Diabetic Cardiomyopathy Expert Forum

TUESDAY, NOVEMBER 07 **8AM ET**

APPLIED THERAPEUTICS

WEBCAST WILL BEGIN SHORTLY

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Forward Looking Statements

Various statements in this presentation concerning the Company's future expectations, plans and prospects, including without limitation, the Company's current expectations regarding its strategy, its product candidate selection and development timing, its management team capabilities, and the ability of the Company's product candidates to have a clinically meaningful effect on the target patient populations, constitute forward-looking statements. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," or "continue," the negative of these and other similar expressions are intended to identify such forward looking statements. Such statements, based as they are on the current analysis and expectations of management, inherently involve numerous risks and uncertainties, known and unknown, many of which are beyond the Company's control. Such risks include, but are not limited to: the impact of general economic conditions, general conditions in the biopharmaceutical industries, changes in the global and regional regulatory environments in the jurisdictions in which the Company does or plans to do business, market volatility, fluctuations in costs and changes to the competitive environment, the Company's ability to fund its working capital requirements and expectations regarding the sufficiency of our capital resources and the Company's ability to achieve the anticipated benefits from the agreements entered into in connection with our partnership with Advanz Pharma. Consequently, actual future results may differ materially from the anticipated results expressed in the forward-looking statements. In the case of forward-looking statements regarding investigational product candidates and continuing further development efforts, specific risks which could cause actual results to differ materially from the Company's current analysis and expectations include: failure to demonstrate the safety, tolerability and efficacy of our product candidates; final and quality controlled verification of data and the related analyses; the expense and uncertainty of obtaining regulatory approval, including from the U.S. Food and Drug Administration and European Medicines Agency; the possibility of having to conduct additional clinical trials and our reliance on third parties such as our licensors and collaboration partners regarding our suite of technologies and product candidates; the Company's ability to take advantage of expedited regulatory pathways for any of our product candidates; the Company's intellectual property position and the duration of its patent rights; developments or disputes concerning the Company's intellectual property or other proprietary rights. Further, even if regulatory approval is obtained, biopharmaceutical products are generally subject to stringent on-going governmental regulation, challenges in gaining market acceptance and competition.
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1. Diabetic Cardiomyopathy Disease Overview
2. ARISE-HF Registrational Phase 3 Trial Overview

James L. Januzzi Jr, MD, FACC, FESC
Hutter Family Professor of Medicine, Harvard Medical School
Director, GDMT Clinic, Massachusetts General Hospital
Director, Heart Failure and Biomarker Trials, Baim Institute for Clinical Research

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Diabetic Cardiomyopathy Disease Overview

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What is Diabetic Cardiomyopathy?

- Diabetic Cardiomyopathy (DbCM) is a form of Stage B Heart Failure in patients with diabetes
- DbCM is caused by underlying metabolic changes in the cardiac tissue, leading to fibrosis of the heart
- DbCM can occur in both Type 1 and Type 2 diabetic patients despite adequate glucose control

Parim B, et al. Heart Failure Rev 2019:24:279-299.; Grewal AS, et al. Min Rev Med Chem 2016; 16:120-62.; Data on file. Decision Resources Group “Epidemiology of DbCM” Report. July 2020.

How is Diabetic Cardiomyopathy Diagnosed?

Demonstration of structural and/or functional cardiac abnormalities in the absence of coronary artery disease or uncontrolled hypertension in diabetic patients

Include

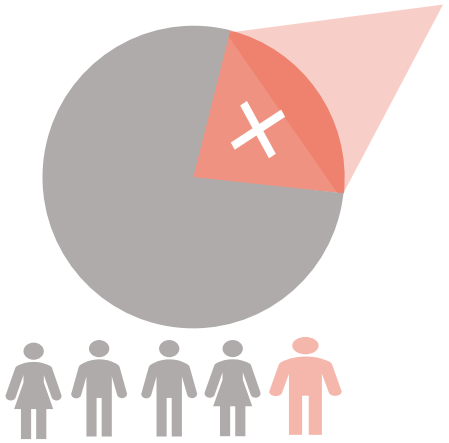
- ☑ **Type 1 or Type 2 Diabetes**
- ☑ **Structural and/or functional cardiac functional abnormalities via:**
  - **Echo abnormalities**
  - **Abnormal CPET or 6MWT**
  - **Elevated cardiac biomarkers (NT-proBNP or HS-troponin)**

Exclude

- ☒ **Coronary Artery Disease**
- ☒ **Uncontrolled Hypertension**

Parim B, et al. Heart Failure Rev 2019:24:279-299.; Grewal AS, et al. Min Rev Med Chem 2016; 16:120-62.; Data on file. Decision Resources Group "Epidemiology of DbCM" Report. July 2020.

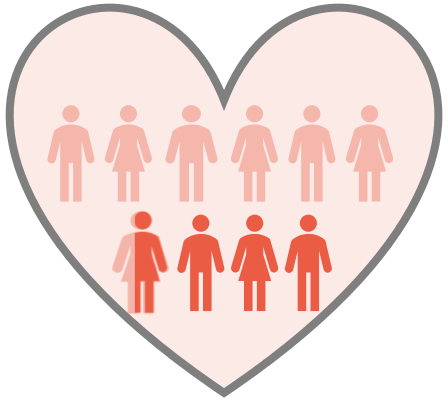
Prevalence of DbCM and High Unmet Medical Need



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

Risk Factors for Developing DbCM

Risk factors for developing DbCM include a diagnosis of Type 2 Diabetes and:

Age ≥ 60 years

OR

Long duration of diabetes

(>10 years)

OR

Renal impairment

(eGFR <60 mL/min/1.73 m^2)

OR

Presence of other diabetic complications

(peripheral or autonomic neuropathy; nephropathy; retinopathy)

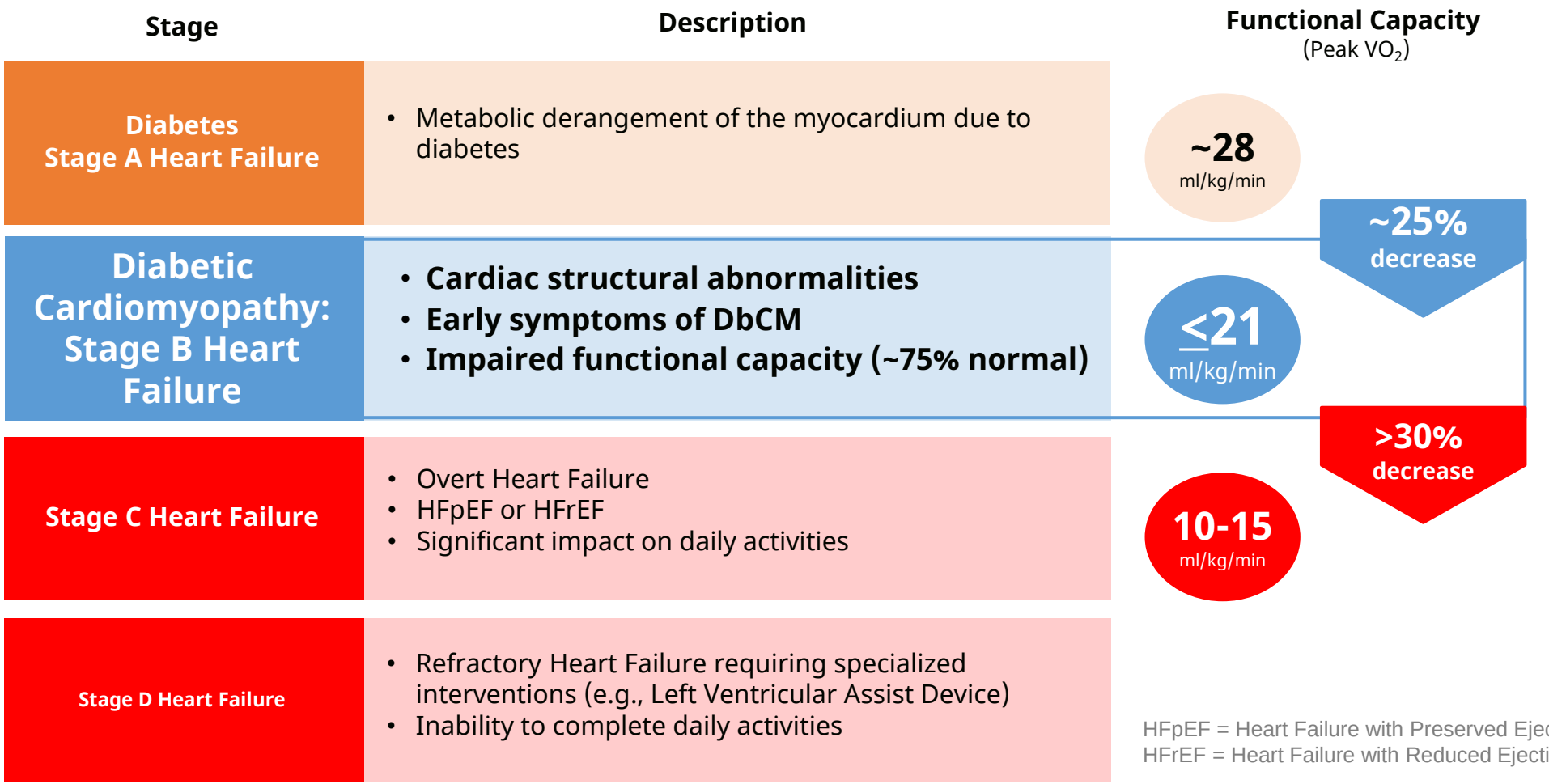
- Wang Y, Marwick TH. Diagnosis of Nonischemic Stage B Heart Failure in Type 2 Diabetes Mellitus Optimal Parameters for Prediction of Heart Failure JACC: CV Imaging 2018 VOL. 11, NO. 10, 2018

What is Cardiac Functional Capacity?

- Cardiac functional capacity is a measure of the heart's ability to circulate oxygen during physical activities
- Peak VO2 is the metric used to describe a person's oxygen level during maximal physical exertion
- Peak VO2 is measured by asking a patient to exert themselves physically to their maximum level (on a treadmill or a stationary bicycle) and a machine measures their oxygen consumption
- Various measures are used to ensure that maximum physical exertion is reached – will be discussed in the next section by Dr. Lewis

Peak VO2	Example Activity
3.5	Rest
7.0-10.5	Walking 2mph, eating, dressing
14.0-17.5	Walking 4mph, household tasks
21.0-24.5	Walking up stairs
28.0-31.5	Swimming, tennis
35.0-38.5	Jogging 10 min/miles
42.0-49.0	Intense aerobic sports, squash
>70.0	Professional Athletes/Olympians

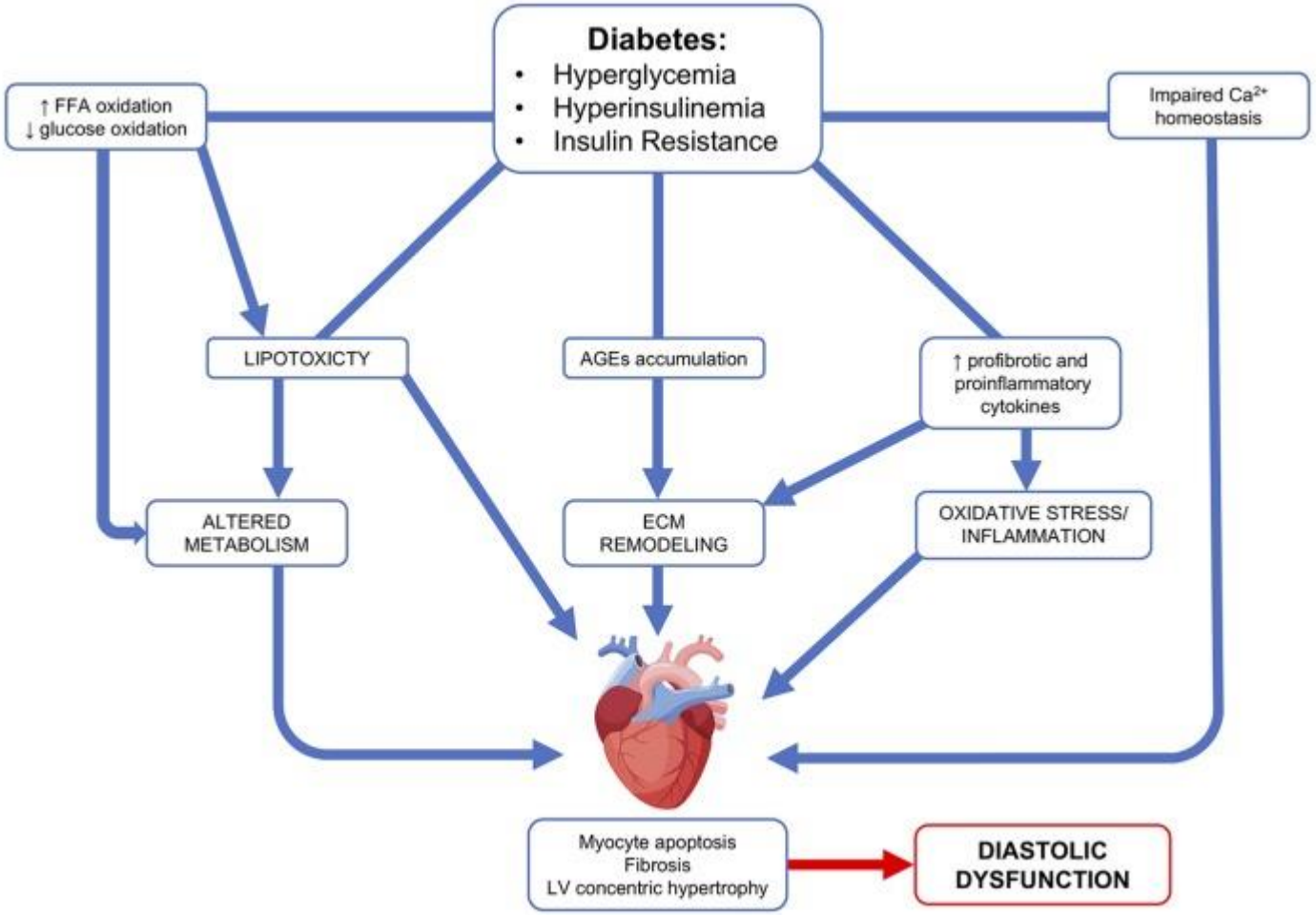
Cardiac Functional Capacity is Impaired in DbCM



HFpEF = Heart Failure with Preserved Ejection Fraction
HFrEF = Heart Failure with Reduced Ejection Fraction

Kosmala et al, JACC V O L . 6 5 , NO . 3 , 20 1 5; Swank et al. Circ HF 2012; Wang et al. JACC: ; Cardiovasc Imaging 2018; From et al. JACC 2010

DbCM: Mechanisms of Disease



- Impaired cardiac energetics (↑ fatty acid oxidation)
  - Lipotoxicity
  - ↓ Glucose utilization
- Accumulation of AGE
- Myocardial remodeling (fibrosis)
- Inflammation
- Impaired calcium handling

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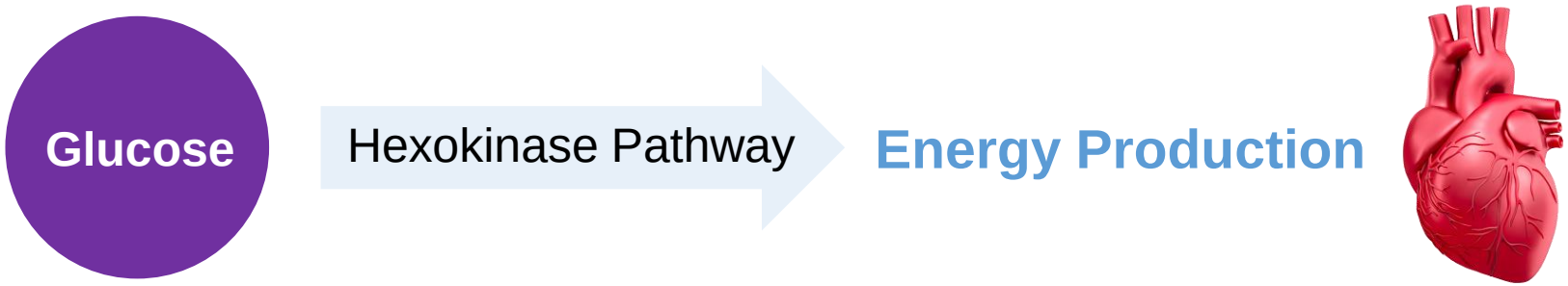
Aldose Reductase Inhibition in DbCM

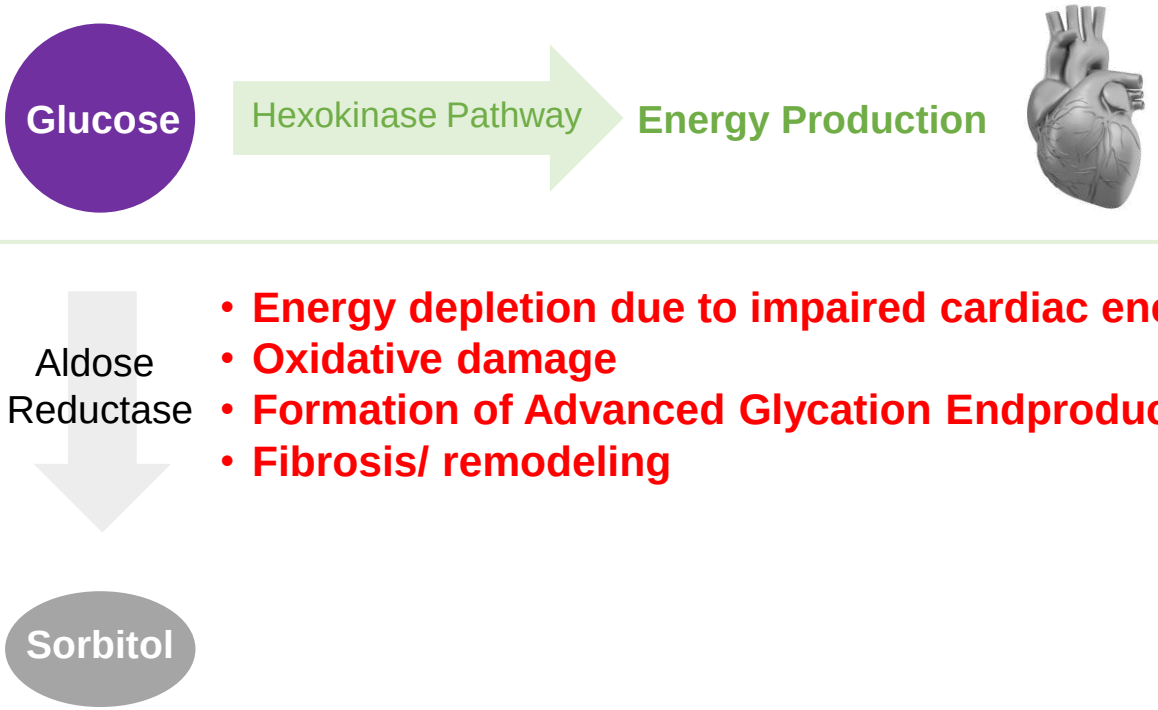
Normal Energy Production



Cardiomyocytes have the highest energy requirements of any cell type in the body[1]

Pascual F, Coleman RA. Fuel availability and fate in cardiac metabolism: A tale of two substrates. Biochim Biophys Acta. 2016 Oct;1861(10):1425-33. doi: 10.1016/j.bbalip.2016.03.014. Epub 2016 Mar 16. PMID: 26993579; PMCID: PMC4983230.

In Diabetes, Aldose Reductase Converts Glucose to Sorbitol and Causes Damage to Cardiomyocytes



Changjin Zhu, Diabetes Mellitus – Insights and Perspectives, Chapter 2 Aldose Reductase Inhibitors as Potential Therapeutic Drugs of Diabetic Complications, 2013. http://dx.doi.org/10.5772/54642

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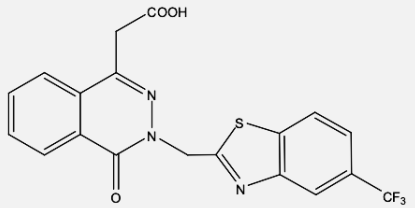
Next Generation Aldose Reductase Inhibitor AT-001 vs. “Old” Compounds

- The role of Aldose Reductase in DbCM is well supported by both clinical and preclinical evidence
- Old Aldose Reductase Inhibitors were limited by off-target hepatoxicity

Zopolrestat (Old ARI)



Inhibition of Aldose Reductase → Clinical Efficacy

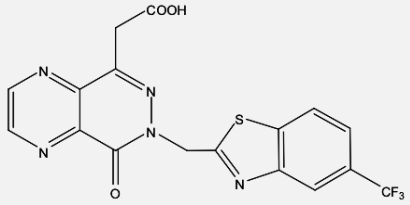
(Off-Target) Hepatotoxicity

Competitive Inhibition of Aldehyde Reductase

AT-001 was developed to selectively inhibit Aldose Reductase without off-target inhibition of Aldehyde Reductase [2]

- 1,000x more potent than old drugs
- Broad exposure in cardiac and nerve tissue

AT-001



Selective Inhibition of Aldose Reductase → Clinical Efficacy

Johnson, et al. Diabetes Care, 2004 pp 448-454; 2. Poster # 632: “Addressing safety and specificity with aldose reductase inhibition: development of AT-001 for diabetic cardiomyopathy” 56th Annual Meeting of the European Association for the Study of Diabetes (EASD) Sept 2020

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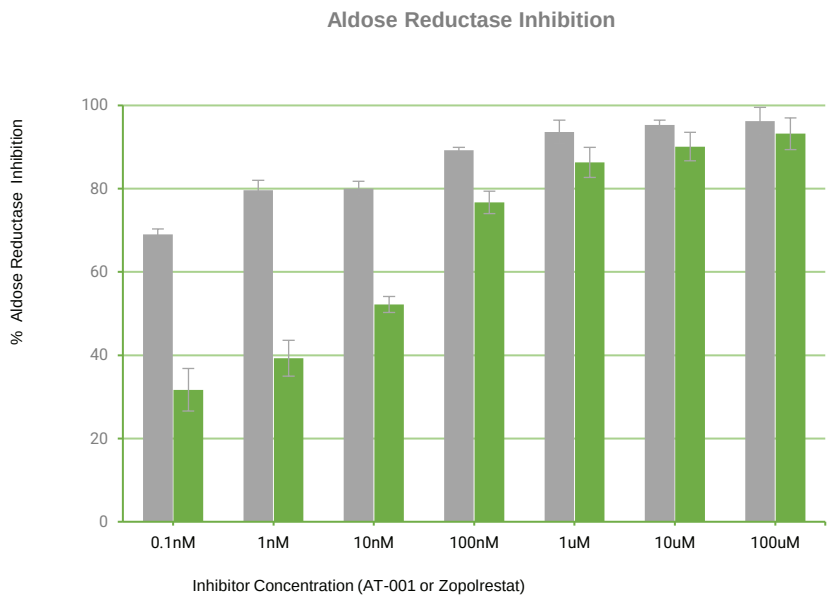
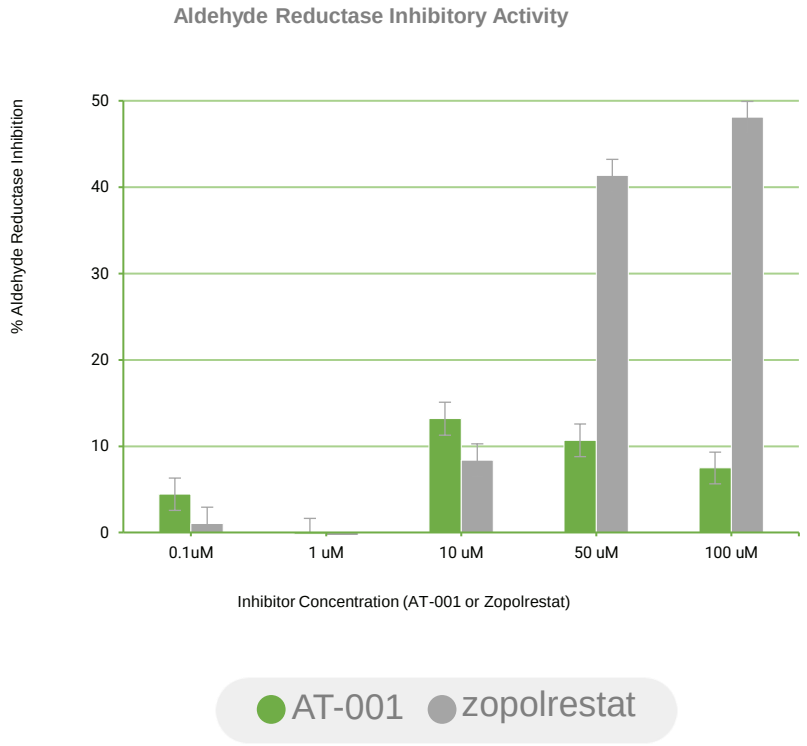
AT-001 Provides Greater Potency and Improved Target Selectivity vs. “Old” ARI, Zopolrestat

AT-001 demonstrated improved Aldose Reductase Inhibition



AT-001 does not inhibit Aldehyde Reductase



Data based on In Vitro Enzyme Inhibition & Cultured Hepatocytes

Poster # 632. 56th Annual Meeting of the European Association for the Study of Diabetes (EASD) Sept 2020

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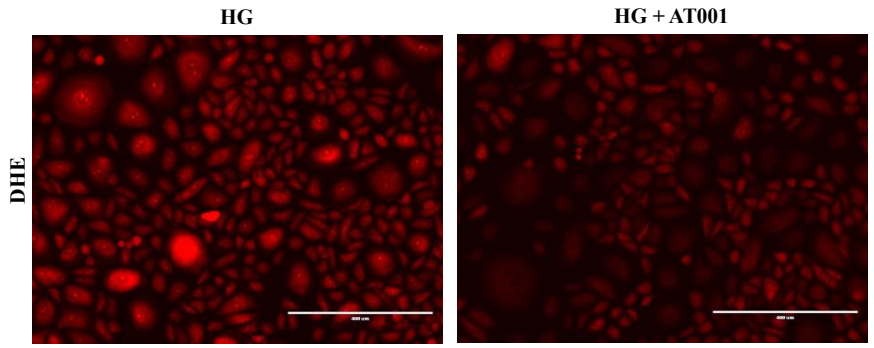
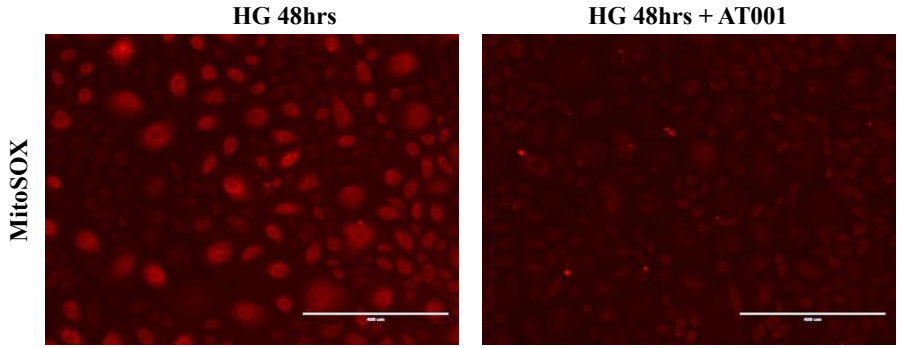
AT-001 Treatment Prevents Cytosolic ROS Generation, Mitochondrial Stress & Cell Aging Caused by High Glucose

Dihydroethidium (DHE) Staining for Cytosolic ROS

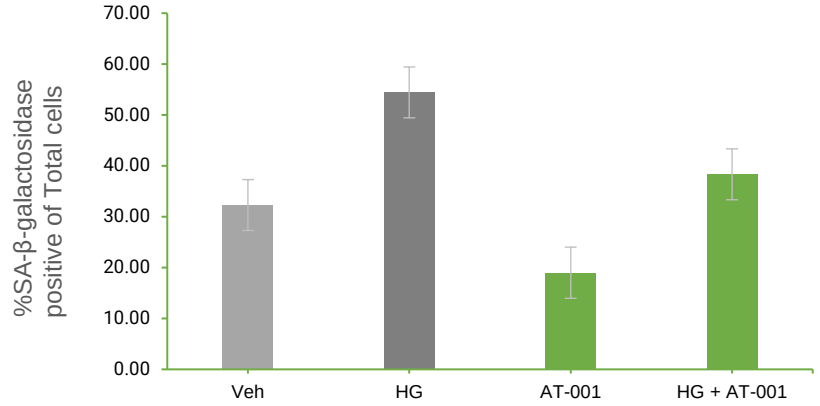


MitoSOX™ Staining for Mitochondrial ROS



HG- NHK cells exposed to 25mM glucose (high glucose) for 48hrs
HG + AT-001 - cells treated with 0.18nM AT-001 along with above mentioned HG exposure

Quantitation of Cell Senescence Via SA-β-gal Staining



- In patients with diabetes, metabolism of glucose through the polyol pathway results in generation of Reactive Oxygen Species (ROS), which has been identified as a key mediator of tissue damage and causal in diabetic complications. Selective inhibition of AR reduces oxidative stress and mitigates these complications.
- AT-001 prevents the production and accumulation of ROS as assessed by both DHE quantitation and MitoSOX™ staining, demonstrating effective reduction of oxidative damage in the cytosol and mitochondria of cells.
- Evaluation of cellular aging via SA-β-gal staining showed less senescence in cells exposed to high glucose in the presence of AT-001

Poster #629: “AT-001 a new aldose reductase inhibitor with improved selectivity and specificity protects from cellular damage” 56th Annual Meeting of the (EASD) Sept 2020

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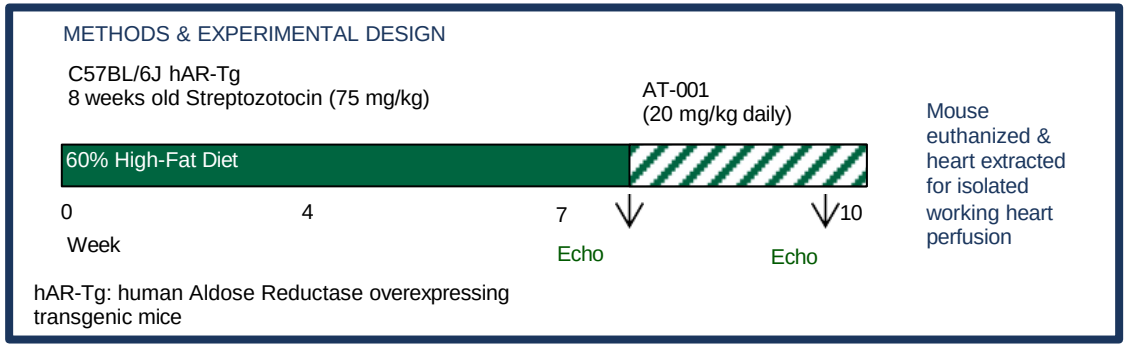
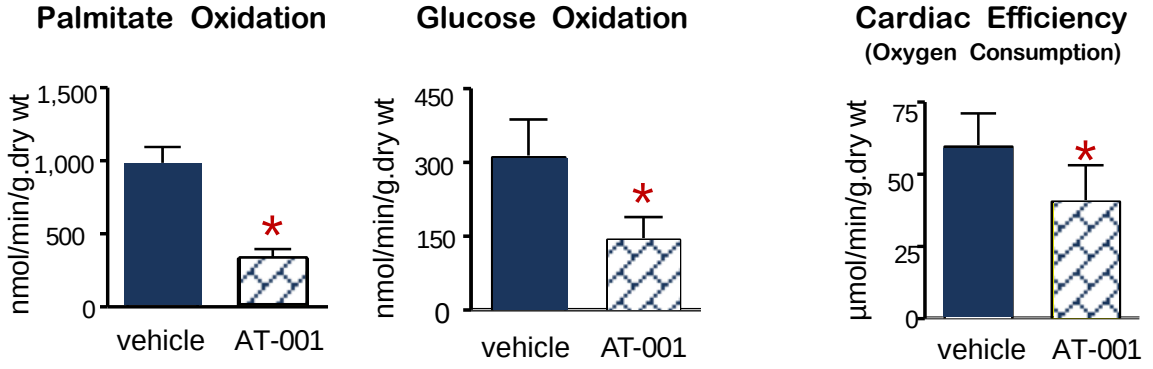
AT-001 Improves Cardiac Energetics, Prevents Cardiac Dysfunction and Prevents Fibrosis in an Animal Model of DbCM

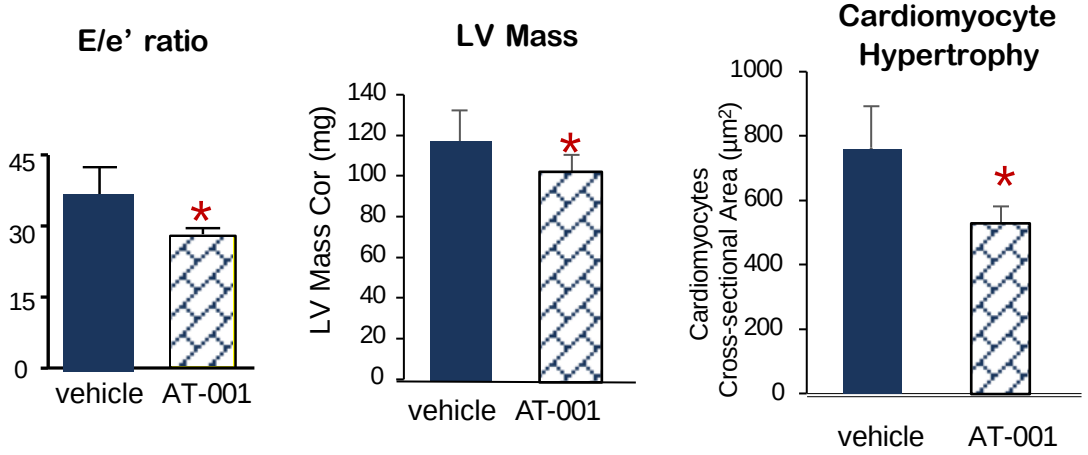
AT-001 Treatment in a DbCM Mouse Model (Design)



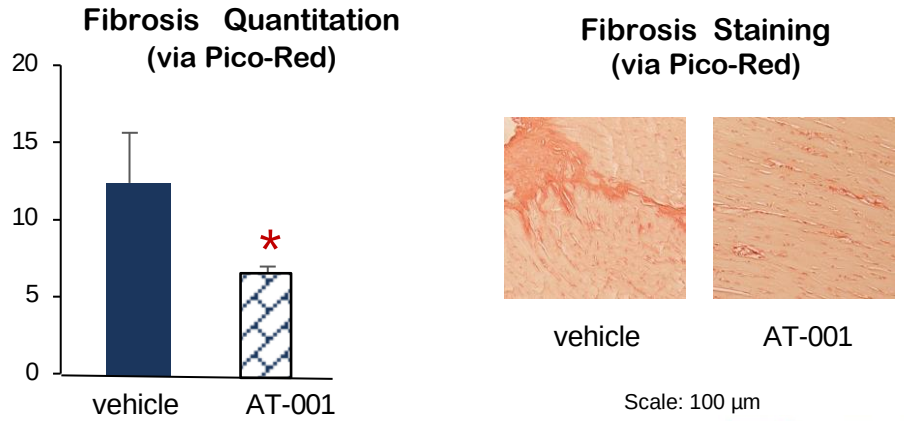
AT-001 Improves Cardiac Energetics



AT-001 Improves Cardiac Function and Prevents LVH



AT-001 Prevents Fibrosis and Adverse Remodeling



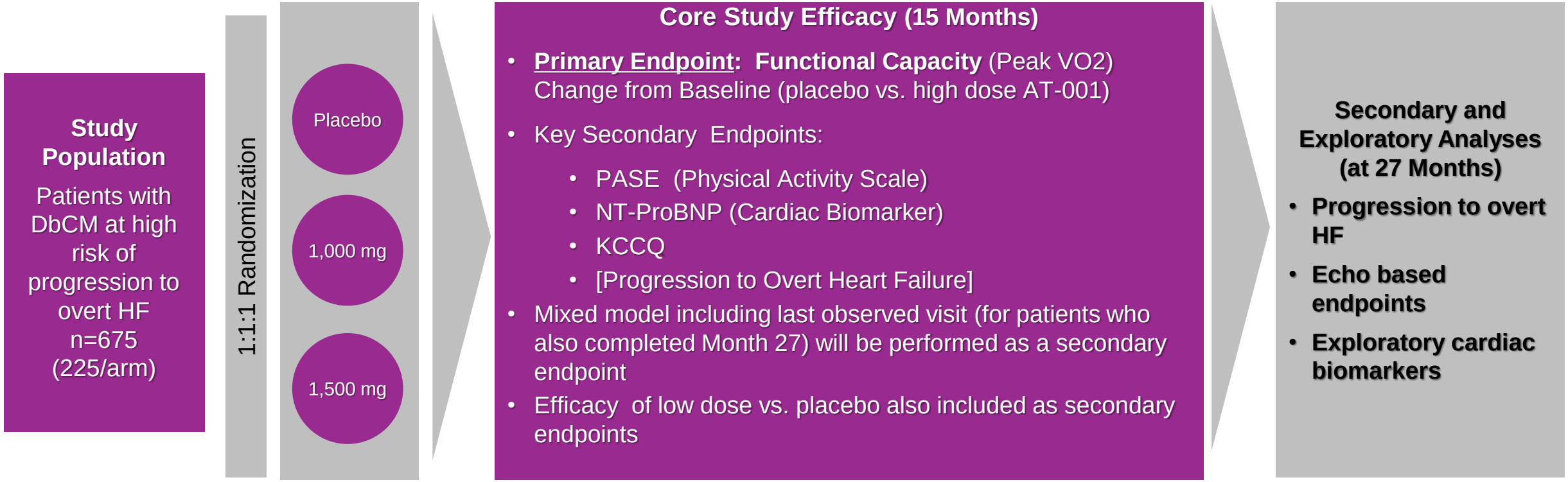
* = p<0.01

Keshav et al Pharmacological Inhibition of Aldose Reductase by AT-001 Prevents Abnormal Cardiac Energy Metabolism and Improves Heart Function in an Animal Model of Diabetic Cardiomyopathy, AHA 2020;
Keshav et Al Aldose Reductase Inhibition By At-001 Alleviates Fibrosis and Adverse Remodeling In Diabetic Cardiomyopathy By Reducing Myocardial Fatty Acid Oxidation, AHA 2022

Design of the ARISE-HF Study

ARISE-HF: Registrational Phase 3 Trial for AT-001 in DbCM

Randomized, Placebo-Controlled Trial in Patients with DbCM at High Risk of Progression to Overt HF



Primary Study Readout YE 2023

Source: NCT04083339

Januzzi JL Jr, Butler J, Del Prato S, et al Am Heart J. 2023 Feb;256:25-36.

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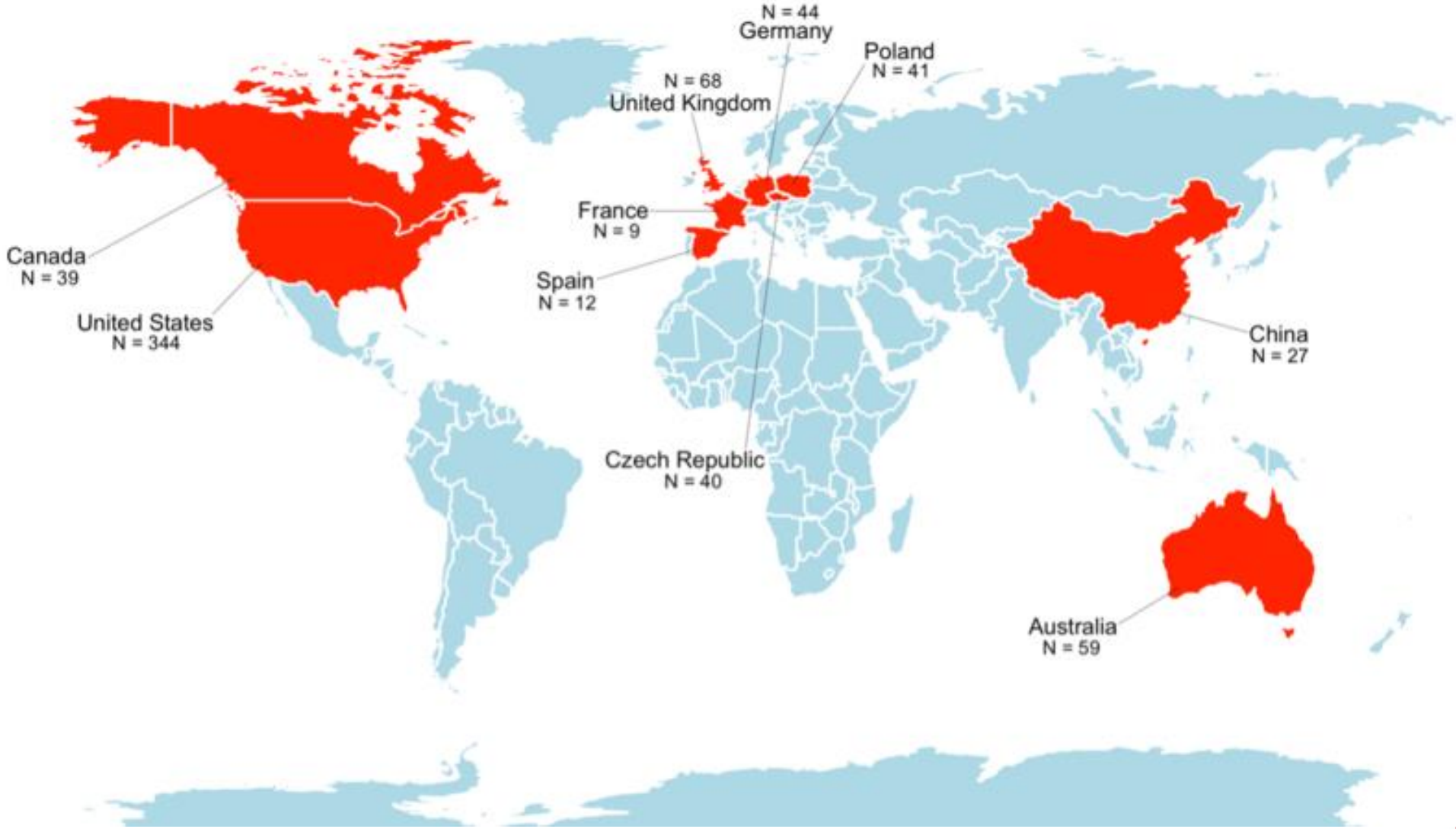
ARISE-HF Enrollment Across North America, Europe, AsiaPac



ARISE-HF Key Enrollment and Exclusion Criteria

Inclusion

1. Diagnosis of Type 2 DM
2. Age:
   - ≥60 years, or
   - ≥40 years, with duration of diabetes >10 years
3. Demonstration of DbCM/ Stage B Heart Failure

   LVEF≥ 45% and at least one of the following

   - Echocardiographic abnormalities

   or

   - NTProBNP ≥ 50 pg/ml
   - HsTNT ≥ 6 ng/L
4. Impaired functional capacity on max CPET
   - RER > 1.05
   - Peak VO2 <75% of age/gender predicted normal

Exclusion

1. Diagnosis or signs of overt/symptomatic heart failure
2. Use of a loop diuretic
3. History of CAD, MI, ACS, CABG, PCI, stroke
4. History of severe valve disease, clinically significant arrhythmia, or other cause of cardiomyopathy
5. Severe disease impacting implementation of the protocol or performance of a CPET
6. SBP >140 mmHg or DBP >90 mmHg
7. BMI ≥45 kg/m2
8. HbA1c >8.5%
9. eGFR <45 mL/min/1.73 m^2

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CPET = Cardio-pulmonary Exercise Test SBP = Systolic Blood Pressure DBP = Diastolic Blood Pressure ACS = Acute Coronary Syndrome CABG = Coronary artery bypass graft Percutaneous Coronary Intervention
CAD = Coronary Artery Disease

Patient Stratification, Adjudication and Monitoring in ARISE-HF

- To ensure balance between active and placebo-treated groups, patients were stratified at baseline based on:
  - Age
  - Gender
  - Concomitant use of a GLP-1 or SGLT2
  - Baseline cardiac functional capacity
- Determination of progression to overt heart failure is adjudicated by a central committee
- Patient safety is monitored by a firewalled unblinded Data Monitoring Committee
- Study conduct is overseen by a blinded Steering Committee

ARISE-HF Baseline Characteristics

Older, equally balanced between men and women, with longstanding T2DM, and prevalent risk factors with abnormal CV markers and imaging

n	691
Age, years, mean (SD)	67.4 (7.2)
Female, N (%)	348 (50.4)
Body-mass index, Kg/m^2, mean (SD)	30.6 (4.57)
Medical history, N (%)	
Hypertension	523 (75.7)
Dyslipidemia	117 (16.9)
Duration of T2DM, years, mean (SD)	14.5 (10.1)
Concomitant medications, N (%)	
Statins	558 (80.8)
ACE inhibitor or ARB	519 (75.1)
Beta blocker	161 (23.3)
MRA	21 (3.0)
Hydrochlorothiazide	133 (19.2)
SGLT2 inhibitor	221 (32.0)
GLP1-RA	173 (25.0)
Metformin	512 (74.1)
Insulin	188 (27.2)
Sulfonylurea	160 (23.2)
DPP-IV inhibitor	85 (12.3)

Laboratory tests, median (Q1, Q3) unless specified	
NT-proBNP, ng/L	71 (35, 135)
hs-cTnT, ng/L	9 (6, 12)
Hemoglobin A1c, mean ± SD	6.98 (0.79)
Hemoglobin, g/L, mean ± SD	13.7 (1.4)
CKD-Epi, eGFR, mL/min/1.73m^2, mean ± SD	80.5 (16.3)
Albumin/Creatinine	15 (8, 41)
Echocardiographic measurements, median (Q1, Q3)	
E/e’	9.40 (7.80, 11.90)
Global longitudinal strain, %	-17.7 (-19.5, -15.2)
LAVi, mL/m^2	23.4 (19.1, 28.9)
LVEF, %	62 (59, 66)
LVMI, g/m^2	74 (64, 88)
Right ventricular systolic pressure, mmHg	23 (19, 28)
Abnormal echocardiogram, N, %	
Global longitudinal strain > -16%	175 (25.3)
E/e’ ≥ 13	122 (17.7)
Left atrial volume index > 34 mL/m^2	82 (11.9)
LVMI≥ 115 g/m^2 in men and ≥ 95 g/m^2 in women	82 (11.9)
Right ventricular systolic pressure > 35 mmHg	27 (3.9)

Januzzi JL, et al, Submitted

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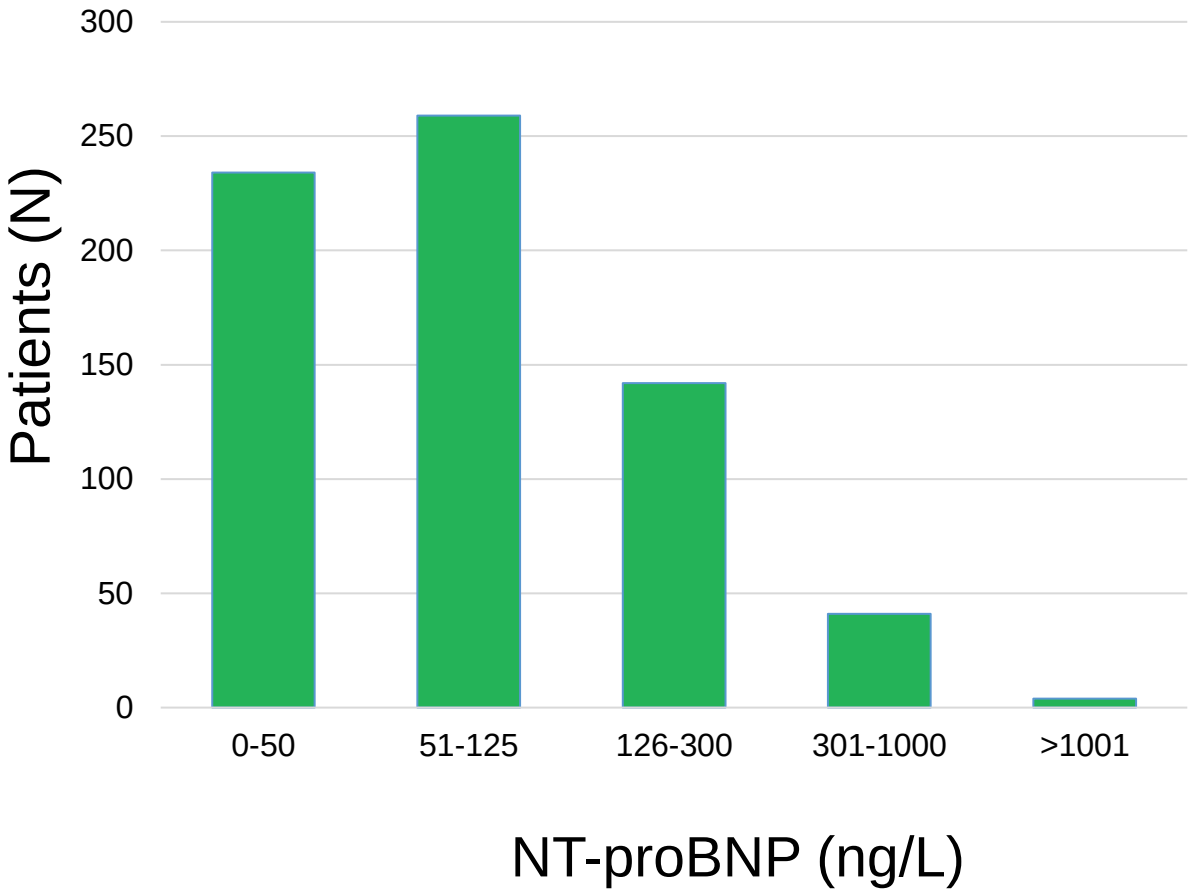
ARISE-HF: Baseline NT-proBNP

NT-proBNP (ng/L)
Mean (SD): 115 (217)
Min 5
Q1: 35
Median: 71
Q3: 134
Max 4284*



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NT-proBNP in DbCM

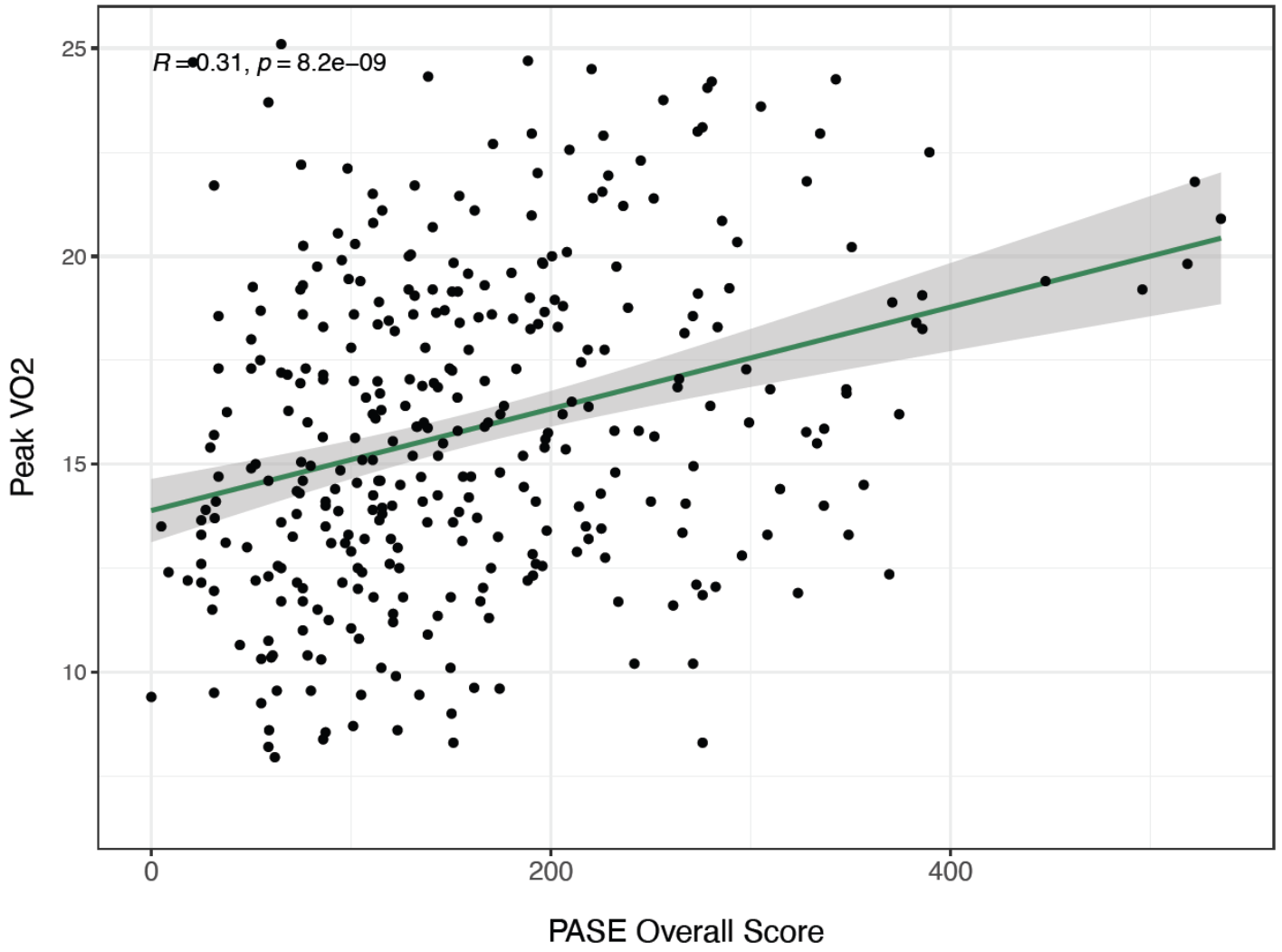
NT-proBNP is associated with worse health status and reduced activity level

	Quartile 1 (n=174)	Quartile 2 (n=171)	Quartile 3 (n=172)	Quartile 4 (n=168)	P
NT-proBNP Range, ng/L	5-35	36-71	72-135	136-4284	
KCCQ physical limitation score, mean ± SD	92 (15)	89 (16)	89 (16)	86 (19)	0.02
KCCQ clinical summary score, mean ± SD	93 (11)	90 (15)	90 (15)	88 (15)	0.01
KCCQ overall summary score, mean ± SD	92 (12)	90 (15)	90 (15)	88 (16)	0.10
PASE score, mean ± SD	163 (95)	169 (100)	152 (79)	135 (82)	0.008

NT-proBNP is associated with decreased exercise capacity and meaningful functional endpoints

	Quartile 1 (n=174)	Quartile 2 (n=171)	Quartile (n=172)	Quartile 4 (n=168)	P
NT-proBNP Range, ng/L	5-35	36-71	72-135	136-4284	
Duration of CPET test, min, mean ± SD	10.55 (2.31)	9.92 (2.41)	9.70 (2.31)	8.80 (2.25)	<0.001
Peak VO_2, mL/Kg/min, mean ± SD	17.18 (3.81)	15.79 (3.63)	15.34 (3.93)	14.55 (3.34)	<0.001
VE/VCO2 slope, mean ± SD	30.58 (4.70)	30.70 (5.13)	31.53 (5.55)	32.08 (6.05)	0.03
Peak respiratory exchange rate, mean ± SD	1.17 (0.09)	1.18 (0.11)	1.18 (0.09)	1.18 (0.09)	0.81

Cardiac Functional Capacity (Peak VO2) Statistically Correlates with PASE Score at Baseline in ARISE-HF



p<0.0001

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Conclusions

- Diabetic Cardiomyopathy is serious complication of diabetes, affecting ~20% of the diabetic population
- There are currently no treatments approved for DbCM
- ARISE-HF is the first registrational study in patients with DbCM
- Baseline data suggest that the “right” target patient population is enrolled in the study
- ARISE-HF primary study readout is expected at the end of this year
- AT-001 may be the first treatment approved for DbCM

Cardiac Functional Capacity

Gregory Lewis, MD

Director, Cardiopulmonary Exercise Testing Laboratory and Section Head, Heart Failure, Massachusetts General Hospital

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Cardiac Functional Capacity

Peak VO2 is a “gold standard” measurement of cardiac functional capacity

It is calculated as the product of cardiac output and arteriovenous oxygen (a−V̇o2) difference at “physical exhaustion”

$$\dot{V}o_{2max} = (HR \times SV) \times a\text{–}\dot{V}o_2diff$$

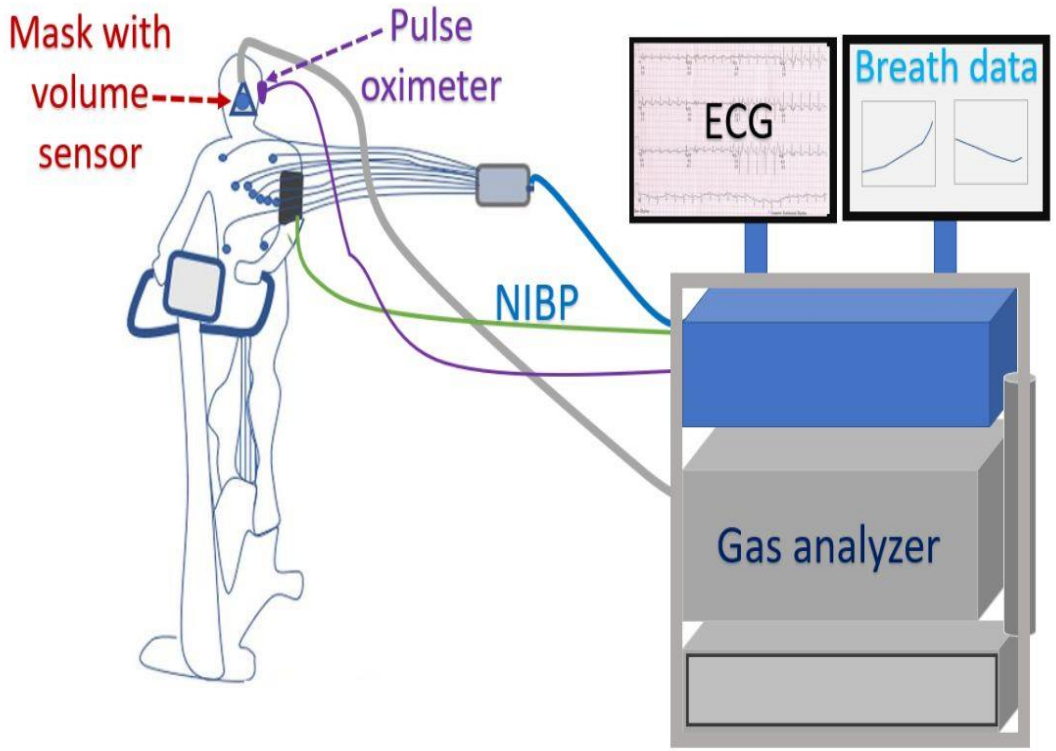
(Peak VO2) can be measured directly using a CPET machine (metabolic cart)

Peak VO2	Example Activity / Bruce Protocol Stage
3.5	Rest
7.0-10.5	Walking 2mph, eating, dressing
14.0-17.5	Walking 4mph, household tasks
21.0-24.5	Walking up stairs, Stage 2 Bruce: 2.5mph, 12%
28.0-31.5	Swimming, tennis
35.0-38.5	Jogging 10 min/miles, Stage 3 Bruce: 3.4mph, 14%
42.0-49.0	Intense aerobic sports, squash Stage 4 Bruce: 4.2mph, 16%
>70.0	Professional Athletes/Olympians

Arena et al, Assessment of Functional Capacity in Clinical and Research Settings Circulation. 2007;116:329–343

How is Cardiac Functional Capacity Measured?

- The CPET machine is comprised of:
  - Cycle or treadmill (to achieve maximal exercise through a programmed protocol)
  - Pulse oximeter (to measure blood oxygen levels)
  - ECG (to measure heart rate)
  - Gas analyzer (to measure expired O2 and CO2 levels)
- Use of ventilary expired gas techniques to measure Peak VO2 have greatly improved the precision, accuracy and reproducibility of CPET



How Do We Ensure Quality in CPET Measurement?

- CPET is reliable and reproducible
- Equipment must be maintained, serviced and quality checked regularly
- All sites must use the same protocol during the trial to control ramp/slope to maximum exercise capacity
- A central core lab promptly reviews data to ensure CPET was performed correctly
- Subjects must achieve maximal exercise as defined as a Respiratory Exchange Ratio (RER) >1.05 in order for the CPET to be considered as having measured Peak VO_2

The Importance of a CPET Core Lab for ARISE-HF

- Training and qualification of all sites performing CPET in the study
- Central oversight to ensure a consistent methodology across clinical sites
- Prompt evaluation of each individual CPET to ensure quality of the test results
- Any tests that were performed incorrectly or aberrant results are repeated
- Central reading and reporting of all CPET values for the primary endpoint

Clinical Meaningfulness of Cardiac Functional Capacity

- A 6% difference in Peak VO2 has been shown to be clinically meaningful in predicting mortality
- In the HF-ACTION trial (2331 patients), a 6% change in Peak VO2 predicted hospitalization for HF and mortality

Relation of 6% change in peak VO_2	p value
All-cause mortality or all-cause hospitalization	<.0001
Cardiovascular mortality or hospitalization	0.001
Cardiovascular mortality or HF hospitalization	0.001
Mortality	0.001

Swank AM et al Circ Heart Fail. 2012 Sep 1;5(5):579-85. doi: 10.1161/CIRCHEARTFAILURE.111.965186. Epub 2012 Jul 6. PMID: 22773109; PMCID: PMC3732187.

Peak VO2 as a Preferred Endpoint in Clinical Trials

- CPET measurements are more precise and reproducible than other measures of physical function
- Direct measurement of cardiac performance, in contrast to other endpoints like 6 minute walk test, which could be dependent on non-cardiac conditions
- No training effect – optimal for repeated measures
- Precise measurement
- High reproducibility

ARISE-HF Baseline Cardiac Functional Capacity

PeakVO2 (ml/kg/min)
Mean (SD): 15.7 (3.8) **Median: 15.6** Q1: 12.9 Q3: 18.6

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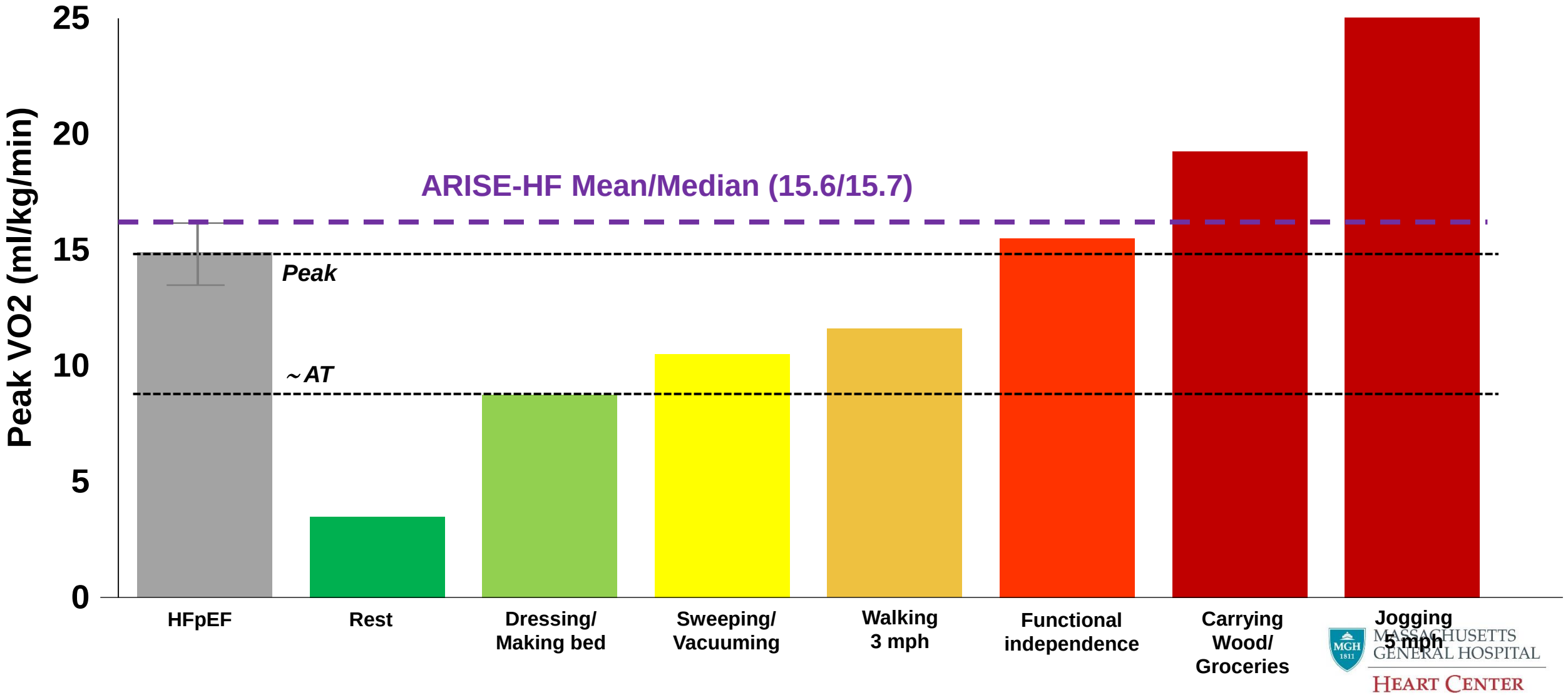
Activities of Daily Living as a Percent Mean Peak VO_2



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Peak VO2 as the Primary Endpoint in ARISE-HF

- The ARISE-HF study is designed to measure the difference in Peak VO2 between the active (high dose) AT-001 treated group and placebo
- Based on the natural history of DbCM, the placebo group is expected to decline on Peak VO2 over the 15 months of the study
- AT-001 treatment is expected to prevent further damage caused by Aldose Reductase activity, and improve cardiac energetics
- By preventing damage and improving cardiac energetics, AT-001 is expected to slow decline (or improve) Peak VO2 from baseline as compared to placebo

Statistical Powering and Correlation with Secondary Endpoints

- The ARISE-HF study is 90% powered to demonstrate a $\geq$ 6% difference in Peak VO2 change from baseline to 15 months between the active and placebo treated groups
- 6% was chosen specifically, as it has been shown to represent a meaningful clinical difference
- In the ARISE-HF study at baseline there is a statistically significant correlation between:
  - Peak VO_2 and PASE score
  - Peak VO_2 and NT-ProBNP
- This suggests that if the study meets the primary endpoint, several secondary endpoints may be met as well

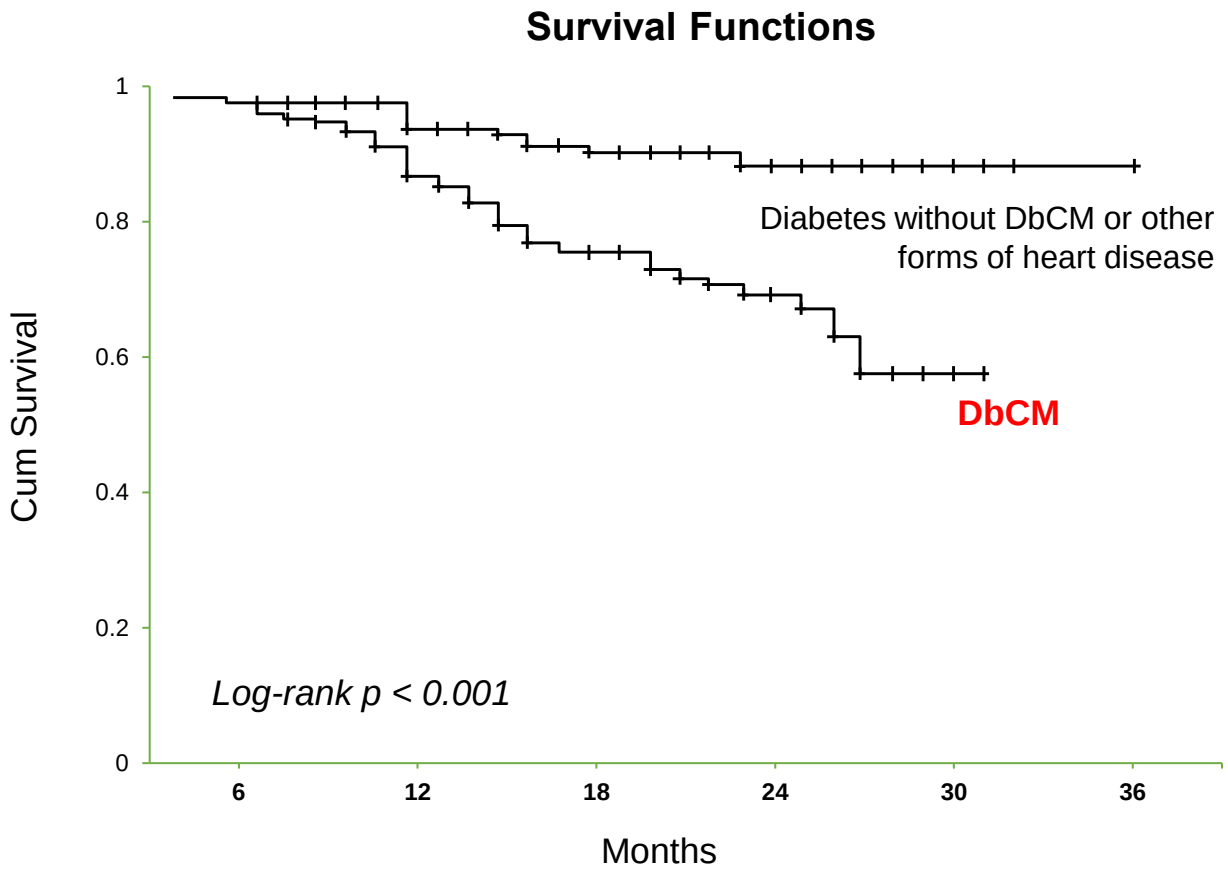
Standby For Q&A

APPLIED THERAPEUTICS
DIABETIC CARDIOMYOPATHY EXPERT FORUM

November 7, 2023

Backup

Diabetic Cardiomyopathy Mortality



- Wang Y, Marwick TH. Diagnosis of Nonischemic Stage B Heart Failure in Type 2 Diabetes Mellitus Optimal Parameters for Prediction of Heart Failure JACC: CV Imaging 2018 VOL. 11, NO. 10, 2018

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