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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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TITLE: 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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Key Words

Aldose reductase inhibitor, diabetic cardiomyopathy, DbCM, heart failure, polyol pathway, sorbitol, type 2 diabetes mellitus

Highlights

- Diabetic cardiomyopathy (DbCM) is a specific form of heart failure secondary to diabetes in absence of other known causes of cardiac dysfunction.
- Hyperactivation of the polyol pathway is one of the primary mechanisms leading to DbCM.
- Aldose reductase catalyzes the first step of the polyol pathway, and its inhibition has been proposed to reduce diabetic complications.
- AT-001 is a new highly selective aldose reductase inhibitor.
- ARISE-HF (NCT04083339) is a phase-3 randomized, placebo-controlled clinical study evaluating the effect of AT-001 to prevent the progression of DbCM.

Abstract

Diabetic cardiomyopathy (DbCM) is a specific form of heart muscle disease that may result in substantial morbidity and mortality in individuals with type 2 diabetes mellitus (T2DM).

Hyperactivation of the polyol pathway is one of the primary mechanisms in the pathogenesis of diabetic complications, including development of DbCM. There is an unmet need for therapies targeting the underlying metabolic abnormalities that drive this form of Stage B heart failure (HF). Aldose reductase (AR) catalyzes the first and rate-limiting step in the polyol pathway, and AR inhibition has been shown to reduce diabetic complications, including DbCM in animal models and in patients with DbCM. Previous AR inhibitors (ARIs) were limited by poor specificity resulting in unacceptable tolerability and safety profile. AT-001 is a novel investigational highly specific ARI with higher binding affinity and greater selectivity than previously studied ARIs. ARISE-HF (NCT04083339) is an ongoing Phase 3 randomized, placebo-controlled, double blind, global clinical study to investigate the efficacy of AT-001 (1000 mg twice daily [BID] and 1500 mg BID) in 675 T2DM patients with DbCM at high risk of progression to overt HF. ARISE-HF assesses the ability of AT-001 to improve or prevent decline in exercise capacity as measured by functional capacity (changes in peak oxygen uptake [peak VO_2]) over 15 (and possibly 27) months of treatment. Additional endpoints include percentage of patients progressing to overt HF, health status metrics, echocardiographic measurements, and changes in cardiac biomarkers. This report describes the rationale and study design of ARISE-HF.

Introduction

Heart failure (HF) is an increasingly recognized complication of Type 2 diabetes mellitus (T2DM)(1). An under-appreciated cause of HF in T2DM is a specific form of heart muscle disease called diabetic cardiomyopathy (DbCM)(2). Formation of this type of heart muscle disease is independent of other known causes of cardiac dysfunction, such as coronary artery disease, cardiac valvular disease, or hypertension (3-6). Multiple factors such as hyperglycemia, metabolic dysregulation, and oxidative stress(7, 8)lead to structural and functional changes to the myocardium (8) which are characteristic of DbCM.

When considered in recent framework for classifying the Stages of HF, DbCM may start with stage B (or “pre”) HF (9) (10), described by the presence of one of the following: structural cardiac abnormality (e. g. ventricular hypertrophy, chamber enlargement), evidence of increased filling pressure, and/or elevated biomarkers (natriuretic peptide or persistently elevated troponin levels). Individuals with stage B HF are at higher risk for progression to overtly symptomatic stages of the disease, and those with DbCM are no exception. Depending on the diagnostic criteria used, the prevalence of DbCM among individuals with T2DM ranges from 11.7% to 67.7% (3) (4) (5) (11) and early-stage DbCM is thought to be at high risk for progression to symptomatic HF.

Despite advances in imaging, technology, and the use of biomarkers to identify cardiac damage, DbCM is not proactively evaluated in the clinical practice, although recent consensus recommendations from the American Diabetes Associations recommends use of biomarkers and other means for the early diagnosis of cardiac dysfunction in those with T2DM(1); some with abnormal biomarkers in this context will have DbCM. Elevated concentrations of N-terminal pro-B type natriuretic peptide (NT-proBNP) have been identified in patients with T2DM without

any known cardiovascular disease (12), and increased natriuretic peptides demonstrate predictive value for both short and intermediate term CV events in patients with diabetes (13) (14, 15). Moreover, among individuals with diabetes a high-sensitivity cardiac troponin T (hs-cTnT) was able to refine identification of patients at higher risk of incident HF (11). Accordingly, a biomarker-based approach for the initial evaluation of those suspected of DbCM appears promising.

Although newer glucose-lowering therapies such as sodium glucose co-transporter 2 inhibitors (SGLT2 inhibitors) and glucagon-like peptide 1 (GLP1) receptor agonists have demonstrated a beneficial role in reducing the risk for adverse cardiovascular (CV) outcome, there is still a large residual risk of HF and CV death in patients with diabetes despite optimal medical therapy(16). Moreover, there are currently no approved therapies that target the upstream abnormalities in cardiomyocyte metabolism that cause DbCM and eventual progression to overt HF(17) . A drug that targets abnormal cardiomyocyte metabolism may have unique benefits due to a mechanism of action that acts upstream to the pathogenic abnormality believed to be involved in the development of the DbCM phenotype.

Increased polyol pathway activity is a primary mechanism in the pathogenesis of diabetic complications including DbCM (**Figure 1**) (18) (19) (20), (21). Aldose reductase (AR) is the first and rate-limiting step in the polyol pathway, which reduces glucose to sorbitol (**Figure 1**). Studies in animal models of diabetes and in humans have established AR as a key driver of the functional and metabolic impairment in the diabetic heart and a potential therapeutic target(20, 22). AR inhibitors (ARIs) were developed in the past for the prevention and treatment of diabetic complications, particularly diabetic neuropathy, and retinopathy. However, these agents were limited by low specificity and off-target effects (23). Despite the efficacy of some ARIs like

sorbinil or zenarestat in increasing nerve fiber density in sural nerve biopsies in patients with diabetic neuropathy, their clinical use was hampered by safety concerns.

AT-001 is a highly selective novel ARI with higher AR binding affinity than previously studied compounds in this class(24). Early studies indicate that AT-001 has improved efficacy, specificity and selectivity compared with previous ARIs and may prevent the decline in functional capacity in patients with DbCM at high risk of progression to overt HF(24). In Phase 2a trials, treatment with AT-001 at 1000mg TID and 1500mg BID significantly reduced NT-proBNP levels over 28 days versus placebo. AT-001 was well-tolerated, with no SAEs or dose-limiting toxicity reported (24).

The Phase 3 ARISE-HF study is currently underway evaluating the efficacy and safety of AT-001 versus placebo in patients with DbCM. The primary objective of the study is to evaluate the effect of AT-001 on cardiac functional capacity as measured by performance on a cardiopulmonary exercise test (CPET) in patients with DbCM. This report describes the design of this study (NCT04083339 on www.clinicaltrials.gov).

Overview of Study Design

ARISE-HF is a Phase 3, randomized, placebo-controlled study to assess the efficacy of AT-001 compared with placebo for preservation or improvement of exercise capacity as measured by peak oxygen uptake (peak VO₂) during a cardiopulmonary exercise testing (CPET) as well as assess the safety and tolerability of AT-001 over the long-term in adult study participants with T2DM and DbCM. The study has been registered at ClinicalTrials.gov under identifier NCT04083339.

The study consists of 2 placebo-controlled parts, with the study participants continuing from Part A to Part B without interruption and maintaining the original treatment allocation from the time of administration of the first dose of the study drug or placebo (**Figure 2**). The two-part study design of ARISE-HF is commonly used for pivotal studies of efficacy and safety with a long-term extension beyond the time of evaluation of the primary and key secondary endpoints.

- Part A runs from screening through the Month 27 Visit (which can occur between 27 and 30 months after randomization) to evaluate the impact of AT-001 on the primary endpoint, key secondary endpoints and safety assessments.
- Part B is a ≥ 12 -month extension after completion of Part A through to the study close or post-treatment follow-up visit (whichever occurs later) to evaluate the impact of AT-001 on additional secondary and exploratory endpoints along with safety assessments.
- The study also includes neuropathy and retinopathy sub-studies.

The key inclusion and exclusion criteria for the ARISE-HF Trial are listed in **Table 1**; full criteria are detailed in **Supplementary Appendix 1**. Briefly, patients must have T2DM, age ≥ 60 years (or age ≥ 40 to < 60 years with duration of diabetes ≥ 10 years or estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²), left ventricular ejection fraction (LVEF) $\geq 45\%$ on echocardiogram, and presence of stage B HF defined by at least one of the 3 following criteria: abnormal cardiac structure or function indicated by any one of absolute value of global longitudinal strain (GLS) $< -16\%$, left ventricular hypertrophy (LVH), defined as left ventricular mass index (LVMI) ≥ 95 g/m² in women and ≥ 115 g/m² in men, left atrial enlargement (LAE) defined as left atrial volume index (LAVi) > 34 mL/m², abnormal myocardial relaxation as defined by the ratio of early transmitral diastolic filling velocity/early mitral annular velocity (E/E', where E' represents average of the lateral and septal velocities) ≥ 13 , right ventricular

systolic pressure (RVSP) >35 mmHg OR increased cardiac biomarkers, indicated by any one of the following: NT-proBNP \geq 50 ng/L OR hs-cTnT \geq 6 ng/L.

The cut off for eligibility to participate to the study based on NT-proBNP level is lower than the cut-off level of \geq 125 ng/L used to support the definition of ambulatory HF (25); the value was selected as natriuretic peptide levels are substantially lower in individuals who are obese, compared with those who are not (4, 5), and since obesity is a common comorbidity in individuals with diabetes it justified consideration for a lower threshold (26). Moreover, recent data from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that an NT-proBNP concentration from as low as 25 to 150 ng/L is associated with an incidence rate difference for HF (per 1000 person years) of 11.0 among individuals with severe obesity and 5.1 among those with normal weight(27).The eligibility cut-off for hs-cTnT (\geq 6 ng/L) was selected based on reported evidence that is predictive of incident HF in patients with diabetes and pre-diabetes (11).

CPET eligibility to participate to the study is based on the demonstration of impaired functional capacity (peak oxygen uptake [VO_2]) equivalent or lower than 75% of predicted, based on age, gender, and ability of maximal effort (respiratory exchange ratio [RER] \geq 1.05).

Patients are excluded if they have a prior/current diagnosis of overt HF or its treatment, including use of a loop diuretic; history of acute coronary syndrome, coronary artery bypass graft, or percutaneous coronary intervention; history of significant valve disease; blood pressure > 140 mmHg (systolic) or > 90 mmHg (diastolic); history of congenital, infective, toxic (e.g., chemotherapy or radiation), infiltrative (e.g., amyloidosis, sarcoidosis, or hemochromatosis), post-partum, or hypertrophic cardiomyopathy.

All glucose lowering treatments are allowed except for thiazolidinediones; treatment with SGLT2 inhibitors is one of the bases for treatment stratification at study entry. Cardiovascular (CV)/renal medications for the treatment of comorbidities are permitted during the study. The use of any diuretic after randomization is permitted. Any inhibitor of the renin-angiotensin-aldosterone system (RAAS) must have been stable for at least 12 weeks prior to screening (see Supplementary **Appendix 1** for definitions used in this study).

Study Organization

This study is conducted at 62 global sites across Australia, Canada, Czech Republic, France, Germany, Hong Kong, Poland, Spain, United Kingdom, and United States (US).

Study conduct involves the following independent committees:

- Data Monitoring Committee (DMC)
- Steering Committee (SC)
- Cardiovascular Endpoint Committee (CEC)
- Echocardiography Reading Committee (ERC)
- Cardiopulmonary Exercise Test Committee (CPET-C)

All committees, except for the DMC, are blinded to the patients' treatment allocations. The DMC reviews unblinded study data on a regular basis to make recommendations to the sponsor regarding study continuation. The DMC is also responsible for reviewing unblinded results of the first CPET performed at Month 15 (window: 15 to 18 months after randomization). The Steering Committee (SC) supports study design, conduct, and reporting for the study. The Cardiovascular Endpoint Committee (CEC) adjudicates all deaths and HF endpoints related to progression from SBHF to SCFH. Central committees oversee CPET administration, site certification and analyze

peak VO₂ data (CPET Committee [CPET-C]) and oversee echocardiograms, certify the sites and analyze echocardiography data (Echocardiography Reading Committee [ERC]).

Treatment and Procedures

Approximately 675 patients will be randomized 1:1:1 to receive high-dose AT-001 (1500 mg twice daily [BID], given as oral capsules), low-dose AT-001 (1000 mg BID), or placebo (**Figure 2**). Each patient, on AT-001 or placebo, receives three capsules twice daily. The doses of AT-001 to be used in ARISE-HF are based on a previous three-part, randomized, placebo-controlled Phase 1/2 study to assess the safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AT-001 in adults with T2DM (28). This study included a single ascending dose (SAD), a 7-day multiple ascending dose (MAD), and a 28-day MAD extension. Based on the entirety of the data analyzed, it was estimated that the minimum dose of AT-001 likely to achieve a permanent and effective lowering of sorbitol was a total daily dose of 2000 mg/day. The highest dose of 3000 mg/day dose results in drug exposure 10-fold lower than the maximum tolerated dose (MTD) based on the pre-clinical toxicology studies.

The visit schedules for Parts A and B are shown in **Supplementary Appendix 2**. Patients are provided with a study diary and instructions on what information to record in between study visits. Following administration of study medication on Day 1 in Part A of the study, on-site assessment visits take place at monthly intervals for the first 3 months, then every 3 months thereafter until Month 27. In Part B, on-site assessment visits take place every 6 months until the end of the study. Patients are also followed by telephone or video-teleconference monthly throughout the study to review their study diaries, collect adverse event (AE) and concomitant medication data, provide medication instruction reminders, and schedule the next visit. A post-

treatment follow-up visit takes place approximately 30 ± 3 days after the last dose of study drug (whether premature discontinuation or per protocol end of treatment).

Study Endpoints

The complete list of study endpoints is provided in **Supplementary Appendix 3**.

Exercise limitation with dyspnea and fatigue at low levels of effort or at rest are cardinal symptoms of HF (29). Accordingly, the primary endpoint of ARISE-HF is the change in CPET performance (peak VO_2) from baseline to Month 15. A CPET may be repeated at Month 27 if the assessment at Month 15 data does not demonstrate a statistically significant difference between placebo and at least one of the two doses of AT-001. Although peak exercise performance is limited not only by cardiac function but also by pulmonary and peripheral skeletal muscle changes (29) functional capacity was chosen as the primary endpoint as it is a widely accepted marker of disease severity and prognosis. Furthermore, impairment of functional capacity is often the only clinical manifestation of underlying cardiac structural abnormalities before the onset of overt HF (30, 31). Peak VO_2 is a strong prognostic indicator and even modest changes are correlated with clinical outcomes such as HF hospitalization and CV death (31, 32). All CPET outcomes are assessed in a uniform manner by a central committee (CPET-C) blinded to individual patients' treatment allocations. All participating sites follow the same trial specific CPET protocol (**Supplementary Appendix 4**). Peak VO_2 is derived from assessment of primary breath-by-breath data with use of the highest median 30-second value during the final 90 seconds of exercise for peak VO_2 .

Key secondary outcomes of ARISE-HF include progression to symptomatic stages of HF, change in NT-proBNP, change in health status as assessed by the modified Kansas City

Cardiomyopathy Questionnaire (mKCCQ) score (**Supplementary Appendix 5**), and the percentage of patients with a clinically significant decrease (i.e., >6%) in peak VO₂ from baseline to Month 27.

Progression to symptomatic stages of HF (stage C or D) is defined as occurrence of at least 1 of the following events by Month 27:

- CV death
- Hospitalization for HF
- Urgent HF visit
- New diagnosis of HF (requiring initiation of a loop diuretic)

All the above events potentially indicative of progression to stage C or D HF are adjudicated by the independent CEC in a treatment-blinded manner, using standardized definitions (33).

Preventing or delaying the progression to overt HF in patients with DbCM is an important clinical benefit because the transition from SBHF to SCHF is associated with a 5-fold increased risk of mortality (34).

The percentage of patients with worsening of DbCM is an additional secondary endpoint that is analyzed at Month 15 and at Month 27 if the primary endpoint is statistically significant. Worsening of DbCM is defined by either: 1) a $\geq 20\%$ increase in NT-proBNP, or 2) a ≥ 5 -point decrease in the mKCCQ score. The KCCQ is a validated measure of health status in individuals with HF and has been previously used in at-risk patients (i.e., not diagnosed with HF at baseline). The current study uses the 23-question KCCQ that has been modified to consider that the patient population does not have overt HF at baseline (35).

Changes in biomarker (other than NT-proBNP) concentration from baseline to Months 15 and 27 are assessed as an exploratory endpoint. This includes biomarkers which are known to be or have been implicated in the pathophysiology of cardiovascular, renal, and metabolic diseases and include sorbitol, hs-cTnT, reactive oxygen species (ROS), and markers of fibrosis including PRO-C6, and Titin Degradation Molecule (TIM).

Safety endpoints include treatment-emergent adverse events (TEAEs) and changes in laboratory parameters, vital signs, and electrocardiogram (ECG) parameters.

Sample Size Calculation

A sample size of 675 patients was determined to be appropriate for ARISE-HF. The sample size is based on calculations for the Month 15 analysis, with an additional assessment of data at Month 27 if a statistically significant difference in the primary outcome between at least one the 2 doses of AT-001 and placebo is not observed at Month 15. A 2-sided $\alpha=2.5\%$ is proposed for each of the analysis timepoints. A sample size of 181 patients per treatment group was calculated to provide >90% power to detect a difference in peak VO_2 of 1.2 mL/kg/min between active treatment and placebo at either analysis timepoint assuming a common standard deviation of 3 within each group. This difference in peak VO_2 of 1.2 mL/kg/min is considered clinically significant for patients with HF (36). The required sample size of 675 patients (225 randomized 1:1:1 to the 3 treatment groups) assumes a drop-out rate of approximately 20% by Month 27. The primary endpoint of the change from baseline to Month 15 (and potentially Month 27) in peak VO_2 in patients with DbCM will be analyzed using a mixed model for repeat measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix. Interaction term and randomization stratification factors (region, use of SGLT2is or GLP1-RA at baseline, baseline RER) will be fixed effects, with a random effect at the patient level. Sensitivity

analyses for the primary endpoint will be assessed using a ‘tipping point’ methodology. This analysis will use multiple imputation to assess a missing-not-at-random structure, in search for a ‘tipping point’ that reverses the analysis results from statistical significance to non-significance. A supportive analysis using an ANCOVA on observed data only will also be presented.

Analysis of the key secondary efficacy outcome of progression from stage B to stages C or D HF at Month 27 will be based on a composite endpoint on the full analysis set, assessed over Part A of the study, using a win-ratio method (37). Treatment groups will be compared on the distribution of four components in the composite endpoint using the Finkelstein-Schoenfeld statistic and p-value. The win-ratio will be used as one estimate of the overall treatment effect size regarding this distribution. This method requires ordering of importance of each of the components in the composite endpoint from high to low to determine the ‘winner,’ ‘loser’ or tie for this analysis, namely: CV death, hospitalization for HF, urgent HF or a new diagnosis of HF requiring loop diuretic therapy. Sensitivity analysis for this endpoint will be performed using a log rank. The p-values from the log rank test for active treatment comparisons vs placebo will be reported. In addition, hazard ratios and 95% confidence intervals from a Cox proportional hazards regression model with treatment included as the sole covariate will be reported.

Analysis of the changes in NT-proBNP and mKCCQ score from baseline to Month 27 will be performed using an MMRM and equivalent methodology to those proposed for the primary efficacy outcome. Analysis of the percentage of patients with a decrease in peak VO_2 of $\geq 6\%$ from baseline to Month 27 will be performed using a logistic regression model for the odds of the decrease with treatment group as a factor and adjusting for covariates based on randomization stratification factors. The estimated odds ratio (OR) and associated 2-sided 95% confidence interval of the estimated OR will be presented.

Statistics

All efficacy analyses will be conducted using the intent-to-treat (ITT) principle with treatment groups allocated according to the randomization schedule, irrespective of the treatment actually received. The primary efficacy population will be the full analysis set (FAS), which will include all randomized patients regardless of compliance with the study procedures or investigational study treatment.

A multiple testing strategy will be used to assess the primary endpoint at Month 15 and again at Month 27 if AT-001 (at least one dose level) is not superior to placebo at Month 15 (**Figure 3**). Safety analyses will be conducted on the safety population, which will consist of all patients who have been randomized and have received at least one dose of study drug. Patients will be reported under the actual treatment received during the study.

Ethics and Regulatory Considerations

This research is carried out in accordance with the protocol, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP) Consolidated Guidance (E6), and applicable regulatory requirements including clinical research guidelines established by the Basic Principles defined in the US 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312; other applicable regional/local regulations, and the principles of the Declaration of Helsinki.

For all study centers, the protocol and informed consent form (ICF) are reviewed and approved by an appropriate institutional review board (IRB), research ethics board (REB), or independent ethics committee (IEC) in accordance with the principles and requirements in applicable regional or local regulations. Written informed consent is obtained from each patient

prior to performing any study-specific procedures. One copy of the signed and dated ICF is provided to the patient and the original retained by the investigator or site.

ARISE-HF is posted on www.clinicaltrials.gov with the clinical trial number: NCT04083339. The first patient was screened on 18 SEP 2019 and enrollment is projected to continue through 30 Sept 2022. As of 21 July 2022, 530 patients have been randomized.

Discussion

Diabetes is a major risk factor for several adverse CV outcomes including HF (38). Epidemiological and observational studies have shown that T2DM increases the risk for new onset HF independently of other traditional risk factors (38). Together with the alarming increase in global prevalence of T2DM these data imply a substantial likelihood for parallel rise in HF owing to DbCM and its progression.

Despite the increased risk of progression to overt HF in individuals with DbCM, there are still no approved therapies that address the underlying complex metabolic abnormalities associated with its development and progression (8, 17). The lack of etiological therapies addressing the underlying mechanism of disease (25) highlights the urgent need for research on disease modifying interventions and the importance of the ARISE-HF clinical trial. Until recently, trials of glucose-lowering therapies demonstrated little benefit of intensive glycemic control on HF-related outcomes (39). Although SGLT2 inhibitors (16) (40) (41), (42) have demonstrated reductions in CV mortality particularly keyed to their effects on HF, the precise mechanisms behind the observed CV benefits remain to be determined (43) and whether SGLT2 inhibitors address the pathophysiology of DbCM or reduce its progression is not known. In

ARISE-HF, analyses will be stratified by the presence or absence of SGLT2i therapy as well as glucagon-like peptide receptor agonist-1 treatment.

ARISE-HF explores the ability of AT-001 to mitigate the pathophysiologic effects of DbCM. Several mechanisms play critical roles in the pathogenesis of DbCM including changes in cardiac metabolism and substrate utilization (44, 45). Hyperactivation of the polyol pathway by chronic and abnormal influx of extracellular glucose has been implicated as the primary pathway involved in the pathogenesis of diabetic complications including damage to peripheral nerves and blood vessels (18, 19, 23). The first and rate-limiting step in the polyol pathway, AR, is activated by hyperglycemic and ischemic conditions(23, 46). The presence and levels of AR vary in tissues and cells with sciatic nerve, lens, cornea, testis, and heart expressing the highest levels(47). Within the heart, AR is present in cardiomyocytes, endothelial cells, smooth muscle cells, and fibroblasts(23). Glucose is reduced to sorbitol by AR using NADPH as a co-factor; sorbitol is then metabolized to fructose by sorbitol dehydrogenase that uses NAD^+ as a co-factor, with several consequences that lead to cellular damage and death:

- Intracellular accumulation of sorbitol and subsequent altered osmotic equilibrium(48, 49)
- Generation of advanced glycation end products (AGEs) following the further breakdown of fructose (49, 50)
- Exposure of cells to oxidative stress through diminished antioxidant reserves and the generation of reactive oxidative species (49, 51-53)

Studies in humans have linked specific polymorphic variants of AR to the risk of developing diabetic microvascular(54-57) and macrovascular(58, 59) complications, suggesting that individuals who over express AR are more likely to develop the vascular complication of diabetes. Blockade of AR with earlier-generation inhibitors was found to dramatically reduce

acute ischemia-reperfusion-induced cardiac damage in diabetic rat hearts and in non-diabetic rat and rabbit hearts(22, 60, 61), and to improve echocardiographic indicators of DbCM in patients with type 2 diabetes(62) and in animal models of disease (22). Taken together, these studies established AR as a key driver of the functional and metabolic impairment in the diabetic heart and highlighted the potential value of AR as a therapeutic target.

Until recently, attempts to develop ARIs for the treatment of diabetic complications including DbCM have been largely unsuccessful, due to low AR binding affinity and poor specificity. Many of the first generation ARIs such as irestatin, imirestat, ponalrestat, and sorbinil have been withdrawn from trials either due to a lack of efficacy or adverse effects, including hepatotoxicity, fever, nausea, diarrhea and Stevens-Johnson syndrome(63). At present, epalrestat is the only ARI approved in Japan, India and China to treat patients with diabetic neuropathy(58, 63-65). In clinical trials, epalrestat was shown to delay the progression of diabetic peripheral neuropathy and improve associated symptoms including motor and sensory nerve conduction velocity (64).

AT-001 is a novel ARI with higher potency and selectivity for AR compared with ARIs previously studied(24). *In vitro* data provided proof-of-concept evidence that AT-001 has greater potency and no off target binding compared to previous small molecule ARIs developed for DbCM. In a transgenic mouse model of DbCM (mice overexpressing human AR), AT-001 was shown to significantly reduce 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 (66).

In Phase 2a trials, treatment with AT-001 at 1000mg TID and 1500mg BID significantly reduced NT-proBNP levels over 28 days versus placebo. AT-001 was well-tolerated, with no SAEs or dose-limiting toxicity reported (24).

Inevitable limitations to the study design exist. First, excluding occult coronary ischemia as the cause of exercise limitation is not entirely possible. Nonetheless, CPET is highly sensitive for the detection of a coronary limitation to exercise and it is implausible many patients with limiting coronary ischemia would enter the trial; effects of AT-001 on myocardial ischemia in this setting are speculative. Presently, an echocardiographic examination is proposed at 27 months. Earlier imaging might inform benefit of AT-001.

In conclusion, ARISE-HF is designed to investigate the potential benefit of AT-001 to prevent worsening of cardiac functional capacity in DbCM, with secondary goals of reducing the risk of developing overt HF or HF progression and provide data to support clinical decision-making in patients with T2DM. In view of the risk of progression to overt HF in individuals with DbCM, the ARISE-HF Trial will shed light on a potential new intervention for this specific form of cardiomyopathy.

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Methods

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Declarations of Interest Disclosure Statement

- Dr. Januzzi is a Trustee of the American College of Cardiology; is a board member of Imbria Pharmaceuticals; has received research support from Abbott, Applied Therapeutics, Innolife, Novartis Pharmaceuticals, and Roche Diagnostics; has received consulting income from Abbott, Beckman, Bristol Myers, Boehringer-Ingelheim, Janssen, Novartis, Pfizer, Merck, Roche Diagnostics and Siemens; and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Bayer, CVRx, Intercept, Janssen, and Takeda.
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- Dr. Lawson was an employee and a stock owner of Applied Therapeutics.
- Dr Perfetti is the CMO and a stock owner of Applied Therapeutics.
- Dr. Urbinati is an employee and a stock owner of Applied Therapeutics.

Table 1: Key Inclusion/Exclusion Criteria for the ARISE-HF Trial. Full criteria are listed in Appendix 1.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> ● Diagnosis of T2DM ● High risk for HF including advanced age, longstanding T2DM or CKD ● Demonstration of DbCM with at least one of the following: <ul style="list-style-type: none"> ○ Structural or functional heart disease on echocardiography* ○ NT-proBNP \geq 50 ng/L ○ hs-cTnT \geq 6 ng/L ○ Impaired exercise tolerance on cardiopulmonary exercise testing, with peak oxygen uptake $<$ 75% of predicted and adequate exercise effort with a respiratory exchange ratio \geq 1.05 	<ul style="list-style-type: none"> ● Past or present diagnosis of symptomatic (stage C/D) HF or other forms of heart muscle disease ● Previous documentation of LVEF $<$ 40% ● Past or present use of loop diuretics ● Prior acute coronary syndrome or stroke ● Significant coronary artery disease with or without revascularization ● Severe valvular heart disease ● Recent cardiac arrhythmia ● Uncontrolled hypertension ● Hemoglobin A1c $>$ 8.5% ● Hemoglobin $<$ 10.0 g/dL ● eGFR $<$ 45 mL/min/1.73m² ● Body-mass index \geq 45 Kg/m² ● Inability to exercise ● Recurrent kidney stones

T2DM denote: Type 2 diabetes mellitus; HF denotes: heart failure; CKD denotes: chronic kidney disease; DbCM denotes: diabetic cardiomyopathy; NT-proBNP denotes: N-terminal pro-B type natriuretic peptide; hs-cTnT denotes: high sensitivity cardiac troponin T; ng/L denotes: nanograms per liter; LVEF denotes: left ventricular ejection fraction; g/dL denotes: grams per deciliter; mL/min denotes: milliliters/minute; Kg/m² denotes: kilograms per meter squared

*Absolute value of global longitudinal strain (GLS) $<$ 16%; left ventricular mass index \geq 95 g/m² in women and \geq 115 g/m² in men; Left atrial volume index $>$ 34 mL/m²; Diastolic Dysfunction defined as E/E' \geq 13; Right ventricular systolic pressure $>$ 35 mmHg

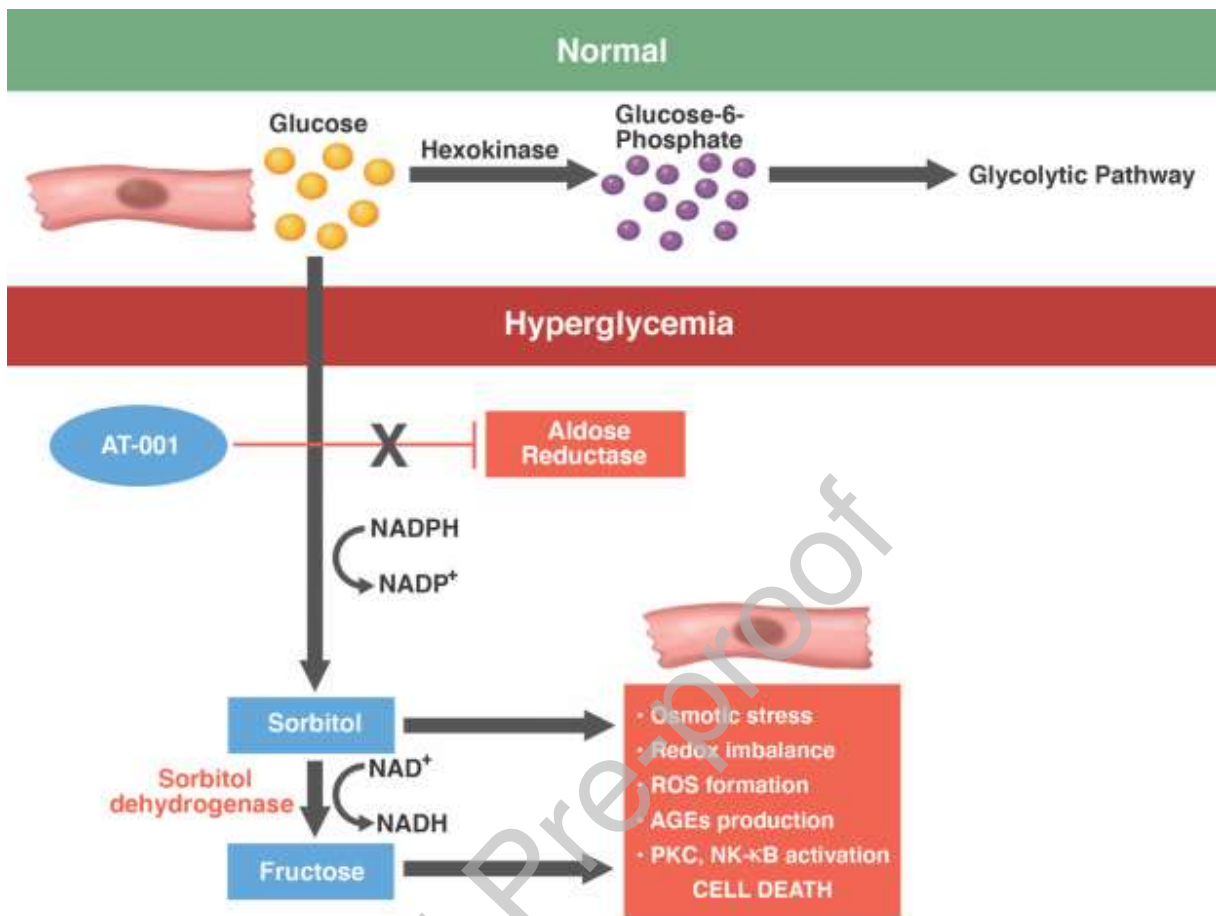


Figure 1: Glucose metabolism in the polyol pathway and AT-001 mechanism of action

AGEs = advanced glycation end-products; NADP^+ = nicotinamide adenine dinucleotide phosphate (oxidized form); NADPH = nicotinamide adenine dinucleotide phosphate (reduced form); $\text{NF-}\kappa\text{B}$ = nuclear factor kappa-light-chain-enhancer of activated B cells; PKC = protein kinase C; ROS = reactive oxygen species

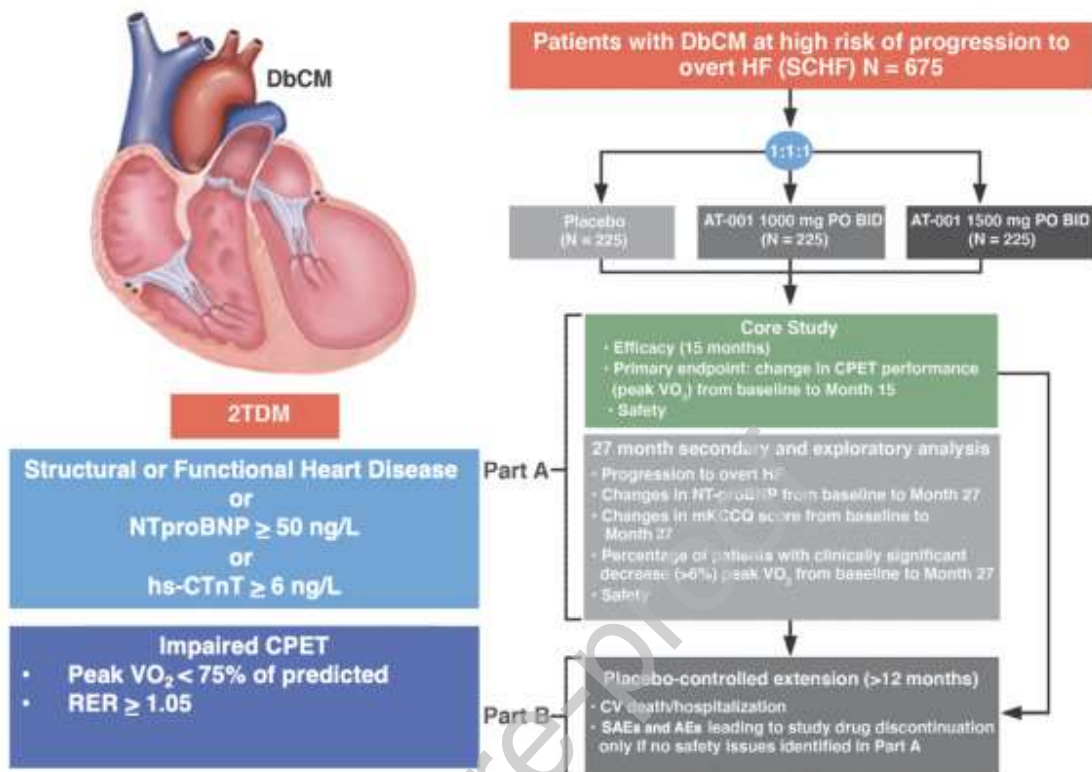


Figure 2: Study Design and main inclusion criteria

AE = adverse event; BID = twice daily, CPET = cardiopulmonary exercise test;

CV = cardiovascular; DbCM = diabetic cardiomyopathy; hs-CTnT= high sensitivity cardiac troponin T; HF = heart failure; mKCCQ = modified Kansas City Cardiomyopathy Questionnaire;

NT-proBNP = N-terminal pro-B-type natriuretic protein; peak VO_2 = peak volume of oxygen

uptake; PO = per oral; RER= respiratory exchange ratio; SCHF = Stage C heart failure.

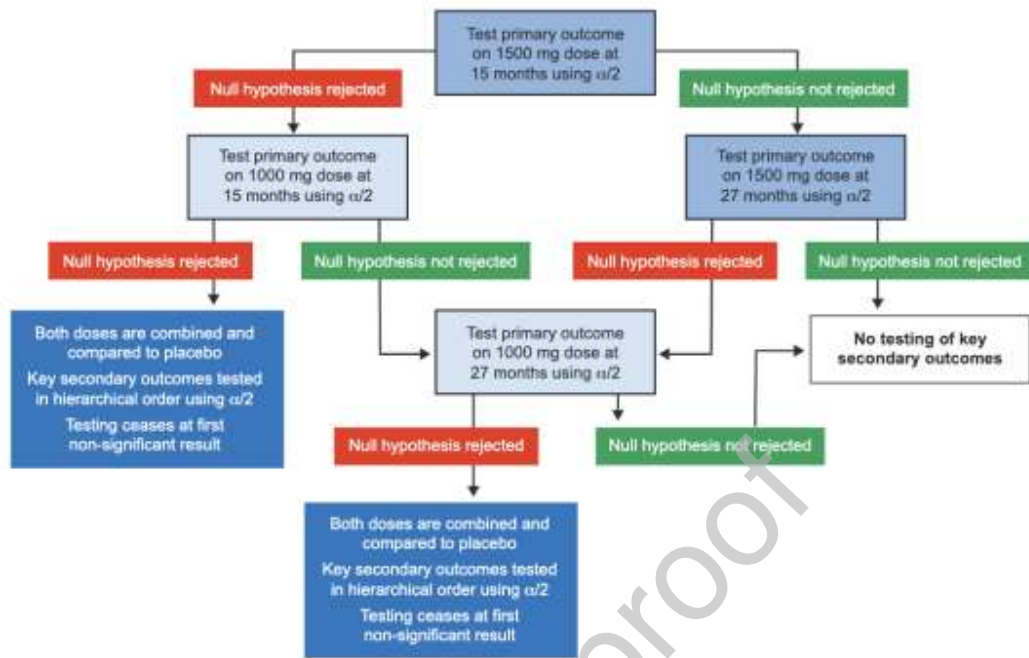


Figure 3: Multiple testing strategy in ARISE-HF

1. Pop-Busui R, Januzzi JL, Bruemmer D, Butalia S, Green JB, Horton WB, et al. Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association. *Diabetes Care*. 2022.
2. Avagimyan A. The Pathophysiological Basis of Diabetic Cardiomyopathy Development. *Curr Probl Cardiol*. 2022;101156.
3. Pham I, Cosson E, Nguyen MT, Banu I, Genevois I, Poignard P, 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.
4. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia*. 2012;55(8):2154-62.
5. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, 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.
6. Authors/Task Force M, Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2013;34(39):3035-87.
7. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. *J Diabetes Res*. 2018;2018:3086167.
8. Dal Canto E, Ceriello A, Ryden L, Ferrini M, Hansen TB, Schnell O, 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.
9. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):1810-52.
10. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):1757-80.
11. Segar MW, Khan MS, Patel KV, Butler J, Tang WHW, Vaduganathan M, et al. Prevalence and Prognostic Implications of Diabetes With Cardiomyopathy in Community-Dwelling Adults. *J Am Coll Cardiol*. 2021;78(16):1587-98.
12. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. *Diabetes Care*. 2004;27(8):1929-35.
13. Clodi M, Resl M, Neuhold S, Hulsman M, Vila G, Elhenicky M, et al. A comparison of NT-proBNP and albuminuria for predicting cardiac events in patients with diabetes mellitus. *Eur J Prev Cardiol*. 2012;19(5):944-51.
14. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a

- history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;62(15):1365-72.
15. Neuhold S, Resl M, Huelsmann M, Strunk G, Adlbrecht C, Rath C, et al. Repeat measurements of glycated haemoglobin A(1c) and N-terminal pro-B-type natriuretic peptide: divergent behaviour in diabetes mellitus. *Eur J Clin Invest*. 2011;41(12):1292-8.
 16. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol*. 2021;6(2):148-58.
 17. Tate M, Grieve DJ, Ritchie RH. Are targeted therapies for diabetic cardiomyopathy on the horizon? *Clin Sci (Lond)*. 2017;131(10):897-915.
 18. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54(6):1615-25.
 19. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: pathophysiology and clinical features. *Heart Fail Rev*. 2013;18(2):149-66.
 20. Ido Y, Nyengaard JR, Chang K, Tilton RG, Kilo C, Mylari BL, 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.
 21. Ramasamy R, Goldberg IJ. Aldose reductase and cardiovascular diseases, creating human-like diabetic complications in an experimental model. *Circ Res*. 2010;106(9):1449-58.
 22. Ramasamy R, Oates PJ, Schaefer S. Aldose reductase inhibition protects diabetic and nondiabetic rat hearts from ischemic injury. *Diabetes*. 1997;46(2):292-300
 23. 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.
 24. PERFETTI R, YEPURI G, QUADRI NA, GHANNAM AF, RAMASAMY R, SHENDELMAN S. 1080-P: Addressing the Safety Challenges of Aldose Reductase Inhibition: Development of AT-001 for Diabetic Cardiomyopathy, a Potent and Selective Next Generation Aldose Reductase Inhibitor. *Diabetes*. 2020;69(Supplement_1).
 25. Dandamudi S, Slusser J, Mahoney DW, Redfield MM, Rodeheffer RJ, Chen HH. The prevalence of diabetic cardiomyopathy: a population-based study in Olmsted County, Minnesota. *J Card Fail*. 2014;20(5):304-9.
 26. Singh S, Pandey A, Neeland IJ. Diagnostic and prognostic considerations for use of natriuretic peptides in obese patients with heart failure. *Prog Cardiovasc Dis*. 2020;63(5):649-55.
 27. Ndumele CE, Matsushita K, Sang Y, Lazo M, Agarwal SK, Nambi V, et al. N-Terminal Pro-Brain Natriuretic Peptide and Heart Failure Risk Among Individuals With and Without Obesity: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2016;133(7):631-8.
 28. Perfetti R, Shendelman S. Abstract 13475: Clinical Assessment of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy: A 28-Day Proof of Concept Study. *Circulation*. 2019;140(Suppl_1):A13475-A.
 29. <eurjpc0485.pdf>.
 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):257-66.
 31. Forman DE, Arena R, Boxer R, Dolansky MA, Eng JJ, Fleg JL, 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.

32. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, et al. Modest increase in peak VO₂ is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail*. 2012;5(5):579-85.
33. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *J Am Coll Cardiol*. 2018;71(9):1021-34.
34. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr., et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation*. 2007;115(12):1563-70.
35. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circ Cardiovasc Qual Outcomes*. 2015;8(5):469-76.
36. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, 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):1268-77.
37. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33(2):176-82.
38. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. 2018;17(1):83.
39. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J*. 2011;162(5):938-48 e2.
40. Neal B, Perkovic V, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(21):2099.
41. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347-57.
42. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-28.
43. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. *Cardiovasc Diabetol*. 2020;19(1):98.
44. Athithan L, Gulsin GS, McCann GP, Levelt E. Diabetic cardiomyopathy: Pathophysiology, theories and evidence to date. *World J Diabetes*. 2019;10(10):490-510.
45. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac Energy Metabolism in Heart Failure. *Circ Res*. 2021;128(10):1487-513.
46. Hwang YC, Sato S, Tsai JY, Yan S, Bakr S, Zhang H, et al. Aldose reductase activation is a key component of myocardial response to ischemia. *FASEB J*. 2002;16(2):243-5.
47. Tanimoto T, Maekawa K, Okada S, Yabe-Nishimura C. Clinical analysis of aldose reductase for differential diagnosis of the pathogenesis of diabetic complication. *Analytica Chimica Acta*. 1998;365(1):285-92.

48. Gabbay KH. The sorbitol pathway and the complications of diabetes. *N Engl J Med*. 1973;288(16):831-6.
49. Lorenzi M. The polyol pathway as a mechanism for diabetic retinopathy: attractive, elusive, and resilient. *Exp Diabetes Res*. 2007;2007:61038.
50. Szwergold BS, Kappler F, Brown TR. Identification of fructose 3-phosphate in the lens of diabetic rats. *Science*. 1990;247(4941):451-4.
51. Barnett PA, Gonzalez RG, Chylack LT, Jr., Cheng HM. The effect of oxidation on sorbitol pathway kinetics. *Diabetes*. 1986;35(4):426-32.
52. Lassegue B, Clempus RE. Vascular NAD(P)H oxidases: specific features, expression, and regulation. *Am J Physiol Regul Integr Comp Physiol*. 2003;285(2):R277-97.
53. Williamson JR, Chang K, Frangos M, Hasan KS, Ido Y, Kawamura T, et al. Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes*. 1993;42(6):801-13.
54. Demaine A, Cross D, Millward A. Polymorphisms of the aldose reductase gene and susceptibility to retinopathy in type 1 diabetes mellitus. *Invest Ophthalmol Vis Sci*. 2000;41(13):4064-8.
55. Deng Y, Yang XF, Gu H, Lim A, Ulziibat M, Snellingen T, et al. Association of C(-106)T polymorphism in aldose reductase gene with diabetic retinopathy in Chinese patients with type 2 diabetes mellitus. *Chin Med Sci J*. 2014;29(1):1-6.
56. Gupta B, Singh SK. Association of aldose reductase gene polymorphism (C-106T) in susceptibility of diabetic peripheral neuropathy among north Indian population. *J Diabetes Complications*. 2017;31(7):1085-9.
57. Sivenius K, Pihlajamaki J, Partanen J, Niskanen L, Laakso M, Uusitupa M. Aldose reductase gene polymorphisms and peripheral nerve function in patients with type 2 diabetes. *Diabetes Care*. 2004;27(8):2021-6.
58. So WY, Wang Y, Ng MC, Yang X, Ma RC, Lam V, et al. Aldose reductase genotypes and cardiorenal complications: an 8-year prospective analysis of 1,074 type 2 diabetic patients. *Diabetes Care*. 2008;31(11):2148-53.
59. Watarai A, Nakashima E, Hamada Y, Watanabe G, Naruse K, Miwa K, et al. Aldose reductase gene is associated with diabetic macroangiopathy in Japanese Type 2 diabetic patients. *Diabet Med*. 2006;23(8):894-9.
60. Ramasamy R, Trueblood N, Schaefer S. Metabolic effects of aldose reductase inhibition during low-flow ischemia and reperfusion. *Am J Physiol*. 1998;275(1):H195-203.
61. Tracey WR, Magee WP, Ellery CA, MacAndrew JT, Smith AH, Knight DR, et al. Aldose reductase inhibition alone or combined with an adenosine A(3) agonist reduces ischemic myocardial injury. *Am J Physiol Heart Circ Physiol*. 2000;279(4):H1447-52.
62. Johnson BF, Nesto RW, Pfeifer MA, Slater WR, Vinik AI, Chyun DA, et al. Cardiac abnormalities in diabetic patients with neuropathy: effects of aldose reductase inhibitor administration. *Diabetes Care*. 2004;27(2):448-54.
63. Quattrini L, La Motta C. Aldose reductase inhibitors: 2013-present. *Expert Opin Ther Pat*. 2019;29(3):199-213.
64. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, Shichiri M, et al. Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. *Diabetes Care*. 2006;29(7):1538-44.

65. Maccari R, Ottana R. Targeting aldose reductase for the treatment of diabetes complications and inflammatory diseases: new insights and future directions. *J Med Chem.* 2015;58(5):2047-67.
66. GOPAL K, KARWI QG, DAKHILI SAT, WAGG CS, PERFETTI R, RAMASAMY R, et al. 379-P: Aldose Reductase Inhibition by AT-001 Prevents Diabetic Cardiomyopathy via Reducing Myocardial Fatty Acid Oxidation Rates. *Diabetes.* 2021;70(Supplement_1).

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