Early Diagnosis of Diabetic Cardiomyopathy: What can be Done? ADA 2023

Diagnosis of Diabetic Cardiomyopathy Based on Circulating Biomarkers

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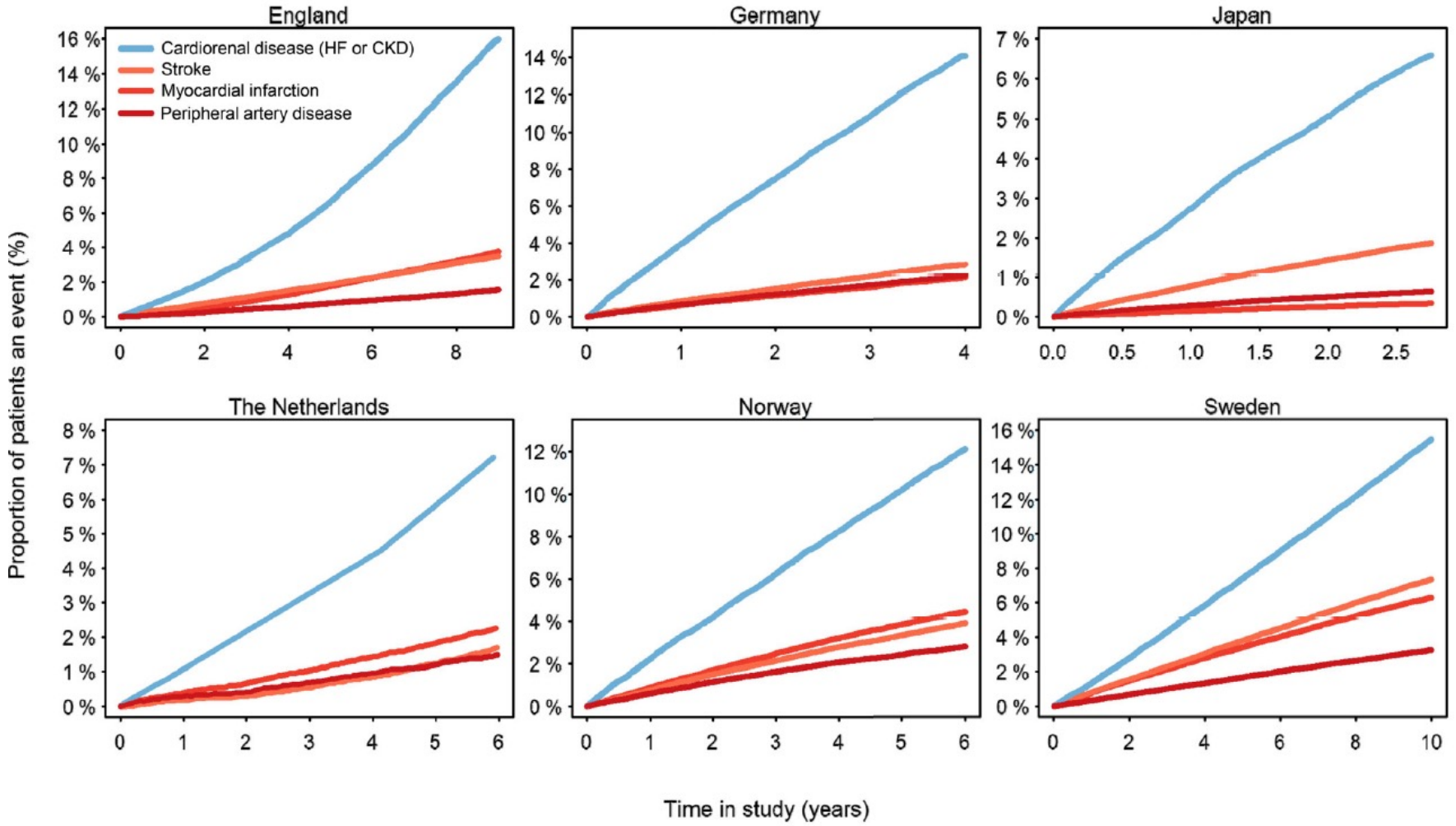
Agenda

- What is diabetic cardiomyopathy?
- How common is diabetic cardiomyopathy?
- How do I make the diagnosis of diabetic cardiomyopathy?

Cardiovascular Manifestation During Follow-Up in Initially CV- and Renal Disease-Free T2D Patients



Birkeland KI, et al. *Diabetes Obes Metab*. 2020;22:1607-1618.

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HF in diabetes: frequent, forgotten, and often fatal

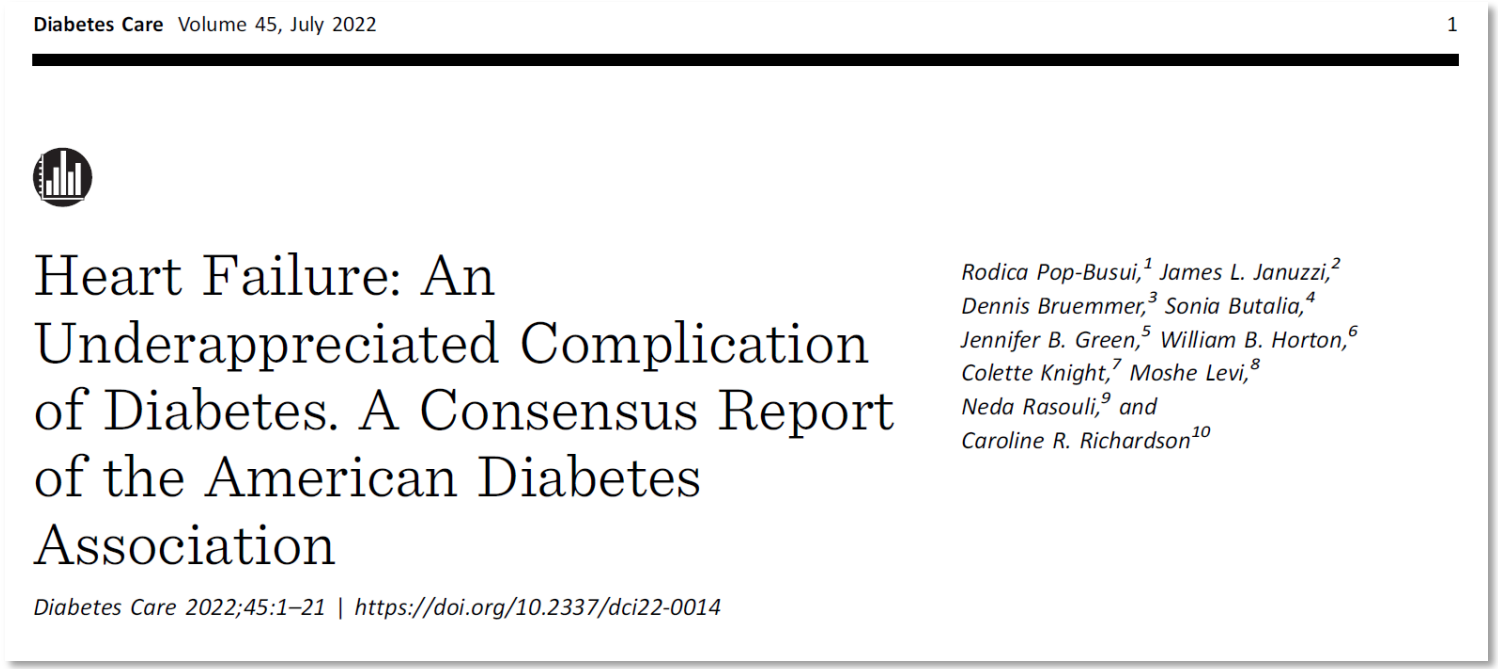
Heart Failure

The frequent, forgotten, and often fatal complication of diabetes

DAVID S.H. BELL, MB, FACE

Overall, it appears that diabetic patients would benefit from more aggressive preventive programs that set more stringent standards likely to reduce the incidence of cardiovascular morbidity and mortality in this high-risk population.

Forgotten no longer: ADA consensus



Diabetes Care Volume 45, July 2022 1

Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association

Rodica Pop-Busui,[1] James L. Januzzi,[2] Dennis Bruemmer,[3] Sonia Butalia,[4] Jennifer B. Green,[5] William B. Horton,[6] Colette Knight,[7] Moshe Levi,[8] Neda Rasouli,[9] and Caroline R. Richardson[10]

Diabetes Care 2022;45:1–21 | https://doi.org/10.2337/dci22-0014

- **A multi-disciplinary consensus statement**
- **Endorsed by the American College of Cardiology**

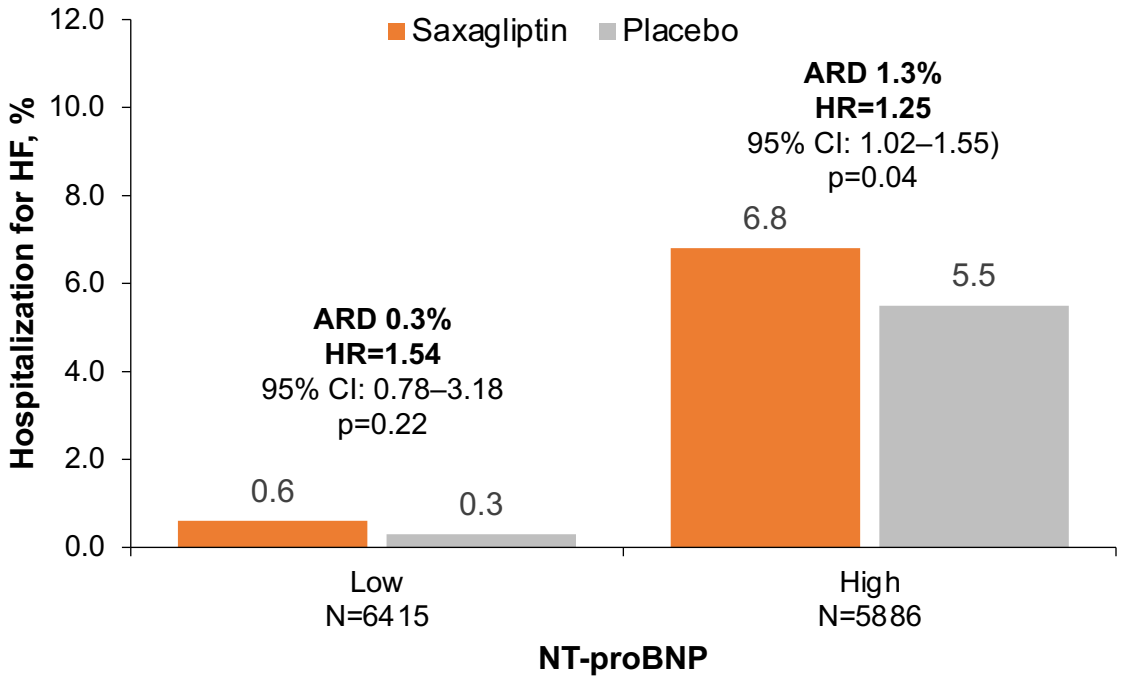
Pop-Busui R, et al. Diabetes Care 2022;45(7):1670–1690.

NT-proBNP cut-off of 125 pg/mL shows good discrimination ability

- Randomized Phase 4 study of 16,492 patients with T2D and a history or risk of CV events
- NT-proBNP measured in 12,301 patients

- NT-proBNP cut-off of >125 pg/mL (for age <75 years) was associated with a significantly increased risk of hospitalization for HF in 12,301 patients with T2D.[1]

- In another study, NT-proBNP cut-off of <25 pg/mL **had a negative predictive value** of 97.6% and sensitivity of 0.795% in predicting the combined endpoint of CV hospitalization or death in 631 patients with diabetes with and without history of CVD.[2]



(High >125 pg/mL if <75 years old, or >450 pg/mL if ≥75 years old)

NT-proBNP cut-off of 125 pg/mL shows good discrimination ability in patients with and without a history of cardiovascular disease.[1,2]

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ARD, absolute risk difference; CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

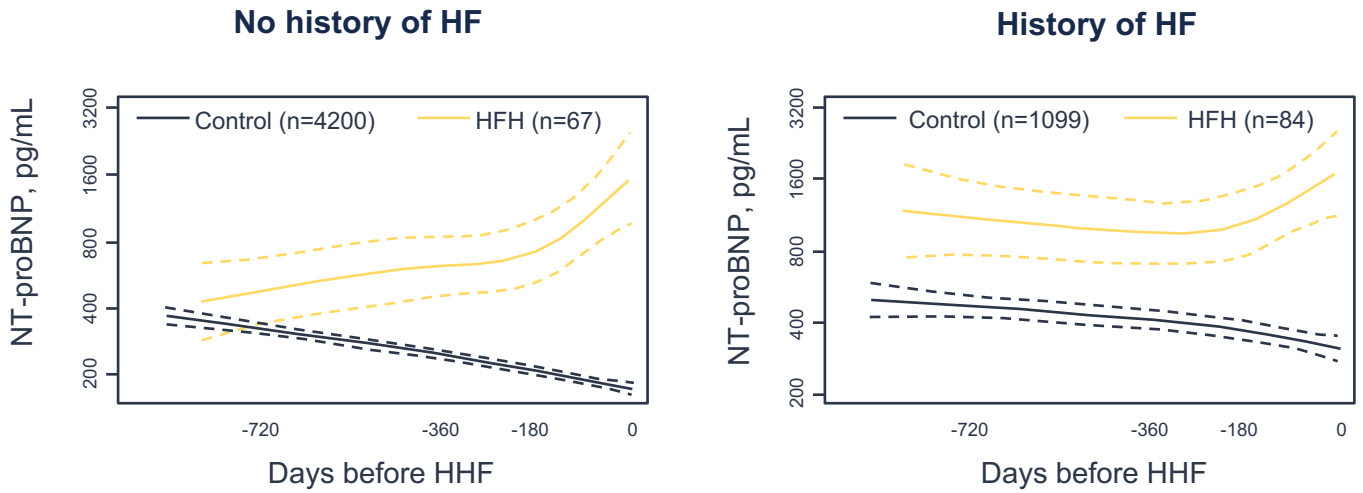
1. Scirica et al. Circulation. 2014; (Supp)130:1579-88; 2. Huelsmann et al. Eur Heart J. 2008;6629:2259-64.

Sharp increase in NT-proBNP preceding hospitalization for heart failure in patients with T2D

- Randomized Phase 3 study including 5450 patients with T2D with a recent coronary event, with and without history of HF
- NPs measured at baseline and at 24 weeks
- Median follow-up: 26 months

- Levels of natriuretic peptides (BNP and NT-proBNP) were significantly greater when measured closer to the time of the event in those who experienced HF hospitalization (BNP, p<0.001; NT-proBNP, p<0.001).
- At the time of HHF, patients with and without a history of HF reached comparable levels of natriuretic peptides .

NP levels in the 6 months preceding heart failure hospitalization

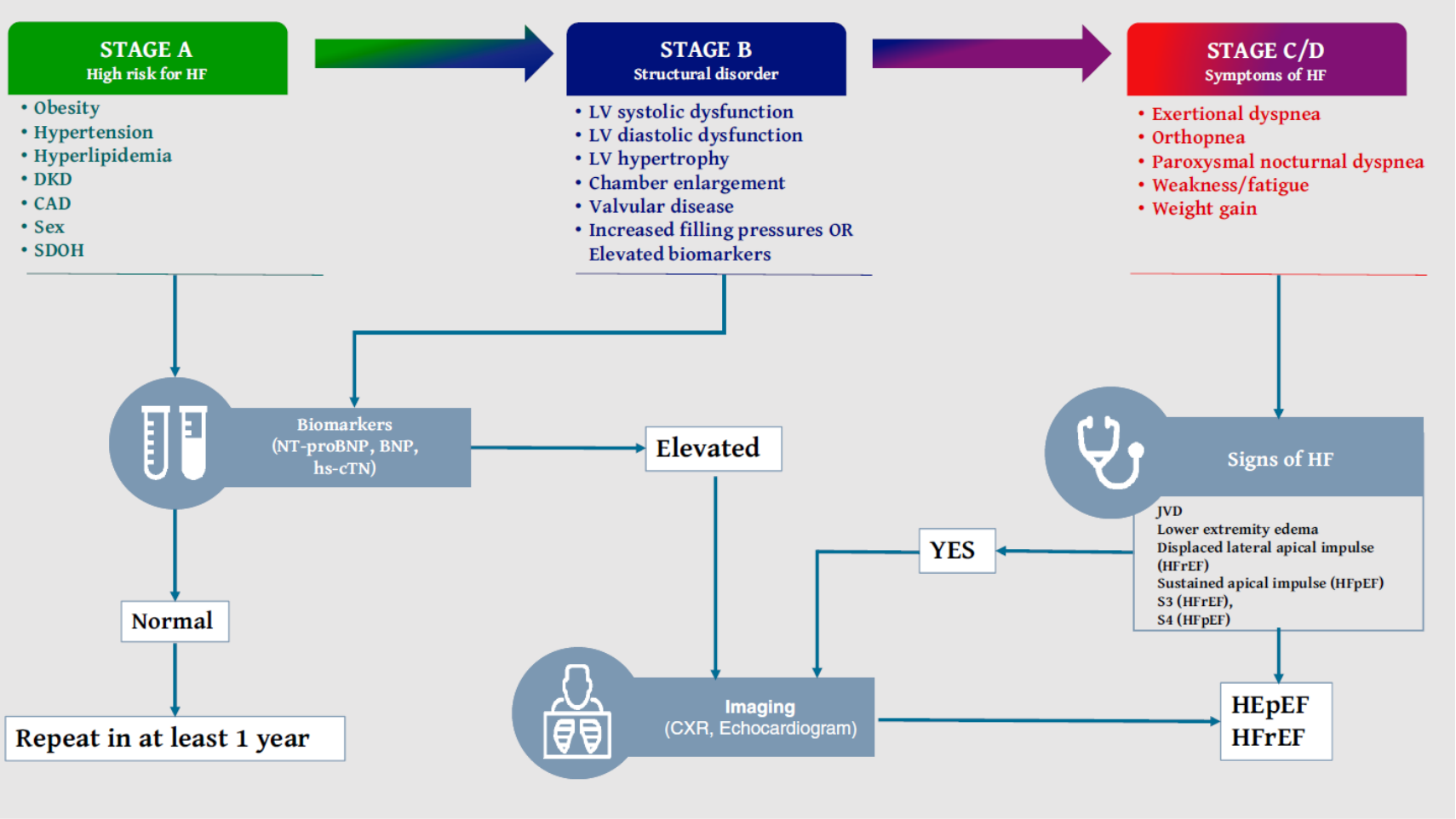


NT-proBNP may help identify patients with type 2 diabetes at risk for hospitalization for heart failure 6 months before the cardiac event, regardless of the history for heart failure

BNP, B-type natriuretic peptide; HHF, hospitalization for heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Wolsk et al. Circulation. 2017;136:1560-2.

Evaluation and Diagnosis



- **Among those with diabetes, routine assessment for symptoms and control of risk factors is crucial**
- **Measurement of a natriuretic peptide or high sensitivity troponin at least yearly is recommended in Stages A/B**
- **In those with abnormal biomarkers and/or symptoms/signs of HF, referral for imaging is recommended**

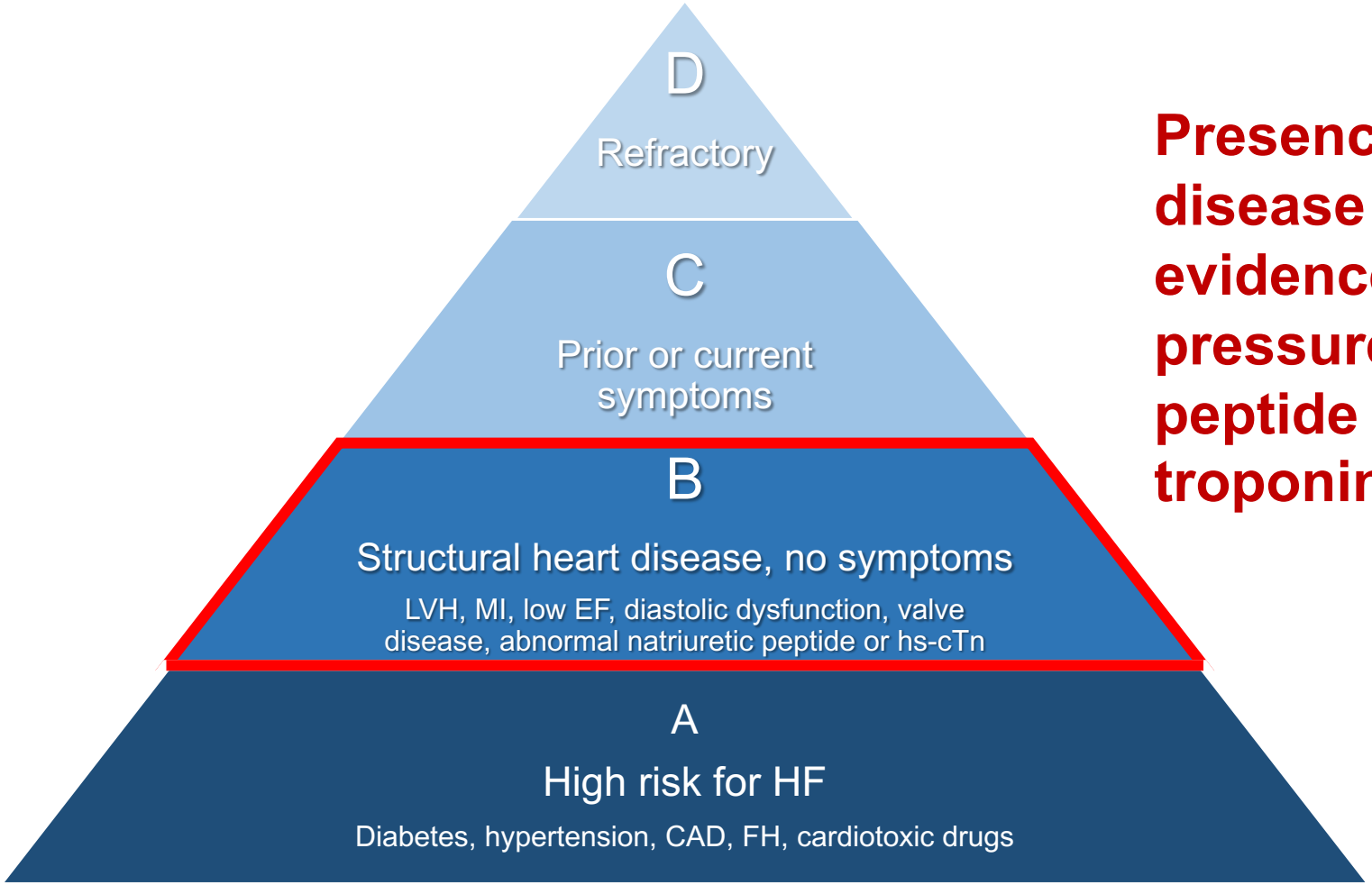
Pop-Busui R, et al; Diabetes Care, 2022;45:1-21

What is Diabetic Cardiomyopathy?

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

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

Stages of heart failure: Stage B (pre-HF)



Presence of structural heart disease and/or congestion as evidenced by elevated filling pressures or abnormal natriuretic peptide or high sensitivity cardiac troponin

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Risk Factors for DbCM

Risk factors for developing DbCM include a diagnosis of diabetes and:

Age ≥ 60 years

OR

Long duration of diabetes

(>10 years)

OR

Renal impairment

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

OR

Presence of other diabetic complications

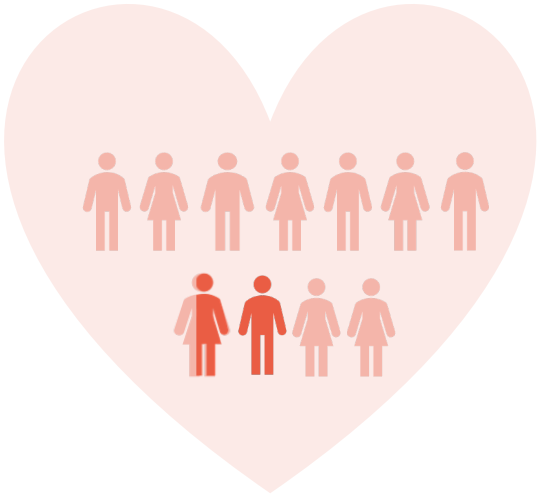
(peripheral or autonomic neuropathy; nephropathy; retinopathy)

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

What is the prevalence of DbCM?

US Study:

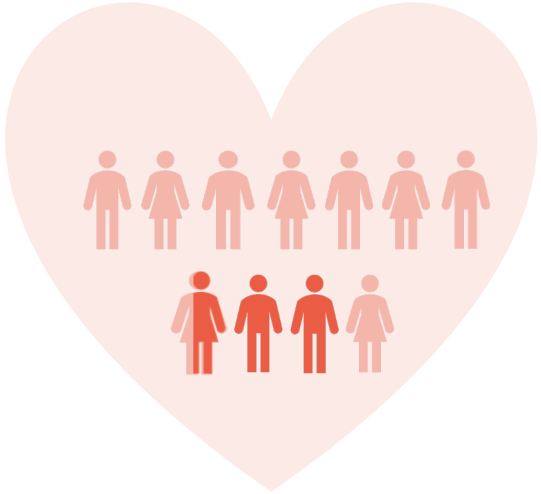
17% of diabetic patients



Dandamudi, S, et al. J. Card. Fail. 2014.

France Study:

24% of diabetic patients



Pham, I. Int J Endocrinol. 2015

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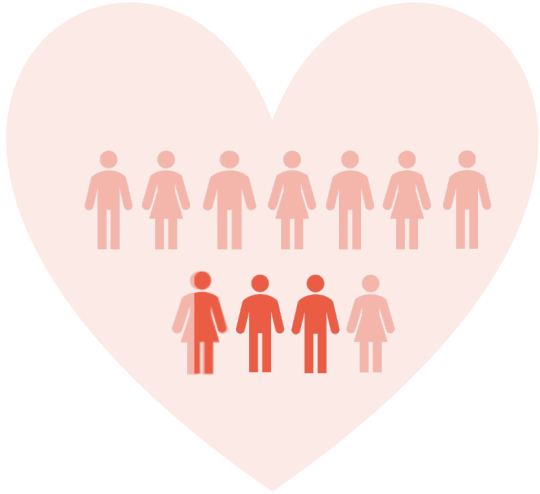

Segar, M. Jour Am Coll Cardiol 2021

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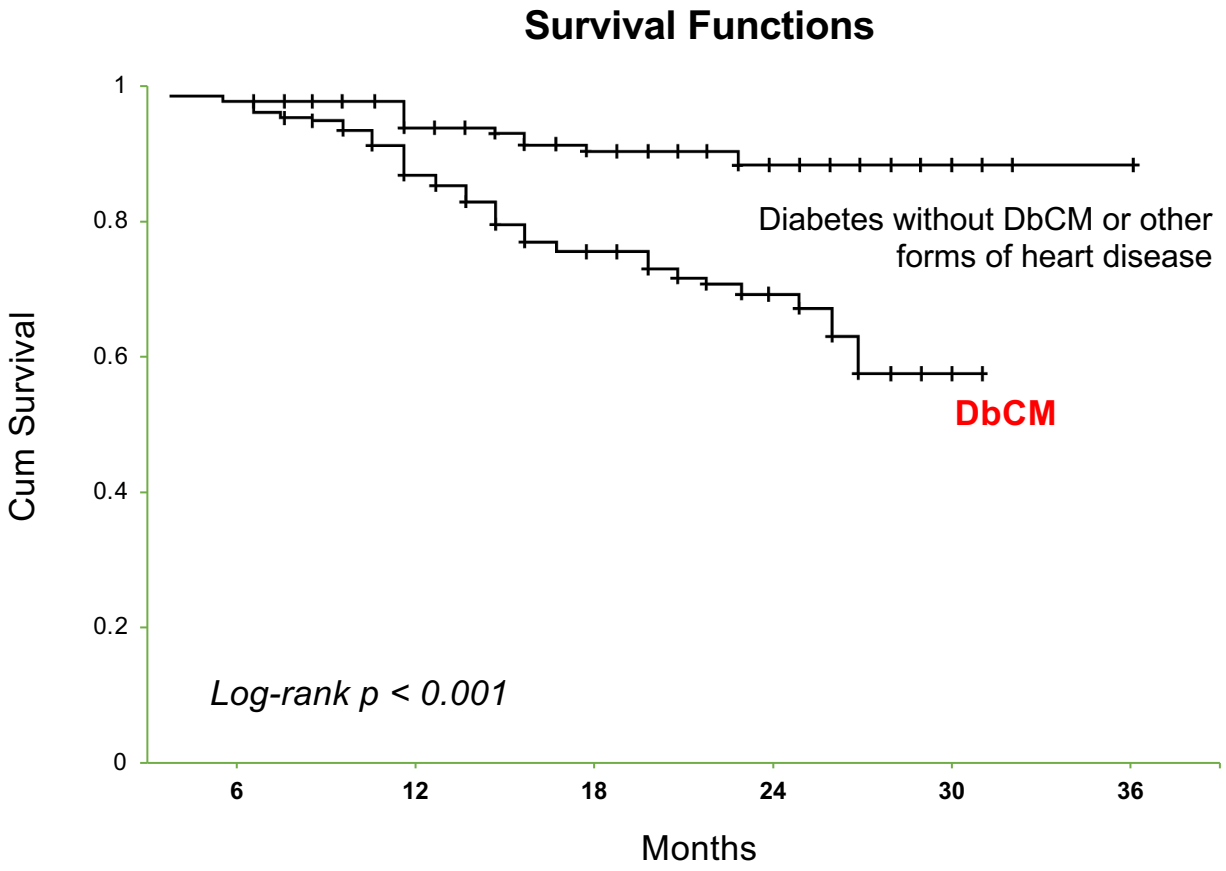
Diabetic Cardiomyopathy Can Rapidly Progress to Overt Heart Failure and Death

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

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



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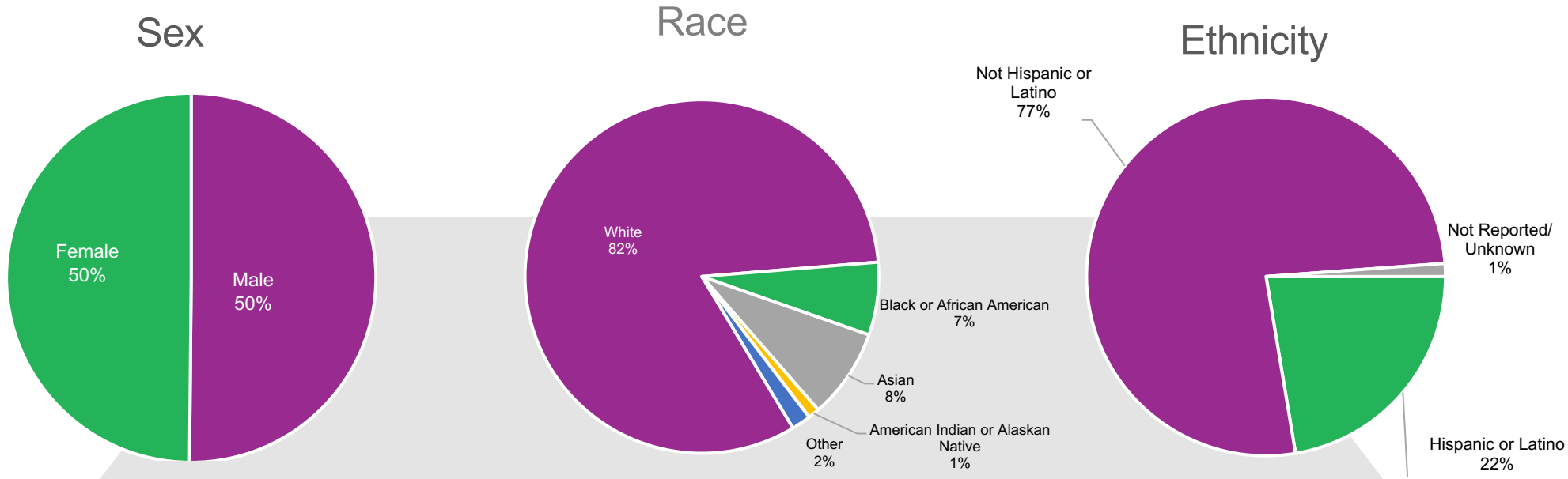
How is DbCM diagnosed?

- Patients with DbCM may report minimal to no symptoms but if tested will be found to have reduced exercise capacity
- Echocardiogram abnormalities and cardiac biomarkers in the absence of other causes of heart failure are common
  - LVH, LAE, increased E/E', and reduced global longitudinal strain
  - NT-proBNP >50-125 pg/mL, BNP >35-50 pg/mL or hs-cTn >99th %
- Absence of other causes, including CAD, uncontrolled hypertension, valve disease, etc

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

The face of DbCM



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

Data as of 15-Dec-2022

The face of DbCM

Laboratory tests	
NTproBNP, ng/L	71 (35-134)
Hs-Tnt, ng/L	9 (6-12)
HbA1c, %	6.99 (0.79)
Hgb, g/L	13.4 (1.4)
eGFR, mL/min/1.73	80.4 (16.3)
UACR, mg/g	8 (15-42)
Abnormal Echocardiogram, n, %	
GLS < -16%	167 (25%)
E/e' ≥ 13	163 (24%)
LAVI > 34 mL/m2	84 (12%)
LVMI ≥95 g/m² in men and ≥115 g/m² in women	77 (11%)
RVSP > 35 mmHg	26 (4%)
Questionnaires	
mKCCQ	90.3 (14.6)
PASE score	154.3 (89.6)
CPET	
PeakVO_2, ml/kg/min	15.7 (3.8)
VE/VCO_2 slope	31.2 (5.4)

- Prevalent biomarker abnormalities
- Abnormal cardiac structure/function
- Substantially reduced exercise capacity

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ARISE-HF: -Baseline Peak VO_2 (n= 680)

PeakVO2 (ml/kg/min)

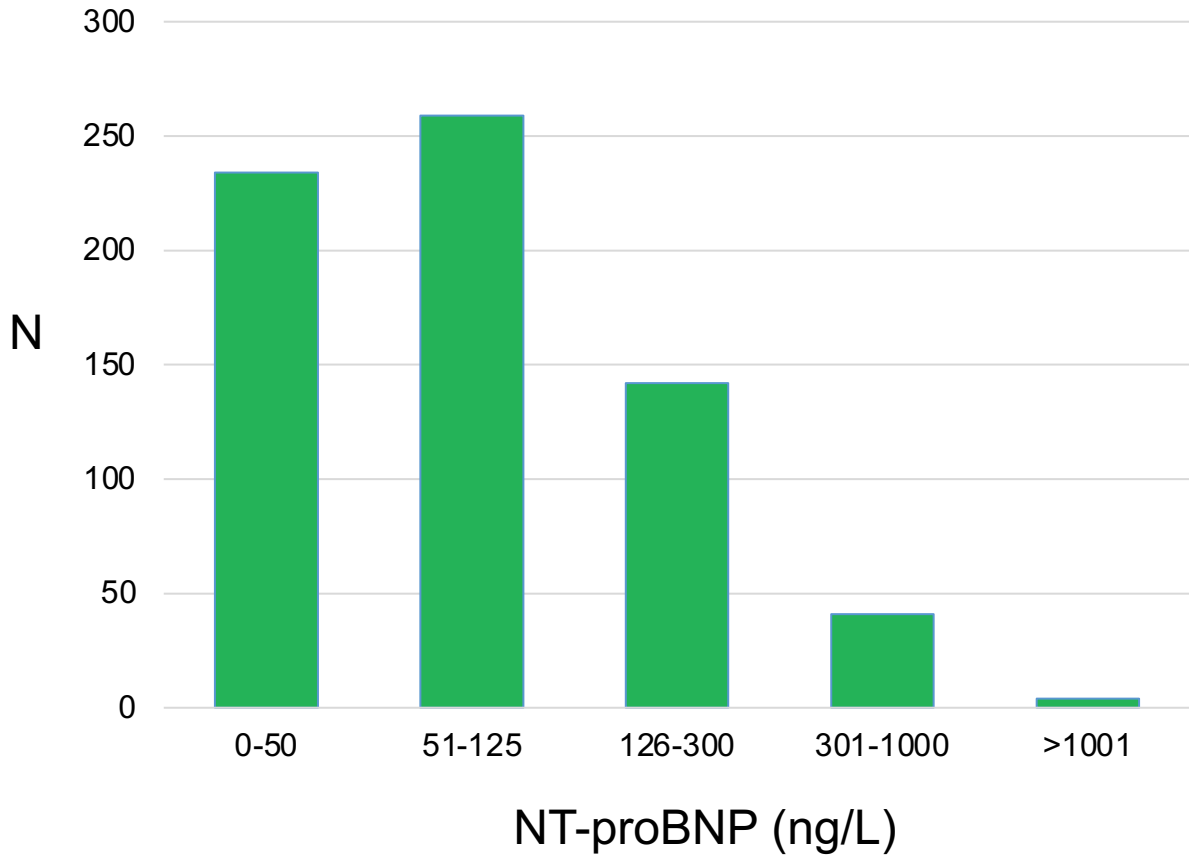
Mean (SD): 15.7 (3.8)
Min 6.7
Q1: 12.9
Median: 15.6
Q3: 18.6
Max 25.2

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

Data as of 15 Dec 2022

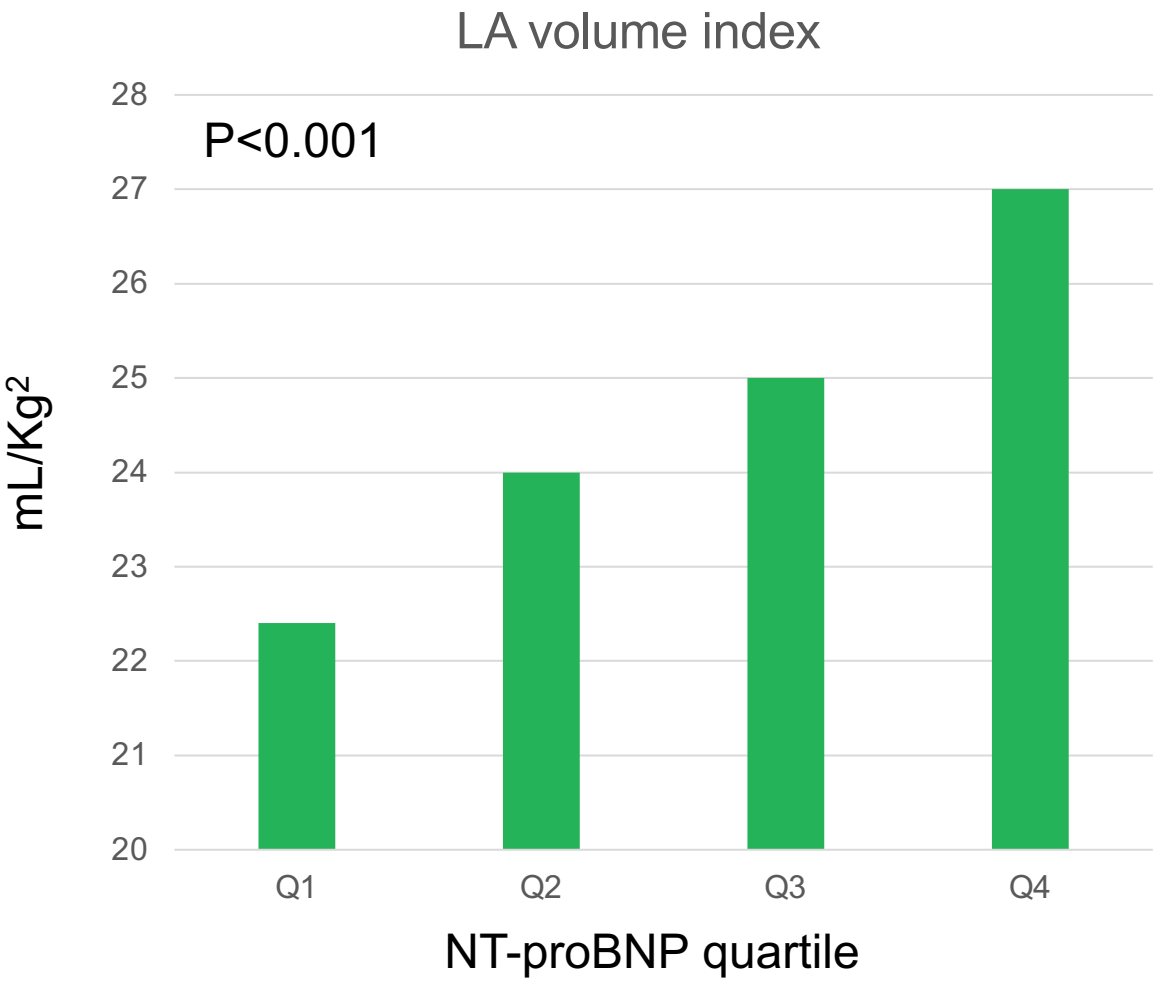
ARISE-HF: Baseline NT-proBNP

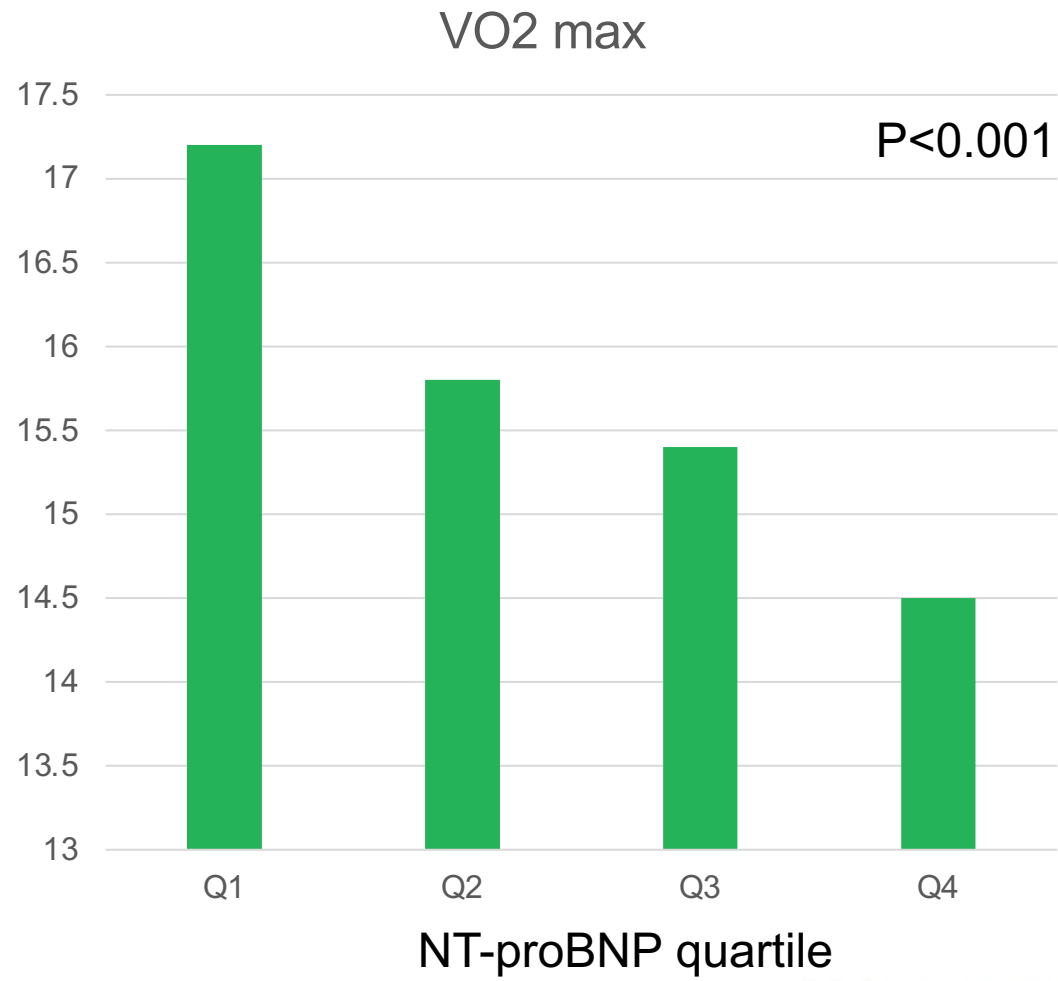
NT-proBNP (ng/L)
Mean (SD): 115 (217)
Min 5
Q1: 35
Median: 71
Q3: 134
Max 4284*



Data as of 15 Dec 2022

ARISE-HF: Baseline NT-proBNP





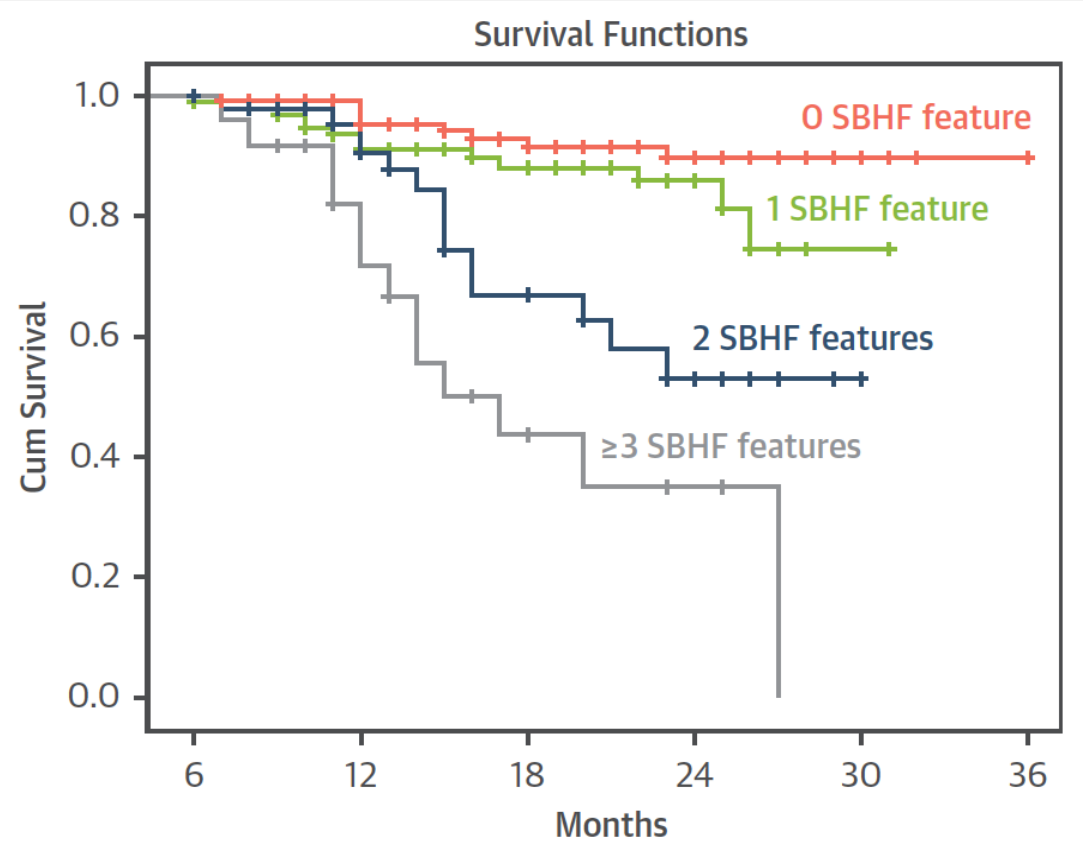
ARISE-HF: Baseline NT-proBNP

The combination of elevated biomarkers and echo = worst clinical picture

	Elevated biomarkers of heart disease N=278	Systolic/LVH cluster N= 177	Diastolic cluster N= 160	Overlap cluster N= 47	p
Echocardiogram					
LVEF, %	63.3 ± 5.2	61.2 ± 4.7	62.1 ± 5.4	60.0 ± 8.5	<0.001
GLS, %	-19.5 ± 2.0	-14.9 ± 1.9	-19.0 ± 2.4	-15.2 ± 3.2	<0.001
LAVI, ml/m^2	22.3 ± 5.2	22.0 ± 5.4	29.4 ± 8.5	31.1 ± 10.0	<0.001
LVMI, g/m^2	70.9 ± 14.0	85.3 ± 24.8	73.3 ± 14.7	101.5 ± 28.2	<0.001
E/e'	8.7 ± 1.9	9.1 ± 2.0	13.4 ± 5.8	14.8 ± 7.6	<0.001
RVSP, mmHg	21.5 ± 6.1	22.2 ± 6.5	26.0 ± 8.8	27.8 ± 7.4	<0.001

New Onset of HF or Death Significantly Increased for Patients with T2D and SBHF Markers

Prospectively study with 310 asymptomatic T2DM patients aged ≥65 years with preserved LVEF from a community-based population in Tasmania from 2013 and 2015[1]



- ~24% of DbCM patients progress to overt heart failure or death within 1.5 years
- Cumulative event-free survival decreased with increasing numbers of echocardiographic features

SBHF abnormality cutoff:

1) DD (E'/e'>13);
2) LAE >34 ml/m^2 ;
3) LVH (>115 g/m^2 for men, > 95 g/m^2 for women;
4) GLS<16%

1. Wang Y, et al. JACC Cardiovasc Imaging 2018

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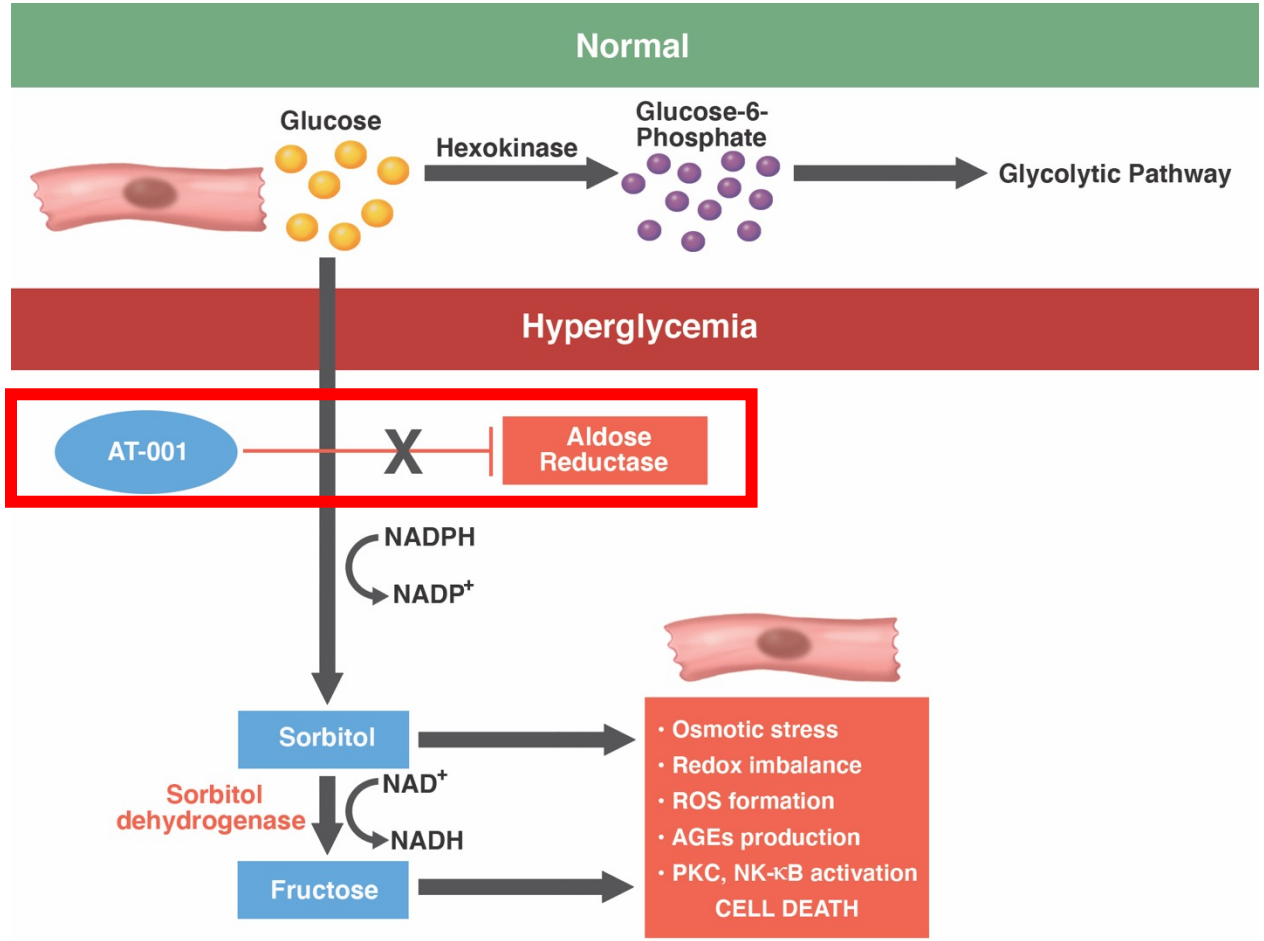
Blocking aldose reductase in DBCM



- **Aldose reductase inhibitors (ARIs) had previously been developed for treatment of microvascular complications**
- **Most 1st generation of ARIs were low potency and poorly tolerated due to inhibition of aldehyde reductase**
- **AT-001 is a highly potent and safe ARI**

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

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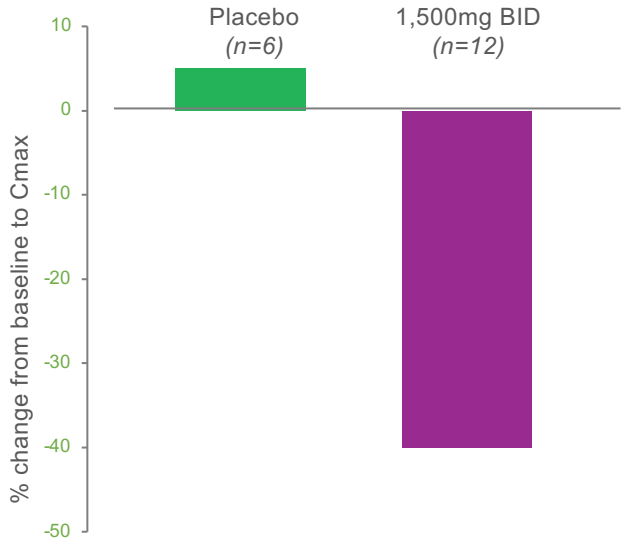
Effect of AT-001 on NT-proBNP

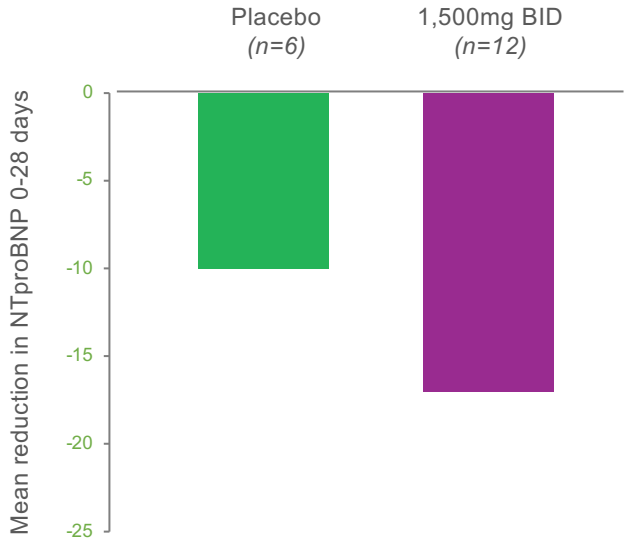
Sorbitol Normalization



Significant sorbitol reduction achieved by 1,500mg BID AT-001

Higher Cmax achieved with BID slightly beneficial — normalizes sorbitol to healthy volunteer levels

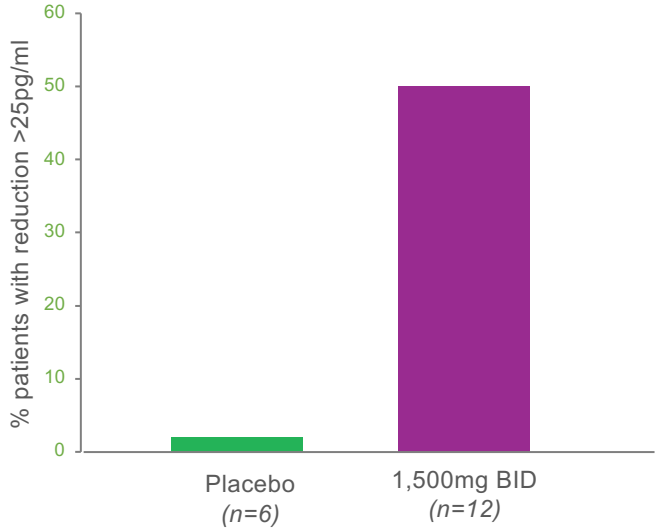
Mean Reduction in NT-proBNP



Mean reduction in NTproBNP seen over 28 days vs. placebo

Mean baseline NTproBNP was 65pg/ml

Clinical Responder Analysis



~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days

>25pg/ml reduction from baseline

Poster, “Phase 1/2 Safety and Proof of Biological Activity Study of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy” American Diabetes Association 79th Scientific Sessions in San Francisco (June 7-11, 2019); Poster “Clinical Assessment of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy: a 28 day proof of concept study” American Heart Association (AHA) Scientific Sessions

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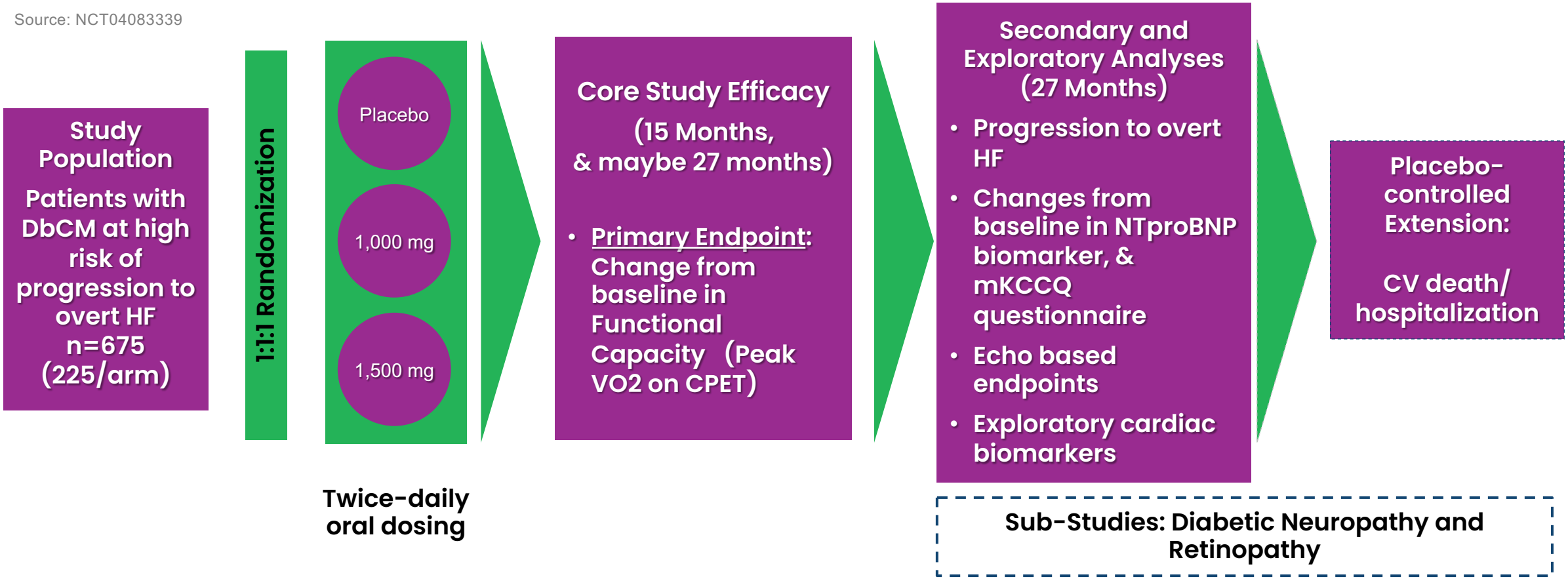
ARISE-HF: Phase 2/3 Trial for AT-001 in DbCM

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

Source: NCT04083339



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Agenda

- What is diabetic cardiomyopathy?
- How common is diabetic cardiomyopathy?
- How do I make the diagnosis of diabetic cardiomyopathy?

Conclusions

- Diabetic cardiomyopathy is an increasingly recognized complication of chronic diabetes
- DbCM is associated with impaired exercise capacity, risk for structural heart disease and potential for progression to symptomatic HF
- It may be diagnosed using cardiac biomarkers or imaging
- Emerging therapies are being developed for treatment of DbCM