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Representativeness of the PIONEER-HF Clinical Trial Population in Patients Hospitalized with Heart Failure and Reduced Ejection Fraction

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Abstract

Background: In PIONEER-HF, the in-hospital initiation of sacubitril/valsartan in patients hospitalized for acute decompensated heart failure (ADHF) was well-tolerated and led to improved outcomes. We aim to determine the representativeness of the PIONEER-HF trial among patients hospitalized for ADHF using real-world data.

Methods: The study population was derived from all patients discharged alive for ADHF in the Get With The Guidelines-HF (GWTG-HF) registry from 2006 to 2018 with HF with reduced ejection fraction (HFrEF) (“all HFrEF with ADHF”). We then determined the proportion of patients meeting PIONEER-HF eligibility criteria (“PIONEER-HF eligible”) and those meeting a set of limited eligibility criteria (“actionable” cohort). Rates of HF readmissions and all-cause mortality were then compared between the “all HFrEF with ADHF”, “PIONEER-HF eligible”, and “actionable” cohorts using linked Medicare claims data.

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Results: A total of 99,767 patients with HFrEF in GWTG-HF were hospitalized for ADHF. PIONEER-HF inclusion criteria were met by 71,633 (71.8%) patients, and both inclusion and exclusion criteria were met by 20,704 (20.8%) patients. 68,739 (68.9%) patients met the criteria for the "actionable" cohort. Among the CMS-linked patients, the HF rehospitalization rate at 1 year was 35.1% (95% CI 34.5, 35.8) for "all HFrEF with ADHF" patients, 32.6% (95% CI 31.3, 33.9) for the "PIONEER-HF eligible" cohort, and 33.1% (95% CI 32.3, 33.9) for the "actionable" cohort. The 1-year all-cause mortality was 36.7% (95% CI 36.1, 37.4) for "all HFrEF with ADHF" patients, 31.6% (95% CI 30.3, 32.9) for the "PIONEER-HF eligible" cohort, and 32.2% (95% CI 31.4, 33.0) for the "actionable" cohort.

Conclusions: Patient characteristics and clinical outcomes for patients eligible for PIONEER-HF only modestly differ when compared with those encountered in routine practice, suggesting that the in-hospital initiation of sacubitril/valsartan should be routinely considered for patients with HFrEF hospitalized for ADHF.

Keywords

Sacubitril valsartan; heart failure with reduced ejection fraction; clinical trial; registry

Nearly 1 million people are hospitalized annually for acute decompensated heart failure (ADHF) in the United States alone 1, Despite national efforts to improve transitional and post-discharge care, unplanned 30-day readmission and 30-day mortality rates after a hospitalization for ADHF remain high at 21% and 10%, respectively 2, 3. In addition, the costs associated with unplanned readmissions for heart failure (HF) are >$900 million annually for Medicare patients alone 4. Improving post-discharge outcomes after a hospitalization for ADHF is an important goal for multiple stakeholders, including patients, clinicians and payers.

The *PIONEER-HF* trial (Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-pro BNP in Patients Stabilized From an Acute Heart Failure Episode) was conducted to determine the safety and efficacy of in-hospital initiation of sacubitril/valsartan vs enalapril in patients with heart failure with a reduced ejection fraction (HFrEF) who were hospitalized for ADHF [5]. The in-hospital initiation of sacubitril/valsartan, compared with enalapril, in trial participants hospitalized for ADHF was safe and well-tolerated, achieved an approximately 30% reduction in NT-proBNP levels, and reduced CV death or rehospitalization for HF within 8 weeks of discharge [5–7].

Given this, it is important to determine if the results of the *PIONEER-HF* trial apply to patients encountered in routine care. In this study, we aimed to: (1) determine the eligibility for the *PIONEER-HF* trial among patients in a contemporary, United States-based registry cohort with acute HFrEF ("all HFrEF with ADHF"), (2) determine the eligibility for sacubitril/valsartan using criteria most relevant to daily clinical practice ("actionable" cohort), and (3) compare long-term outcomes between the "all HFrEF with ADHF", "*PIONEER-HF* eligible", and "actionable" cohorts using linked Medicare claims data.

Methods

Data sources

The registry population utilized in this analysis encompassed patients enrolled in Get with the Guidelines – Heart Failure (GWTG–HF). GWTG–HF is a contemporary registry established by the American Heart Association (AHA), and includes a diverse cohort of patients hospitalized for HF or who developed significant HF symptoms during hospitalization in the United States [8]. Baseline characteristics and subsequent data is collected via case report forms and includes demographics, medical history, laboratory and biochemical data, in –hospital treatment and subsequent outcomes [8].

In this study, we included patients discharged alive in GWTG-HF between January 2006 – June 2018 across 317 sites in the United States. Only patients with non – missing information on age, quantitative or qualitative left ventricular ejection fraction (LVEF), and NT – proBNP or brain natriuretic peptide (BNP) were included in the *PIONEER-HF* cohort comparison. The baseline characteristics of the *PIONEER-HF* trial participants that were used for comparison have been previously published and described [9].

Study cohorts

The initial study cohort ("all HFrEF with ADHF") was derived by selecting for all patients discharged alive in GWTG-HF between January 2006 – June 2018 with LVEF < 40% on quantitative assessment. Next, we derived two separate groups by applying: (1) *PIONEER-HF* trial inclusion and exclusion criteria ("*PIONEER-HF* eligible") and (2) a minimal set of clinically relevant criteria ("actionable") to the overall HFrEF population in GWTG-HF. This "actionable" cohort was constructed to allow an understanding of the number of HFrEF patients encountered in clinical practice for whom clinicians might consider sacubitril/valsartan therapy, and comprised of three criteria: (i) estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2, (ii) systolic blood pressure (SBP) ≥ 100 mmHg, and (iii) no evidence of advance HF as determined by the use of a left –ventricular assist device, inotropes, or post –cardiac transplant.

Data on all-cause mortality, and HF readmission rate at 1 year were obtained by linking the GWTG-HF registry with the Center for Medicare & Medicaid (CMS) Part A inpatient fee-for-service claims. Medicare Part A is national health insurance program in the United States that covers inpatient treatment for individuals aged over 65. By linking the Medicare Part A claims of individuals over age 65 with a diagnosis of HFrEF in GWTG-HF between the year 2006 and 2015 (Supplemental Table 1), we were able to determine post-discharge outcomes in HFrEF patients and infer how each cohort faired following index HF discharge.

Statistical analysis

All analyses were carried out in SAS version 9.4 (SAS Institute, Cary, North Carolina). The Institutional Review Board of Duke Clinical Research Institute approved the study and granted a waiver of analyzing de-identified patient data for research purposes.

Results

A total of 206,207 patients were discharged alive in the GWTG-HF registry between January 2006 – June 2018. Of this cohort, a total of 99,767 (N) patients in GWTG-HF were hospitalized for acute HF in the setting of HFrEF. *PIONEER-HF* inclusion criteria were met by 71,633 (71.8%) patients, and both inclusion and exclusion criteria were met by 20,704 (20.8%) patients. 68,739 (68.9%) patients met the criteria for the "actionable" cohort (Table 1, Figure 1, Supplementary Figure 1). The most common reasons GWTG–HfrEF patients were excluded from the *PIONEER-HF* study were the following: patients with contraindications to ARB therapy (17.6% of N), patients with contraindications to sacubitril/valsartan therapy (7% of N), and eGFR <30 ml/min/1.73 m^2 as calculated by the Modification in Diet in Renal Disease (5.9% of N). The most common reason the GWTG–HfrEF patients were excluded from the "actionable" cohort was not meeting the criteria for eGFR ≥ 30 ml/min/1.73 m^2 (23.6% of N excluded).

Population characteristics

Table 1/Supplementary Table 2 compares the baseline characteristics between the *PIONEER-HF* trial participants and the three GWTG-HF cohorts. There were notable differences between *PIONEER-HF* trial participants and GWTG-HF cohorts. A notable, difference was a lower median age of *PIONEER-HF* trial participants when compared to any of the three GWTG cohorts [*PIONEER-HF* 61 (51–71) years vs. "all-HfrEF with ADHF" – 70 (58–81) years vs. "actionable" 69 (57–80) years vs. "*PIONEER-HF* eligible" 71 (59–82) years]. The proportion of women was lower in the *PIONEER-HF* trial when compared to the GWTG cohorts ("*PIONEER-HF* eligible" 25.7% vs. "all-HfrEF with ADHF" – 36.6% vs. "actionable" 35.2% vs. "*PIONEER-HF* eligible" 38.2%). Further, the proportion of patients in *PIONEER-HF* who self-identified as black were higher in the *PIONEER-HF* trial (35.9%) compared to 25.5% of the "all HfrEF with ADHF", 27.2% of the "actionable" cohort, and 25.1% of *PIONEER-HF* eligible.

Within the GWTG cohorts, "*PIONEER-HF* eligible" patients generally had lower rates of comorbid disease when compared to the "all-HfrEF with ADHF" and "actionable" patient cohorts (atrial fibrillation: 28.1% vs. 33.3% vs. 32.9 %; coronary artery disease: 50.4% vs. 52.9% vs. 51.1%; hypertension: 79.9% vs. 79.7% vs 80.8%; diabetes: 41.5% vs. 43.8% vs. 42.5% and renal insufficiency: 8.9% vs 20.2% vs 11.5%).

Outcomes

A total of 21,627 patients were linked within CMS to determine post discharge outcomes (47.4% of total) (Supplementary Table 3). Among the CMS-linked patients, the 1-year all-cause mortality and its 95% CI in the "all HfrEF with ADHF" cohort was higher (36.7%, 95% CI 36.1, 37.4) than then the upper limits of the "actionable" (32.2%, 95% CI 31.4, 33.0) and the "*PIONEER-HF* eligible" cohorts (31.6%, 95% CI 30.3, 32.9). This indicates significantly higher all-cause mortality in "all HfrEF with ADHF" than in the "actionable" or "*PIONEER-HF* eligible" cohorts (Table 2, Figure 2). The all-cause readmission rate at 1 year for "*PIONEER-HF* eligible" patients was the lowest with 64.5% (95% CI 63.2, 65.8), 65.5% (95% CI 64.7, 66.3) for the "actionable" cohort and 67.3% (95% CI 66.7, 68.0) for

the “all HfrEF with ADHF” cohort. The HF rehospitalization rate at 1 year was 35.1% (95% CI 34.5, 35.8) for “all HfrEF with ADHF” patients, 33.1% (95% CI 32.3, 33.9) for the “actionable” cohort and 32.6% (95% CI 31.3, 33.9) for the “*PIONEER-HF* eligible” cohort.

Discussion

In a contemporary HF registry of patients hospitalized for ADHF in the United States, one out of every five individuals (20.8%) met the *PIONEER-HF* inclusion and exclusion criteria. Relaxing the criteria to an “actionable” cohort increased the eligibility to 68.9% of all patients with HfrEF. Baseline characteristics and clinical outcomes at 1 year within the GWTG-HF cohorts indicated an all-over comparable but somewhat lower risk profile of patients eligible for *PIONEER-HF* as compared with patients with HfrEF encountered in routine practice.

With nearly one in three patients experiencing mortality within 1 year of hospitalization for ADHF in clinical practice, there is a substantial opportunity to improve the care and outcomes of these patients. *PIONEER-HF* provided data on the safety and efficacy of sacubitril/valsartan in patients recently treated for ADHF. The *PIONEER-HF* data suggests that in-hospital initiation of sacubitril/valsartan can both reduce NT-proBNP levels and readmissions through 8 weeks [7, 10]. Our analysis found that *PIONEER-HF* trial participants were comparable to patients with HfrEF hospitalized for ADHF in routine clinical practice in the United States. Yet, the *PIONEER-HF* trial participants and the selected GWTG-HF cohorts had some notable differences in the distribution of age, sex, and race as well as comorbid burden, suggesting that GWTG-HF registry cohort was all-over sicker. While the clinical outcomes seem mostly comparable between the “*PIONEER-HF* eligible” and the “actionable” cohort, patients who did not meet either the *PIONEER-HF* trial inclusion and exclusion criteria as well as the reduced “actionable” criteria were associated with a worse clinical outcome. Thus, the impact of *PIONEER-HF* on the in-hospital initiation of sacubitril/valsartan in patients with ADHF is poised to be significant, especially when extended to capture a broader population (“actionable” cohort). The importance of starting GDMT during hospitalization, in order to leverage this critical timepoint to optimize a patient’s HF treatment plan appears to be safe, is likely to improve adherence to medication and clinical outcomes [11–14].

The *PIONEER-HF* trial was novel in several ways. It was the first study to suggest benefit of in-hospital initiation of sacubitril/valsartan in a diverse population of patients hospitalized for HF. Over a third of patients enrolled in the trial identified as black, and approximately half were not being treated with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) at the time of their admission [9]. Successful therapies for the treatment of ADHF or evidence to support initiation of chronic treatments instituted in the setting of a HF hospitalization have been limited. In regards to sacubitril/valsartan the early uptake of this drug was slow, amounting to only 2.3% of patients hospitalized for HfrEF in the US in the first 12 months post approval by the Food and Drug Administration [15].

PIONEER-HF demonstrated that initiating patients on sacubitril/valsartan at this critical juncture in their disease course can positively impact both the trajectory of disease-specific biomarkers and patient outcomes [9, 10]. Our findings are distinct from results by Parikh et al. who compared the scope of sacubitril/valsartan eligibility in the PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor) which enrolled outpatients with a more narrow LVEF inclusion criterion (≤ 35%). Yet, more patients in the GWTG-HF registry met PARADIGM-HF eligibility criteria, given in parts to more relaxed natriuretic peptide [PARADIGM-HF: LVEF ≤ 35%, NT-proBNP ≥ 600 pg/mL or BNP ≥ 150 pg/mL (or, if hospitalized for HF within 6 months, NT-proBNP ≥ 400 pg/mL or BNP ≥ 100 pg/mL) and PIONEER-HF: LVEF < 40%, NT-proBNP ≥ 1600pg/mL or BNP ≥ 400 pg/mL][16].

The use of pharmacological therapies to block neurohormonal pathways has improved outcomes for patients in the stable, chronic phase of HF. Thus, it is important that the majority of patients be considered for these medications following stabilization of acute HF. Despite improving outcomes in patients with HfrEF, several missed opportunities to improve clinical outcomes remain. Recent work emphasized the low rates of guideline directed medical therapy (GDMT) in outpatients with HfrEF. Among eligible patients, 27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and mineralocorticoid receptor antagonist therapy, respectively. Further, when medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%) [17]. Only 1% of the eligible patient population received recommended target doses of all classes of medications. Unfortunately, up-titration of medications does not occur frequently during follow-up thus the majority of patients either do not get started on the appropriate medications or their target doses [18]. In many instances a hospitalization for HF presents an opportunity to start or up-titrate patients on their GDMT for HF. Yet, in the setting of a hospitalization, in many instances medications for HF get discontinued or dose reduced due to hemodynamic or cardiorenal considerations [19]. Not surprisingly the use of GDMT at discharge is low [20]. This represents an extensive gap in how the medical therapy for HF could be further optimized and lends further support to ensuring that patients are on the most efficacious doses of their GDMT prior to discharge [21–25].

As shown in our analysis the number of patients who could potentially benefit from sacubitril/valsartan can be significantly increased when only a reduced number of inclusion and exclusion criteria is applied ("*PIONEER-HF* eligible" to "actionable"). It seems reasonable to offer sacubitril/valsartan therapy to a wider population of symptomatic HfrEF patients in the absence of absolute contraindications such as persistent hypotension and advanced renal disease [26]. Our analysis confirms that patient characteristics are similar amongst patients meeting *PIONEER-HF* inclusion and exclusion criteria and those in the actionable cohort. It is likely that the expansion to patients outside of the *PIONEER-HF* trial inclusion and exclusion criteria may derive a comparable benefit as it was seen with other HF medical therapies [27].

Limitations

Notably, not all *PIONEER-HF* inclusion and exclusion criteria were available in GWTG-HF, thus some criteria were replaced by surrogate criteria. Further, although prior studies have suggested patients enrolled in GWTG-HF have similar characteristics to national cohorts, GWTG-HF may not represent all patients hospitalized for ADHF in the United States. Next, the "actionable" and "*PIONEER -HF* eligible" cohorts originate from the "All HfrEF" cohort. Thus, the interpretation of the results needs to be considered in this context. Finally, we acknowledge that the definition of the "actionable cohort", while clinically meaningful is subjective.

Conclusions

Patient characteristics and clinical outcomes in patients eligible for *PIONEER-HF* only modestly differ when compared with those encountered in routine practice, indicating that result from *PIONEER-HF* may be broadly generalizable. These results further support clinicians to apply guideline recommendations to optimize GDMT for their patients prior to discharge for their ADHF hospitalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms:

ADHF	acute decompensated heart failure
BNP	brain natriuretic peptide
CMS	Center for Medicare and Medicaid
GWTG-HF	Get With The Guidelines – Heart Failure
HFrEF	heart failure with a reduced ejection fraction
LVEF	left ventricular ejection fraction

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What is new?

- In a contemporary HF registry of patients hospitalized for ADHF in the United States, one out of every five individuals (20.8%) met the PIONEER-HF inclusion and exclusion criteria.
- Relaxing the criteria to an “actionable” cohort increased the eligibility to 68.9% of all patients with HFrEF.
- Baseline characteristics and clinical outcomes at 1 year indicated an all-over comparable but somewhat lower risk profile of patients eligible for PIONEER-HF as compared with patients with HFrEF encountered in routine practice.

What are the clinical implications?

- Patient characteristics and clinical outcomes in participants enrolled in *PIONEER-HF* only modestly differ when compared with those encountered in routine practice, indicating that result from *PIONEER-HF* may be broadly generalizable.
- These results further support clinicians to apply guideline recommendations to optimize GDMT for their patients prior to discharge for their ADHF hospitalization.

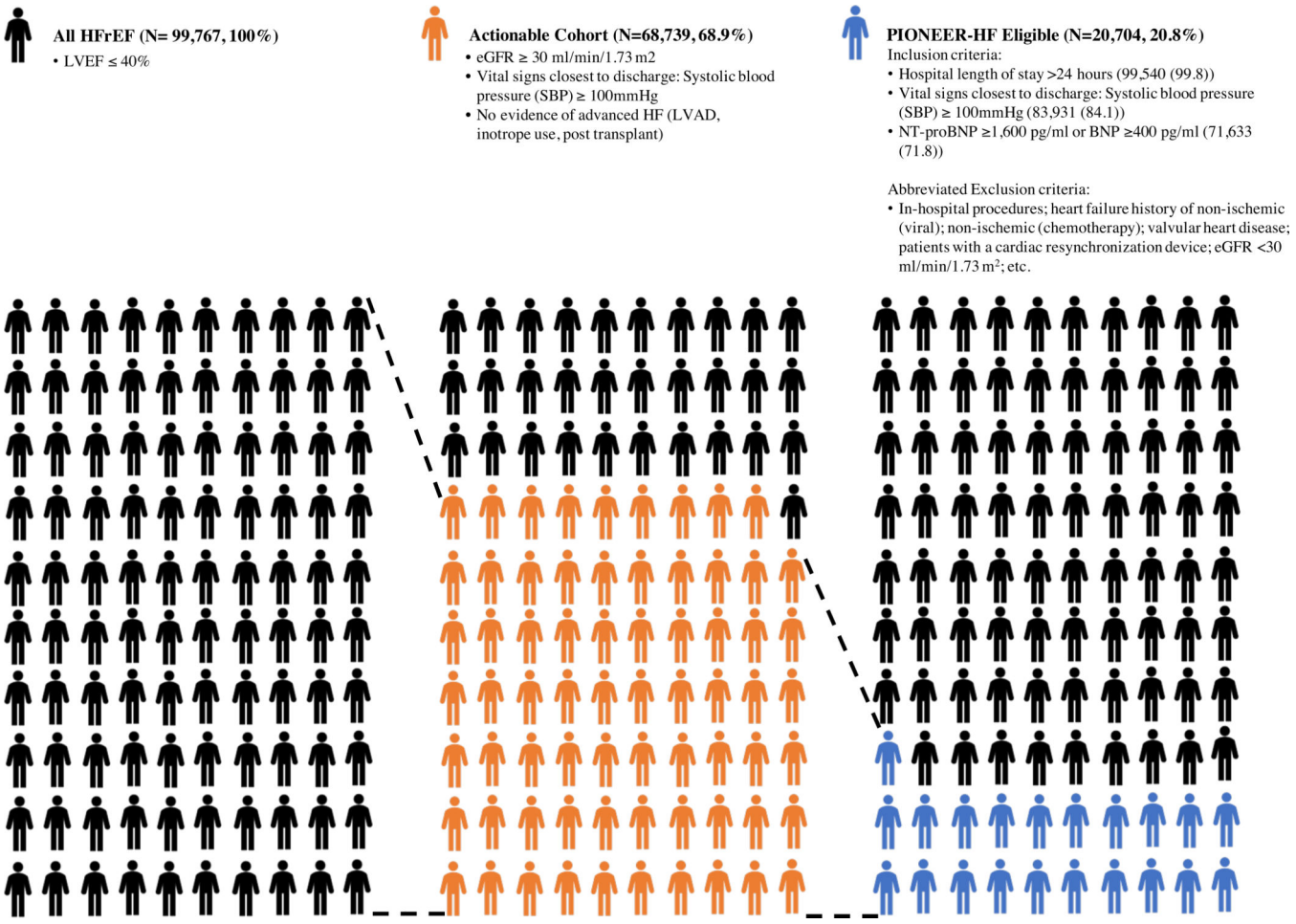

Figure 1.

Abbreviated flow diagram for the derivation of the "all HFrEF with ADHF", "*PIONEER-HF* eligible" and "actionable" cohort.

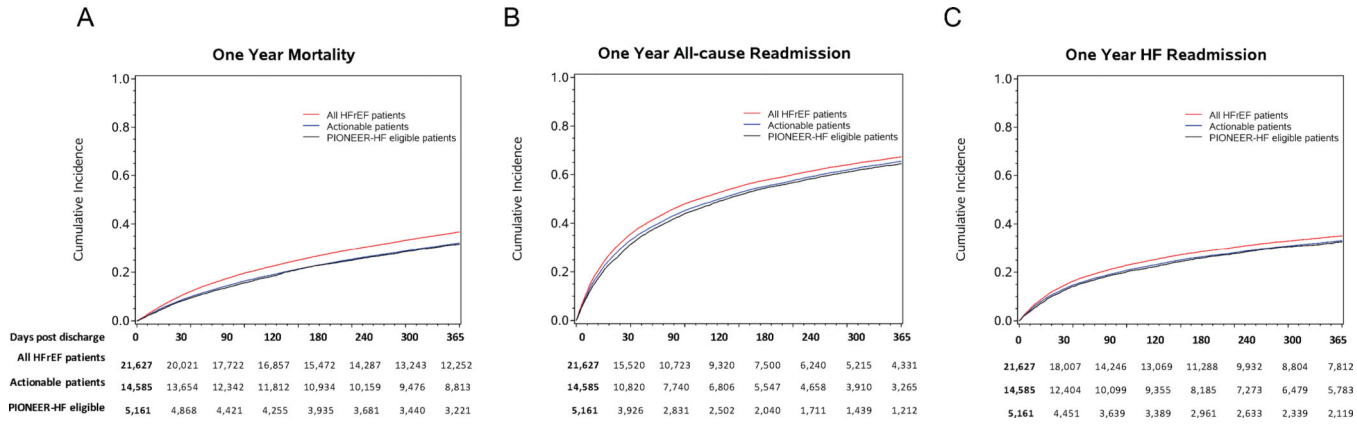

Figure 2.

Cumulative incidence plots for the three cohorts: “all HFrEF with ADHF”, “*PIONEER-HF* eligible” and “actionable”. (A) One year mortality; (B) One year all-cause readmission; (C) One year HF readmission

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Table 1.

Baseline characteristics

Variable	PIONEER-HF trial participants (9)	All HFrEF patients in GWTG	PIONEER-HF eligible patients in GWTG	Actionable patients in GWTG	% Std. Diff. vs PIONEER-HF patients		
	(N=440)	N=99,767	N=20,704	N=68,739	HFrEF	Eligible	Actionable
Demographics							
Age	61 (51 – 71)	70 (58 – 81)	71 (59 – 82)	69 (57 – 80)			
Female	113 (25.7)	36,490 (36.6)	7,905 (38.2)	24,182 (35.2)	23.7	27.1	20.8
Race							
Black	158 (35.9)	25,488 (25.5)	5,204 (25.1)	18,671 (27.2)	22.6	23.6	18.9
White	261 (59.3)	61,925 (62.1)	12,878 (62.2)	41,826 (60.8)	5.6	5.9	3.1
Medical History							
Atrial fibrillation/Atrial flutter	147 (33.4)	33,111 (33.3)	5,794 (28.1)	22,581 (32.9)	0.3	11.6	1.0
CVA/TIA	44 (10.0)	15,435 (15.5)	2,918 (14.1)	10,369 (15.1)	16.6	12.7	15.5
Previous myocardial infarction	27 (6.1)	26,996 (27.1)	5,079 (24.6)	17,763 (25.9)	58.7	53.0	55.9
Hyperlipidemia	159 (36.1)	51,580 (51.8)	9,824 (47.6)	34,909 (50.9)	32.0	23.4	30.1
Hypertension	384 (87.3)	79,392 (79.7)	16,478 (79.9)	55,447 (80.8)	20.4	20.1	17.7
Diabetes	79 (18.0)	44,137 (44.3)	8,690 (42.1)	29,596 (43.1)	59.4	54.6	56.8
Renal Insufficiency (SCr>2)	130 (29.5)	20,067 (20.2)	1,827 (8.9)	7,916 (11.5)	21.9	54.4	45.7
Prior percutaneous coronary intervention	2 (0.5)	18,630 (18.7)	3,286 (15.9)	12,558 (18.3)	65.2	58.8	64.3
Prior coronary artery bypass graft	18 (4.1)	20,280 (20.4)	3,471 (16.8)	13,345 (19.5)	51.3	42.5	49.1
Implantable cardioverter defibrillator only	80 (18.2)	18,067 (18.1)	3,552 (17.2)	11,625 (16.9)	0.1	2.5	3.3
Cardiac resynchronization therapy	43 (9.8)	9,343 (9.4)	171 (0.8)	5,913 (8.6)	1.3	40.7	4.0
Medical History panel missing	–	201 (0.2)	68 (0.3)	136 (0.2)	–	–	–
Discharge Measures							
Systolic Blood Pressure, mmHg	118 (110 – 133)	116 (104 – 131)	120 (110 – 134)	120 (110 – 133)			
Heart rate, bpm	81 (72 – 92)	76 (68 – 86)	76 (68 – 86)	76 (68 – 86)			
Body mass index	30.5 (25.9 – 37.1)	27.2 (23.2 – 32.7)	27.1 (23.2 – 32.3)	27.7 (23.5 – 33.3)			
NT-BNP, pg/mL	4,821 (3,109 – 8,767)*	5,196 (2,424 – 10,618)	4,810 (2,448 – 9,245)	4,576 (2,083 – 9,287)			

Variable	PIONEER-HF trial participants (9)	All HFrEF patients in GWTG	PIONEER-HF eligible patients in GWTG	Actionable patients in GWTG	% Std. Diff. vs PIONEER-HF patients		
	(N=440)	N=99,767	N=20,704	N=68,739	HFrEF	Eligible	Actionable
Ejection Fraction Quantitative, %	24 (18 – 30)	25 (20 – 33)	26 (20 – 35)	25 (20 – 34)			
Potassium, mEq	4.2 (4.0 – 5.0)	4.0 (3.7 – 4.4)	4.0 (3.7 – 4.3)	4.0 (3.7 – 4.3)			
Prior Medications							
Sacubitril/valsartan	–	838 (0.9)	–	580 (0.9)	–	–	–
ACEi/ARB	208 (47.3)	49,755 (52.0)	11,890 (61.1)	36,284 (55.1)	9.4	27.9	15.6
Beta-Blocker	262 (59.5)	62,213 (65.0)	11,421 (58.7)	42,099 (63.9)	11.2	1.8	8.9
Aldosterone antagonist	48 (10.9)	16,271 (17.0)	2,655 (13.6)	11,177 (17.0)	17.6	8.3	17.5
Loop diuretics	262 (59.5)	60,307 (63.0)	11,166 (57.3)	40,504 (61.5)	7.1	4.5	3.9
Hydralazine	30 (6.8)	9,118 (9.5)	1,127 (5.8)	5,225 (7.9)	9.9	4.2	4.3
Nitrates	43 (9.8)	17,780 (18.6)	3,094 (15.9)	11,058 (16.8)	25.4	18.4	20.8
Digoxin	41 (9.3)	14,574 (15.2)	2,776 (14.3)	10,074 (15.3)	18.1	15.4	18.2
Prior Medications panel missing	–	4,030 (4.0)	1,231 (5.9)	2,842 (4.1)	–	–	–

Abbreviations: CVA = cerebrovascular accident; TIA = transient ischemic attack; SCr = serum creatinine; NT-proBNP = N terminal pro brain natriuretic peptide; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker. *NT-proBNP at screening. Data presented as median (IQR) and N (%)

Table 2.

All-cause mortality, all-cause and HF-related readmission at 1-year post discharge compared between: All HFrEF, Actionable, and PIONEER-HF eligible.

	At 30 Days		At 90 Days		At 1 Year	
Outcome	**n**	**Cumulative Incidence (95% CI)**	**n**	**Cumulative Incidence (95% CI)**	**n**	**Cumulative Incidence (95% CI)**
All-cause Mortality						
All HFrEF patients	1,410	6.6 (6.2, 6.9)	3,411	16.0 (15.5, 16.4)	7,645	36.7 (36.1, 37.4)
Actionable patients	799	5.5 (5.1, 5.9)	1,894	13.1 (12.6, 13.7)	4,502	32.2 (31.4, 33.0)
PIONEER-HF eligible patients	257	5.0 (4.4, 5.6)	645	12.6 (11.7, 13.5)	1,581	31.6 (30.3, 32.9)
All-cause Readmission						
All HFrEF patients	5,119	23.8 (23.2, 24.4)	9,016	42.3 (41.6, 42.9)	13,975	67.3 (66.7, 68.0)
Actionable patients	3,174	21.9 (21.2, 22.6)	5,679	39.5 (38.7, 40.3)	9,143	65.5 (64.7, 66.3)
PIONEER-HF eligible patients	1,039	20.2 (19.1, 21.3)	1,945	38.2 (36.8, 39.5)	3,207	64.5 (63.2, 65.8)
HF Readmission						
All HFrEF patients	2,195	10.2 (9.8, 10.6)	4,228	19.8 (19.3, 20.4)	7,249	35.1 (34.5, 35.8)
Actionable patients	1,338	9.2 (8.8, 9.7)	2,580	18.0 (17.3, 18.6)	4,596	33.1 (32.3, 33.9)
PIONEER-HF eligible patients	433	8.4 (7.7, 9.2)	886	17.4 (16.4, 18.5)	1,611	32.6 (31.3, 33.9)

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