JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2024

PUBLISHED BY ELSEVIER

Randomized Trial of a Selective Aldose Reductase Inhibitor in Patients With Diabetic Cardiomyopathy

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ABSTRACT

BACKGROUND Progression to symptomatic heart failure is a complication of type 2 diabetes; heart failure onset in this setting is commonly preceded by deterioration in exercise capacity.

OBJECTIVES The study sought to determine whether AT-001, a highly selective aldose reductase inhibitor, can stabilize exercise capacity among individuals with diabetic cardiomyopathy (DbCM) and reduced peak oxygen uptake (Vo_2).

METHODS A total of 691 individuals with DbCM meeting inclusion and exclusion criteria were randomized to receive placebo or ascending doses of AT-001 twice daily. Stratification at inclusion included region of enrollment, cardiopulmonary exercise test results, and use of sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists. The primary endpoint was proportional change in peak Vo_2 from baseline to 15 months. Subgroup analyses included measures of disease severity and stratification variables.

RESULTS The mean age was 67.5 ± 7.2 years, and 50.4% of participants were women. By 15 months, peak Vo_2 fell in the placebo-treated patients by -0.31 mL/kg/min ($P = 0.005$ compared to baseline), whereas in those receiving high-dose AT-001, peak Vo_2 fell by -0.01 mL/kg/min ($P = 0.21$); the difference in peak Vo_2 between placebo and high-dose AT-001 was 0.30 ($P = 0.19$). In prespecified subgroup analyses among those not receiving sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists at baseline, the difference between peak Vo_2 in placebo vs high-dose AT-001 at 15 months was 0.62 mL/kg/min ($P = 0.04$; interaction $P = 0.10$).

CONCLUSIONS Among individuals with DbCM and impaired exercise capacity, treatment with AT-001 for 15 months did not result in significantly better exercise capacity compared with placebo. (Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy [ARISE-HF]; NCT04083339) (J Am Coll Cardiol 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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Harlan Krumholz, MD, SM, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 8, 2024; revised manuscript received March 13, 2024, accepted March 13, 2024.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2024.03.380

ABBREVIATIONS AND ACRONYMS

ANCOVA = analysis of covariance

CPET = cardiopulmonary exercise test

DbCM = diabetic cardiomyopathy

DM = diabetes mellitus

GLP-1RA = glucagon-like peptide-1 receptor agonist

HF = heart failure

hs-cTnT = high-sensitivity cardiac troponin T

KCCQ = Kansas City Cardiomyopathy Questionnaire

LS = least square

MedDRA = Medical Dictionary for Regulatory Activities

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PASE = Physical Activity Scale for the Elderly

RER = respiratory exchange ratio

SGLT2 = sodium-glucose cotransporter 2

T2DM = type 2 diabetes mellitus

Vo_2 = oxygen uptake

Heart failure (HF) is an underappreciated but increasingly recognized major cardiovascular complication of individuals with diabetes mellitus (DM).[1] For example, it is estimated that individuals with type 2 DM (T2DM) have a more than doubling in their risk for incident HF compared to those without DM, and when a person with T2DM develops HF, their risk for mortality is considerably higher than someone without DM.[1] Among individuals with DM, the risk for HF onset persists even when adjusting for factors such as glycemic control, blood pressure control, valvular heart disease, or the presence and severity of ischemic heart disease.[2-4] It is now recognized that DM itself may result in heart muscle disease related to the chronicity and severity of hyperglycemia, abnormalities in myocardial metabolism, and oxidative stress.[5,6] These processes result in diabetic cardiomyopathy (DbCM),[4,7-12] a form of cardiac dysfunction that is initially without overt HF symptoms, classified as stage B HF;[3] this is associated with high risk for progression to overt HF. No treatment is currently offered to DbCM in those without overt HF, which is an ideal opportunity for intervention to reduce the considerable risk in such individuals.

An important cause of DbCM is increased activity of the polyol pathway.[11-15] Stimulated by hyperglycemic conditions, the polyol pathway reduces glucose to sorbitol, followed by further conversion of sorbitol to fructose; this results in tissue injury and fibrosis. Aldose reductase is the initial, rate-limiting step in the polyol pathway;[16] accordingly, inhibition of aldose reductase has been proposed as a treatment for DbCM.[8,17,18] AT-001 is a novel, highly selective aldose reductase inhibitor that demonstrates higher target engagement than other compounds in its class. In early-stage trials of individuals with DbCM, AT-001 lowered concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and circulating sorbitol without dose-limiting toxicity.[9] For this reason, it was hypothesized that AT-001 treatment would result in stabilization of DbCM progression. This phase 3 study evaluated the effect of AT-001 on exercise capacity among individuals with DbCM and reduced exercise capacity at high risk for progression to overt HF.

METHODS

All research procedures were approved by local Institutional Review Boards, and study participants provided informed consent for their participation in the trial.

RATIONALE AND DESIGN. The rationale, design, and baseline characteristics of ARISE-HF (Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart Failure; NCT04083339) have been recently reported.[9,10] The Supplemental Appendix details trial leadership, committees, and study sites.

ARISE-HF was a global, phase 3, randomized, placebo-controlled, double-blind study performed at 62 sites to assess the efficacy of AT-001 compared with placebo for stabilization of exercise capacity (as measured by peak oxygen uptake [Vo_2] during cardiopulmonary exercise testing [CPET]) in adult study participants with T2DM and DbCM.

The full inclusion and exclusion criteria for participation in ARISE-HF are detailed in Supplemental Table 1. In brief, study participants with T2DM were considered for enrollment if they were age ≥60 years (or age ≥40 to <60 years with duration of T2DM of ≥10 years or with an estimated glomerular filtration rate of <60 mL/min/1.73 m^2) and had either abnormal cardiac structure or function or increased concentration of either NT-proBNP or high-sensitivity cardiac troponin T (hs-cTnT). Furthermore, study participants were required to have impaired cardiac functional capacity defined by a peak Vo_2 of ≤75% of predicted based on age and sex[19] and ability to achieve acceptable maximal effort during CPET (defined as a respiratory exchange ratio [RER] of ≥1.05). Importantly, well-controlled blood pressure and hemoglobin A_{1c} of <7.5% were both required for enrollment in the trial. All glucose-lowering treatments were allowed except for thiazolidinediones. Use of sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RA) was permitted.

Following baseline CPET, confirmation of eligibility, and provision of informed consent, study participants were randomized in a 1:1:1 fashion to receive placebo, low-dose AT-001 (1,000 mg twice daily), or high-dose AT-001 (1,500 mg twice daily).

Randomization was stratified by region (North America vs the rest of the world), by the baseline CPET results (RER of ≥1.15 vs RER of <1.15; peak Vo_2 of ≤15 mL/kg/min in study participants with RER of ≥1.15), and by the use of an SGLT2 inhibitor or

GLP1-RA at baseline. The rationale for regional stratification was to evaluate for geographic heterogeneity in baseline DbCM profiles and response to therapy, and the RER stratification was used to ensure adequate distribution of high- and lower-performing study participants. Stratification of SGLT2 inhibitors and/or GLP-1RA use was based on previous evidence suggesting an impact of these therapies on exercise capacity and, conceivably, the residual effect on peak Vo_2 exerted by those drugs may not leave sufficient room to detect an effect of aldose reductase inhibition.[20,21]

The high dose of AT-001 was selected as the target dose, given its ability to lower NT-proBNP in phase 1 and 2 trials, and lower-dose treatment was included to explore the safety and efficacy of lower doses of the drug. Study participants were treated for a planned 15 months with routine study visits as described. A longer treatment duration was initially planned if a neutral finding was returned at 15 months;[9] because of a 2-year study delay caused by the global COVID-19 pandemic, the trial was completed at 15 months without continuation.

STUDY ENDPOINTS. The primary endpoint of ARISE-HF was change in peak Vo_2 from baseline to 15 months between placebo and high-dose AT-001. Initial prespecified subgroups analyzed included region of enrollment, sex, baseline CPET parameters (peak Vo_2, RER), baseline hemoglobin A_{1c}, and baseline use vs nonuse of SGLT2 inhibitor and/or GLP-1 RA.

Key secondary outcomes of ARISE-HF included percentage of study participants with a clinically significant decrease (≥6%) in peak Vo_2, effect of low-dose AT-001, change in NT-proBNP concentrations, change in health status assessed using the 12-question Kansas City Cardiomyopathy Questionnaire (KCCQ),[22] and change in activity assessed using the Physical Activity Scale for the Elderly (PASE).[23] Finally, an additional prespecified endpoint was progression to signs or symptoms suggestive of HF (based on adverse event reporting by site investigators using Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) together with positively adjudicated events (a composite of cardiovascular death and HF hospitalization).

ADVERSE EVENTS. All adverse events and serious adverse events were recorded. Potential cardiovascular serious adverse events, including possible cardiovascular deaths or HF hospitalizations, were adjudicated by a Clinical Events Adjudication Committee.

STATISTICAL ANALYSES. Data frequencies are expressed as mean ± SD or median (Q1-Q3) depending on normality. Original study planning included extension to 27 months if assessment at 15 months did not demonstrate a statistically significant difference between AT-001 and placebo; however, all results shown presently are based on the 15-month timepoint analyzed using $\alpha/2$. Assuming a 20% dropout rate within each group, a sample size of 181 patients per treatment group was calculated to provide the analysis with >90% power to detect a difference in peak Vo_2 of 1.2 mL/kg/min between active treatment and placebo assuming a common SD of 3 mL/kg/min in each stratum. This difference in peak Vo_2 of 1.2 mL/kg/min is considered clinically significant for patients with HF.[24]

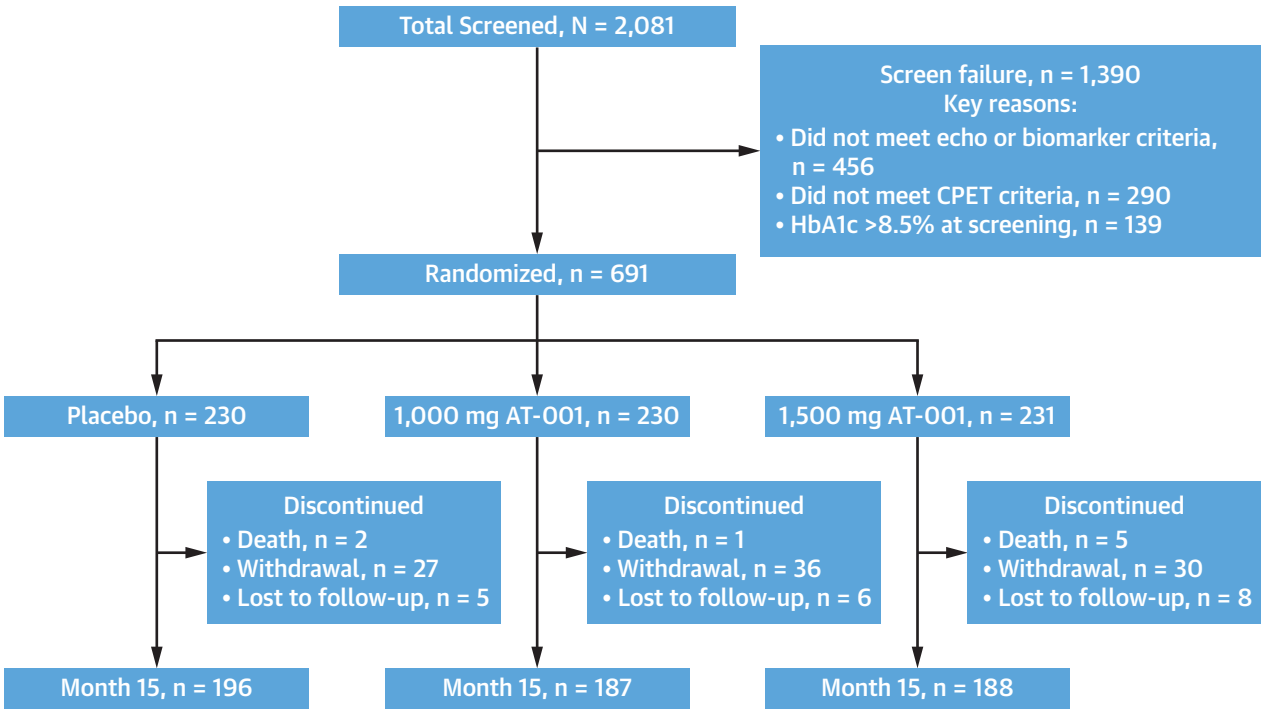
The primary endpoint of the change in Vo_2 from baseline to 15 months was analyzed using a mixed model for repeat measures analysis of covariance (ANCOVA) model with an unstructured covariance matrix using $\alpha/2$; least-square (LS) mean changes (with SE) in peak Vo_2 were examined. Before using the prespecified analysis method of ANCOVA, graphical and visual inspection of the distribution of the primary endpoint was performed to satisfy that the distribution was normal. There were also no issues with using ANCOVA based on the evaluation of residuals.

There were 3 main subgroup analyses based on measures of disease severity at baseline and/or study stratification criteria. These included presence of abnormal NT-proBNP (using a cutpoint of 125 ng/L) or hs-cTnT (using a cutpoint of 14 ng/L), baseline CPET result (RER of ≥1.15 vs RER of <1.15; peak Vo_2 of ≤15 mL/kg/min in study participants with RER of ≥1.15), region of enrollment, and use of SGLT2 inhibitor or GLP1-RA at baseline. These subgroups of interest were included as fixed effects, with a random effect at the patient level. All efficacy analyses were conducted using the intent-to-treat principle.

Analysis of the percentage of patients with a decrease in peak Vo_2 of ≥6% was performed using a logistic regression model adjusting for covariates based on randomization stratification factors. Estimated ORs and associated 2-sided 95% CIs were generated. Analyses of the changes in NT-proBNP, KCCQ score, and PASE score from baseline to 15 months were assessed using a mixed model for repeat measures approach like that for the primary efficacy outcome. The frequency of signs/symptoms suggesting HF with or without development of positively adjudicated HF events were compared using chi-square testing.

All statistics were performed using SAS 9.4 (SAS Institute Inc), with 2-sided P values of <0.05 considered significant.

FIGURE 1 Study Flow for ARISE-HF



A total of 691 eligible individuals with diabetic cardiomyopathy and reduced exercise capacity were randomized. ARISE-HF = Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy; CPET = cardiopulmonary exercise test; HbA1c denotes = hemoglobin A_{1c}.

ROLE OF THE SPONSOR. Applied Therapeutics, Inc participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; review of the manuscript; and decision to submit the manuscript for publication. All statistical analyses were independently confirmed by the investigative team. The sponsor did not have the right to veto publication and did not have control regarding which journal the paper was submitted to. A medical writer was not used for preparation of the manuscript.

RESULTS

BASELINE CHARACTERISTICS. Figure 1 details study flow and patient disposition. Between September 18, 2019, and October 31, 2022, 2,081 individuals were screened for study participation; from these, 691 eligible study participants with stage B HF and reduced exercise capacity were randomized to receive placebo (n = 230) or AT-001 at low dose (n = 230) and high dose (n = 231) or placebo (n = 230). At 15 months, there were 196 study participants in the placebo arm, 187 receiving low-dose AT-001, and 188 receiving high-dose AT-001 with data for analysis.

Baseline characteristics of the study participants as a function of treatment allocation are detailed in Table 1. Characteristics were well balanced between study arms. Overall, the mean ± SD age was 67.5 ± 7.2 years, and 50.4% of participants were women. The race and ethnicity of the study participants reflects the global enrollment; 82.5% were White (of whom 21.9% were of Hispanic ethnicity), 8.4% were Asian, and 7.2% were Black. On average, study participants had obesity, with a body mass index of 30.6 ± 4.6 kg/m^2. The average duration of T2DM was 14.5 ± 10.1 years. Consistent with expectations for well-controlled T2DM, the baseline hemoglobin A_{1c} was 6.98% ± 0.79%; in a similar fashion, although a history of hypertension was prevalent (75.7%), control of blood pressure was acceptable. Study participants received a mixture of glucose-lowering therapies; notably, 32.0% were treated with SGLT2 inhibitors, and 25% were receiving a GLP-1RA. The balance of use of SGLT2 inhibitors or GLP-1RA was similar across study arms, at approximately 38%.

TABLE 1 Baseline Clinical Characteristics of Study Participants Randomized in ARISE-HF as a Function of Treatment Allocation

	All (N = 691)	Placebo (n = 230)	AT-001 1,000 mg (n = 230)	AT-001 1,500 mg (n = 231)
Age, y	67.5 ± 7.2	68.2 ± 6.7	67.4 ± 7.8	66.9 ± 7.0
Female	348 (50.4)	124 (53.9)	107 (46.5)	117 (50.6)
Race				
White	570 (82.5)	195 (84.8)	191 (83.0)	184 (79.7)
Black	50 (7.2)	14 (6.1)	13 (5.7)	23 (10.0)
Asian	58 (8.4)	17 (7.4)	24 (10.4)	17 (7.4)
American Indian or Alaskan Native	5 (0.7)	2 (0.9)	0 (0)	3 (1.3)
Native Hawaiian or other Pacific Islander	1 (0.1)	0 (0)	0 (0)	1 (0.4)
Other	5 (0.7)	1 (0.4)	1 (0.4)	3 (1.3)
Ethnicity				
Hispanic	151 (21.9)	44 (19.1)	48 (20.9)	59 (25.5)
Non-Hispanic	532 (77.1)	183 (79.6)	179 (77.8)	170 (73.6)
Body mass index, kg/m^2	30.6 ± 4.6	30.9 ± 4.8	30.4 ± 4.6	30.5 ± 4.4
Smoking status				
Current smoker	66 (9.6)	21 (9.1)	23 (10.0)	22 (9.5)
Previous smoker	246 (35.6)	85 (37)	81 (35.2)	80 (34.6)
Never	394 (57)	132 (57.4)	130 (56.5)	132 (57.1)
Vital signs at baseline				
Systolic blood pressure, mm Hg	131 ± 17	131 ± 17	132 ± 17	131 ± 16
Diastolic blood pressure, mm Hg	77 ± 10	77 ± 11	77 ± 10	77 ± 10
Heart rate, beats/min	78 ± 13	78 ± 12	79 ± 13	78 ± 13
Medical history				
Hypertension	523 (75.7)	179 (77.8)	179 (77.8)	165 (71.4)
Dyslipidemia	116 (16.8)	45 (19.6)	36 (15.7)	35 (15.2)
Duration of T2DM, y	14.5 ± 9.1	14.4 ± 9.2	14.6 ± 9.2	14.4 ± 9.0
Geographic region				
North America	390 (56.4)	130 (56.5)	129 (56.1)	131 (56.7)
Rest of the world	301 (43.6)	100 (43.5)	101 (43.9)	100 (43.3)
Use of SGLT2i or GLP-1RA at baseline	263 (38.1)	86 (37.4)	89 (38.7)	88 (38.1)
Baseline respiratory exchange rate				
<1.15	296 (42.8)	98 (42.6)	99 (43)	99 (42.9)
≥1.15	394 (57.2)	132 (57.4)	131 (57)	131 (56.7)
Baseline peak Vo_2, mL/kg/min	15.7 ± 3.8	15.6 ± 3.8	15.7 ± 3.8	16 ± 3.9

Values are mean ± SD or n (%).

ARISE-HF = Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy; GLP1-RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus; Vo_2 = oxygen uptake.

Overall, at baseline, the median NT-proBNP was 71 ng/L (Q1-Q3: 25-135 ng/L), and the corresponding hs-cTnT was 9 ng/L (Q1-Q3: 6-12 ng/L). Echocardiographic abnormalities were prevalent, with global longitudinal strain of <16% in 25.3%, E/e′ of >14 in 17.7%, and increased indexed left atrial volume (>34 mL/m^2) or left ventricular mass (>95 g/m^2 in women; >115 g/m^2 in men) in 11.9% each. The results of questionnaire testing at baseline are detailed in Table 2, which demonstrates good balance of objective measures across study arms.

The baseline peak Vo_2 was similar across treatment arms, averaging 15.7 ± 3.8 mL/kg/min. A similar percentage of study participants had an RER of ≥1.15 in each study arm, at approximately 57%.

PRIMARY ENDPOINT. As shown in Figure 2, from baseline to 15 months, LS-mean peak Vo_2 fell in the placebo-treated patients by -0.31 mL/kg/min (SE: 0.18; P = 0.005) compared to baseline. In those receiving high-dose AT-001, peak Vo_2 was essentially unchanged, reduced by -0.01 mL/kg/min (SE: 0.18; P = 0.21) compared to baseline. Despite the difference in change between placebo and high-dose AT-001, the primary endpoint of LS mean change difference between placebo and high-dose AT-001 was 0.30 (SE: 0.23) and did not reach statistical significance (P = 0.19).

In prespecified subgroup analyses, among nonusers of SGLT2 inhibitors and/or GLP-1RA, peak Vo_2 declined by 0.54 mL/kg/min by 15 months, whereas

TABLE 2 Objective Testing Results at Baseline as a Function of Treatment Allocation

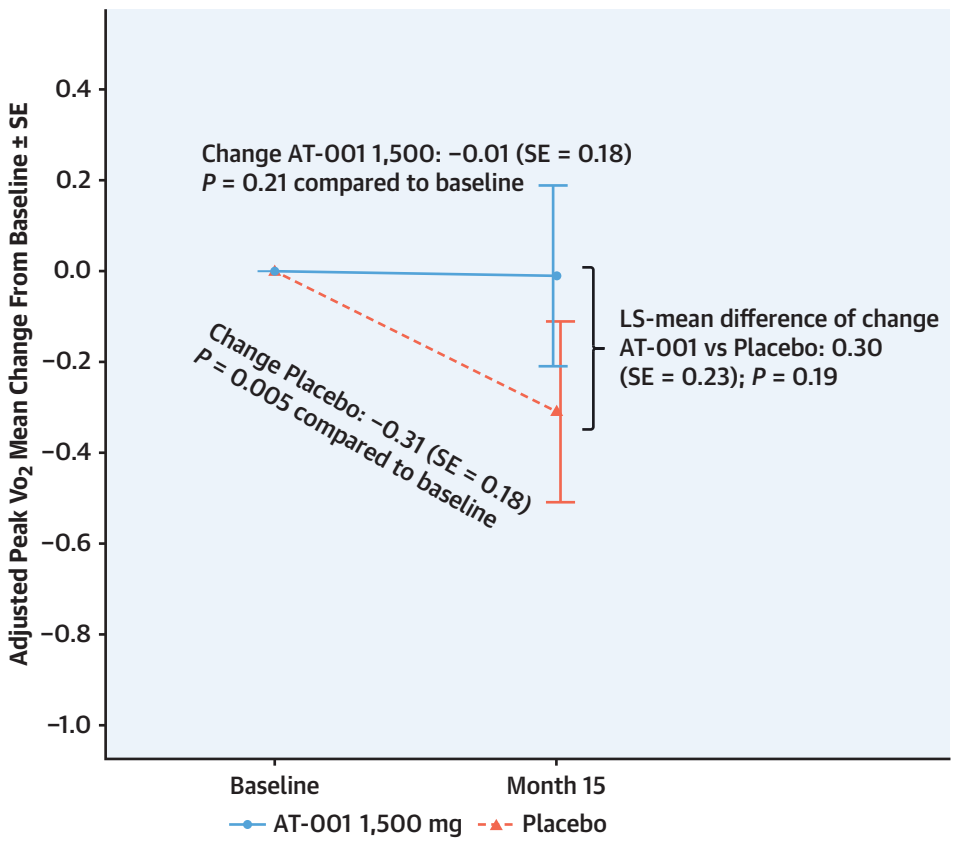
	Placebo	AT-001 1,000 mg	AT-001 1,500 mg
PASE score	159 ± 94	150 ± 90	157 ± 87
KCCQ overall summary score	90 ± 16	90 ± 15	91 ± 13
KCCQ clinical summary score	90 ± 15	91 ± 114	91 ± 13
KCCQ total symptom score	92 ± 15	92 ± 15	94 ± 13
KCCQ physical limitation score	88 ± 17	90 ± 17	89 ± 16
KCCQ symptom stability score	52 ± 10	52 ± 11	51 ± 9
KCCQ symptom frequency score	91 ± 15	91 ± 15	93 ± 13
KCCQ symptom burden score	92 ± 15	92 ± 15	94 ± 13
KCCQ self-efficacy score	85 ± 22	85 ± 25	86 ± 22
KCCQ quality of life score	87 ± 20	88 ± 20	87 ± 18
KCCQ social limitation score	92 ± 18	92 ± 18	93 ± 15

Values are mean ± SD.
KCCQ = Kansas City Cardiomyopathy Questionnaire; PASE = Physical Activity Scale for the Elderly.

treatment with high-dose AT-001 was associated with improvement in peak Vo_2 by 0.08 mL/kg/min (LS mean difference between peak Vo_2 in placebo vs high-dose AT-001 in this prespecified subgroup: 0.62; $P = 0.04$; interaction P value = 0.10). The baseline characteristics of those study participants not receiving SGLT2 inhibitor or GLP-1RA at baseline are detailed in Supplemental Table 2. Other examined prespecified subgroups showed no obvious differences in peak Vo_2 related to treatment with placebo vs AT-001.

SECONDARY ENDPOINTS. Relative to secondary endpoints, in those receiving low-dose AT-001, peak Vo_2 declined by -0.29 mL/kg/min (SE: 0.18), which was similar to placebo ($P = 0.84$ for difference).

FIGURE 2 Primary Endpoint of ARISE-HF



Although peak Vo_2 declined in placebo-treated patients and remained the same in those treated with high-dose AT-001, the proportional change in peak Vo_2 between study arms was not significantly different at 15 months. Because of trial termination, the effect of AT-001 at 27 months was not explored. ARISE-HF = Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy; LS = least square; VO2 = oxygen uptake.

TABLE 3 Change in Physical Activity and Health Status From Baseline to 15 Months

Questionnaire	Measure	Change From Baseline to 15 Months		
		Placebo	AT-001 1,000 mg	AT-001 1,500 mg
PASE score	LS mean (SE)	-5.84 (7.34)	-6.96 (7.24)	-7.46 (7.22)
	LS mean difference (SE)		-1.12 (9.2)	-1.62 (9.11)
	P		0.90	0.86
KCCQ overall summary score	LS mean (SE)	-1.62 (1.02)	-0.18 (1.02)	-2.61 (1)
	LS mean difference (SE)		1.44 (1.29)	-0.99 (1.27)
	P		0.27	0.44
KCCQ clinical summary score	LS mean (SE)	-2.99 (0.99)	-1.05 (0.99)	-3.72 (0.97)
	LS mean difference (SE)		1.94 (1.26)	-0.74 (1.24)
	P		0.12	0.55
KCCQ total symptom score	LS mean (SE)	-3.3 (1.03)	-0.49 (1.03)	-4.42 (1.01)
	LS mean difference (SE)		2.81 (1.31)	-1.12 (1.29)
	P		0.03	0.39
KCCQ physical limitation score	LS mean (SE)	-2.72 (1.21)	-1.85 (1.21)	-2.65 (1.18)
	LS mean difference (SE)		0.88 (1.54)	0.07 (1.51)
	P		0.57	0.96
KCCQ symptom stability score	LS mean (SE)	-1.01 (1.2)	-0.44 (1.2)	-0.36 (1.18)
	LS mean difference (SE)		0.57 (1.52)	0.65 (1.5)
	P		0.71	0.67
KCCQ symptom frequency score	LS mean (SE)	-3.34 (1.12)	-0.06 (1.12)	-4.05 (1.1)
	LS mean difference (SE)		3.28 (1.42)	-0.71 (1.4)
	P		0.02	0.61
KCCQ symptom burden score	LS mean (SE)	-3.25 (1.08)	-0.96 (1.09)	-4.8 (1.06)
	LS mean difference (SE)		2.28 (1.37)	-1.55 (1.35)
	P		0.10	0.25
KCCQ self-efficacy score	LS mean (SE)	-1.55 (2.01)	2.68 (2)	-2.43 (1.96)
	LS mean difference (SE)		4.23 (2.54)	-0.89 (2.5)
	P		0.10	0.72
KCCQ quality of life score	LS mean (SE)	0.21 (1.45)	0.72 (1.45)	-0.52 (1.42)
	LS mean difference (SE)		0.51 (1.84)	-0.73 (1.81)
	P		0.78	0.69
KCCQ social limitation score	LS mean (SE)	-0.62 (1.52)	0.97 (1.49)	-2.44 (1.49)
	LS mean difference (SE)		1.59 (1.94)	-1.82 (1.93)
	P		0.41	0.34

LS = least square; other abbreviations as in Table 2.

Overall, a ≥6% decline in peak Vo_2 was observed in 41.8% of placebo-treated patients and 36.2% of those treated with high-dose AT-001 (OR: 0.80; 95% CI: 0.52-1.21; $P = 0.29$). Among nonusers of SGLT2 inhibitors or GLP-1RA, the difference was 46.0% vs 32.7% (OR: 0.56; 95% CI: 0.33-0.96; $P = 0.04$).

No significant differences were seen in NT-proBNP concentrations between study arms from baseline to 15 months. For example, the difference in LS mean change difference between placebo and high-dose AT-001 was 10.2 (SE: 9.8; $P = 0.30$). Similarly, no significant difference in PASE score or consistent effect on KCCQ domains was seen from baseline to 15 months in those treated with AT-001 vs placebo (**Table 3**). There was 1 adjudicated HF hospitalization in the placebo arm and 2 adjudicated cardiovascular deaths (both high-dose AT-001). In a prespecified analysis that considered potential cardiovascular adverse events identified using MedDRA terms (Supplemental Table 3) together with adjudicated endpoints, placebo-treated patients had 26 events, low-dose AT-001 patients had 11 events, and high-dose AT-001 patients had 14 events (chi-square $P = 0.01$).

ADVERSE EVENTS. The most frequent adverse events were mild to moderate and with no major differences in frequency among study groups (**Table 4**). Nausea and constipation events were numerically slightly more frequent in those treated with AT-001, but these were typically mild and not associated with a higher likelihood of treatment discontinuation. Treatment with AT-001 was not associated with any evidence of significant liver injury (Supplemental Table 4). Frequency of rise in

TABLE 4 Adverse Events Occurring at >5% During 15 Months of Treatment in ARISE-HF

	Overall	Placebo	AT-001 1,000 mg	AT-001 1,500 mg
COVID-19	131 (19.0)	44 (19.1)	53 (23.2)	34 (14.7)
Urinary tract infection	96 (13.9)	25 (10.9)	34 (14.9)	37 (16.0)
Constipation	49 (7.1)	11 (4.8)	17 (7.5)	21 (9.1)
Nausea	51 (7.4)	13 (5.7)	20 (8.8)	18 (7.8)
Decrease in estimated glomerular filtration rate	39 (5.7)	2 (0.9)	16 (7.0)	21 (9.1)
Diarrhea	58 (8.4)	23 (10)	20 (8.8)	15 (6.5)
Fatigue	54 (7.8)	22 (9.6)	12 (5.3)	20 (8.7)
Back pain	40 (5.8)	9 (3.9)	14 (6.1)	17 (7.4)
Nasopharyngitis	45 (6.5)	15 (6.5)	19 (8.3)	11 (4.8)
Dizziness	37 (5.4)	10 (4.3)	5 (2.2)	22 (9.5)
Arthralgia	42 (6.1)	16 (7.0)	11 (4.8)	15 (6.5)
Headache	35 (5.1)	11 (4.8)	10 (4.4)	14 (6.1)
Upper respiratory tract infection	37 (5.4)	13 (5.7)	12 (5.3)	12 (5.2)
Fall	37 (5.4)	14 (6.1)	7 (3.1)	16 (6.9)
Peripheral edema	36 (5.2)	14 (6.1)	10 (4.4)	12 (5.2)

Values are n (%).
ARISE-HF = Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy.

serum creatinine at any time during the trial was infrequent (Supplemental Table 5). Rise in serum creatinine (and other adverse events) was generally transient in people who discontinued the study medication as well as in those who did not interrupt the daily intake of the study medication; there was not an imbalance in drug discontinuation attributable to deterioration of renal function between the patients on the study drug (Supplemental Table 6) compared to placebo.

DISCUSSION

DbCM is an increasingly recognized cause of HF in persons with T2DM but lacks a proven, specific treatment.[7,12] In this prospective, randomized controlled trial of individuals with well-controlled T2DM complicated by stage B HF and impaired exercise capacity, 15 months of a highly selective, well-tolerated aldose reductase inhibitor (AT-001) did not result in higher peak Vo_2 vs placebo (**Central Illustration**). In a prespecified subgroup of individuals not prescribed an SGLT2 inhibitor or GLP-1RA at baseline (accounting for 62% of the study population), AT-001 treatment was associated with better exercise capacity at 15 months; although exploratory, such a finding is of note and suggests that AT-001 may have an impact on a relevant outcome measure in certain patients with DbCM.

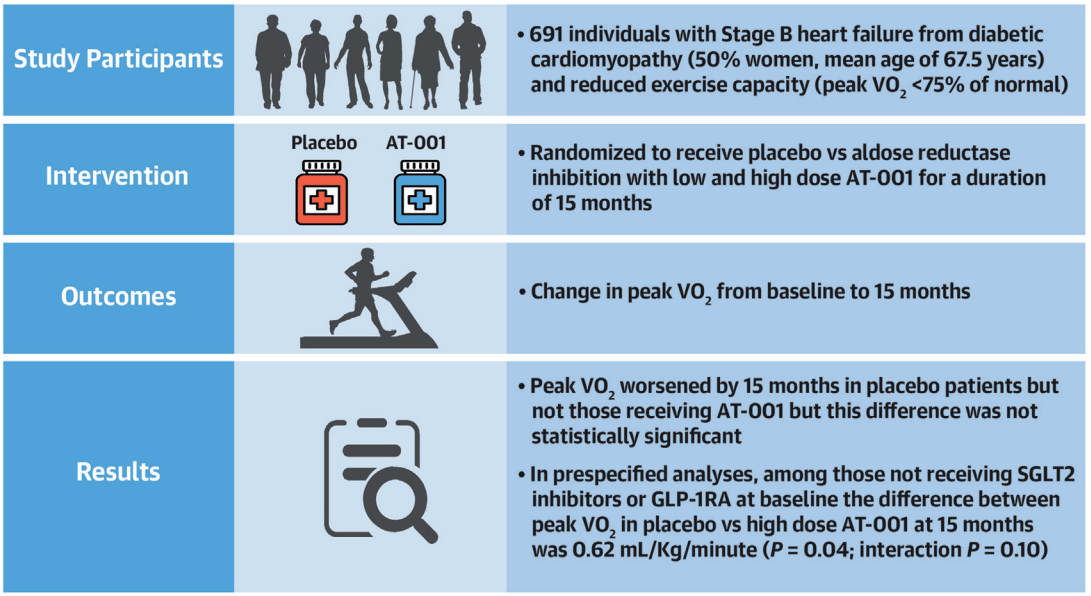
The diagnosis of DbCM—a heart muscle disease related to chronic hyperglycemia—is recognized as an important cause of HF in those with chronic DM.[2,4,7,11,12] Changes in myocardial substrate use have been implicated as a cause of DbCM,[25] with overactivation of the polyol pathway from chronic exposure to hyperglycemia a leading culprit. Such overactivation of the polyol pathway has been linked to development of neuropathy and nephropathy;[16,17,26] it has also been implicated in the myocardial injury associated with DbCM. Aldose reductase catalyzes the rate-limiting step of the polyol pathway, identifying it as an important target for reducing complications of diabetes. In preclinical models, increased aldose reductase activity has been shown to increase oxidative damage and deterioration of functional activities of various cell types,[27] and in human epidemiology studies, individuals overexpressing aldose reductase are more likely to manifest various complications of the diabetes.[28] Attempts to develop inhibitors of aldose reductase for the treatment of diabetic complications had been largely unsuccessful because of low binding affinity and poor specificity for the target. Many of the first generation agents in the class were withdrawn from clinical trials because of either a lack of efficacy or adverse effects, including hepatotoxicity, fever, nausea, diarrhea, and Stevens-Johnson syndrome.[29]

Despite these drawbacks, early studies of aldose reductase inhibition suggested a potentially favorable impact on cardiac structure, function, and associated exercise capacity among individuals with neuropathy from DM.[18] The development of AT-001, which has higher potency and selectivity than other drugs in the class,[9] allowed for exploration of its use for treatment of DbCM. In a transgenic mouse model of DbCM, treatment with AT-001 reduced cardiac fatty acid oxidation rates and cardiac oxygen consumption, preventing cardiac structural and functional abnormalities present in DbCM with improved diastolic function and reduced LV mass.[8]

Given the totality of evidence pointing toward benefit from inhibiting aldose reductase in those with DbCM together with development of AT-001, this study examined the effect of potent aldose reductase inhibition with AT-001 in persons with chronic, well-controlled T2DM, DbCM, and reduced exercise capacity reflected by reduced peak Vo_2 on CPET. Although impairment of peak Vo_2 is limited by cardiac and noncardiac factors (including pulmonary and peripheral muscle limitations), it is nonetheless a strong prognostic indicator for risk of HF onset.[19,30] This population with DbCM and impaired exercise tolerance therefore represents a high-risk group in transition toward overt, severe HF.

In ARISE-HF, randomized allocation to high-dose AT-001 was associated with no change of peak Vo_2 over 15 months, whereas those treated with placebo

CENTRAL ILLUSTRATION Design and Main Results From ARISE-HF



Januzzi Jr., JL, et al. J Am Coll Cardiol. 2024;■(■):■-■.

Persons with diabetic cardiomyopathy and reduced exercise capacity were treated with AT-001 for 15 months to explore the impact of aldose reductase inhibition on peak oxygen uptake. ARISE-HF = Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy; VO_2 = oxygen uptake.

experienced a significant decline. However, the difference in peak Vo_2 between the 2 arms at 15 months was not statistically significant. Whether a longer treatment time or inclusion of those with less well-controlled T2DM would be expected to result in further divergence in exercise capacity remains uncertain. Because the overall study result was neutral, other outcomes are to be viewed as exploratory only. However, in a prespecified and stratified subgroup analysis of the primary endpoint among those study participants not receiving SGLT2 inhibitor or GLP-1RA therapy at baseline, high-dose AT-001 appeared to be associated with favorable impact on the primary endpoint, also reducing the number of study participants in this sizeable subgroup experiencing a meaningful reduction in peak Vo_2. This finding was accompanied by an interaction P value of 0.10, implying lack of heterogeneity; the nonsignificant trend in the interaction analysis may reflect reduced power in this relatively small subgroup. Study participants were randomly stratified based on use of SGLT2 inhibitors and/or GLP-1RA, and this categorization was a prespecified subgroup of interest owing to the fact that these agents may affect exercise capacity through cardiovascular and skeletal muscle effects.[20,21] The possible efficacy of AT-001 in those not receiving these drugs is thus of note.

Treatment with AT-001 was safe and well tolerated in ARISE-HF. This is important, given the off-target toxicities observed with other drugs in this class.[16,29] Treatment with AT-001 did not lead to liver injury during 15 months of treatment in ARISE-HF, and transient changes in kidney function in the study associated with AT-001 were infrequent and did not lead to discontinuation of treatment.

During the 15 months of treatment, serious adverse events, such as HF hospitalization or cardiovascular death, were rare, reflecting the short follow-up time of the trial. However, in prespecified outcome analyses, the frequency of HF symptoms, physical findings, and site-reported clinical adverse cardiovascular events as identified using MedDRA preferred terms appeared higher among those study participants treated with placebo. More information is needed regarding the potential effect of AT-001 to reduce progression to overt, symptomatic HF.

STUDY LIMITATIONS. First, the study participants in ARISE-HF were a unique population with well-controlled T2DM and blood pressure, which may not reflect patients with DbCM more generally.

Restriction of uncontrolled T2DM or hypertension was a regulatory requirement, imposed to remove influence of hyperglycemia or elevated blood pressure on CPET performance or risk for overt HF. On the other hand, given that the polyol pathway is activated (and produces sorbitol) in the setting of hyperglycemia, it is possible that AT-001 might be less effective in individuals whose glucose is well controlled; in this setting, near-normoglycemia may have normalized sorbitol levels, mitigating potential benefit from inhibiting aldose reductase. Indeed, because hyperglycemia is the main driver of sorbitol generation, the near-normoglycemic control in our population may have mitigated favorable effects of aldose reductase inhibition. The combination of tight blood pressure and glycemic control is a unique aspect of the study participants in ARISE-HF compared to general practice; thus, effects of AT-001 in a more generalizable population with T2DM and DbCM remain unknown. It is plausible that among those with more advanced stage B HF (such as those with more elevated biomarker concentrations or worse echocardiographic parameters), the effect of AT-001 would be more evident. Baseline data from ARISE-HF reveals clusters of participants with varying clinical profiles, including those with worse biomarker concentrations and more remodeled hearts.[10] Exploratory analyses based on these populations are planned. Second, the diagnosis of DbCM lacks a gold standard test for its identification, and disease heterogeneity may be present. The diagnosis of DbCM was made based on stage B HF (characterized by structural heart disease or elevated cardiac biomarkers without overt past or present symptoms of HF)[3] and a lack of other obvious causes of HF. It is plausible that study participants had a mixture of other causes of stage B HF besides DbCM, or they may have had different manifestations of the DbCM. Subgroup analyses based on phenotypic clusters are planned. Third, the time horizon of this trial was only 15 months; during this timeframe, those treated with high-dose AT-001 showed potential stabilization of exercise capacity, whereas placebo-treated patients showed a decline. We speculate that a longer treatment duration might have been necessary to identify an impact on exercise capacity in this population. Fourth, although peak Vo_2 is a relevant and important prognostic measure that predicts future events in chronic HF, it is possible that by the point of such significant impairment (with an average peak Vo_2), study participants might not have been treatment responsive. Finally, with increasing use of SGLT2 inhibitors and GLP-1RA in the care of higher-risk individuals with T2DM, the additive value of aldose reductase inhibition requires further study.

CONCLUSIONS

In conclusion, in this 15-month study, aldose reductase inhibition with AT-001 did not result in a statistically significant difference in peak Vo_2 among persons with very-well-controlled T2DM affected by DbCM and reduced exercise capacity. Despite these overall results, given the urgency to reduce risk for HF in those with chronic DM, more investigation is needed regarding the potential role of AT-001 to reduce HF risk. Future studies should evaluate longer treatment with AT-001 in a more generalizable population of patients with T2DM with hyperglycemia. Furthermore, the additive value of AT-001 with SGLT2 inhibitors or GLP-1RA bears further scrutiny.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by Applied Therapeutics, Inc. Dr Januzzi is supported in part by the Adolph Hutter Professorship at Harvard Medical School; is a trustee of the American College of Cardiology; is a Board member of Imbria Pharmaceuticals; is a director at Jana Care; has received research support from Abbott, Applied Therapeutics, Bayer, Bristol Myers Squibb, HeartFlow Inc, Innolife, Medtronic and Roche Diagnostics; has received consulting income from Abbott, AstraZeneca, Bayer, Beckman, Boehringer Ingelheim, Cytokinetics, Janssen, Merck, Novartis, Prevencio, Quidel/Ortho, and Roche Diagnostics; and participates in Clinical Endpoint Committees/Data Safety Monitoring Boards for Abbott, AbbVie, Axon, Bayer, CVRx, Medtronic, Pfizer, Roche Diagnostics, and Takeda. Dr Butler is a consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll. Dr Del Prato has served as president of the European Society for the Study of Diabetes/European Foundation for the Study of Diabetes (2020-2022); has received research grants to the institution from AstraZeneca and Boehringer Ingelheim; has served as an advisor for Abbott, Amarin Corporation, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co, EvaPharma, Jiangsu Hengrui Pharmaceuticals Co, Menarini International, Merck Sharpe & Dohme, Novartis Pharmaceutical Co, Novo Nordisk, Sanofi, and Sun Pharmaceuticals; and has received fees for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co, Laboratori Guidotti, Menarini International, Merck Sharpe & Dohme, and Novo Nordisk. Dr Ezekowitz has received research support for trial leadership, honoraria, or grants from American Regent, Applied Therapeutics, AstraZeneca, Bayer, Cytokinetics, Merck & Co, Novo Nordisk, and Otsuka. Dr Ibrahim has served as a consultant for Cytokinetics; and has served on the Steering Committee for Applied Therapeutics. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Novo Nordisk and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/

WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd, Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and serves as cofounder and nonexecutive director of Us2.ai. Dr Lewis has received research funding from the National Institutes of Health (U01 HL160278, R01-HL 151841, R01-HL131029, R01-HL159514), Amgen, Cytokinetics, Applied Therapeutics, AstraZeneca, Imbria, Pfizer, Rivus, and SoniVie; has received honoraria for consulting and Advisory Boards outside of the current study from American Regent, Amgen, Cytokinetics, Edwards, Pfizer, Merck, Boehringer Ingelheim, NXT, and Amgen; and receives royalties from *UpToDate* for scientific content authorship related to exercise physiology. Dr Perfetti is an employee of Applied Therapeutics. Dr Rosenstock has served on Scientific Advisory Boards and received honoraria or consulting fees from Applied Therapeutics, Biomea Fusion, Boehringer Ingelheim, Eli Lilly, Endogenex, Hanmi, Novo Nordisk, Oramed, Regor, Sanofi, Scholar Rock, Structure Therapeutics, Terns Pharma, and Zealand; and has received grants/research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi, Merck, Oramed, Novartis, Novo Nordisk, Pfizer, and Sanofi. Dr Solomon has received a research grant to his institution from Applied Therapeutics for the conduct of the trial; has received research grants to his institution from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, the National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI outside the submitted work; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo outside the submitted work. Dr Tang has served as consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, Boston Scientific, WhiteSwell, Kiniksa Pharmaceuticals, Intellia Therapeutics, CardiaTec Biosciences, Bristol Myers Squibb, and Alleviant Medical; and has received honoraria from Springer Nature, Belvoir Media Group, and the American Board of Internal Medicine. Dr Zannad has received personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, Bristol Myers Squibb, CVRx, Cambrian, Cardior, Cereno Pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, Novo Nordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, and USa2; holds stock options at G3Pharmaceutical and equities at Cereno, Cardiorenal, and Eshmoun Clinical Research; and is the founder of Cardiovascular Clinical Trialists. Dr Marwick has reported that he has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Treatment with an investigational selective aldose reductase inhibitor (AT-001) for 15 weeks does not improve exercise capacity in patients with diabetes mellitus and heart failure attributed to diabetic cardiomyopathy.

TRANSLATIONAL OUTLOOK: More data are needed to determine the potential role of selective aldose reductase inhibition in patients with diabetic cardiomyopathy.

REFERENCES

1. Pop-Busui R, Januzzi JL, Bruemmer D, et al. Heart failure: an underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care*. 2022;45(7):1670-1690.

2. Boonman-de Winter LJ, Rutten FH, Cramer MJ, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia*. 2012;55(8):2154-2162.

3. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail*. 2021;27:387-413.

4. Pham I, Cosson E, Nguyen MT, et al. Evidence for a specific diabetic cardiomyopathy: an observational retrospective echocardiographic study in 656 asymptomatic type 2 diabetic patients. *Int J Endocrinol*. 2015;2015:743503.

5. Dal Canto E, Ceriello A, Ryden L, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol*. 2019;26(2 suppl):25-32.

6. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of diabetes 2017. *J Diabetes Res*. 2018;2018:3086167.

7. Avagimyan A, Popov S, Shalnova S. The pathophysiological basis of diabetic cardiomyopathy development. *Curr Probl Cardiol*. 2022;47(9):101156.

8. Gopal K, Karwi QG, Tabatabaei Dakhili SA, et al. Aldose reductase inhibition alleviates diabetic cardiomyopathy and is associated with a decrease in myocardial fatty acid oxidation. *Cardiovasc Diabetol*. 2023;22(1):73.

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

10. Januzzi JL, Del Prato S, Rosenstock J, et al. Characterizing diabetic cardiomyopathy: baseline results from the ARISE-HF trial. *Cardiovasc Diabetol*. 2024;23(1):49.

11. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res*. 2018;122(4):624-638.

12. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: pathophysiology and clinical features. *Heart Fail Rev*. 2013;18(2):149-166.

13. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54(6):1615-1625.

14. Ido Y, Nyengaard JR, Chang K, et al. Early neural and vascular dysfunctions in diabetic rats are largely sequelae of increased sorbitol oxidation. *Antioxid Redox Signal*. 2010;12(1):39-51.

15. Ramasamy R, Goldberg IJ. Aldose reductase and cardiovascular diseases, creating human-like diabetic complications in an experimental model. *Circ Res*. 2010;106(9):1449-1458.

16. Grewal AS, Bhardwaj S, Pandita D, Lather V, Sekhon BS. Updates on aldose reductase inhibitors for management of diabetic complications and non-diabetic diseases. *Mini Rev Med Chem*. 2016;16(2):120-162.

17. Jannapureddy S, Sharma M, Yepuri G, Schmidt AM, Ramasamy R. Aldose reductase: an

emerging target for development of interventions for diabetic cardiovascular complications. *Front Endocrinol (Lausanne)*. 2021;12:636267.

18. Johnson BF, Nesto RW, Pfeifer MA, et al. Cardiac abnormalities in diabetic patients with neuropathy: effects of aldose reductase inhibitor administration. *Diabetes Care*. 2004;27(2):448-454.

19. Forman DE, Arena R, Boxer R, et al. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2017;135(16):e894-e918.

20. Peng Y, Qin D, Wang Y, Xue L, Qin Y, Xu X. The effect of SGLT-2 inhibitors on cardiorespiratory fitness capacity: a systematic review and meta-analysis. *Front Physiol*. 2022;13:1081920.

21. Wu L, Zhou M, Li T, et al. GLP-1 regulates exercise endurance and skeletal muscle remodeling via GLP-1R/AMPK pathway. *Biochim Biophys Acta Mol Cell Res*. 2022;1869(9):119300.

22. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. *Circ Cardiovasc Qual Outcomes*. 2015;8(5):469-476.

23. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993;46(2):153-162.

24. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309(12):1268-1277.

25. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. *Circ Res*. 2021;128(10):1487-1513.

26. Hwang YC, Sato S, Tsai JY, et al. Aldose reductase activation is a key component of myocardial response to ischemia. *FASEB J*. 2002;16(2):243-245.

27. Tang WH, Martin KA, Hwa J. Aldose reductase, oxidative stress, and diabetic mellitus. *Front Pharmacol*. 2012;3:87.

28. Li W, Chen S, Mei Z, Zhao F, Xiang Y. Polymorphisms in sorbitol-aldose reductase (polyol) pathway genes and their influence on risk of diabetic retinopathy among Han Chinese. *Med Sci Monit*. 2019;25:7073-7078.

29. Quattrini L, La Motta C. Aldose reductase inhibitors: 2013-present. *Expert Opin Ther Pat*. 2019;29(3):199-213.

30. Kosmala W, Jellis CL, Marwick TH. Exercise limitation associated with asymptomatic left ventricular impairment: analogy with stage B heart failure. *J Am Coll Cardiol*. 2015;65(3):257-266.

KEY WORDS aldose reductase inhibitor, diabetes, heart failure

APPENDIX For supplemental tables, please see the online version of this paper.