Ivabradine in Heart Failure

The Representativeness of SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) in a Broad Population of Patients With Chronic Heart Failure

See Editorial by Eckman

BACKGROUND: The sinus node inhibitor ivabradine was approved for patients with heart failure (HF) after the ivabradine and outcomes in chronic HF (SHIFT [Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial]) trial. Our objective was to characterize the proportion of patients with HF eligible for ivabradine and the representativeness of the SHIFT trial enrollees compared with those in the Swedish Heart Failure Registry.

METHODS AND RESULTS: We examined 26 404 patients with clinical HF from the Swedish Heart Failure Registry and divided them into SHIFT type (left ventricular ejection fraction <40%, New York Heart Association class II–IV, sinus rhythm, and heart rate ≥70 beats per minute) and non-SHIFT type. Baseline characteristics and medication use were compared and change in eligibility over time was reported at 6 months and 1 year in a subset of patients. Overall, 14.2% (n=3741) of patients were SHIFT type. These patients were more likely to be younger, men, have diabetes mellitus, ischemic heart disease, lower left ventricular ejection fraction, and more recent onset HF (<6 months; all, P<0.001). Although 88.9% of SHIFT type and 88.5% of non-SHIFT type (P=0.421) were receiving selected β-blockers, only 58.8% and 67.3% (P<0.001) were on >50% of target dose. From those patients who had repeated visits within 6 months (n=5420) and 1 year (n=6840), respectively, 10.2% (n=555) and 10.6% (n=724) of SHIFT-type patients became ineligible, 77.3% (n=4188) and 77.3% (n=5287) remained ineligible, and 4.6% (n=252) and 4.9% (n=335) of non-SHIFT–type patients became eligible for initiation of ivabradine.

CONCLUSIONS: From the Swedish Heart Failure Registry, 14.2% of patients with HF were eligible for ivabradine. These patients more commonly were not receiving target β-blocker dose. Over time, a minority of patients became ineligible and an even smaller minority became eligible.

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WHAT IS NEW?

- Ivabradine, a sinus node inhibitor, was shown in the SHIFT (Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial) trial to improve outcomes in patients with chronic HF and reduced ejection fraction with heart rate > 70 bpm despite guidelines-directed medical therapy. With ivabradine being widely introduced over the last year, understanding whether the participants in the SHIFT trial are representative of the larger population with chronic HF becomes important.
- In a registry of Swedish patients with chronic HF, our study highlights that 14.2% would be eligible for ivabradine with 5% and 11% becoming eligible and ineligible over a course of 12 months.
- The SHIFT–type patients from our study reached target β-blocker dose less often than non-SHIFT–type patients.
- Optimizing β-blocker dose before initiating ivabradine remains a key step and is supported by international guidelines.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Identifying and monitoring patient eligibility for addition of ivabradine to guidelines-directed medical therapy is important as ivabradine becomes available in general practice.
- Further observational and comparative effectiveness data will inform clinical practice, especially related to β-blocker doses achieved and other medications that can alter heart rate.

An elevated resting heart rate (HR) is a known risk marker and likely risk factor for adverse outcomes in patients with heart failure (HF). Ivabradine is a specific sinus node inhibitor that decreases the HR.[1–3] The ivabradine and outcomes in chronic heart failure (SHIFT [Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial]) clinical trial randomized 6558 patients with stable (≥4 weeks) but symptomatic chronic HF with reduced ejection fraction, hospitalized with HF decompensation in the previous 12 months, New York Heart Association class II–IV, left ventricular ejection fraction (LVEF) ≤35%, and sinus rhythm with HR >70 beats per minute to ivabradine versus placebo. The primary end point was a composite of cardiovascular death or HF hospitalization, and over a median follow-up time of 23 months, a 18% reduction in this composite was seen.[4,5] Ivabradine was approved by the European Medical Association in 2005 for treatment of chronic angina and in 2012 for treatment of chronic HF with reduced ejection fraction and by the Food and Drug Administration in 2015 for the treatment of patients with chronic HF with reduced ejection fraction and LVEF ≤35%.[6,7]

Although randomized clinical trials are the gold standard to assess efficacy and safety of novel therapeutics, clinical trial populations may not represent the broader population and have limited external validity.[8] Nonselective clinical registries provide information on generalizability and are important in understanding the context of new pharmacotherapy in relation to the current standard of practice. The prevalence of eligibility for ivabradine in the general HF with reduced ejection fraction population is unknown, and SHIFT did not report prescreening and screening data. Using the well-established Swedish Heart Failure (SwedeHF) Registry, our objective was to determine proportions of and characterize patients eligible for ivabradine, assess the representativeness of the SHIFT clinical trial criteria in patients with HF, and assess how eligibility changed over time.

METHODS

Study Design and Setting

The SwedeHF, which has been described previously, provided the study population and baseline clinical characteristics and medications.[9] SwedeHF is a nationwide continuous health quality and research registry founded in 2000. The inclusion criterion is clinician-judged HF regardless of LVEF, which is categorized as <30%, 30% to 39%, 40% to 49%, and ≥50%. Variables (≈100) are recorded at discharge from hospital or outpatient visits at cardiology, internal medicine, geriatrics, and primary care clinics by a local physician or nurse and entered into a database managed by Uppsala Clinical Research Center (www.ucr.se). The protocol, case report form, and annual reports are available at www.SwedeHF.se. SwedeHF covers ≈53% of all inpatients HF encounters with a smaller percentage of outpatient coverage.

The Swedish Board of Health and Welfare (www.socialstyrelsen.se) maintains the Patient Registry, which provided additional baseline comorbidities. It contains *International Statistical Classification of Diseases*, Tenth Revision codes for encounters as inpatients and as outpatients at specialty clinics and is updated and validated annually (last update for the present merged database and thus end of inclusion for this study, December 31, 2012). The positive predictive value for most diagnoses is between 85% and 95%.[10]

Patients and SHIFT Criteria

Patients were included in this study if the index date was between July 1, 2005, and December 31, 2012. Patients were excluded if they had missing information on EF, NYHA class, HR, rhythm, or baseline β-blocker use and dose, or <3 months of follow-up. Patients were subsequently divided into SHIFT type defined as LVEF <40%, NYHA class II–IV, HR >70 beats per minute, sinus rhythm and non-SHIFT type defined as did not meet ≥1 of the eligibility criteria, that is, any of LVEF ≥40%, NYHA class I, HR <70 beats per minute, atrial fibrillation or atrial flutter, hypotension (systolic blood pressure <100 mm Hg) or significant hypertension (systolic blood pressure >180 mm Hg). Baseline characteristics of SHIFT-type and non-SHIFT–type patients are shown in Table 1. These data are also subdivided into inpatients and outpatients to identify any distinct clinical profiles between these groups (Table I in the Data Supplement).

Table 1. Baseline Characteristics of Patients From the Swedish Heart Failure (SwedeHF) Registry Subdivided by SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) Type and Non-SHIFT Type

Characteristics	SHIFT Type (n=3741; 14.2%)	Non-SHIFT Type (n=22 663; 85.8%)	*P* Value	Missing Data, %
Age, y	70 [60–79]	75 [66–82]	<0.001	0
Sex, male, %	68	65	<0.001	0
Location			<0.001	0
Inpatients	51	45		
Outpatient (physician)	6	8		
Outpatient (heart failure nurse-based clinic)	43	47	<0.001	
Year of first registration			0.373	0
2005–2008	43	43		
2009–2012	57	57		
Specialty			0.219	4
Cardiology	58	57		
Internal Medicine/Geriatrics	42	43		
Medical history: cardiovascular				
Duration of heart failure, mo			<0.001	0.5
<6	59	48		
≥6	41	52		
NYHA class				0
I	0	14		
II	51	47		
III	45	36		
IV	4	3		
Ischemic heart disease	51	47	<0.001	4
Myocardial infarction	42	38	<0.001	0
Percutaneous coronary intervention	18	16	0.015	0
Coronary artery bypass surgery	23	23	1.000	0
Atrial fibrillation/flutter	0	52		0
Valve disease	18	24	<0.001	0
Device therapy			<0.001	0.7
Pacemaker (non-CRT, non-ICD)	2	8		
CRT+ICD	1	1		
CRT only	1	1		
ICD only	3	2		
Medical history: noncardiovascular				
Stroke or TIA including ICH	13	16	<0.001	0
Hypertension	44	61	<0.001	0
Diabetes mellitus	31	26	<0.001	0
Renal dialysis	0.8	0.6	0.170	0
Lung disease	29	28	0.240	0
Physical examination				
Blood pressure				0
Systolic	125 [110–140]	125 [110–140]	0.191	
Diastolic	75 [70–80]	70 [65–80]	<0.001	
Mean arterial pressure	92 [83–100]	90 [82–100]	<0.001	

(*Continued*)

Table 1. Continued

Characteristics	SHIFT Type (n=3741; 14.2%)	Non-SHIFT Type (n=22 663; 85.8%)	*P* Value	Missing Data, %
Heart rate, beats per minute	80 [73–86]	70 [60–80]		0
Laboratory/investigations				
LVEF, %				0
<30	58	26		
30–39	42	25		
eGFR	70 [47–96]	62 [44–86]	<0.001	5
Potassium, mEq/L	4.2 [3.9–4.4]	4.2 [3.9–4.4]	0.312	35
NT-proBNP, pg/mL	3070 [1250–6812]	2269 [1018–4960]	<0.001	64
Chest x-ray: cardiomegaly	47	45	0.081	37
Chest x-ray: pulmonary congestion	48	43	<0.001	37

Values are % or medians unless otherwise stated. Median (interquartile range) also reported. CRT indicates cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; ICH, intracranial hemorrhage; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and TIA, transient ischemic attack.

Percentages of non-SHIFT–type patients who met individual SHIFT entry criteria are also reported. Both non-SHIFT–type and SHIFT-type patients with repeat registrations within 6 and 12 months were assessed for change in eligibility and ineligibility over time. After their initial enrollment in SwedeHF, those individuals selected for analysis had an additional registration closer to 6 and 12 months.

β-Blocker Use and Dose

Medication profiles at first clinical visit between SHIFT-type and non-SHIFT–type patients were compared including the use of β-blockers and whether >50% of the recommended target dose was used. The American Heart Association/American College of Cardiology and European Society of Cardiology HF guidelines were used to determine the target doses of specific β-blockers.[11–13] Additional cardiac medications were also reported.

Statistical Analysis

Baseline continuous variables were shown as medians with interquartile range and compared between SHIFT-type and non-SHIFT–type patients using the Wilcoxon rank-sum test. Categorical variables including medication use were reported as percentages and compared with a Pearson χ^2 test. A $P<0.05$ was considered to be statistically significant, and the above comparison provides unadjusted differences between SHIFT-type and non-SHIFT–type patients.

To determine the independent predictors of eligibility for ivabradine, that is, of being a SHIFT-type patient, and to determine the predictors of eligibility and ineligibility over the following 12 months, logistic multivariable models were performed including variables that were significantly associated with eligibility/ineligibility at the univariate level. Analysis for eligibility and ineligibility over time was restricted for patients who were initially ineligible and eligible, respectively. Missing data in variables that were not reported as inclusion/criteria for our study were managed by multiple imputation.

Ethics

Ethics approvals for the establishment of SwedeHF and for this study were provided by a multisite ethics committee. Individual patient consent is not required for entry into national registries, but patients are informed of entry and allowed to opt out.

RESULTS

Starting with 80 772 registrations, after excluding patients with missing values for variables reported in the inclusion/exclusion criteria listed above and repeat registrations for the same individual, there were 26 404 patients remaining (Figure 1).

A total of 14.2% (n=3741) were SHIFT type and 85.8% (n=22 663) were non-SHIFT type. Of the 26 404 patients, 45.5% (n=12 024) were inpatients with 15.8% (n=1895) individuals being SHIFT type and 84.2% (n=10 129) being non-SHIFT type. The remaining 54.5% (n=14 380) were outpatients and included 12.8% (n=1846) of SHIFT-type and 87.2% (n=12 534) of non-SHIFT–type patients (Table I in the Data Supplement). Some non-SHIFT–type patients met one but not all individual SHIFT eligibility criteria including NYHA class II–IV (86.0%), LVEF <40% (51.3%), HR >70 beats per minute (50.6%), baseline sinus rhythm (48.4%), currently on β-blockers (88.8%). Of the total 26 404 patients included, 58.1% had an LVEF <40% (n=15 367). This includes 3741 SHIFT type (24.3%) and 11 626 non-SHIFT type (75.7%).

SHIFT-type patients were more likely to be younger, men, to have history of diabetes mellitus, and ischemic heart disease but not of hypertension and valve disease, a more recent onset of HF (ie, duration <6 months), higher estimated glomerular filtration rate, and NT-proBNP (N-terminal pro-B-type natriuretic peptide)

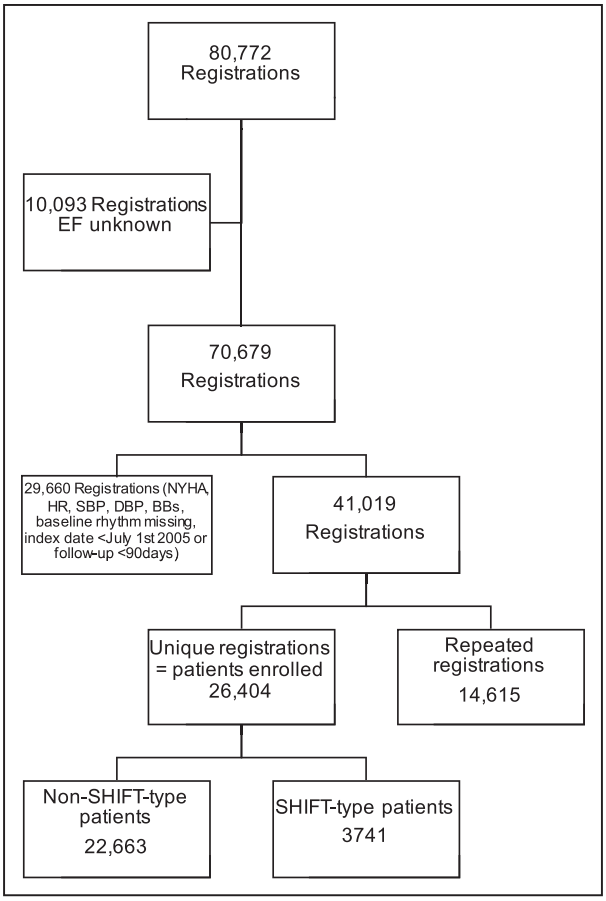

Figure 1. Flowchart of SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) eligible patients with chronic heart failure from the Swedish Heart Failure Registry.

Index date refers to the date of discharge if the patient was an inpatient and the date of clinic visit if the patient was an outpatient. BBs indicate β-blocker use; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; NYHA, New York Heart Association; and SBP, systolic blood pressure.

when compared with non-SHIFT–type patients (P<0.05; Tables 1 and 2). After dividing both groups of patients into inpatients and outpatients, these clinical characteristics remained consistent for SHIFT-type inpatients (Table I in the Data Supplement).

From their baseline clinical visit and registration into SwedeHF, the majority of both SHIFT-type and non-SHIFT–type patients were prescribed selected β-blockers (88.9% and 88.5%, respectively; Table 2). When comparing both groups to prespecified target doses of selected β-blockers (American Heart Association/American College of Cardiology and European Society of Cardiology guidelines), only 58.8% of SHIFT-type patients versus 67.3% of non-SHIFT–type patients met >50% of target β-blocker dose (P<0.001). Medication profiles differed between both groups as well with SHIFT-type patients being more likely to be on angiotensin-converting enzyme inhibitors, diuretics, mineralocorticoid receptor antagonists, and antiplatelet agents where non-SHIFT–type patients were more likely to be prescribed angiotensin receptor blockers, digoxin, nitrates, and oral anticoagulants. When further subdividing patient groups into inpatients and outpatients, a similar pattern was seen with the majority of patients being prescribed β-blockers. Importantly, non-SHIFT–type inpatients and outpatients were more likely to be at >50% of target β-blocker dose than SHIFT inpatients and outpatients (Table I in the Data Supplement).

From the multivariate analysis, variables associated with baseline SHIFT eligibility included age, HF duration, smoking, estimated glomerular filtration diuretics, mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, digoxin, platelet inhibitors, oral anticoagulants, diabetes mellitus, hypertension, ischemic heart disease, severe bleeding, and percutaneous coronary intervention (P<0.05; Table 3). Whereas those associated with SHIFT eligibility >12 months included age, type of clinic, use of digoxin, or mineralocorticoid receptor antagonist (P<0.05; Table 4). Female sex (odds ratio, 0.75 [0.58–0.96]; P=0.025), duration of HF (OR, 0.68 [0.53–0.88]; P=0.003), oral anticoagulants use (OR, 1.68 [1.20–2.36]; P=0.003), and diabetes mellitus (OR, 0.76 [0.59–0.98]; P=0.035) were associated with SHIFT ineligibility over the same period.

When assessing the change in SHIFT eligibility over time, a total of 5420 and 6840 patients had repeat registrations within 6 and 12 months, respectively. At 6 months, 10.2% (n=555 of 5420 patients) of SHIFT-eligible patients became ineligible and 4.6% (n=252 of 5420 patients) of non-SHIFT–type patients became eligible (Figure 2). In addition, 7.8% (n=425 of 5420 patients) of eligible individuals remained eligible and 77.3% (n=4188 of 5420 patients) of ineligible individuals remained ineligible at 6 months (Figure 2). At 12 months, 10.6% (n=724 of 6840 patients) of SHIFT-type patients became ineligible and 4.9% (n=335 of 6840 patients) non-SHIFT–type patients became eligible (Figure 2). Among those who stayed in the same eligibility group, 7.2% (n=494 of 6840 patients) and 77.3% (n=5287 of 6840 patients) remained eligible and ineligible, respectively (Figure 2). At 6 months and 12 months, patients became ineligible for initiation of ivabradine, primarily because of lack of HF hospitalization (84.7% and 85.2%, respectively), HR <70 beats per minute (76.4% and 75.1%, respectively), with a smaller percentage driven by LVEF >40% (10.6% and 15.3%, respectively), NYHA class I (9.4% and 10.8%, respectively), and baseline rhythm atrial fibrillation and atrial flutter (9.4% and 10.5%).

DISCUSSION

Application of clinical trial results can pose a substantial challenge when applied to a broader and more

Table 2. Medication Profile of SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial)-Type and Non-SHIFT–Type Patients From the Swedish Heart Failure Registry

Current Medications	SHIFT Type (n=3741; 14.2%)	Non-SHIFT Type (n=22,663; 85.8%)	*P* Value	Missing Data, %
β-blocker (all)	89	89	0.593	0
β-blocker (selected)	89	89	0.421	0
β-blocker (selected) with >50% target dose	59	67	<0.001	0
Angiotensin-converting enzyme inhibitors	73	67	<0.001	0.3
Angiotensin receptor blocks	22	24	0.002	1
Digoxin	6	19	<0.001	0.4
Mineralocorticoid receptor antagonists	33	30	<0.001	0.4
Diuretic	79	77	0.013	0.3
Statin	50	47	0.002	0.3
Nitrates	13	15	0.001	0.5
Oral anticoagulants	20	46	<0.001	0.3
Platelet inhibitor	63	47	<0.001	0.4

Values are % unless otherwise stated. β-blocker (selected) includes those recommended from the American Heart Association/American College of Cardiology and European Society of Cardiology guidelines.

generalized patient population. Using the SwedeHF registry to analyze 26 404 patients with HF, first, we found that 14.2% patients would be eligible for therapy with ivabradine based on broad SHIFT clinical trial entry criteria. Second, we identified that the majority of patients did not change eligibility or ineligibility over 6 and 12 months. Third, approximately 10% of patients became ineligible, mainly because of lack of HF hospitalization and HR <70 beats per minute, whereas approximately 5% of patients became eligible over time. There were also no clear predictors that would aid the clinician in predicting future eligibility for ivabradine.

β-blocker use was similar among all groups including the clinical trial population and patients from the SwedeHF registry with ≈90% of individuals on β-blocker therapy. However, non-SHIFT–type patients from SwedeHF were more likely to be at >50% of target β-blocker dose than SHIFT-type patients. Although we cannot assess specifically why SHIFT-type patients were not reaching target β-blocker dose, it is most plausible that HR was the most important limiting factor. A portion of non-SHIFT–type patients were those with preserved EF, in whom β-blocker use may be related to alternative reasons including post–myocardial infarction, angina relief from ischemic heart disease, and rate control for atrial fibrillation or flutter. In the OPTIMIZE-HF registry (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) using data from 2003 to 2004, authors found that the majority of patients with HF were often discharged with <25% or 25% to 49% of the target β-blocker dose.[14] In both groups of patients in OPTIMIZE-HF, the average HR was 78 and 75 beats per minute at the time of discharge, respectively.[14] This is of particular importance as resting HR is a well-established risk factor for worse outcomes in patients with chronic HF.[15] In the SwedeHF cohort, the higher percentage of patients with >50% target dose of a β-blocker may indicate potential for more aggressive

Table 3. Multivariate Analysis of Variables Associated With Baseline SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) Eligibility From the Swedish Heart Failure Registry

Variable	Odds Ratio	95% CI	*P* Value
Age (per 10 y)	0.75	0.71–0.78	<0.001
Duration of heart failure (≥6 vs <6 mo)	0.72	0.65–0.76	<0.001
Smoking			
Previous vs no smoking	1.16	1.07–1.27	<0.001
Smoking vs no smoking	1.47	1.31–1.65	<0.001
Estimated glomerular filtration rate (per 10 mL/min 1.73 m^2)	0.97	0.96–0.99	0.002
Diuretic	1.59	1.44–1.75	<0.001
Angiotensin-converting enzyme inhibitors	1.23	1.10–1.38	<0.001
Mineralocorticoid receptor antagonists	1.23	1.13–1.33	<0.001
Digoxin	0.37	0.32–0.43	<0.001
Oral anticoagulants	0.35	0.32–0.39	<0.001
Platelet inhibitor	1.12	1.01–1.23	0.03
Diabetes mellitus	1.36	1.25–1.48	<0.001
Hypertension	0.85	0.78–0.92	<0.001
Ischemic heart disease	1.22	1.11–1.34	<0.001
Severe bleeding	0.78	0.71–0.87	<0.001

CI indicates confidence interval.

Table 4. Multivariate Analysis of Variables Associated With SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) Eligibility From the Swedish Heart Failure Registry at 12 Months

Variable	Odds Ratio	95% CI	*P* Value
Age (per 10 U)	0.82	0.74–0.90	<0.001
Type of Clinic (Cardiology vs Internal Medicine/ Geriatrics)	1.58	1.24–2.01	<0.001
Mineralocorticoid receptor antagonist	1.47	1.16–1.86	0.001
Digoxin	0.41	0.26–0.64	<0.001
Oral anticoagulant	0.44	0.32–0.62	<0.001
Percutaneous coronary intervention	0.84	0.76–0.94	0.002

CI indicates confidence interval.

up-titration. Nevertheless, maximizing β-blocker dose before initiating ivabradine remains a key step.[12,16,17]

Interestingly, as ivabradine became available, there were concerns that the use of β-blocker therapy would be altered because of concerns of bradycardia. However, Borer et al[18] reported from the SHIFT trial that the addition of ivabradine did not significantly affect β-blocker usage, suggesting a valuable role for both agents. From an outpatient perspective, titration of HF medications occurs less frequently and patients are often undertreated leading to worse outcomes.[19,20] Although specialized HF clinics have made substantial improvements for this patient population, the expected mean or median optimal dosages of β-blockade in clinical practices are not known.[21,22] It is also noteworthy that our cohort experienced, over a 12-month follow-up, a relatively small 5% net reclassification of ivabradine eligibility, which was likely at least partially related to the nature of HR variability. Our study suggests that despite higher prescription and doses of β-blockers in Sweden there were ≈14% SHIFT-eligible patients among those with chronic HF enrolled in the SwedeHF.

The largest group not meeting SHIFT entry criteria was those who were not in sinus rhythm. Although the majority of non-SHIFT–type patients were in either atrial fibrillation or atrial flutter, the total number may have been underestimated when including those individuals with a pacemaker, cardiac resynchronization device, or an implantable defibrillator. Although our study did not report the development of new atrial arrhythmias over time, it is often underestimated in the literature.[23]

Strengths and limitations of our study deserve consideration. Strengths include the use of SwedeHF, which enabled the use of a large generalized HF population and the collection of comprehensive baseline data, medication profiles, and patient demographics. Although SHIFT-type and non-SHIFT–type patients had

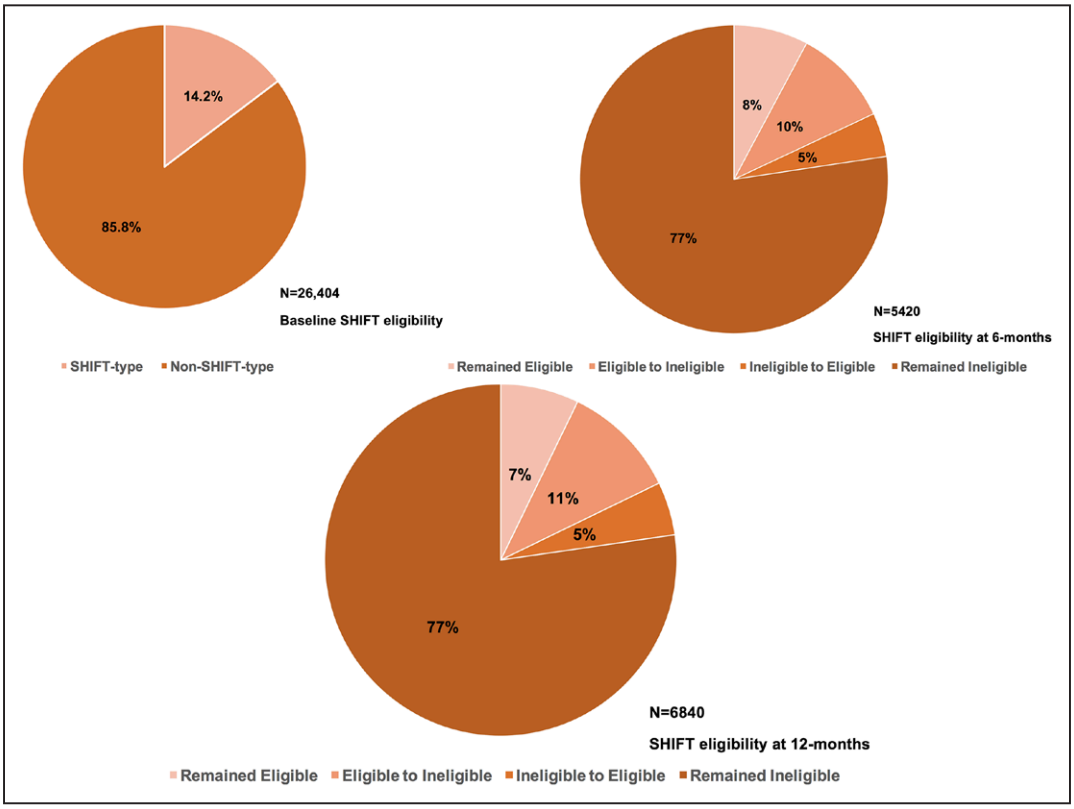

Figure 2. Assessment of SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) eligibility from the Swedish Heart Failure Registry at baseline, 6 mo, and 12 mo after initial registration/clinical visit.

a distinct clinical profile, many baseline features including age, sex, and hypertension may be explained by reduced versus preserved LVEF. Unlike SHIFT, we did not exclude patients on dialysis; however, this represented a fraction of our included population (0.8% SHIFT type and 0.6% non-SHIFT type; P=0.1) and thus was considered to have a minimal effect on our overall analysis.

Another relevant limitation is that although SwedeHF reflected similar β-blocker prescription when compared with other registries such as the European Society of Cardiology HF Long Term Registry, the percentage of individuals meeting >50% of target β-blocker dose from SwedeHF are much higher than reported in the literature.[24] Patients achieving >50% of target β-blocker in SwedeHF were similar to clinical trial data and are not reflective of global practice patterns of β-blocker use.[4,25] Another important limitation to our study was the inability to assess for HF hospitalization before SwedeHF registration and an inability to specifically assess patients with an LVEF ≤35% (LVEF is reported as a categorical variable in SwedeHF [<30%, 30%–39%, 40%–49%, and ≥50%]), which may have overestimated the number of SHIFT-type patients. We also did not have data on ivabradine use from SwedeHF, and although a reduction in HR to <70 beats per minute rendered a patient ineligible, we cannot rule out that this may be a result of ivabradine and do not imply that such patients should discontinue therapy. In addition, we had limited longitudinal data, this means that not all patients had registrations at 12 months had registrations at 6 months. This represents a limitation in our change in eligibility/ineligibility over time analysis.

The original SHIFT trial also required patients to be on stable treatment for at least 4 weeks before enrollment in the trial. Although this was an inherent limitation, our study does represent clinical practice where stability of therapy may not be guaranteed before initiation of a new medication. Finally, from our study was an inability to ascertain why patients were not meeting target doses of β-blocker therapy. From previously published data, we expect a combination of β-blocker intolerance and contraindications to comprise the majority of this population but are unable to comment on true lack of therapy.

CONCLUSIONS

SHIFT-type patients from SwedeHF represent 14.2% of patients with chronic HF who are eligible for treatment with ivabradine. SHIFT-type patients have a distinct clinical profile with a large percentage of individuals not achieving target β-blocker dose compared with non-SHIFT–type patients. With 5% and 11% of patients becoming eligible and ineligible, respectively, for ivabradine over a 12-month period, monitoring of patients for eligibility is essential. As therapeutics for chronic HF continue to advance, appreciating the use of these agents in the context of a broader population will be important and necessary to ensure the delivery of effective care.

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DISCLOSURES

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FOOTNOTES

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Ivabradine in Heart Failure: The Representativeness of SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) in a Broad Population of Patients With Chronic Heart Failure

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Baseline characteristics of patients from SwedeHF registry regarding inpatients and outpatients

Characteristics	Inpatients			Outpatients		
	SHIFT-Type (n=1,895; 15.8%)	Non-SHIFT-Type (n=10,129; 84.2%)	P-Value	SHIFT-Type (n=1,846; 12.8%)	Non-SHIFT-Type (n=12,534; 87.2%)	P-Value
Age (years)	72 [61– 81]	78 [69 – 84]	<0.001	67 [59 – 76]	72 [64 – 79]	<0.001
Sex, Male, %	67	59	<0.001	70	69	0.744
Location			0.117			0.006
Inpatients	100	100		0	0	
Outpatients (Physician)	0	0		13	15	
Outpatients (HF Nurse-based clinic)	0	0		87	85	
Year of First Registration			0.024			0.121
2005-2009	48	45		39	41	
2009-2012	52	55		61	60	
Specialty			0.117			0.663
Cardiology	63	61		53	54	
Internal Medicine/Geriatrics	37	39		47	47	
Medical History - Cardiovascular						
Duration of HF			<0.001			<0.001
< 6 months	59	47		60	49	
≥ 6 months	41	53		40	51	

NYHA Class			<0.001			<0.001
I	0	13		0	15	
II	45	44		57	50	
III	48	39		41	33	
IV	7	4		2	2	
Ischemic Heart Disease	54	48	<0.001	48	47	0.205
Myocardial Infarction	46	40	<0.001	38	36	0.139
Percutaneous Coronary Intervention	18	15	<0.001	17	17	0.691
Coronary Artery Bypass Surgery	23	22	0.654	23	24	0.768
Atrial Fibrillation / Flutter	0	59	<0.001	0	45	<0.001
Valve Disease	20	27	<0.001	17	21	<0.001
Device Therapy			<0.001			<0.001
Pacemaker (non-CRT, non-ICD)	2	10		2	7	
CRT + ICD	0.9	1		1	1	
CRT Only	1	1		0.7	2	
ICD Only	3	2		3	2	
Medical History – Non-Cardiovascular						
Stroke or TIA including ICH	15	19	<0.001	10	14	<0.001
Hypertension	57	65	<0.001	55	57	0.107
Diabetes	32	30	<0.001	31	22	<0.001
Renal Dialysis	0.9	0.7	0.479	0.7	0.5	0.276
Lung Disease	31	32	0.114	28	25	0.008
Physical Exam						

Blood Pressure						
Systolic	122 [110 – 140]	125 [110– 140]	0.001	125 [115 – 140]	125 [110 – 140]	0.164
Diastolic	75 [68 – 80]	70 [65 – 80]	<0.001	75 [70 – 80]	70 [65 – 80]	<0.001
MAP	90 [83 – 100]	90 [82 – 100]	0.055	93 [83 – 100]	90 [82 – 100]	<0.001
Heart Rate, bpm	80 [74 – 88]	72 [64 – 84]	<0.001	78 [72 – 85]	67 [60 – 76]	<0.001
Laboratory/Investigations						
LVEF, %			<0.001			<0.001
<30%	61	25		56	27	
30-39%	39	21		44	29	
eGFR	63 [44 – 89]	55 [39 – 78]	<0.001	77 [54 – 103]	68 [49 – 92]	<0.001
Potassium (mEq/L)	4.1 [3.8 – 4.3]	4.1 [3.8 – 4.3]	0.724	4.2 [4.0 – 4.5]	4.2 [4.0 – 4.5]	0.955
NT-proBNP (pg/mL)	5267 [2320 – 10650]	3740 [1700 – 7490]	<0.001	2100 [908 – 4908]	1810 [790 – 3773]	<0.001
Chest X-ray – Cardiomegaly	47	44	0.061	48	47	0.534
Chest X-ray – Pulmonary Congestion	53	49	0.006	42	37	0.004

NYHA: New York Heart Association; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter Defibrillator; TIA: Transient Ischemic Attack; ICH: Intracranial Hemorrhage; BNP: B-Type Natriuretic Peptide; LVEF: Left Ventricular Ejection Fraction; eGFR: Estimated Glomerular Filtration Rate