ARTICLE 1: The Clinical and Economic Burden of Worsening Heart Failure

Disease State Overviewx

Heart failure (HF) is a chronic disease affecting approximately 7 million Americans, with numbers continuing to rise as the aging population increases.[Heidenreich,2013;p608,table1][Benjamin,2019;pE62,col1,bullet6] By 2030, the prevalence in the United States is expected to be 8 million or nearly 3% of the population.[Heidenreich,2013;p608,table1;p607,col2,para4;p608,col2,para1] Among those aged 65 and over, the incidence of HF in the U.S. is approximately 21 per 1000 people per year.[Benjamin,2019;pE440,col1,bullet2]

Worsening HF, defined as chronic HF that has progressed in signs and symptoms to the point of requiring escalation of therapy and/or hospitalization(s), carries a ve[illegible]oor prognosis.[Greene,2018;p253,figure1;p257,col2,para3] [Cooper,2015;p603,col2,para2(entire);col1,p[illegible]es cited within the American College of Cardiology's (ACC's) 2019 ex[illegible]ent on managing patients hospitalized with heart failure indicat[illegible]ents with HF do not adequately improve during a hospitalization,[illegible]n for them to experience additional, subsequent hospitalizations wi[illegible].[Hollenberg,2019;p1987,col2,para3-4;p1988,col1,para1];note:Hollenberg cites to Allen, w[illegible],JCF,2008;p780,col1para3,ln9-11;p780,figure1;p781,table2] It has b[illegible]odes of acute decompensated HF requiring hospitalizations mark[illegible]e in the clinical disease course of chronic HF and are likely indicati[illegible]rgan damage which leaves patients with a permanently increas[illegible]es.[Hollenberg,2019;p1968,col1,para4][Greene,2018;p253,col1,para2]

[illegible]College of Cardiology Foundation/American Heart Association (ACCF/A[illegible]tages of HF and the New York Heart Association (NYHA) functional classes

provide different, yet complementary, information regarding disease status in HF.[Yancy,2013;pE155,col2,para3,ln1-4] The two systems are summarized in **Table 1.** AHA structural stages are progressive; that is, once a patient moves to a higher stage, they cannot regress to a lower stage.[Yancy,2013;pE155,col2,para4,ln3-4;pE156,col1,para1,ln1] The NYHA functional classes, on the other hand, focus on the symptomology a patient is experiencing at a given time point; thus, assignment of NYHA is more fluid and subject to change throughout the histori e course of disease.[Yancy,2013;pE156,col1,para1,ln7-11;pE155,col2,para3,ln7-8][Yancy,2013;pE156,col1,para al characterizations of HF (reduced ejection fraction and preserved lso summarized in **Table 1**.[Yancy,2018;p203,col1,para4,ln1-5]

Table 1. AACF/AHA Stages of HF, NYHA Functional Classifications, and Ejection Fraction Cut-Points[Yancy,2013;pE155,table3,table4][Buglioni,2015;p3,col2,para2,ln7-15][Hollenberg,2019;p1969,col2,para9-10][Yancy,2017;p785,para6,ln5-7]

AACF/AHA Stages			NYHA Functional Classes		
Stage	Description		Functional Class	Description	
	Structural Disease	Signs and Symptoms (current or prior)		HF symptoms occur during ordinary physical activities	HF symptoms during less ordi…
A	*(at risk)*		*(n/a)*		
B	✓	*(none)*	I		
C	✓	✓	I		
			II		*(none)*
			III		*(none)*
			IV		✓
D	✓	✓ *(refractory requiring specialized interv…*			✓

…on Cut-Points	
Type	**EF %**
Reduced Ejection Frac… (HFrEF)	…HF ≤ 40%
	… > 40% and < 50%
Preserve… Frac…	Diastolic HF > 50%

NT-proBNP Biomarker Cut-Points	
…Normal	< 125 pg/mL for age < 75 < 450 pg/mL if age ≥ 75
Unstable HF	> 450 pg/mL for age < 50 > 900 for age ≥ 50
Mild to Moderate HF	≥ 600 pg/mL -or- ≥ 400 pg/mL + prior hospitalization in the preceding 12 months

pg/mL, picogram per milliliter

AACF, American College of Cardiology Foundation; AHA, American Heart Association; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; n/a, not applicable; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide (N-terminus of the pro-hormone of BNP)

Epidemiology

In an observational cohort analysis of patients with reduced left ventricular ejection fraction HF (HFrEF; N = 11,064) identified in the NCDR PINNACLE registry (ACC's National Cardiovascular Data Registry [NCDR]), 16.7% (or approximately 1 in 6; n = [illegible] developed worsening HF within an average of 1.5 years from their initial diagnosis.[Butler,JACC,2019;p936,col2,para3,ln9-14;para4,ln3-8;p938,col2,para4,ln2-6; 167 = 1/6] In the study, worsening HF was defined as requiring at le[illegible] diuretic treatment in any health care setting or an HF-related hospital[illegible]ed worsening, patients were required to have received at least 30[illegible]rapy following their diagnosis and to have been stable for at leas[illegible]ir diagnosis (no EF-related emergency care, hospitalizations, or o[illegible]eatment during this 90-day window).[Butler,JACC,20[illegible]omorbidities such as diabetes mellitus and atrial fibrillation w[illegible]common among those that developed worsening HF versus those [illegible] that worsening HF may be correlated with a high comorbidity burden.[illegible]939,col1,para2,ln2-12]

In this same study, the subsequent 2-year mortality rate following a worsening-defining event was 22.5% and the mean survival time after such an event was just under 20 months.[Butler,JACC,2019;p939,col2,para2,ln1-4] The mean number of HF-related re-hospitalizations more than doubled following the worsening event, from 0.7 per patient at 30-days post-worsening event to 2.0 per patient at 24 months post-worsening event.[Butler,JACC,2019;p940,col1,para1(entire);p943,figure4b] It was also observed that the proportion of patients with hospitalizations in the worsening HF cohort at 1 month, 3 months, 12 months, and 24

months following the index worsening event was high, ranging from [illegible] 70%.[Butler,JACC,2019;p939,col2,para2,ln9-10;p943,figure4b]

In the American Heart Association's (AHA's) 2[illegible]sease and stroke statistics, it was noted that rates of HF rehospitali[illegible]ar death in the United States are greatest among those previousl[illegible]with an average incidence of recurrent HF-related hospitalizatio[illegible]00 people per year.[Benjamin,2019;pE442,col1,bullet[illegible]ame report also indicated that the age-adjusted case fatality rates aft[illegible] HF were 10.4% at 28 days and 29.4% at 1 year.[Benjamin,20[illegible]arly, the ACC cited a 1 year mortality rate following a HF hospit[illegible]Hollenberg,p1968,col2,para1]

[illegible]d HF events, approximately half (53%) are associated with HFrEF and the other half ([illegible]%) are associated with HFpEF.[Benjamin,2017;E151,col2,bullet9][Benjamin,2019;pE62,col2,bullet2;pE442,col2,bullet2][Buglioni,2015;p4,col1,para1,ln5-6] In general, mortality rates for those with HFrEF are usually much higher than they are for HFpEF.[Buglioni,2015;p4,col1,para1,ln11-12]

Economics

HF is one of the largest burdens of managed care, with HF hospitalizations and re-hospitalizations occupying the majority of total costs.[Hollenberg,2019;p1968,col1,para3][Heindenreich,2013;p608,col1,para2;p610,col2,para2] Of the total U.S. healthcare budget, 1%-2% is spent on HF and one-half of this is attributable to inpatient admissions for HF.[Hollenberg,2019;p1968,col1,para3] It is therefore not surprising that HF is one of the 6 conditions and procedures covered under the Center for Medicare and Medicaid Services' (CMS's) Hospital Readmission Reduction Program (HRRP) to incentivize acute care hospitals to reduce the rate of

30-day unplanned readmissions for Medicare beneficiaries.[HRRP_CMS,2020;p1,para1-3][HRRP_FedReg_Aug2019;p42049] Under this program, hospitals participating in the Inpatient Prospective Payment System (IPPS) whose 30-day readmission rates for covered conditions are higher than the national average receive reduced a reduced reimbursement rate when tre beneficiaries.[HRRP_FedReg_Aug2019;p42046;p42049]

CMS estimates that the HRRP will save the U.S. gove $563 million in FY2020 as a result of nearly 2,600 hospitals receivi ties for excess readmissions.[HRRP_FedReg_Aug2019;p42051] This sugg portion of hospitals are expected to face penalties for HF and the ered under HRRP. Given that the proportion of patients with HF wh r is projected to increase to over 70% by the year 2030, HF hospitali ation costs to providers who participate in Medicare's IPPS ar ntial both now and in the future.[Heidenrei 2.2million)/(8.5million)=0.718*100=71.8%][Fitch,2018;p855,para1,ln2-4]

Pathop hormonal Activation

HF p iology is complex, involving the activation of several neurohormonal mechanisms designed to compensate for a poorly functioning heart pump and the accompanying decrease in cardiac output.[Buglioni,2015;p3,col1,para1;p5,col1;para1;p5,col1,para3;p5,col2,para2][Jackson,2000;p167,col1,para1;p167,col1,para2;p167,col2,figure1][Khan,2020;p11,para1(entire)] These compensatory mechanisms are helpful in normal physiological conditions, but their chronic activation in the setting of HF becomes maladaptive and problematic.[Jackson,2000;p167,col1,para3(entire);p167,col1,para5,ln4-6][Khan,2020;p13,para1(entire)][Khan,2020;p13,para3,ln7-9]

There are 3 main neurohormonal systems that become activated in HF and which play a role in the pathophysiology of disease.[Buglioni,2015;p4,col2,para3,ln1-3] They are the sympathetic nervous

system (SNS), the renin-angiotensin-aldosterone system (RAAS), and the natriuretic peptide (NP) system.[Buglioni,2015;p4,col2,para3,ln1-3] The effects of these 3 systems in HF have be summarized in **Figures 1, 2, and 3.**

Briefly, in the setting of a failing heart pump, the SNS attem output and blood perfusion to organs by releasing catecholam norepinephrine), which make the heart pump harder a opic and chronotropic effects, respectively) and which c eral vasoconstriction to maintain blood pressure.[Buglioni,2015;p4,col2, on,2000;p167,col1,para2,ln5-9] The RAAS attempts to increase blood pressu ction and by increasing blood volume.[Buglioni,2015;p4,col2,para 1,para2,ln9-12] Renin is released, which cleaves angiotensinogen in tensin I is subsequently converted to angiotensin II by the angioten (ACE).[Jackson,2000;p167,col1,para4,ln1-3;p167,col2, ,para3,ln12-14] Angiotensin II is a potent vasoconstrictor and also activates aldos synthesis and release from the adrenal glands.[Bugioni,2015;p5,col1,para3,ln14-16][Jackson,2000;p167,col1,para4,ln3;p167,col2,figure2] Aldosterone acts at mineralocorticoid receptors in the kidney tubules to increase sodium and water retention, which action increases blood volume.[Buglioni,2015;p5,col1,para1,ln3-6;p5,col1,para3,ln17-20][Jackson,2000;p167,col2,figure2]

The NP system attempts to counteract the vasoconstriction and the fluid retention brought about by the SNS and RAAS by releasing the natriuretic peptides ANP and BNP.[Buglioni,2015;p4,col2,para3,ln6-8;p4,col2,para4,ln1-3][Jackson,2000;p168,col1,para3-5(entire)] These hormonal peptides bring about natriuresis (excretion of sodium and water in the urine), vasodilation, and inhibition of aldosterone synthesis, as well as several cardioprotective mechanisms.[Buglioni,2015;p4,col2,para4,ln11-16;p4,col2,para4,ln18-20] The NP is successful at compensating for the deleterious effects of the SNS

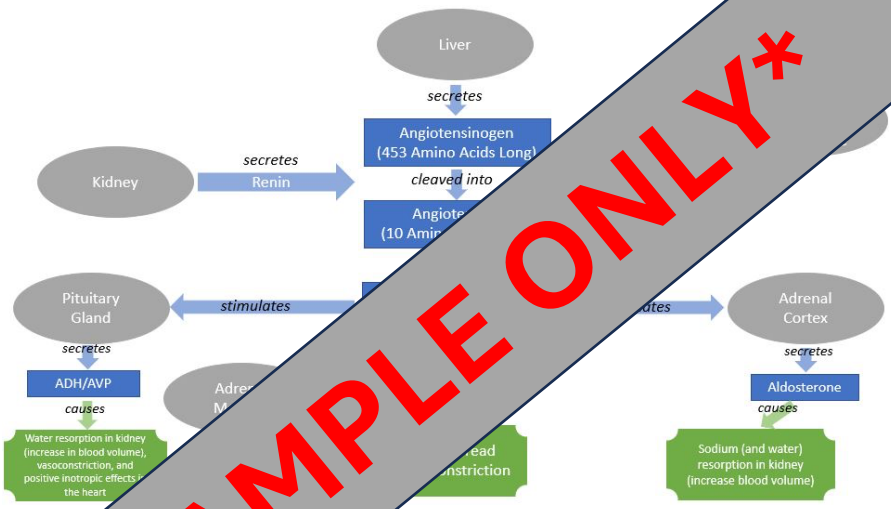
and RAAS for a time. However, as HF progresses, the actions of the SNS and RAAS overwhelm the NP system's beneficial and protective effects, and the imbalance that ensu bout symptomatic decompensation.[Buglioni,2015;p5,col1,para1,ln10-13;p5,col1,para3,ln20-23;

One of the natriuretic peptides and its inactive fragment [N-terminal pro-B-type natriuretic peptide, respectively) hav ostic biomarkers in HF. [Yancy,2013;pE163,sect6.3.A.1;sect6.3.A.2;sect6.3.B.1][Yancy,2 5;p6,col1,para3] [Jackson,2000;p169,col1,para2] The precursor to both is the peptide proBNP$_{108}$, which is released by cardiomyocyte rdial stretch secondary to cardiac congestion.[Yancy,2013;pE164,col1,p sing, proBNP$_{108}$ is cleaved into BNP (active form) and an N-termi s) fragment, NT-proBNP.[Yancy,2013;pE164,col1,para2(entire)] Levels of these HF worsening and go down when HF is stable.[Y][Hollenberg,2019;p1977,table5][Hollenberg,2019;p1978,col1,para3,ln9-17] Higher levels are associate ier risk for poor clinical outcomes, including hospital readmission and mortality.[Yancy,2017;p782,sect6.3.3] Cut-points for NT-proBNP useful in the clinical setting are provided in **Table 1.**

Conclusion

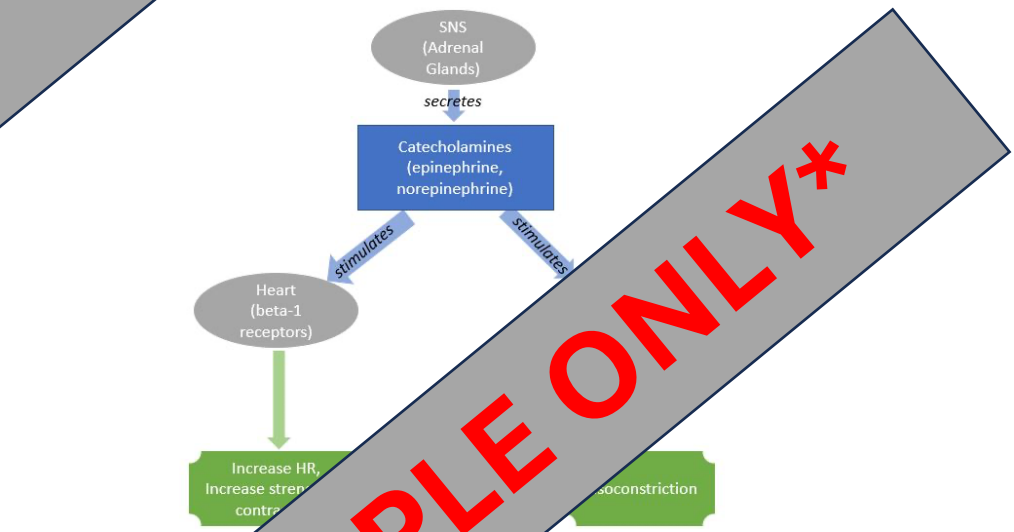
Patients with worsening HF represent a subgroup of patients with HF who are the sickest and hardest to treat, as evidenced by their high re-hospitalization and mortality rates.[Hollenberg,p1968,col2,para1] Given that HF is a covered condition through CMS's HRRP, optimizing therapies in this patient population is beneficial for improving outcomes and lowering costs.

Figure 1. Effects of the renin-angiotensin aldosterone system (RAAS) in the setting of reduced cardiac output during heart failure.[Eaton,2020;p10,figure7.5;p13-14,figure7.8;p15,para1(entire)][Khan,2020;p12,para1,ln3][Khan,2020;p13,para3(entire);p14,para1,ln1-2;p14,para2(entire);para2_section_title;ln1-2;p15,para1,ln1-4][Barrett,2020;p2,para1,ln1-3;p3,para3-4(entire);p4,para6,ln1-2;p4,para6,ln6-8;p6,para2(entire);p9,para2,ln8-10;p9-10,figure38.5;p11,para4,ln1-2;p11-12,figure38.6;p12-13,figure38.7;p13,para2;p13,para2(entire);p14,para6(entire);p15,para2(entire);p15,para3(entire);p16,para1,ln6-8;p19,table38.3]



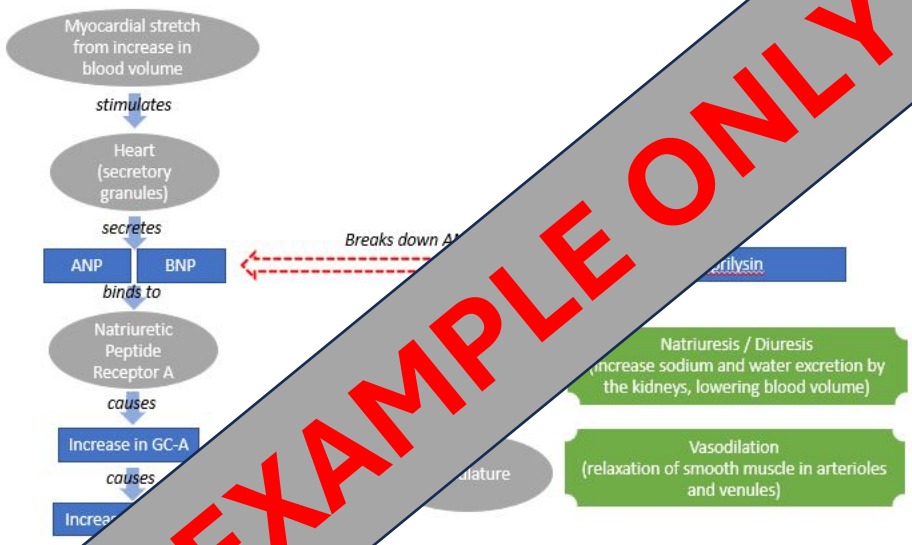
ACE, angiotensin conv… …idiuretic hormone / arginine vasopressin

Figure 2. F… …e nervous stimulation (SNS) in the setting of reduced cardiac output …han,2020;p11,para2(entire)]



HR, heart rate; SNS, sympathetic nervous s…

Figure 3. Effects of the natriuretic peptide (NP) system in the setting of heart failure.[Barrett,2020;p9,para2,ln10-12;p11,para3,ln2-3;p19,para2(entire);p20,para1(entire);p20,para2(entire);p21,para1(entire);p21,para2(entire);p21,para3,ln1-4;ln9-11][Braunwald,2015;p1031,central_illustration][Braunwald,2015;p1032,col2,para2,ln14-18;p1033,col1,para1,ln1-2;p1033,col1,para2(entire);p1033,col1,para3,ln6-9;p1033,col2,para1(entire);p1034,col2,para2(entire)]



ANP is secreted w… …P is secreted when the ventricles are stretched.
A-type natriure… …om the atria of rats, so was named atrial natriuretic peptide. B-type natriuretic peptide was first … …ain, so was given the name brain natriuretic peptide; it also found in the human brain, but more is found v… …art. C-type natriuretic peptide was the third in the sequence to be isolated, but does not play a central role in … …st two natriuretic peptides had already received the designation of A-type and B-type, it was named C-type. CNP is … …the brain, pituitary gland, kidneys, and vascular endothelial cells, but very little is found in the heart and in the general ci…ulation.
ANP, A-type natriuretic peptide; BNP, B-type natriuretic peptide; GC-A, guanylyl cyclase A; cGMP, cyclic guanosine monophosphate

ARTICLE 2: TREATMENT APPROACHES AND UNMET NEEDS IN WORSENING HF

Targeting maladapted neurohormonal systems in HF

Central to HF therapy management is the targeting of one or all of the maladapted neurohormonal systems and/or their deleterious effects.[Buglioni,2015;p6,col2,para2,ln5-10] Pharmaceutical agents that directly suppress the sympathetic nervous system (SNS) and/or renin-angiotensin-aldosterone system (RAAS); ameliorate fluid retention, vasoconstriction, and/or rapid heart rate; and/or leverage the beneficial effects of the natriuretic peptide (NP) system would be advantageous in the setting of heart failure (HF).[Buglioni,2015;p6,col2,para2,ln5-10][Y para1,ln2-4;p220,table15] The set of agents recommended by evidence-based pra ting HF with reduced ejection fraction (HFrEF), along with the s y target, are provided in **Table 3.**

Guideline-based medical therapy for HFrEF

Guideline-based therapy recom ng HFrEF are summarized in **Figure 4.** Briefly, the American Foundation/American Heart Association (ACCF/AHA) guidelines ocker ***plus*** either an angiotensin-converting enzyme inhibitor (in receptor blocker (ARB) as the backbone of therapy to reduce mor ncy,2013;pE173,figure1][Yancy,2018;p206,figure2] Added to this backbone are: 1) a gonist, provided that the patient's kidney function and potassium levels are wit acceptable range (creatinine clearance > 30 mL/min and serum K+ < 5.0 mEq/dL, respectively); 2) hydralazine and isosorbide dinitrate if the patient is African American; and 3) a loop diuretic in the setting of volume overload.[Yancy,2013;pE173,figure1]

Since the publication of the 2013 ACCF/AHA guideline document, several novel therapies have been added to the recommendations based upon key clinical trials. These new

recommendations were included in the 2017 ACCF/AHA focused guideline update, and include the addition of ivabradine, an agent that functions at the sinoatrial node to reduce heart rate, and valsartan-sacubitril, an angiotensin receptor blocker combined with a neprilysin inhibitor (ARNI). [Yancy,2017;p784,section7.3.2.10;p786,sect7.3.2.11]

The results of the SHIFT trial showed that adding ivabradine to a background of guideline-directed medical therapy in patients who had a persistently elevated resting heart rate significantly lowered HF-related hospitalizations.[Yancy,2018;p210,col2,para1,ln1-8][Yancy,2017;p786,section7.2.3.11][Swedberg,2010;p880,table3;p879,col1,para4(entire);p879,col2,para1(entire)] Ivabradine reduces heart rate without concomitantly lowering blood pressure by selectively inhi[illegible] the potassium funny channel current (I_f) in the sinoatrial node.[Yancy,2017;p786,sect7.3.2.11][illegible]ara1,ln1-4][Bashore,2020;p5,para4,ln15-17] Candidates for ivabradine are those al[illegible]tolerated dose of a beta blocker and in sinus rhythm with a restin[illegible] bpm.[Yancy,2018;p206,figure2;p210,table2][Yancy,2017;p786,sect7.3[illegible]1,para3,ln6-9] For patients who need resting heart rate control but w[illegible]thm (i.e., in atrial fibrillation), digoxin can be considered, althou[illegible]out of favor in recent years due to its high risk for various drug t[illegible]long the elderly.[Hollenberg,2019;p1991,col1,para3,ln15-23] [Yancy,2013;pE179,col2,sect7[illegible]ra1,ln4-5;pE180,col2,para1(entire)] [Khan,2020;p24,par[illegible]

The P[illegible]A-HF, and VICTORIA trials

[illegible]the SHIFT trial, several other key trials have shed new light on how HF can be treated [illegible]mprove outcomes. They include PARADIGM-HF, DAPA-HF and VICTORIA. Highlights of these 3 pivotal trials PARADIGM-HF, DAPA-HF, and VICTORIA trials have been summarized in **Table 4**, and will be discussed at length in this supplement.

The beneficial effects of valsartan-sacubitril were shown in the PARADIGM-HF trial, a randomized, double-blind, parallel group active-controlled, two-arm, eve ial comparing enalapril (an angiotensin-converting enzyme inhibitor acubitril in patients with chronic HFrEF.[McMurray,2013;p1063,col2,para2,ln1-4] outcome in this trial was a composite of death from cardiovasc spitalization for heart failure.[McMcurray,NEJM,2014;p997,col1,para3,ln1-3] Ove valuated (n = 4,187 in the valsartan-sacubitril arm and n = 4,21 and the mean left ventricular ejection fraction at baseline ac pproximately 29%.[McMcurray,EJHF,2014;p82 characteristics to note were that approximately 5% had symptoms c lass I, 70% with class II, 24% with class III, and only 1% with class ,table2] Approximately 37% had atrial fibrillation/flutter, 15% ha overter-defibrillator (ICD), and 7% had a biventricular pacemaker (i.e., were re diac resynchronization therapy) at baseline.[McMurray,EJHF,2014;p821-822,table2] The median NT-proBNP level at baseline across both groups was 1608 pg/mL.[McMurray,EJHF,2014;p823,table4] Baseline kidney function, as measured by the mean estimated glomerular filtration rate (eGFR) was 68 mL/min/1.73m^2 across both groups.[McMurray,EJHF,2014;p821,table2] The proportion of patients having a primary outcome event (either death from cardiovascular causes or a first hospitalization for heart failure) was significantly lower in the valsartan-sacubitril arm compared to the enalapril arm, with a hazard ratio of 0.80 and a 95% CI of 0.73-0.87.[McMurray,NEJM,2014,table2]

Based on the 20% reduction in relative risk of cardiovascular death or first hospitalization associated with valsartan-sacubitril compared to enalapril in the PARADIGM-HF trial, the 2017 ACCF/AHA focused guideline update included a recommendation to utilize valsartan-sacubitril

as an alternative to an ACEI or an ARB in the treatment backbone.

[Hollenberg,2019;p1985,col1,para2(entire)][Yancy,2018;p210,table2][McMurray,2014;table2][Yancy,2017;p[illegible]

[Yancy,2018;p206,figure2][1-0.80=0.20] Specifically, the update recommends [illegible]an ARB with an ARNI for patients who are already tolerating an AC[illegible]r to further reduce morbidity and mortality.[Yancy,2017;p785,middle_sec[illegible] Valsartan-sacubitril carries an FDA approved indication for redu[illegible]vascular death and hospitalization for HF in adult patient[illegible]Entresto_PI;sect1.1(entire)]

The DAPA-HF trial ev[illegible]n patients with HFrEF. Dapagliflozin is a sodium-glucose cotrans[illegible]T2) inhibitor that blocks the re-uptake of glucose within the proxi[illegible]y.[Dapaglifozin_PI;sect12.1(entire)] The increased amount of glucose i[illegible]smotic gradient wherein water is also pulled into the urine, creating a d[illegible][Dapaglifozin_PI;sect12.1(entire)][Wiviott,2019;p348,col1,para2,ln1-4] Dapagliflozin was originally appro[illegible]d for use in type 2 diabetes mellitus (T2DM) as an agent to improve glycemic control. [Dapagliflozin_PI;sect1(entire)] However, based on the results of more recent trials, including the DECLARE-TIMI 58 trial and DAPA-HF trial, it has also gained FDA approval for an expanded set of indications, including 1) reducing the risk of cardiovascular death among adult patients with T2DM who have established cardiovascular disease or multiple cardiovascular risk factors; and 2) reducing the risk of cardiovascular death and hospitalization for heart failure in adults with HFrEF.[Dapagliflozin_PI;sect1(entire)][Wiviott,2019;p347,col1,para2,ln11-13;p350,col2,para2,ln4-8][McMurray,NEJM,2019;p1999,col1,para3(entire)] The DECLARE-TIMI 58 trial showed that dapagliflozin significantly reduced the risk of a first hospitalization for heart failure or cardiovascular death in patients with type 2 diabetes mellitus (T2DM) compared to placebo.[Wiviott,2019;p347,col1,para2,ln11-13;p350,col2,para2,ln4-8] The DAPAP-HF evaluated the ability of dapagliflozin to prevent HF

worsening, as defined by the reduction in HF hospitalizations or outpatient visits, in a more general HF population regardless of their T2DM status.[McMurray,NEJM,2019;p1996,col1,para1,ln22-29;p1996,col2,para2-4(entire);p1997,col2,para2(entire)]

The DAPA-HF was a phase 3, randomized controlled trial comparing dapagliflozin to placebo in evaluating a primary composite outcome of worsening heart failure or death from cardiovascular causes.[McMurray,NEJM,2019;p1995,para2,ln1(note: this is the abstract, but this information does not appear elsewhere);p1997,col2,para2,ln1-3] In the trial, a worsening event was defined as an unpl ed HF-related hospitalization or an outpatient visit involving urgent use of IV diuretics.[McMurray,NEJM,2019;p1997,col2,para2,ln3-6] Over 4,500 patients w /3 in the dapagliflozin arm and n = 2,371 in the placebo arm), and ar ejection fraction at baseline across both groups was approx EJM,2019;p2000,table1] Other baseline characteristics to note were that th this trial that had symptoms consistent with NYHA class I, but i ed as NYHA II, III, or IV (approximately 67%, 32%, a cMurray,NEJM,2019;p2000,table1;estimates made to generalize across both groups] Approxi ibrillation, approximately 26% had an ICD, and about 7% had ker (i.e., were receiving cardiac resynchronization therapy) able1;estimates made to generalize across both groups] The median NT-proBNP level 28 pg/mL in the dapagliflozin group and 1446 pg/mL in the placebo group.[Mc M,2019;p2000,table1] Baseline kidney function, as measured by the mean estimated glomerular filtration rate (eGFR) was approximately 66 mL/min/1.73m^2 across both groups.[McMurray,NEJM,2019;p2000,table1;estimates made to generalize across both groups] The proportion of patients having a primary outcome event was significantly lower in the dapagliflozin arm compared to

the placebo arm, with a hazard ratio of 0.74 and a 95% CI of 0.65-0.85.[McMurray,NEJM,2019;p2002,table2] Thus, dapagliflozin lowered the risk of a primary event by 26% compared to placebo.[1-0.74=0.26]

The VICTORIA trial was a phase 3, randomized, double-blind trial evaluating an oral soluble guanylate cyclase stimulator, vericiguat, against placebo.[Armstrong,NEJM,2020;p1883,para2,ln1(note: this is the abstract, but this information does not appear elsewhere);p1884,col1,para2,ln1-2;p1884,para3,ln1-2] Stimulating the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway (NO-sGC-cGMP) is a novel approach to the treatment of HF and addresses a deficit in this pathway likely to be present in patients with worsening HFrEF.[Gheorgiade,2015;p2552,col1,para2,ln1-4;p255 para2,ln12-14;p2552,col1,para3,ln1-5] During certain physiologic stimuli, NO is gene l cells and diffuses into vascular and cardiac muscle cells. Once inside ts intracellular receptor, sGC, an action which stimulates sGC to ge duction of cGMP exerts vasodilatory, antifibrotic, and cardiopr ed bioavailability of NO is thought to occur in the setting of HF, r in cGMP and its beneficial effects. A reduced level of endogenous nding decline in cGMP synthesis) has been correlated with cardiom tial fibrosis, and coronary microvascular dysfunction, all t te to worsening HF. Thus, by directly stimulating sGC in a manner dent of, endogenous NO, it is hypothesized that cGMP levels wil e effects can be restored.[Armstrong,NEJM,2020;p1884,col1,para2,ln1-8][,col1,para2(entire);p97,col2,para1,ln1-11;p97,col2,para1,ln15-26]

In addition to having a diagnosis of chronic HFrEF like the DAPA-HF and PARADIGM-HF trials, patients enrolled in the VICTORIA trial also had to have evidence of worsening HF, a feature that sets it apart from the other two trials.[Armstrong,NEJM,2020;p1884,col2,para2,ln1-5;p1884,col2,para3,ln1-8][McMurray,NEJM,2019;p1996,col2,para2(entire)][McMurray,NEJM,2014;p994,col2,para4(entire)] Worsening HF was defined

as a previous HF hospitalization within 6 months prior to randomization or outpatient IV diuretic treatment for HF without hospitalization within 3 months before randomization.[Armstrong,NEJM,2020;p1884,col2,para3,ln1-8] The primary efficacy outcome in the VICTORIA trial was a composite of first hospitalization for HF or death from cardiovascular causes.[Armstrong,NEJM,2020;p1885,col1,para3,ln1-3]

Over 5,000 patients were evaluated (n = 2,526 in the vericiguat arm, 2,524 in the placebo arm), and the mean left ventricular ejection fraction at baseline was approximately 29%.[Armstrong,NEJM,2020;p1887,table1] Other baseline characteristics were that the distribution of patients who had symptoms consistent with NYHA class II, III, and IV were < 0.1%, 59%, 39.7%, and 1.3%, respectively.[Armstrong,NEJM,2020;p1887,table1] Approximately 45% had atrial fibrillation, approximately 28% had diabetes, and 5% had a biventricular pacemaker (i.e., were receiving cardiac resynchronization therapy).[Armstrong,NEJM,2020_supplement;p38-39,tableS1] The median NT-proBNP level across both groups was 2816 pg/mL.[Armstrong,NEJM,2020_supplement;p38-39,tableS1] Baseline kidney function, as measured by the mean estimated glomerular filtration rate (eGFR) was approximately 62 mL/min/1.73m^2 across both groups.[Armstrong,NEJM,2020_supplement;p38-39,tableS1] The proportion of patients having a primary outcome event was significantly lower in the vericiguat arm compared to the placebo arm, with a hazard ratio of 0.90 and a 95% CI of 0.82-0.98.[Armstrong,NEJM,2020;p1889,table2] Thus, vericiguat lowered the risk of a primary event by 10% compared to placebo.[1-0.90=0.10]

Conclusion

The results of the VICTORIA, DAPA-HF, and PARADIGM-HF trials each present the clinician with drug treatment options that may augment the standard of care for patients with chronic HFrEF. Choosing which agent to utilize on top of a background of guideline-directed

medical therapy becomes an important decision point, especially in the setting of worsening HF where care has already been optimized but patients are still experiencing clinical declines. In this case, it is helpful to examine the baseline characteristics and absolute risk reductions for primary outcomes of each the trials against one another. This has been done in T... VICTORIA evaluated a subset of patients whose baseline clinic... worse than those evaluated in both the DAPA-HF and PARADI... enced by an inclusion criteria requirement of a HF hospitalizat... eatment with the past 3-6 months, a higher proportion of patients wi... IV, a higher proportion of patients with a biventricular pacema... proBNP level that was approximately two times as high. A sicker p... CTORIA was also manifested in its shorter trial duration – that is ... ted more primary outcome events within a median follow-up time ... onths, compared to 18 months and 27 months in the DAPA-HF ... M-HF trials, respectively (primary outcome event rates of 35.5% and 38.5%, 16.5... 21.1%, and 21.8% and 26.5%, respectively). In addition, although both DAPA-HF and PARADIGM-HF had greater reductions in relative risk of their primary outcomes compared to the VICTORIA trial (26% and 20% vs 10%, respectively), when reductions in absolute risks (annualized event rates per 100 patient-years) are compared, the results seem more similar (a reduction in 4.2, 4.0, and 2.7 reduction in absolute risk for VICTORIA, DAPA-HF, and PARADIGM-HF, respectively; refer to **Table 4**).

To date, there is no particular agent recommended in the guidelines for improving outcomes in the subset of patients with worsening HF.[Greene,2018;p254,box,bullet3] Evidence-based practice guideline recommendations for these patients are general in nature and focus on optimizing chronic HF therapy.[Greene,2018;p254,box,bullet3] They include: 1) escalation of current

therapies, diuretics, and/or other decongestion strategies; 2) hemodynamic monitoring with right heart catheterization; 3) IV inotropes or pressors; 4) percutaneous or durable mechanical support devices; 5) long-term advanced treatment strategies such as cardiac transplant; 6) re-evaluation of comorbidities and alternative diagnose; and 7) palliative care.[Hollenberg,2019;p1988,figure9;p1979,figure4]

Despite a variety of treatment options, unmet needs remain for patients with worsening HF who are already on standard of care, as evidenced by the 20% to 30% 1-year m y rate following a hospitalization.[Hollenberg,p1968,col2,para1] Arguably, there is a need t al risk for patients with worsening HF who have a history of hospitaliz eady on guideline-based standard of care (beta blocker plus an AC ARNI).[Greene,2018;p254,box,bullet4,bullet8] The VICTORIA tri aluated a novel agent in a population of patients who were clini evaluated in both the PARADIGM-HF and DAPA-HF trials.

Table 3. Evidence-based clinical practice guideline-recommended therapies f t of HFrEF, their pathophysiologic targets, and their effects*

[Yancy,2013;pE174,table14;pE175,table15][Yancy,2017;p788,table3;p784,sect7.3.2.10;p786,sect7.3.2.11]

[Yancy,2018;p210,table1;p220,table15][Hollenberg,2019;p1981,table7]

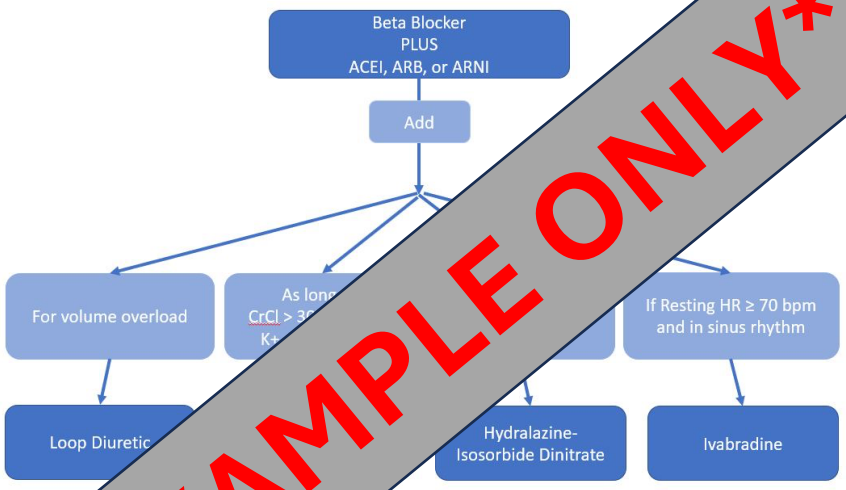
Pharmaceutical Class	Pathophysiologic Target	Effect	
Beta Blocker	SNS (adrenergic receptors in heart)[Khan,2020;p22,para9,ln1]	Antagonist at beta-2 in the heart (blo catecholami	Bisoprolol Carvedilol • Carvedilol CR • Metoprolol succinate CR/XL
ACEI	RAAS (angiotensin converting enzyme)	enzyme I into ecreasing the n II in circulation and onstrictive effects	• Captopril • Enalapril • Fosinopril • Lisinopril • Perindopril • Quinapril • Ramipril • Trandolapril
ARB	RAAS (angiotensin	ntagonist at angiotensin receptors, blocking the vasoconstrictive effects of angiotensin II	• Candesartan • Losartan • Valsartan
ARNI	RAA (enzyme)	Antagonist at angiotensin receptors, blocking the vasoconstrictive effects of angiotensin II; Blocks neprilysin from breaking down ANP	• Valsartan-Sacubitril (combination agent)
Aldosterone Antagonist	tors in kidney)	Antagonist at aldosterone receptors in the kidney, thereby decreasing the amount of sodium and water that gets reabsorbed	• Spironolactone • Eplerenone
Direct-Acting Vasodilator [Khan,2020;p23,para3,title&ln1-3;para4(entire)	Vas e	Vasodilation, thereby decreasing the peripheral resistance the heart has to pump against	• Hydralazine-Isosorbide dinitrate (fixed-dose combination agent) • Hydralazine (individual agent) • Isosorbide dinitrate (individual agent)
Loop Diuretic	Kidney (Na-K-Cl transporter in ascending loop of Henle)[Khan,2020;p23,para7-8]	Blocks the reabsorption of sodium and chloride from the urine back into the bloodstream, thereby decreasing blood volume[Khan,2020;p23,para7-8]	• Bumetanide • Furosemide • Torsemide
I_f Channel Inhibitor [Bashore,2020;p5,para4,ln15-17]	SA node (heart's pacemaker) [Ivabradine_PI;sect11,para1(entire)]	Inhibits the I_f current through the sinoatrial node, thereby slowing firing at the node and decreasing HR [Ivabradine_PI;sect11,para1(entire);sect12.1,para1,ln1-3]	• Ivabradine

*Guideline-based medical therapy for HF includes a beta-blocker ***plus*** an ACEI, ARB, or ARNI. An aldosterone antagonist should be added to the regimen as long as kidney function and serum potassium levels are within an acceptable range. Addition of hydralazine-isosorbide dinitrate is indicated in African American patients. Loop diuretics should be utilized to manage volume overload. Ivabradine can be considered in those who have a resting heart rate ≥ 70 beats per minute while on a maximally-tolerated dose of a beta-blocker and who are in normal sinus rhythm.

ACEI, angiotensin converting enzyme inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CR, controlled release; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; I_f, potassium funny channel (specific to the sinus node); [Bashore,2020;p5,para4,ln15-17] NP, natriuretic peptide system; RAAS, renin-angiotensin-aldosterone system; SA, sinoatrial; SNS, sympathetic nervous system; XL, extended release

Figure 4. Flow chart of guideline based recommended therapy for HFrEF Sta C, NYHA Class I, II, III, or IV*

[Yancy,2013;pE173,figure1][Yancy,2017;p785,middle_section;p786,section7.2.3.11;p787,figure2][Yancy,2018; 2,para1,ln 1-8;p210,table2][Hollenberg,2019;p1991,col1,para3,ln6-9]



*All patients with sta blocker + ACEI/ARB/ARNI backbone, regardless of NYHA functional class. Additional agents blocker + ACEI/ARB/ARNI backbone when they progress to at least NYHA stage II and me the case of African Americans, add on hydralazine-isosorbide dinitrate in the setting of NYHA f angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensi or; bpm, beats per minute; CrCl, creatinine clearance; HR, heart reate; HFrEF, heart failure with reduced min, milliliters per minute; mEq/dL, milliequivalents per deciliter; K+, serum potassium

Table 4. Comparison of highlights from the VICTORIA, DAPAP-HF, and PARADIGM-HF trials.

	VICTORIA [Armstrong,NEJM,2020;table1-2] [Armstrong,NEJM,2020_SupplAppendix;p38-40;tableS1]		DAPA-HF [McMurray,NEJM,2019;p2000,table1;p2001, table1cont'd;p2002,table2]		PARADIGM-HF [McMurray,NEJM,2014;p996,table1;p997,table1cont'd;p999,table2] [McMurray,EJHF,2014;p821,table2] [Packer,Circ,2015;p57,table]	
	Vericiguat (N = 2526)	Placebo (N = 2524)	Dapagliflozin (N = 2373)	Placebo (N = 2371)	Sacubitril/Valsartan (N = 4187)	Enalapril (N = 4212)
Age (mean, years)	67.5 [Armstrong,NEJM,2020;table1]	67.2 [Armstrong,NEJM,2020;table1]	66.2 [McMurray,NEJM,2019;table1]	66.5 [McMurray,NEJM,2019;table1]	63.8 [McMurray,NEJM,2014;table1]	63.8 [McMurray,NEJM,2014;table1]
Left Ventricular Ejection Fraction at Baseline (mean, %)	29.0 [Armstrong,NEJM,2020;table1]	28.8 [Armstrong,NEJM,2020;table1]	31.2 [McMurray,NEJM,2019;table1]	30 [McMurray,NEJM,2019;table1]	29.6 [McMurray,NEJM,2014;table1]	29.4 [McMurray,NEJM,2014;table1]
Median follow-up	10.8 months [Armstrong,NEJM,2020;p1887,col2,para2,ln1]		18.2 months [McMurray,NEJM,2019;p1999,col1]		27 months [McMurray,NEJM,2014;p999,col2,para2,ln11-13]	
NYHA Class (%)						
I	0 [Armstrong,NEJM,2020;table1]	0 [Armstrong,NEJM,2020;table1]	0 [McMurray,NEJM,2019;table1]		4.3 [McMurray,NEJM,2014;table1]	5.0 [McMurray,NEJM,2014;table1]
II	58.6 [Armstrong,NEJM,2020;table1]	59.3 [Armstrong,NEJM,2020;table1]	67.7 [McMurray,NEJM,2019;table1]		71.6 [McMurray,NEJM,2014;table1]	69.3 [McMurray,NEJM,2014;table1]
III	40.0 [Armstrong,NEJM,2020;table1]	39.4 [Armstrong,NEJM,2020;table1]	[McMurray,NEJM,2019;table1]		23.1 [McMurray,NEJM,2014;table1]	24.9 [McMurray,NEJM,2014;table1]
IV	1.4 [Armstrong,NEJM,2020;table1]	1.2 [Armstrong,NEJM,2020;table1]		1.0 [McMurray,NEJM,2019;table1]	0.8 [McMurray,NEJM,2014;table1]	0.6 [McMurray,NEJM,2014;table1]
Comorbidities at baseline (%)						
Atrial fibrillation	43.5 [Armstrong,NEJM,2020_Suppl; p38,tableS1]	46.4 [Armstrong,NEJM,2020_Suppl; p38,tableS1]		38.0 [McMurray,NEJM,2019;table1]	36.2 [McMurray,NEJM,2014;table1]	37.4 [McMurray,NEJM,2014;table1]
Diabetes mellitus	48.6 [Armstrong,NEJM,2020_Suppl; p38,tableS1]	[Armstrong,NEJM,2020_Suppl; p38,tableS1]	41.8 [McMurray,NEJM,2019;table1]	41.8 [McMurray,NEJM,2019;table1]	34.7 [McMurray,NEJM,2014;table1]	34.6 [McMurray,NEJM,2014;table1]
Standard of care treatment type (%)						
ACEI	73.3 [Armstrong,NEJM,2020_Suppl; p38,tableS1]		56.1 [McMurray,NEJM,2019;table1]	56.1 [McMurray,NEJM,2019;table1]	(Pretrial use: 78.7) [McMurray,NEJM,2014;table1]	(Pretrial use: 77.5) [McMurray,NEJM,2014;table1]
ARB			28.4 [McMurray,NEJM,2019;table1]	26.7 [McMurray,NEJM,2019;table1]	(Pretrial use: 22.2) [McMurray,NEJM,2014;table1]	(Pretrial use: 22.9) [McMurray,NEJM,2014;table1]
Beta blocker		[Armstrong,NEJM,2020_Suppl; p38,tableS1]	96.0 [McMurray,NEJM,2019;table1]	96.2 [McMurray,NEJM,2019;table1]	93.1 [McMurray,NEJM,2014;table1]	92.9 [McMurray,NEJM,2014;table1]
Mineralocorticoid Receptor Antagonist		71.4 [Armstrong,NEJM,2020_Suppl; p38,tableS1]	71.5 [McMurray,NEJM,2019;table1]	70.6 [McMurray,NEJM,2019;table1]	54.2 [McMurray,NEJM,2014;table1]	54.2 [McMurray,NEJM,2014;table1]
Neprilysin inhibitor + ARB (sacubitril/valsartan)	[Armstrong,NEJM,2020_Suppl; p38,tableS1]	14.7 [Armstrong,NEJM,2020_Suppl; p38,tableS1]	10.5 [McMurray,NEJM,2019;table1]	10.9 [McMurray,NEJM,2019;table1]	N/A	N/A
Implantable cardioverter-defibrillator (ICD)	27.6 [Armstrong,NEJM,2020_Suppl; p39,tableS1]	27.9 [Armstrong,NEJM,2020_Suppl; p39,tableS1]	26.2 [McMurray,NEJM,2019;table1]	26.1 [McMurray,NEJM,2019;table1]	14.9 [McMurray,NEJM,2014;table1]	14.7 [McMurray,NEJM,2014;table1]
Biventricular pacemaker (AKA cardiac resynchronization therapy)	14.7 [Armstrong,NEJM,2020_Suppl; p39,tableS1]	14.6 [Armstrong,NEJM,2020_Suppl; p39,tableS1]	8.0 [McMurray,NEJM,2019;table1]	6.9 [McMurray,NEJM,2019;table1]	7.0 [McMurray,NEJM,2014;table1]	6.7 [McMurray,NEJM,2014;table1]
Kidney function at baseline						

eGFR (mean, mL/min/1.73m^2)	61.3 [Armstrong,NEJM,2020_Suppl; p39,tableS1]	61.7 [Armstrong,NEJM,2020_Suppl; p39,tableS1]	66.0 [McMurray,NEJM,2019;table1]	65.5 [McMurray,NEJM,2019;table1]	68 [McMurray,EJHF,2014;p821,table2]	
Natriuretic Peptide Level at baseline						
NT-proBNP (median, pg/mL)	2803.5 [Armstrong,NEJM,2020_Suppl; p39-40,tableS1]	2821.0 [Armstrong,NEJM,2020_Suppl; p39-40,tableS1]	1428 [McMurray,NEJM,2019;table1]	1446 [McMurray,NEJM,2019;table1]	1631 [McMurray,NEJM,2014;table1]	1594 [McMurray,NEJM,2014;table1]
Primary Efficacy Outcome						
Composite of death from cardiovascular causes or 1st hospitalization for HF						
Rate (%)	35.5 [Armstrong,NEJM,2020;table2]	38.5 [Armstrong,NEJM,2020;table2]	16.3[a] [McMurray,NEJM,2019;table2]	21.3 [McMurray,N	21.8 M,2014;table2]	26.5 [McMurray,NEJM,2014;table2]
Annualized Event Rate (events / 100 patient-years)	33.6 [Armstrong,NEJM,2020;table2]	37.8 [Armstrong,NEJM,2020;table2]	11.6 [McMurray,NEJM,2019;table2]	[	c;table]	13.2 [Butler,Circ;table]
Absolute Risk Reduction (ARR) (difference in annualized event rates; events / 100 patient-years)	4.2 [Armstrong,NEJM,2020;p1891,col1,para3,ln14;p1891,col2,para1,ln1] [37.8-33.6=4.2][Butler,Circ;table]		4.0 [15.6-11.6=4.0		2.7 [13.2-10.5][Butler,Circ;table]	
Number Needed to Treat (NNT) with study drug for 1 year to prevent a primary-outcome event	24 [Armstrong,NEJM,2020;p1891,col2,para1,ln1-4] [NNT = 1/ARR = 1/(4.2/100) = 23.8]		*note: this dif p1999,e cite NNT = 21; trial period" which ords, they did not use 16.3% and 21.2%, which would if we use annualized rates reported in a better comparison because then it can be ed as NNT for 1 year]		37 [NNT = 1/ARR = 1/(2.7/100) = 37] *note: this differs from what is stated in McMurray,NEJM,2014;they cite NNT = 21; p1001,col1,para2,ln9-13; however, this is cited as "over the duration of the trial" which was 27 months;p999,col2,para2,ln11-13; in other words, they did not use annualized rates and instead used their raw rates of 21.8% and 26.5%, which would produce a NNT = 1/(26.5-21.5) = 0.212→21; if we use annualized rates reported in Butler, then NNT = 37, which provides a better comparison because then it can be interpreted as NNT for 1 year]	
Hazard Ratio (95% CI)	0.90 (0.82-0.98 [Armstrong,NEJM,2020		0.74 (0.65-0.85) [McMurray,NEJM,2019;table2]		0.80 (0.73-0.87) [McMurray,NEJM,2014;table2]	
Relative Risk Reduction in Treatment Group	10 [1-0.90= [Armstrong,NE		26% [1-0.74=0.26*100=26%]		20% [1-0.80=0.20*100=20%]	
Components of the Primary Outcome						
Death from cardiovascular causes						
Rate (%)	[JM,2020;table2]		9.6 [McMurray,NEJM,2019;table2]	11.5 [McMurray,NEJM,2019;table2]	13.3 [McMurray,NEJM,2014;table2]	16.5 [McMurray,NEJM,2014;table2]
Annualized Event Rate (events / 100 patient-years)	13.9 nstrong,NEJM,2020;table2]		6.5 [McMurray,NEJM,2019;table2]	7.9 [McMurray,NEJM,2019;table2]	6.0 [Butler,Circ;table]	7.5 [Butler,Circ;table]
Absolute Risk Reduction (ARR) (difference in annualized event rates; events / 100 patient-years)	.0 0][Butler,Circ;table]		1.4 [7.9-6.5=1.4][Butler,Circ;table]		1.5 [7.5-6.0][Butler,Circ;table]	
Hazard Ratio (95% CI)	0.93 (0.81-1.06) [Armstrong,NEJM,2020;table2]		0.82 (0.69-0.98) [McMurray,NEJM,2019;table2]		0.80 (0.71-0.89) [McMurray,NEJM,2014;table2]	
Relative Rate Reduction in Treatment Group	7% [1-0.93=0.0.7%*100=7%]		18% [1-0.82=0.18*100=18%]		20% [1-0.80=0.20*100=20%]	
Hospitalized for HF (1st occurrence)						
Rate (%)	27.4 [Armstrong,NEJM,2020;table2]	29.6 [Armstrong,NEJM,2020;table2]	9.7 [McMurray,NEJM,2019;table2]	13.4 [McMurray,NEJM,2019;table2]	12.8 [McMurray,NEJM,2014;table2]	15.6 [McMurray,NEJM,2014;table2]
Annualized Event Rate (events / 100 patient-years)	25.9 [Armstrong,NEJM,2020;table2]	29.1 [Armstrong,NEJM,2020;table2]	6.9 [McMurray,NEJM,2019;table2]	9.8 [McMurray,NEJM,2019;table2]	NR [Butler,Circ;table]	NR [Butler,Circ;table]
Absolute Risk Reduction (ARR)	3.2		2.9		1.6	

(difference in annualized event rates; events / 100 patient-years)	[29.1-25.9=3.2][Butler,Circ;table]		[9.8-6.9=2.0][Butler,Circ;tabl		[Butler,Circ;table]	
Hazard Ratio (95% CI)	0.90 (0.81-1.00) [Armstrong,NEJM,2020;table2]		0.70 (0.5 [McMurray		0.79 (0.71-0.89) [McMurray,NEJM,2014;table2]	
Relative Rate Reduction in Treatment Group	10% [1-0.90=0.10*100=10%]				21% [1-0.79=0.21*100=21%]	
Other Outcomes						
Any hospitalization for HF[c]						
Total Number of Hospitalizations	1223 [Armstrong,NEJM,2020;table2]	1336 [Armstrong,NEJM,2020;table2]		742[b] urray,NEJM,2019;table2]	851 [Packer,Circ,2015;table]	1079 [Packer,Circ,2015;table]
Annualized Event Rate (events / 100 patient-years)	38.3 [Armstrong,NEJM,2020;table2]	42.4 [Armstrong,NEJM,2020;table2]		NR	NR	NR
Absolute Risk Reduction (ARR) *(difference in annualized event rates; events / 100 patient-years)*	4.1 [42.4-38.3=4.1]		N/A		N/A	
Hazard Ratio (95% CI) **interpretation = the occurrence of a hospitalization (event vs patient-level risk)**	0.91 (0.84-0.9 [Armstrong,NEJM,2		0.75 (0.65-0.88) [McMurray,NEJM,2019;table2]		0.77 (0.67-0.89) [Packer,Circ,2015;table]	
Relative Rate Reduction in Treatment Group **interpretation = the occurrence of a hospitalization (event vs patient-level risk)**	[1 The risk of a the treatm ne		25% [1-0.75=0.25*100=25%] The risk of a HF hospitalization occurring was 25% lower in the treatment group than in the placebo group		23% [1-0.77=0.23*100=23%] [Packer,Circ,2015;p55,para2,ln6-7;p58,col1,para1,ln2-7] The risk of a HF hospitalization occurring in the treatment group was 23% lower than in the enalapril group OR "The patients in the treatment group had 23% fewer hospitalizations for worsening heart failure." [Packer,Circ,2015;p55,para2,ln6-7;p58,col1,para1,ln2-7]	

ACEI, angiotensin converting enzym sin receptor blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; NR, not reported; NT-p B-type natriuretic peptide

[a]In the case of the DAPA-HF trial, an urg th IV treatment for HF (without hospitalization) was also counted as part of the primary outcome[McMurray,NEJM,2019;p1997,col2,para2,ln3-6;p19 a3,ln1-3]

[b]In the case of the DAPA-HF trial, total number of hospitalizations for HF also included hospitalizations where a cardiovascular death occurred[McMurray,NEJM,2019;p2002,table2;p1999,col1,para5,ln6-12;p1999,col2,para1(entire)]

[c]In all 3 trials, any hospitalization for HF counted the first hospitalization as well as any subsequent hospitalizations[Armstrong,NEJM,2020;p1889,table2_footnote;p1889,col1,para2,ln1-6][McMurray,NEJM,2019;col2,para3,ln3-5][Packer,Circ,2015;p58,col1,para1,ln2-7]

REFERENCES

Bashore TM, Granger CB, Jackson KP, Patel MR. Sinus Arrhythmia, Bradycardia, & Tachycardia. In: Papadakis MA, McPhee SJ, Rabow MW. eds. Current Medical Diagnosis and Treatment 2020. McGraw-Hill; Accessed June 16, 2020. https://accessmedicine-mhmedical-com.proxy.libraries.rutgers.edu/content.aspx?bookid=2683&sectionid=225039960

Regulation of Sodium and Water Excretion. In: Eaton DC, Pooler JP. eds. Vander's Renal Physiology, 9e. McGraw-Hill; Accessed June 16, 2020. https://accessmedicine-mhmedical-com.proxy.libraries.rutgers.edu/content.aspx?bookid=2348&sectionid=185664222

Khan MK, Sanchez A. Congestive Heart Failure and Management Drugs. In: Elmoselhi A. eds. Cardiology: An Integrated Approach. McGraw-Hill; Accessed June 16, 2020. https://accessmedicine-mhmedical-com.proxy.libraries.rutgers.edu/content.aspx?bookid=2224&sectionid=171661368

Regulation of Extracellular Fluid Composition & Volume. In: Barrett KE, Barman SM, Brooks HL, Yuan JJ. eds. Ganong's Review of Medical Physiology, 26e. McGraw-Hill; Accessed June 16, 2020. https://accessmedicine-mhmedical-com.proxy.libraries.rutgers.edu/content.aspx?bookid=2525&sectionid=204298130