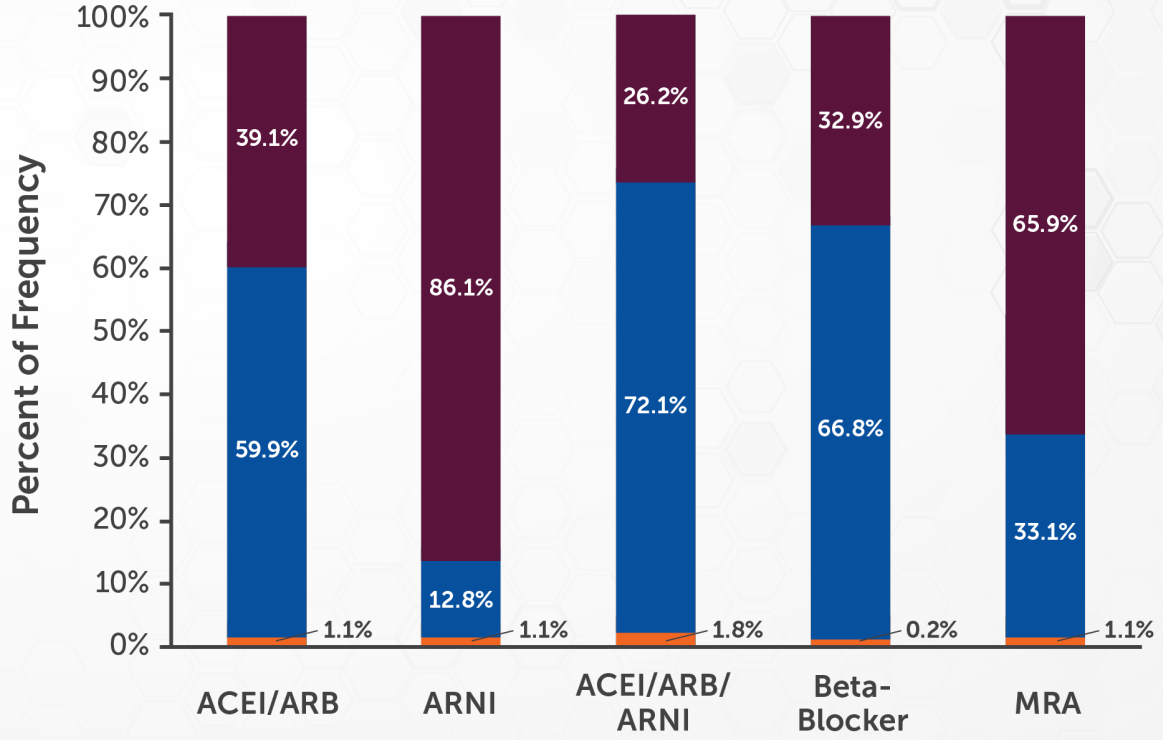
High-Risk HFrEF: Who Will Benefit Most from Novel Therapies?

CHAMP-HF Registry: Gaps in GDMT

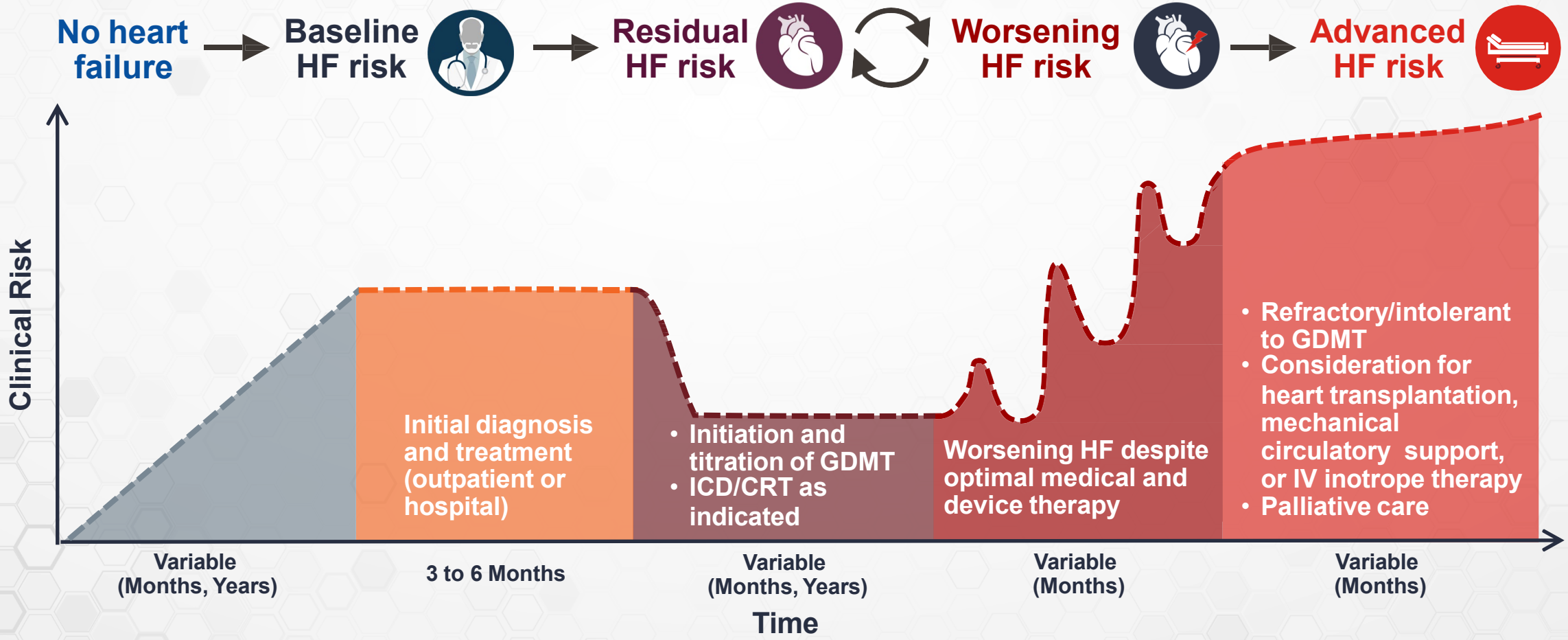
- Significant gaps remain in guideline-directed use and dosing of HFrEF medications



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Greene SJ, et al. *J Am Coll Cardiol*. 2018;72(4):351-366.

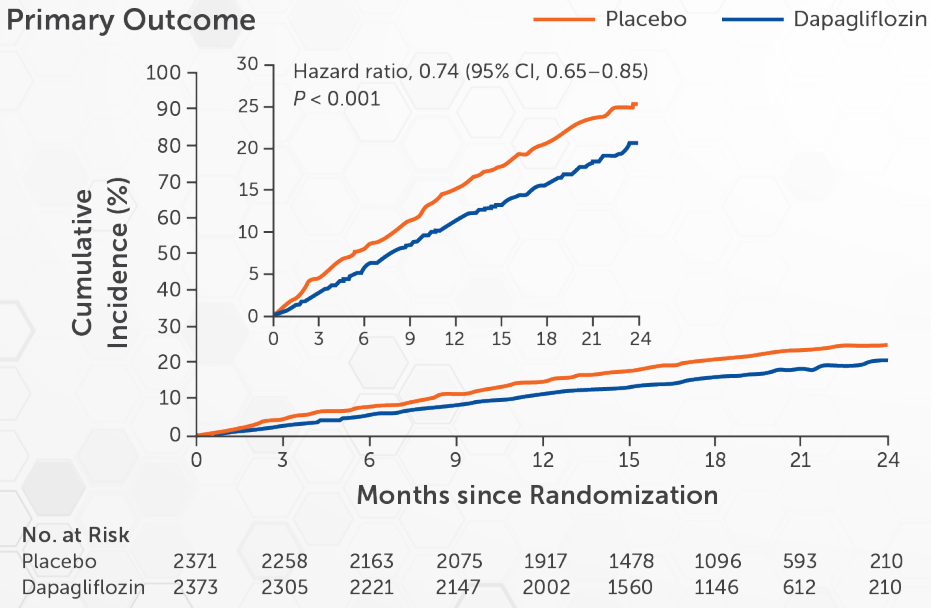
Heart Failure: A Vicious Cycle That Progressively Worsens Over Time

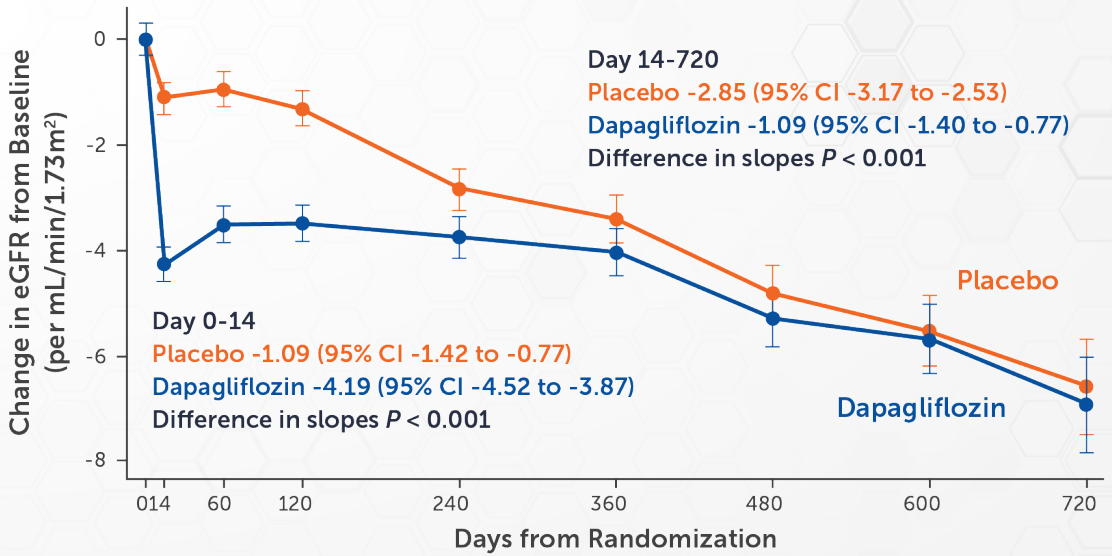


CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; IV, intravenous.

Adapted from Gheorghiade M, et al. *Am J Cardiol*. 2005;96(6A):11G-17G; and Cowie MR, et al. *ESC Heart Fail.* 2014;1(2):110-145.

DAPA-HF: Dapagliflozin Improved CV Outcomes and Slowed the Rate of Decline in eGFR





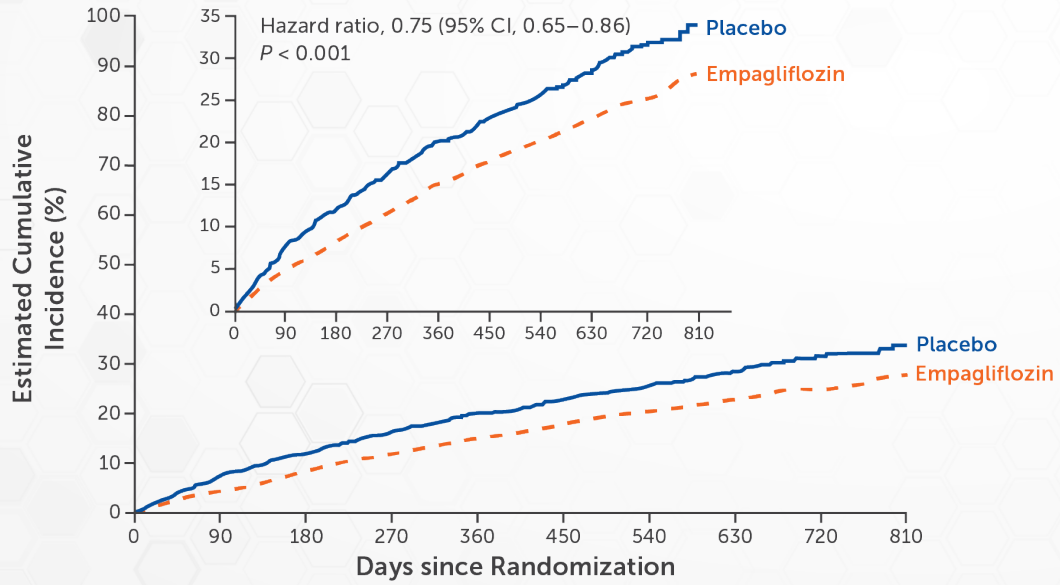
The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure.

Effect of dapagliflozin on change in eGFR. The slope in eGFR from day 0 to 14 from baseline is the slope per mL·min^{-1}·1.73 m^{-2} for over 14 days and from 14 to 720 days expressed as a slope per mL·min^{-1}·1.73 m^{-2} per year.

CV, cardiovascular; eGFR, estimated glomerular filtration rate.

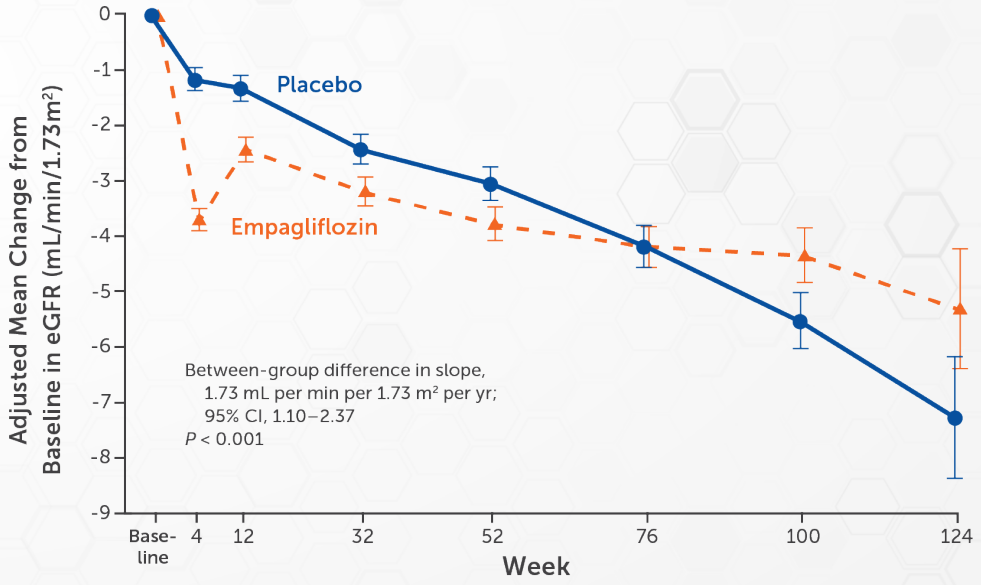
1. McMurray JJ, et al. *N Engl J Med*. 2019;381(21):1995-2008; 2. Jhund PS, et al. *Circulation*. 2021;143(4):298-309.

EMPEROR-Reduced: Empagliflozin Improved CV Outcomes and Slowed the Rate of Decline in eGFR



No. at Risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

The cumulative incidence of the primary composite outcome of cardiovascular death or hospitalization for heart failure.



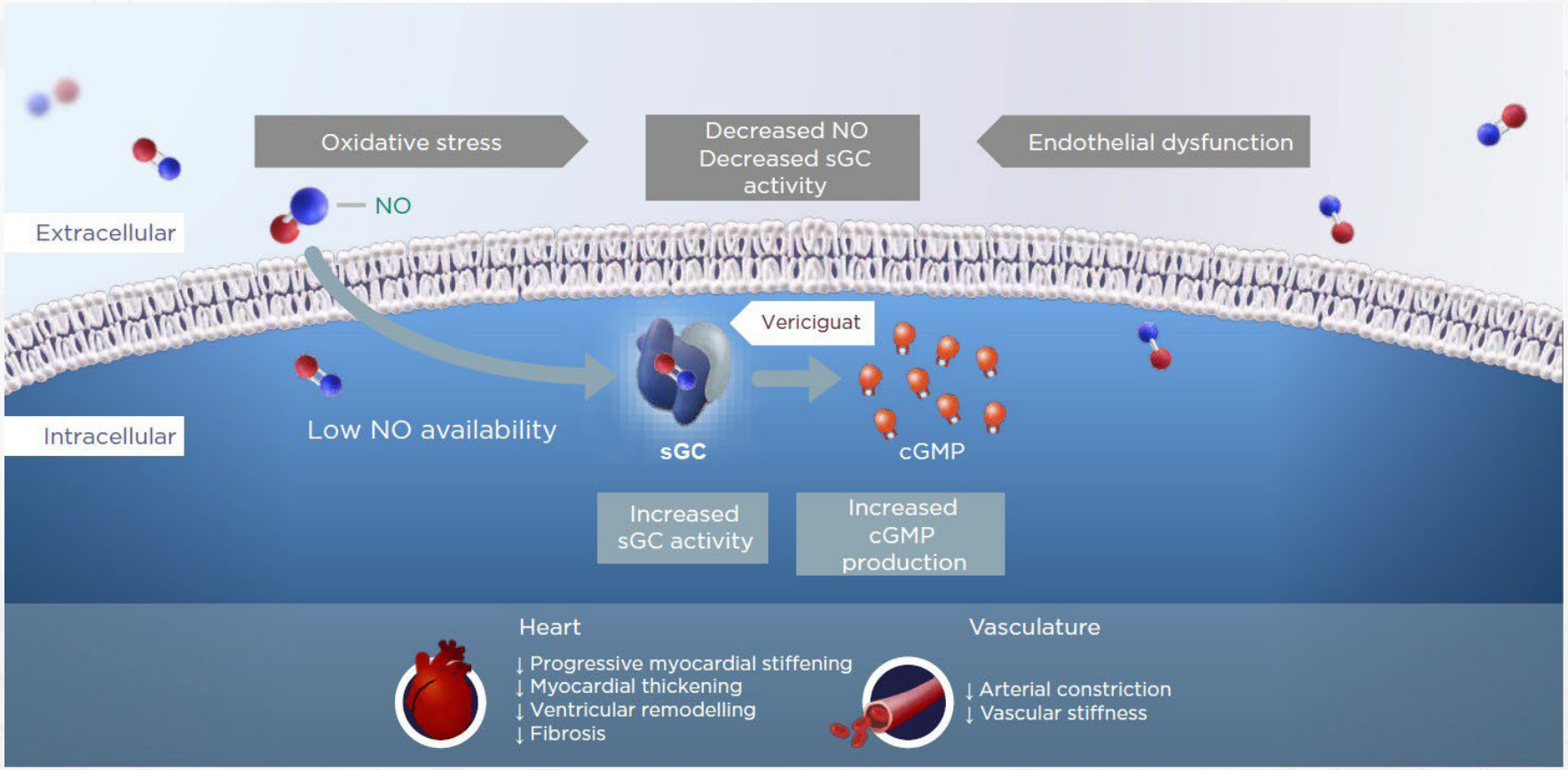
No. at Risk								
Placebo	1792 1765 1683	1500	1146	745	343	76
Empagliflozin	1799 1782 1720	1554	1166	753	356	80

Adjusted mean changes from baseline in the eGFR, as calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

CV, cardiovascular; eGFR, estimated glomerular filtration rate.

Packer M, et al. *N Engl J Med.* 2020;383(15):1413-1424.

Vericiguat Increases Soluble Guanylate Cyclase Activity to Improve Myocardial and Vascular Function



cGMP, cyclic guanosine monophosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.
Lam C, et al. European Society of Cardiology (ESC) Congress 2020 Virtual Symposium; August 29, 2020.

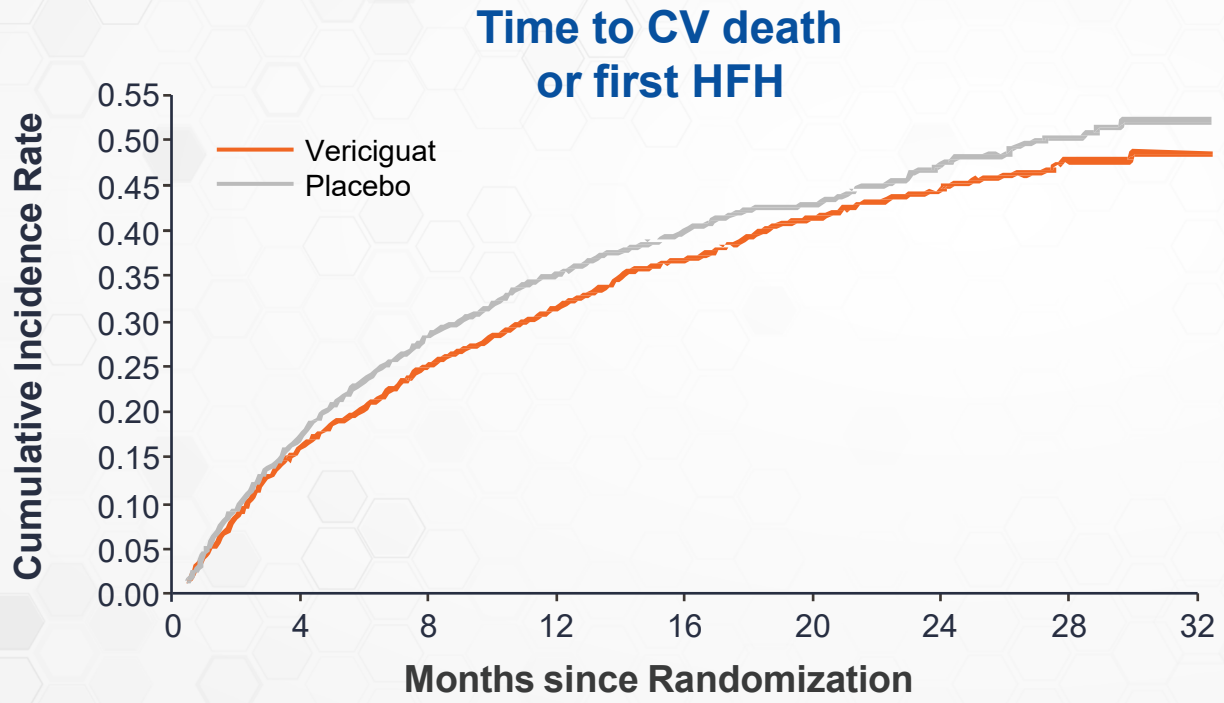
VICTORIA Trial Inclusion andExclusion Criteria

Inclusion Criteria	Main Exclusion Criteria
• Ejection fraction of <45% assessed within 12 months prior to randomization • Elevated natriuretic peptide levels within 30 days prior to randomization; for patients in sinus rhythm, BNP ≥300 pg/mL and for NT-proBNP ≥1,000 pg/mL; for those in atrial fibrillation, BNP ≥500 pg/mL; and for NT-proBNP ≥1,600 pg/mL* • Prior HF hospitalization within 6 months (those >3 months limited to 20%) or outpatient IV diuretic therapy for HF within 3 months prior to randomization	• Clinically unstable • Systolic blood pressure <100 mm Hg • Concurrent or anticipated use of long-acting nitrates of sGC stimulator • PDE5 inhibitors • Receiving IV inotropes, an implantable LV assist device, or awaiting heart transplantation • Correctable, complex, or clinically active cardiac comorbidity • Prior cardiac valve intervention <3 months or coronary revascularization <60 days • Unable to provide informed consent • Females of reproductive age not using an acceptable form of contraception

*For those subjects receiving sacubitril/valsartan, NT-proBNP criteria will be applied.
BNP, brain natriuretic peptide; HF, heart failure; IV, intravenous; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PDE5, phosphodiesterase type 5; sCG, soluble guanylate cyclase; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction.

Armstrong PW, et al. *JACC Heart Fail*. 2018;6(2):96-104.

VICTORIA: Primary Composite Endpoint CV Death or First HF Hospitalization



Number of patients at risk									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

- Median treatment duration for primary endpoint: 10.8 months
- Annual event rates for vericiguat and placebo per 100 PY were 33.6 and 37.8, respectively

HR = 0.90 (95% CI, 0.82-0.98);
***P* = 0.02**
ARR = 4.2 events/100 PY
Annual NNT = 24*

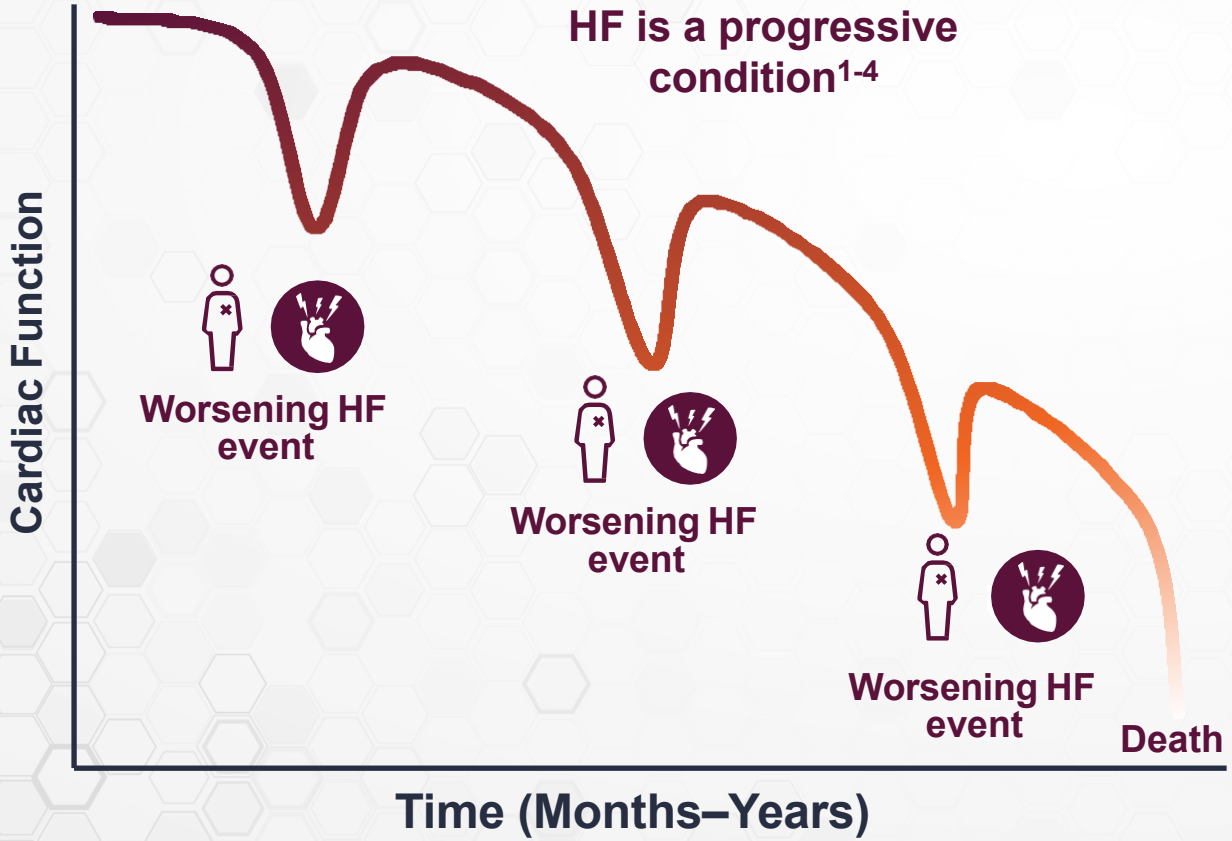
Vericiguat significantly reduced the annualized absolute rate of time to HFH or CV death by 4.2 events/100 PY[1]

*Calculations: annual NNT = 100/4.2 = 24.

ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; NNT, number needed to treat; PY, patient-years.

1. Armstrong PW, et al. *N Engl J Med*. 2020;382(20):1883-1893.

Worsening HF Is Characterized by Repeated HF Events, Resulting in Reduced Cardiac Function[1-5]



Worsening HF events[3-5]

Characterized by:

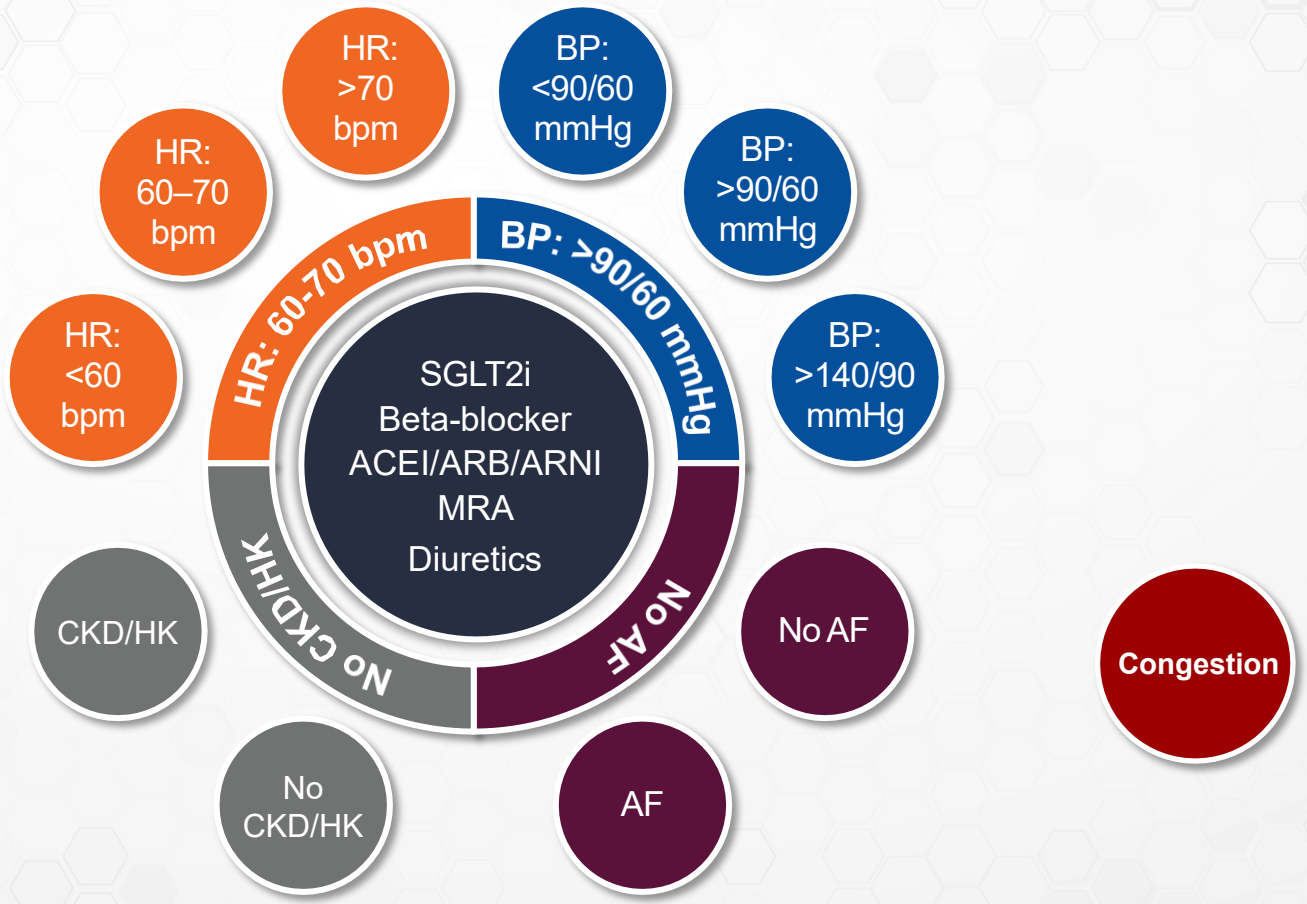
- Progressive signs and symptoms of HF for which medical treatment is warranted despite the use of GDMT
- Experience of a prior worsening HF event
  - Need for IV diuretics, regardless of setting
  - HFH
  - Need for an urgent HF visit

Adapted from Gheorghiade *et al*. *Am J Cardiol*. 2005 and Cowie *et al*. *ESC Heart Fail*. 2014.

GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; IV, intravenous.

1. Gheorghiade M, et al. *Am J Cardiol*. 2005;96(6A):11G-17G; 2. Cowie MR, et al. *ESC Heart Fail*. 2014;1(2):110-145; 3. Greene SJ, et al. *JAMA Cardiol*. 2018;3(3):252-259; 4. Butler J, et al. *J Am Coll Cardiol*. 2019;73(8):935-944; 5. European Medicines Agency. 2017. CPMP/EWP/235/95, Rev.2. Accessed June 2021. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf

Important Characteristics When Considering Medical Therapy in Heart Failure Patients



ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; HK, hyperkalemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Rosano GMC, et al. *Eur J Heart Fail*. 2021;23(6):872-881.