nf-kB is a protein complex that controls transcription of DNA, cytokine production and cell survival

1. Brownlee M. Diabetes Care. 2005;54(6):1615-1625. 2. Miki T, et al. Heart Fail Rev. 2013;18(2):149-166.

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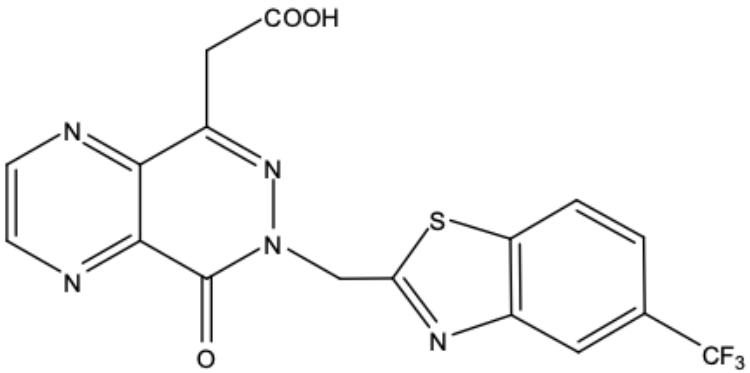
Aldose Reductase Plays a Key Role in Diabetic Cardiomyopathy (DbCM)

- The role of Aldose Reductase (AR) in DbCM is well supported by preclinical and clinical evidence
  - AR knock-out animals are protected from diabetic complications and cardiac damage
  - In humans, over-expression of AR (due to a polymorphism in the promoter) leads to higher risk of diabetic complications
- Early attempts to inhibit AR were unsuccessful due to lack of selectivity, resulting in off-target toxicity issues
  - Off-target inhibition of Aldehyde Reductase (a structurally related enzyme required for normal liver function) led to liver tox issues
- Zopolrestat (an “old” ARI) demonstrated proof of concept efficacy in DbCM in a Phase 2 study

AT-001: A New Generation Aldose Reductase Inhibitor (ARI) for Diabetic Cardiomyopathy (DbCM)

- ~1,000X more potent than prior ARIs in vivo and in vitro
- No off-target inhibition of Aldehyde Reductase
- Broad exposure: cardiac and nerve tissue
- Significant reduction of cardiac damage in an animal model of cardiomyopathy

AT-001



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AT-001: Clinical Development

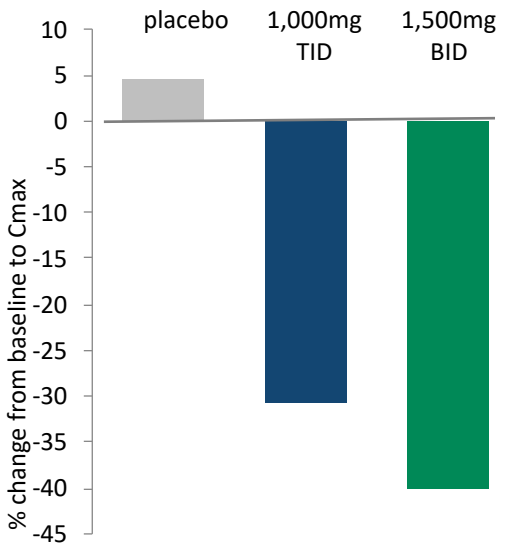
- **Phase 1/2 safety, PK, PD study in patients with T2D**
  - Part A: N=40 Single Ascending Doses (SAD) - 5, 10, 20, 40mg/kg
  - Part B: N=40 Multiple Ascending Doses (MAD - 7 days) - 5, 10, 20, 40mg/kg
  - Part C: N=33 patients with elevated NT-proBNP (mean = 65pg/ml; range = 30-235pg/ml)
    - 3,000mg/day for 28 days: placebo; 1,500mg BID; 1,000mg TID
- **Phase 2/3 pivotal study in patients with Diabetic Cardiomyopathy (DbCM) at high risk of progression**

AT-001: Results of Phase 1/2 Safety, PK, PD Study

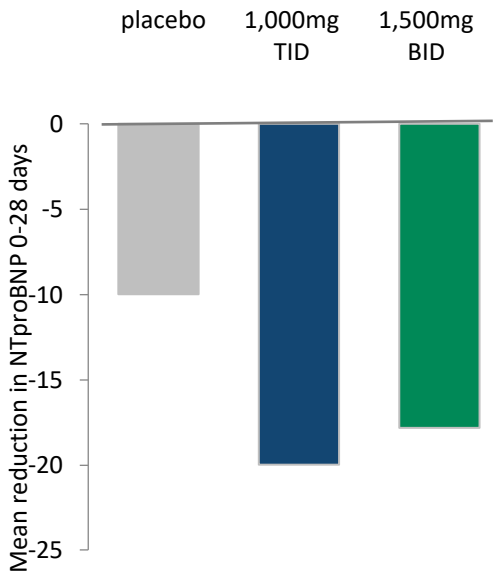
- **Safety:**
  - Well tolerated
    - No treatment-related AEs
    - No treatment-related discontinuations
    - No abnormalities in liver or kidney function
    - No treatment emergent ECG changes
- **Pharmacokinetics:**
  - Supportive of BID administration
- **Pharmacodynamics**:
  - Dose-dependent inhibition of sorbitol allowed dose selection for the phase 2/3 study
  - Proof of concept reduction of NT-proBNP observed in T2D patients with elevated baseline levels

AT-001 Normalized Sorbitol (a PD Biomarker of AR Activity) and Reduced Levels of NT-proBNP Over 28 Days of Treatment

Mean Reduction in Sorbitol



Mean Reduction in NT-proBNP



Preliminary Phase 1/2 data

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DbCM Phase 2/3 Study (ARISE-HF)

Randomized, Placebo-Controlled Study in DbCM Patients at High Risk of Progression

n=675
(225/arm)

Patients with DbCM at high risk of progression to overt HF

1:1:1 Randomization

Placebo

1000 mg

1500 mg

Twice-daily oral dosing

Core Study

Efficacy (15 Months)

- **Primary Endpoint: Functional Capacity (as measured by** Peak VO2 change from baseline)
- Secondary:
- NTproBNP cardiac biomarker
- Quality of life (mKCCQ)

27 Month Secondary and Exploratory Analyses

- Progression to overt HF
- Echo based endpoints
- mKCCQ
- Exploratory cardiac biomarkers

Placebo-controlled Extension:

CV death/ hospitalization

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