Cross-Sectional Analysis of a Large Cohort of Patients with DbCM Enrolled in a Longitudinal Study—The Baseline Results of the ARISE-HF Trial

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26 June 2023

COI / RWA / RWI

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I serve on the Steering Committee of ARISE-HF

ARISE-HF is a phase 3 clinical trial (NCT04083339) sponsored by Applied Therapeutics

Rationale and design of the Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart Failure Trial (ARISE-HF) in patients with high-risk diabetic cardiomyopathy

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AHJ 2023

What is Diabetic Cardiomyopathy?

- Diabetic Cardiomyopathy (DbCM) is a form of Stage B Heart Failure in patients with diabetes
- Patients with DbCM have structural and/or functional cardiac abnormalities and early symptoms of disease
- 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
- There are no treatments approved for DbCM

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.

DbCM is a Form of Stage B Heart Failure

Stage	Description	Functional Capacity (Peak VO_2)
Diabetes Stage A Heart Failure	• Metabolic derangement of the myocardium due to diabetes	**~28** ml/kg/min
Diabetic Cardiomyopathy: Stage B Heart Failure	• **Cardiac structural abnormalities** • **Early indicators of DbCM** • **Impaired functional capacity (~75% normal)**	**~25% decrease** **≤21** ml/kg/min
Stage C Heart Failure	• Overt Heart Failure • HFpEF or HFrEF • Significant impact on daily activities	**>30% decrease** **10-15** ml/kg/min
Stage D Heart Failure	• Refractory Heart Failure requiring specialized interventions (e.g., Left Ventricular Assist Device) • Inability to complete daily activities	

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

How is Diabetic Cardiomyopathy Diagnosed?

DbCM is diagnosed via echocardiogram abnormalities and cardiac biomarkers in the absence of other causes of heart failure:

☑ **Echocardiographic abnormalities common in DbCM patients:**

- ❑ Left Ventricular Hypertrophy (LVH)
- ❑ Impaired Global Longitudinal Strain (GLS)
- ❑ Left Atrial Enlargement (LAE)
- ❑ Diastolic Dysfunction (abnormal E/e')

☑ **Elevation of NT-ProBNP**

☑ **Elevation of high sensitivity troponin biomarker**

☒ **Exclude:**

- ❑ Coronary Artery Disease
- ❑ Valvular disease
- ❑ Congenital Heart Failure
- ❑ Uncontrolled Hypertension

Early Indicators of Diabetic Cardiomyopathy

- The most common early indicator of DbCM reported by patients is that “physical activities feel harder to do”
- This occurs because cardiac functional capacity has significantly decreased, due to fibrosis of the cardiac tissue
- Patients with DbCM gradually reset their lifestyle to include fewer physical activities because of decreased cardiac functional capacity
- Cardiac functional capacity can be measured by CPET, or cardio-pulmonary exercise testing

Lam CS. Diabetic cardiomyopathy: an expression of stage B heart failure with preserved ejection fraction. Diab Vasc Dis Res 2015;12:234–8

DbCM Impacts Cardiac Functional Capacity & QoL

- Decreased functional capacity impacts patients' ability to perform physical activities spanning from light exercise to activities of daily living, and quality of life
- Patients with DbCM are at high risk of progression from "physical activities feel harder to do" to "inability to perform daily tasks"

	Peak VO2	Example Activity / Bruce Protocol Stage
Light to Moderate Intensity	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%
Vigorous Intensity	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

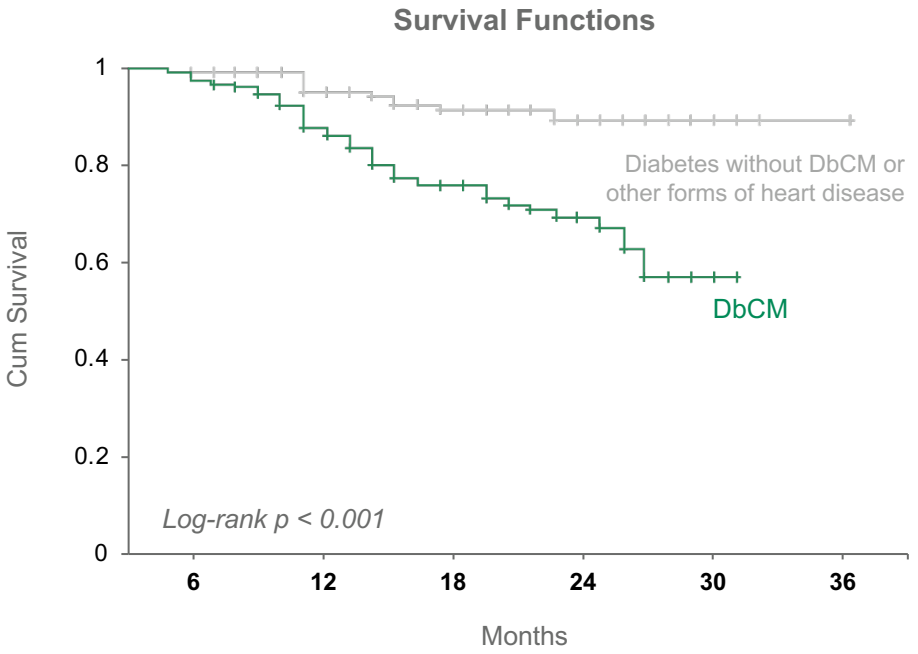
DbCM Functional Capacity ≤21ml/kg/min

QoL, Quality of Life
AMA Guides to the Evaluation of Permanent Impairment, Sixth Edition. Author: Robert D. Rondinelli, MD, PhD

Diabetic Cardiomyopathy Can Rapidly Progress to Overt Heart Failure and Death

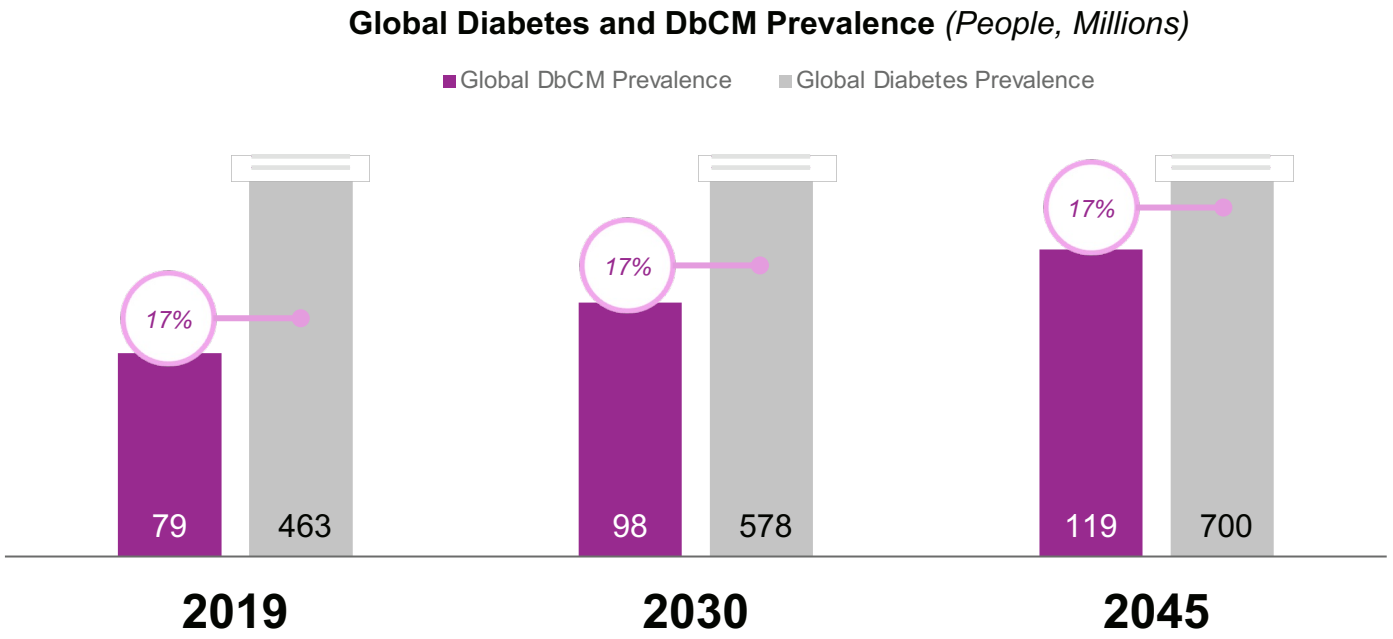
Progression to overt heart failure and death was **~1.5 fold higher** in patients with DbCM compared to diabetic patients without DbCM

290 Patients with type 2 diabetes ≥65 years of age with preserved ejection fraction and no ischemic heart disease



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

DbCM is a Major Health Issue, Which Will Expand with the Increasing Prevalence of Diabetes



DbCM projected as 17% of diabetes population based on Dandamudi et al; Saedi et al Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition 2019, https://doi.org/10.1016/j.diabres.2019.107843

Aldose Reductase Inhibition for Stabilization of Exercise capacity in Heart Failure (ARISE-HF Trial)

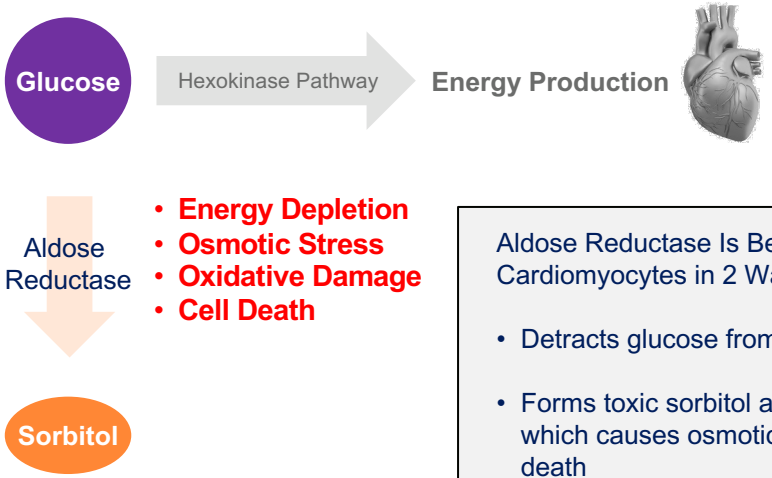
Primary Objective:
Demonstrate the efficacy of AT-001 compared to placebo, to decrease the worsening of performance on a cardio-pulmonary exercise test (CPET) in patients with DbCM.

Key Secondary Objective:
Evaluate efficacy and safety of AT-001 compared to placebo, in preventing progression to overt heart failure.

Source: NCT04083339

ARISE-HF Is An Efficacy Study to Evaluate the Ability of a Novel and Highly Selective Aldose Reductase Inhibitor (AT-001) to Prevent the Worsening of Diabetic Cardiomyopathy

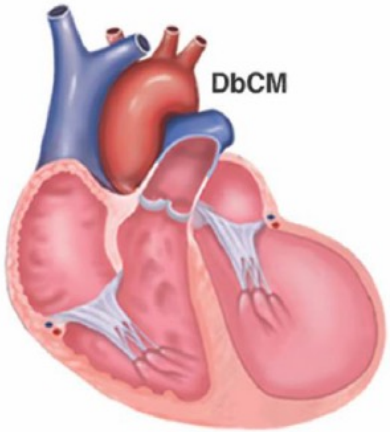
Aldose Reductase Converts Glucose to Sorbitol and Causes Damage to Cardiomyocytes in Patients with Diabetes



Aldose Reductase Is Believed to Cause Damage to Cardiomyocytes in 2 Ways[2]:

- Detracts glucose from energy efficient pathways
- Forms toxic sorbitol and other downstream products, which causes osmotic stress, oxidative damage and cell death

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



2TDM

Structural or Functional Heart Disease
or
NTproBNP ≥ 50 ng/L
or
hs-CTnT ≥ 6 ng/L

Impaired CPET
- **Peak VO_2 < 75% of predicted**
- **RER ≥ 1.05**

Patients with DbCM at high risk of progression to overt HF (SCHF) N = 675

1:1:1

- Placebo (N = 225)
- AT-001 1000 mg PO BID (N = 225)
- AT-001 1500 mg PO BID (N = 225)

Part A

Core Study
- Efficacy (15 months)
- Primary endpoint: change in CPET performance (peak VO_2) from baseline to Month 15
- Safety

27 month secondary and exploratory analysis
- Progression to overt HF
- Changes in NT-proBNP from baseline to Month 27
- Changes in mKCCQ score from baseline to Month 27
- Percentage of patients with clinically significant decrease (>6%) peak VO_2 from baseline to Month 27
- Safety

Part B

Placebo-controlled extension (>12 months)
- CV death/hospitalization
- **SAEs and AEs** leading to study drug discontinuation only if no safety issues identified in Part A

Januzzi, *AHJ* 2023

ARISE-HF: Key Inclusion/Exclusion Criteria

INCLUSION CRITERIA

1. Diagnosis of Type 2 DM
2. Age:
   - ≥60 years, or
   - ≥40 years, with duration of diabetes >10 years or renal impairment (eGFR <60 mL/min/1.73 m^2)
3. Demonstration of DbCM/ Stage B Heart Failure

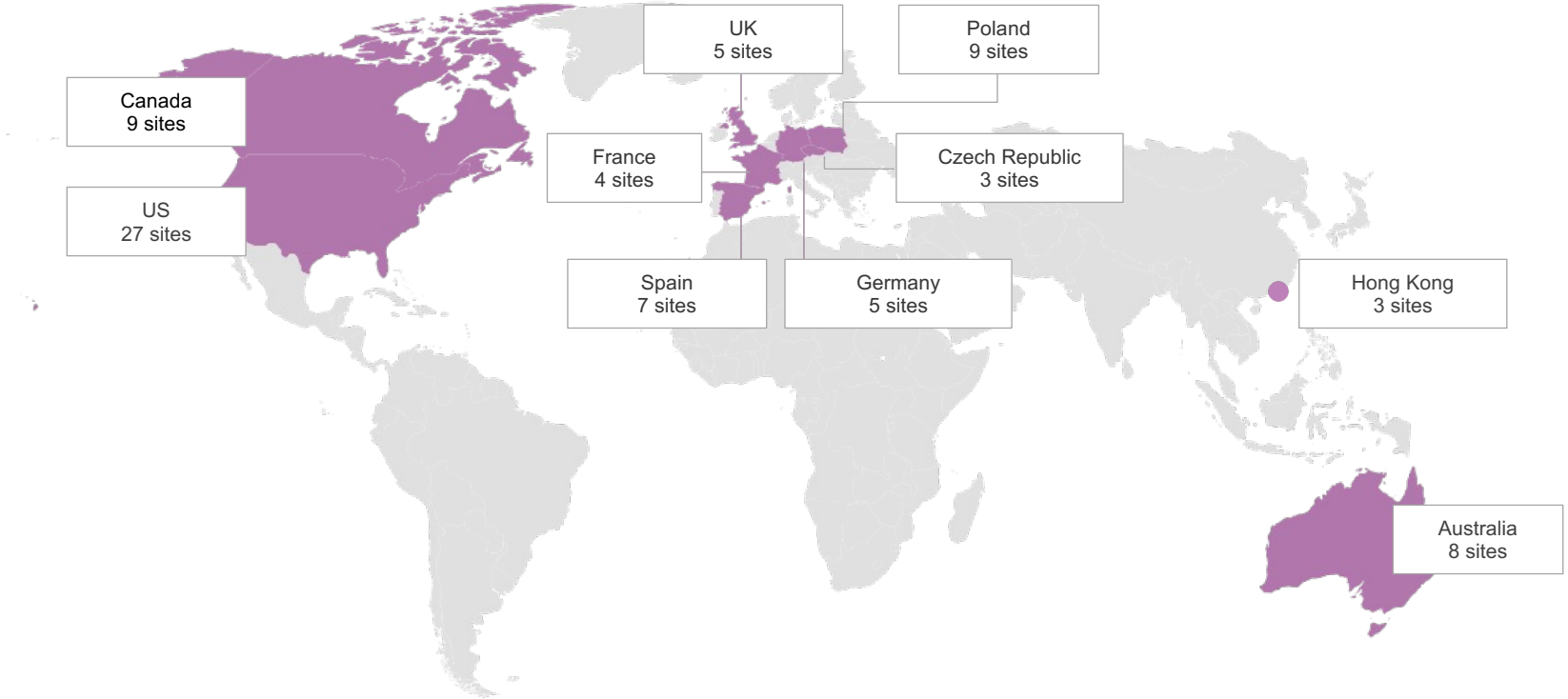
   LVEF≥ 45% and at least one of the following
   - Echocardiographic abnormalities
   - NTProBNP ≥ 50 pg/ml
   - HsTNT ≥ 6 ng/L
4. Impaired functional capacity on max CPET
   - RER > 1.05
   - Peak VO2 <75% of age/gender predicted

KEY EXCLUSION CRITERIA

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

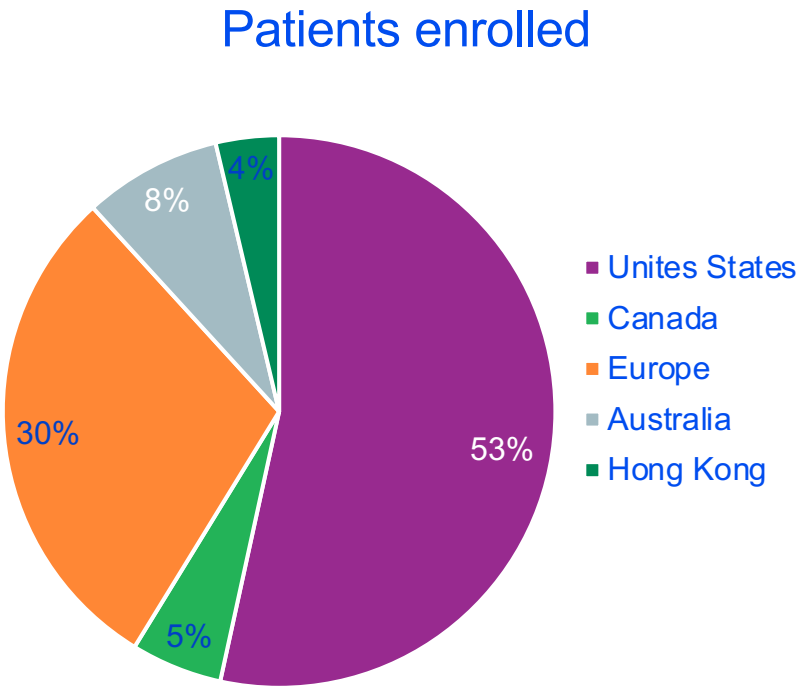
CPET = Cardio-pulmonary Exercise Test SBP = Systolic Blood Pressure DBP = Diastolic Blood Pressure ACS = Acute Coronary Syndrome CABG = Coronary artery bypass graft Percutaneous Coronary Intervention CAD = Coronary Artery Disease

ARISE-HF is Being Conducted at 80 Sites Globally

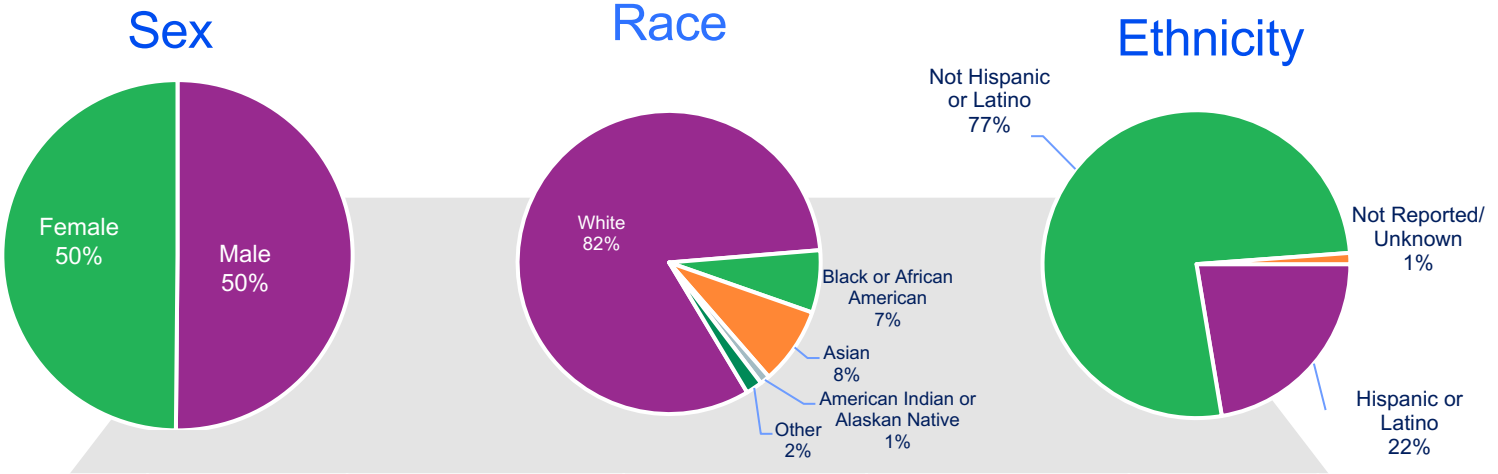


Enrollment Dashboard

	Screenned Overall	Randomized Overall
Overall	**2116**	**691**
North America	***1153***	***390***
Canada	142	39
United States	1011	351
Europe/Israel	***732***	***215***
Czech Republic	106	41
France	31	9
Germany	127	44
Poland	174	41
Spain	80	12
United Kingdom	214	68
Asia Pacific	***231***	***86***
Australia	157	59
Hong Kong	74	27



ARISE-HF: Baseline Characteristics Overview (n= 684)



Age yrs.	BMI Kg/m^2	Duration T2D yrs	Blood Pressure mmHg	HbA1c %	eGFR mL/min/1.73m^2	Hb g/dl	UACR mg/g
67.5 (7.2)	30.5 (4.5)	14.0 (9.2)	SBP 129.8 (12.8) DBP 75.8 (9.1)	6.98% (0.79%)	80.4 (16.3)	13.7 (1.4)	72.6 (255.6)

Data as of 15-Dec-2022

Baseline concomitant medications (n= 684)

Medications	N (%)
Statins	490 (72%)
ACE-I or ARBs	458 (67%)
B-blockers	139 (20%)
MRAs	12 (2%)
Diuretics (HCTZ)	119 (17%)
SGLT2 inhibitors	184 (27%)
GLP1-RA	140 (21%)
Metformin	462 (68%)
SU	133 (19%)
Insulin	163 (24%)

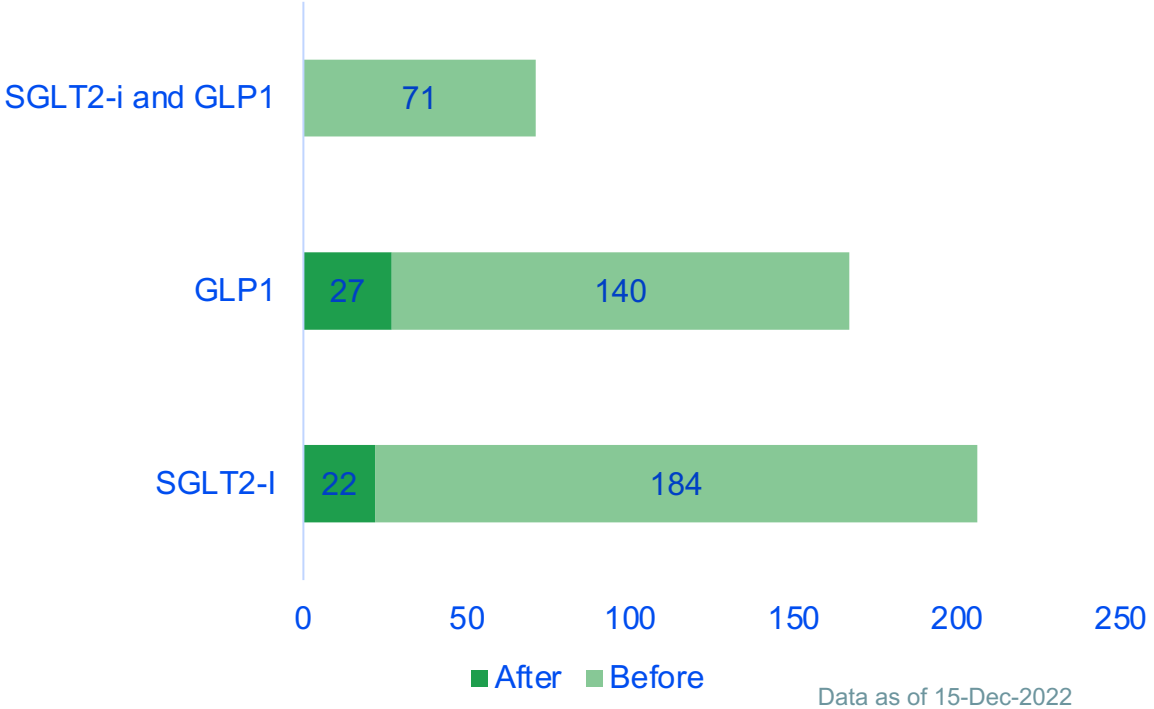
Data as of 15-Dec-2022

SGLT2-I & GLP1 Use (n=684)

10% of pts enrolled are on both SGLT2 and GLP1

3.9% of pts enrolled started GLP1 after Day 1

3.2% of patients enrolled started SGLT2 after Day 1



Data as of 15-Dec-2022

ARISE-HF: Baseline Peak VO2 (n= 680)

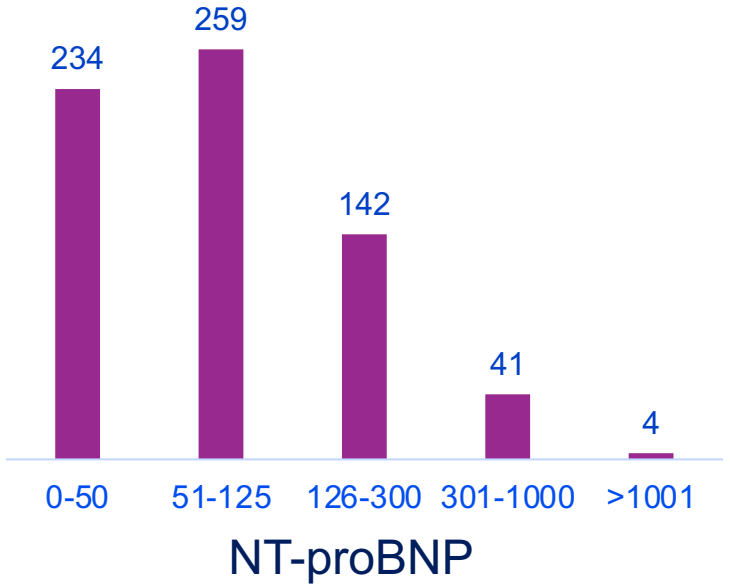
PeakVO2 (ml/kg/min)
Mean (SD) 15.7 (3.8)
Median 15.6 (Q1 12.9 – Q3 18.6)

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

Data as of 15-Dec-2022

NT-proBNP at Screening (n= 674)

NT-proBNP (ng/L = pg/mL)
Mean (SD): 115 (217)
Median: 71 (Q1 35 – Q3 134)
Max 4284*



* Patient who had a history of HFpEF/ Exclusionary Criteria

Data as of 15-Dec-2022

Baseline characteristics and Peak VO2

	Q1 N=170	Q2 N=170	Q3 N=170	Q4 N=170	P
PeakVO_2, ml/min/kg	10.9 (1.5)	14.2 (0.8)	16.9 (0.9)	20.7 (1.7)	<0.001
Age, yrs	68.8 (7.4)	68.6 (6.9)	66.4 (7.1)	66.3 (6.8)	<0.001
Male, n, %	40 (24%)	67 (39%)	87 (51%)	148 (87%)	<0.001
Race, n, %					
White	143 (84%)	143 (84%)	134 (79%)	139 (82%)	0.05
Black or African American	15 (9%)	13 (8%)	13 (8%)	5 (3%)	
Others	11 (7%)	14 (8%)	23 (14%)	26 (15%)	
BMI, kg/m²	31.7 (4.3)	31.0 (4.8)	29.9 (4.6)	29.5 (4.1)	<0.001
SBP, mmHg	127.3 (12.0)	130.6 (13.3)	130.5 (13.2)	130.8 (12.5)	0.03
DBP, mmHg	75.4 (9.5)	75.8 (9.0)	76.0 (8.6)	76.2 (9.2)	0.85
Medical History					
Duration of T2DM, yrs	14.8 (9.3)	13.0 (9.8)	15.2 (9.0)	13.0 (8.4)	0.05
Hypertension, n, %	121 (71%)	121 (71%)	110 (65%)	114 (67%)	0.49
Dyslipidemia, n, %	13 (8%)	26 (15%)	36 (5%)	33 (19%)	<0.001

Baseline characteristics and Peak VO2

	Q1 N=170	Q2 N=170	Q3 N=170	Q4 N=170	P
PeakVO_2, ml/min/kg	10.9 (1.5)	14.2 (0.8)	16.9 (0.9)	20.7 (1.7)	<0.001
Concomitant medications, n, %					
ACEI-ARBs	114 (67%)	120 (71%)	109 (64%)	115 (68%)	0.65
B-blockers	45 (27%)	40 (24%)	31 (18%)	22 (13%)	0.01
HCTZ	42 (25%)	30 (18%)	25 (15%)	22 (13%)	0.02
SGLT2 inhibitors	34 (20%)	41 (24%)	52 (31%)	56 (33%)	0.03
GLP1-RA	35 (21%)	28 (17%)	36 (21%)	41 (24%)	0.38
Laboratory test					
NT-proBNP, ng/L	94 (48-165)	73 (40-136)	68 (32-137)	57 (21-91)	<0.001
Hs-Tnt, ng/L	8 (6-11)	9 (6-12)	8 (6-13)	9 (7-13)	0.09
HbA1c, %	7.0 (0.8)	6.9 (0.8)	7.1 (0.8)	7.0 (0.7)	0.19
Hgb, g/dl	13.0 (1.4)	13.5 (1.4)	13.8 (1.3)	14.4 (1.3)	<0.001
eGFR, ml/min/1.73m^2	78.8 (16.9)	78.8 (15.5)	81.3 (17.5)	82.7 (14.9)	0.07
UACR	16 (8-41)	14 (8-46)	14 (8-42)	16 (9-41)	0.45

Baseline characteristics and Peak VO2

	Q1 N=170	Q2 N=170	Q3 N=170	Q4 N=170	P
PeakVO_2, ml/min/kg	10.9 (1.5)	14.2 (0.8)	16.9 (0.9)	20.7 (1.7)	<0.001
Echocardiogram					
LVEF, %	62.3 (5.7)	62.2 (6.0)	62.2 (5.3)	62.1 (5.1)	0.98
GLS, %	-17.5 (3.3)	-17.4 (3.1)	-17.5 (3.3)	-17.6 (2.7)	0.98
LAVI, ml/m^2	23.5 (6.7)	24.7 (7.3)	24.0 (7.5)	25.9 (8.4)	0.03
LVMI, g/m^2	74.9 (20.2)	79.7 (22.1)	77.9 (22.1)	78.1 (19.1)	0.22
E/e'	11.9 (6.0)	10.2 (2.9)	10.4 (5.0)	9.2 (2.7)	<0.001
RVSP, mmHg	24.9 (7.1)	23.7 (6.8)	22.9 (7.4)	21.9 (8.2)	0.03

ARISE-HF: Baseline questionnaires (n= 680)

Questionnaire	Mean (SD)
mKCCQ Overall	90.3 (14.6)
mKCCQ Physical Activity	89.1 (16.3)
PASE Score	154.3 (89.6)

Data as of 15-Dec-2022

Summary

- Diabetic Cardiomyopathy (DbCM) is a serious, progressive disease that can lead to increased hospitalizations, morbidity and mortality
- There are currently no treatments approved for DbCM; AT-001 is being investigated for the treatment of DbCM
- **Baseline characteristics of the ARISE-HF identify a pathological phenotype often unrecognized and susceptible to progress toward overt heart failure**