

Non-Interventional Study (NIS) Protocol

Document Number:	<i><Document number from Document Management System (DMS) for submission documents, if relevant></i>
BI Study Number:	1245-0246
BI Investigational Product(s):	NA
Title:	Prevalence, Incidence and Patient Characteristics of Chronic Heart Failure (CHF) and the Predicted Subtypes HFrEF(<40%), HFpEF(≥40%) in Japan and United States
Brief lay title:	Prevalence, incidence and subtypes of CHF in Japan and US
Protocol version identifier:	Version 1
Date of last version of protocol:	01 February 2021
PASS:	<i>No</i>
EU PAS register number:	<i>NA</i>
Active substance:	<i>NA</i>
Medicinal product:	<i>NA</i>
Product reference:	<i>NA</i>
Procedure number:	<i>If applicable, <Agency or national procedure number(s), e.g. EMA/X/X/XXX></i>
Marketing authorisation holder(s):	<i><Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study></i>
Joint PASS:	<i>No</i>
Research question and objectives:	<i><Summary of the research question and main objectives></i>
Country(-ies) of study:	<i>Japan and United States</i>
Author:	<i>Yasuhisa Ono, M.D. Japan Epidemiology, Nippon Boehringer Ingelheim,</i>

	Shinagawa, Tokyo, Japan yasuhisa.ono@boehringer-ingenlheim.com
Marketing authorisation holder(s):	NA
<i>In case of PASS, add:</i> MAH contact person:	NA
<i>In case of PASS, add:</i> <EU-QPPV:>	NA
<i>In case of PASS, add:</i> <Signature of EU-QPPV:>	NA
Date:	01 February, 2021
Page 1 of 5030	
Proprietary confidential information © 2021 Boehringer Ingelheim Group of companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission	

1. TABLE OF CONTENTS

.....	1
1. TABLE OF CONTENTS	3
2. LIST OF ABBREVIATIONS	5
3. RESPONSIBLE PARTIES	6
4. ABSTRACT	7
5. AMENDMENTS AND UPDATES	1614
6. MILESTONES	1815
7. RATIONALE AND BACKGROUND	1816
8. RESEARCH QUESTION AND OBJECTIVES	2018
9. RESEARCH METHODS	2018
9.1 STUDY DESIGN	2018
9.2 DATA SOURCES	2019
9.3 Study population	21
9.3.1 Claims databases	エラー!ブックマークが定義されていません。 23
9.3.1 EMR databases	エラー!ブックマークが定義されていません。 23
9.4 EXPOSURES AND COVARIATES	23
9.5 KEY OUTCOMES	2426
9.6 MINIMUM SAMPLE SIZE	2426
10. data analysis	2628
10.1 Claims-based HFrEF algorithm	2628
10.2 EMR HFrEF detection	エラー!ブックマークが定義されていません。 30
10.3 Identifying HFrEF in an EMR-Claims linked database	エラー!ブックマークが定義されていません。 30
10.4 analysis of study objectives (post-hfref detection)	エラー!ブックマークが定義されていません。 32
10.4.1 Objective 1: Treatment Patterns and cost among HFrEF patients	エラー!ブックマークが定義されていません。 32
10.4.2 Objective 2: Degree of compliance to guideline-recommended treatment regimen (Pharmacological Therapy for Symptomatic HF due to HFrEF).	エラー!ブックマークが定義されていません。 34
10.4.3 Objective 3: HFrEF population at Index Date	エラー!ブックマークが定義されていません。 41
10.4.3.1 Demographic characteristics	エラー!ブックマークが定義されていません。 42

10.4.3.2 Health status, comorbidities, and concomitant medications [エラー! ブックマークが定義されていません。 43](#)

10.5	Internal Validity for HFrEF algorithm.....	3244
10.6	QUALITY CONTROL	3244
10.7	DATA MANAGEMENT.....	3344
10.8	LIMITATIONS OF THE RESEARCH METHODS.....	3344
11.	PROTECTION OF HUMAN SUBJECTS.....	3347
11.1	STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT	3447
11.2	STATEMENT OF CONFIDENTIALITY	3448
12.	MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	3448
13.	PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	3448
14.	REFERENCES.....	3448
14.1	PUBLISHED REFERENCES.....	3448
	ANNEX 1. LIST OF STAND-ALONE DOCUMENTS.....	3651
	ANNEX 4. commonly performed tests on hfref patients	4665
	ANNEX 5. ENCEPP CHECKLIST FOR STUDY PROTOCOLS	4867
	ANNEX 6. ADDITIONAL INFORMATION.....	4867
	ANNEX 7. REVIEWERS AND APPROVAL SIGNATURES	4968

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CHF	Chronic Heart Failure
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event

Adapt and complete as appropriate

3. RESPONSIBLE PARTIES

Responsibility	Responsible Person, Department, Location
NIS Lead	Yasuhisa Ono, Japan Epidemiology, Tokyo Japan
RWE CoE and Project Statistician	Ling Zhang, RWE CoE, Global Epidemiology, Conn, USA
Global TM Epi	Qing Qiao, Global Epidemiology, CV, Ingelheim, Germany
NIS DM	Ling Zhang, RWD CoE, Global Epidemiolgy, Conn, USA

ABSTRACT

Name of company: Boehringer Ingelheim		NA	
Name of finished medicinal product:			
Name of active ingredient:			
Protocol date: 01 FEB 2021	Study number: 1245-0246	Version/Revision: Version 1	Version/Revision date:
Title of study:	Prevalence, Incidence and Patient Characteristics of Congestive Heart Failure and the Predicted Subtypes HFrEF(<40%), HFpEF(≥40%) in Japan and United States		
Rationale and background:	Congestive heart failure can be defined as inability of the heart to keep up with the demands on it, with failure of the heart to pump blood with normal efficiency. When this occurs, the heart is unable to provide adequate blood flow to other organs, such as the brain, liver, and kidneys. Abbreviated as CHF, CHF can be due to failure of the right or left ventricle, or both. The symptoms can include shortness of breath, asthma due to the heart, pooling of blood (stasis), swelling, cyanosis and enlargement of the heart. CHF can be divided into three categories based on the ejection fraction measured; (1) HF with preserved ejection fraction $\geq 50\%$ (HFpEF), HF with moderately reduced EF of 40-49% (HFmrEF) and (2) HF with reduced ejection fraction <40% (HFrEF).¹ CHF is a major and growing public health problem in the developed countries. In the United States, approximately 6.2 million individuals have HF with prevalence estimates of 2.2% reported in 2016.² Japanese Circulation Society Treatment Guideline 2018 states that there are approximately 1.2 million Japanese CHF patients in Japan.³ However, this figure is based on a study conducted in 2002 reported by Okura et al, captures only the HFrEF population with EF<50%, and evaluating the prevalence of patients who had echo cardiogram results in 15 hospitals located in Niitata City, thus the data is outdated and only reflective of HFrEF population, when prevalence estimates should reflect both HFrEF and HFpEF.⁴ In the US, prevalence estimates do not reflect the most recent data in the past few years, and the methods applied to estimate the prevalence in studies conducted in and US are different with various study population in terms of age distribution, baseline comorbidities, etc. The primary objective of this study is to estimate the prevalence of Japan and US CHF patients using large population based claims and EMR databases. The secondary objectives are to estimate the incidence of CHF patients in Japan and USA; in addition, comparison of CHF patient characteristics and treatment pattern in the two countries will be made. Furthermore, as an exploratory objective, we will estimate the ratio of HFrEF/HFpEF using predictive modeling (Desai et al <i>Circ Cardiovasc Qual Outcomes</i>. 2018) for comparison with previously published ratio using Japanese heart failure registry data (Tsuchihashi-Makana et al, <i>Circ J</i> 2013)		

Research question and objectives:	Primary objective: - To assess the crude, as well as age (≤ 44, 45-64, ≥ 65) and gender standardized prevalence (annual and cross year) of CHF in Japan from January 1, 2014 to November 30, 2019; in United States from January 1, 2014 to December 31, 2019 for US data. Secondary objectives are: - To assess the incidence rate of CHF in Japan from January 1, 2014 to November 30 and in United States from January 1, 2014 to December 31, 2019. - To describe the patient characteristics of incident and prevalent cases of CHF, (age, gender, co-morbidities in the one year look-back period prior to the incident CHF diagnosis) and the current use of CHF medication by type Exploratory objective: - To predict subtype of heart failure (rEF, <0.45 and pEF, >0.45) based Desai's predictive models.
Study design:	Non interventional study (NIS) using existing data.
Population:	The starting population are any patients included in the Japan Medical Data Center, Medical Data Vision or Optum database with any claims record during the period of January 1, 2014 to end of data period. <i>Inclusion criteria:</i> - A code indicating a confirmatory diagnosis of heart failure in JMDC, MDV or Optum database prior to December 31, 2019 - For JMDC and MDV, ICD 10 codes to identify heart failure cases will be: cardiac edema (I50.0), chronic congestive heart failure (I50.0), right heart failure (I50.0), insufficiency of left heart (I50.1), cardiac dyspnea (I50.1), acute cardiac failure (I50.9), cardiac failure (I50.9), chronic cardiac failure (I50.9), cardiogenic pulmonary edema (I50.0), myocardial failure (I50.9), bi-ventricular failure (I50.9), right ventricular failure (I50.0). - For Optum, at least 2 outpatient diagnosis or 1 inpatient diagnosis will be identified as confirmed cases. The following ICD 9-CM codes in addition to ICD 10 codes above) will be used to identify the CHF population of interest. Congestive heart failure: 428.0, 428.1, 428.2, 428.3, 428.4, 428.9, Heart failure with hypertensive heart disease: 402.01, 402.11, 402.91, Heart failure with hypertensive and renal disease: 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 <i>Exclusions:</i> < 18 years at study entry - Patients with missing or ambiguous age or gender information.

Variables:	<i>The identification and definition of exposures, outcomes, and covariates may differ, depending on the type of database used and the variables available.</i> <u>Covariates will include:</u> • Age (years) • Gender (male/female) • Smoking status (never, ex, current, missing) [as determined by all available codes prior to index]. • BMI, proBNP in one year prior to index date (proBNP is expected to be obtained in very few patients) • Prevalent and Current CHF medication usage (diuretic, ACE inhibitor, ARB, sacubitril-valsartan (ENTRESTO), beta-blocker, mineralocorticoid receptor antagonist, digitalis, ivabradine). Current use is defined as having at least one prescription within 12 months after the index date]. Baseline medication of prevalent CHF case will be defined as presence of prescription claim within 6 months preceeding the index diagnosis of Heart failure. The frequency (%) with at least one prescription of each type of medication will be described with 95% confidence interval. • Comorbidid conditions [all defined by ever presence of codes prior to index in JMDC and Optum] ○ Hypertension ○ Hyperlipidemia ○ T2DM ○ T1DM ○ Previous MI (ever and in 3 months prior to index) ○ Previous stroke (ever and in 3 months prior to index) ○ Cardiac procedure (ever and in 3 months prior to index) ○ Other covariates, such as : anemia, maglinant cancer, valvular disease, ischemia heart disease ○ COPD ○ Atrial Fibrillation (AF) ○ CKD (as defined by code indicating CKD (ever) or two consecutive eGFRs < 60 in the year prior to index). • Geographic region if available in Optum As an exploratory analysis, a published algorithm (Desai, 2018) will be used to identify HF patients by subtypes (rEF, <0.40 mEF of 40-50%, and pEF, >0.50). Heart Failure patients with rEF will be identified by • HF-related variables (specific ICD-9 and ICD-10 codes indicating systolic, diastolic, left, rheumatic, hypertensive, or unspecified HF, number of HF hospitalizations, site of recorded HF diagnosis at study entry [inpatient or outpatient], history of implantable cardioverter-defibrillator, cardiac resynchronization therapy, left ventricular assist device), HF-related medication use, and comorbid conditions. The published algorithm had a positive predictive value of 0.73 (95% CI: 0.68-0.78) for rEF. <u>Outcomes:</u> Primary outcome: • To assess the crude, as well as age (≤ 44, 45-64, ≥ 65) and gender standardized prevalence (annual and cross years) of CHF in Japan from January 1, 2014 to December 31, 2019; in United States from January 1, 2014 to December 31, 2019 for US data. Secondary outcomes:
-------------------	--

- | | |
|--|---|
| | <ul style="list-style-type: none">• To assess the incidence rate of CHF in Japan from January 1, 2014 to November 30 and in United States from January 1, 2014 to December 31, 2019.• To describe the patient characteristics of incident and prevalent cases of CHF, (age, gender, co-morbidities in the one year look-back period prior to the incident CHF diagnosis) and the current use of CHF medication by type within 6 months after the incident diagnosis of HF. <p>Exploratory outcome:</p> <ul style="list-style-type: none">• To predict the ratio of subtype of HFrEF, HFmrEF and HFpEF based upon the latest publication of predictive models published by Desai et al. |
|--|---|

Data sources:	<i>Japan Medical Data Center (JMDC)</i> JMDC database is a commercially available claims database in Japan. It is employment insurance based, and collected from over 7 million insured employees and their dependants across Japan. The limitation of the database is that the retired population is not well represented, with less individuals above age 65, and virtually no representation of those above 75 years of age. <i>Medical Data Vision Database (MDV)</i> MDV database contains hospital administrative claims data from more than 25 million uniquely identifiable in- and outpatients treated at more than 300 acute care hospitals within secondary medical care blocs around Japan. These hospitals used the Diagnosis Procedure Combination (DPC) case-mix classification system for inpatient reimbursement claims. The database contains pseudonymous information from health insurance claims for outpatients, administrative data for in- and out-patients, prescriptions, operations and medical procedures, hospitalization and results of laboratory tests from some of the participating hospitals. The age group ≥ 75 is much better represented in MDV at approximately 24% of patients compared to virtually 0% in JMDC, thus, it will be used to estimate the prevalence ≥ 75 in combination with JMDC <i>Optum Database</i> Commercially available claims and electronic medical record (EMR) database in the United States, holding approximately 180 million patients with claims records and 80 million patients with EMR data. Elderly population (age >65) consists of approximately 20% of the entire population, and considered to be well represented. <i>Study period</i> The study period will be from January 1st 2014 to November 30, 2019(JMDC) or December 31, 2019(Optum).
----------------------	---

Study size:

{The following should be crafted for the specific country and database being considered:}

An initial feasibility analysis in JMDC suggests that there were 6.4 million individuals enrolled at least for 1 day between Jan 1st, 2014 to November 31, 2019. Each year, the total number of patients enrolled remain around 3 to 4 million. With the estimated prevalence 1.5%, one sample proportion power analysis indicates the power is above 0.9 for overall population each and every year between the years 2014 to 2019. For the elderly group (age between 70 to 80) in JMDC with higher prevalence (~5%) from feasibility analysis, sample size is around 30,000 per year, and the power is more than 0.9. Similar analyses have been conducted for reference data from 2009 to 2013, the results also show we have sufficient sample size with statistical power of more than 0.9 in our analyses.

For Optum, with even large denominator population as 39.8 million from 2014 to 2019, and around 12 million enrollees each year. When looking at each age group with sample size of at least 1 million and published prevalence as 2.2%, the statistical power is close to 0.99 at overall, annual population.

In JMDC, it is estimated that more than 70,000 HF patients are studied in descriptive analysis. Similarly, in Optum analyses, the estimated HF patients are around 750,000, from 2014 to 2019, which is an adequate sample size to provide accurate information on HF population.

Below, we report the prevalence with confidence interval (CI) estimated in feasibility study.

There were 6,208, 941 enrollees in the JMDC database during the period of Jan 1, 2016 to May 31, 2019. Assuming the prevalence rate ranges from 2/1000 to 14 /1000, the expected prevalence with 95% confidence interval will be:

Population Size	Prevalence per 1000 persons with CHF	95% CI	
		Lower	Upper
6,000,000	2	1.96	2.04
6,000,000	4	3.95	4.05
6,000,000	6	5.94	6.06
6,000,000	8	7.93	8.07
6,000,000	10	9.92	10.00
6,000,000	12	11.91	12.08
6,000,000	14	13.91	14.09

There were 371,721 enrollees in JMDC in 60-70 year old age group during the period between January 2016 and May 2019. Assuming 300,000 enrollees, ranging the prevalence from 10 to 50 per 1000 persons will give the following 95% CI's.

Population Size	Prevalence per 1000 persons with CHF	95% CI	
		Lower	Upper
300,000	10	9.92	10.08
300,000	15	14.90	15.10
300,000	20	19.89	20.11
300,000	25	24.88	25.12
300,000	30	29.86	30.14
300,000	35	34.85	35.15
300,000	40	39.84	40.16

There were 40,326 enrollees in JMDC in the 70-80 year old age group during the period between Jan 2016 to May 2019. Assuming 40,000 enrollees, ranging the prevalence from 50 to 200 per 1000 persons will give the following 95% CI's.	300,000	45	44.83	45.17
	300,000	50	49.83	50.17
	There were 40,326 enrollees in JMDC in the 70-80 year old age group during the period between Jan 2016 to May 2019. Assuming 40,000 enrollees, ranging the prevalence from 50 to 200 per 1000 persons will give the following 95% CI's.			
	<i>Population Size</i>	<i>Prevalence per 1000 persons with CHF</i>	<i>95% CI</i>	
			<i>Lower</i>	<i>Upper</i>
	30,000	50	49.83	50.17
	30,000	75	74.79	75.21
	30,000	100	99.76	100.24
	30,000	125	124.74	125.26
	30,000	150	149.71	150.29
	30,000	175	174.70	175.30
	30,000	200	199.68	200.32
Sample Size of Prevalence Estimates by Optum				
	<i>Population Size</i>	<i>Prevalence per 1000 persons with CHF</i>	<i>95% CI</i>	
			<i>Lower</i>	<i>Upper</i>
	32,000,000	10	9.97	10.03
	32,000,000	15	14.96	15.04
	32,000,000	20	19.95	20.05
	32,000,000	25	24.95	25.05
	32,000,000	30	29.94	30.06
	32,000,000	35	34.94	35.06
	32,000,000	40	39.93	40.07
	32,000,000	45	44.93	45.07
	32,000,000	50	49.92	50.08

Data analysis:	Primary outcome: prevalence - Yearly prevalence over the study period will be calculated as the number of HF patients under follow up on the 30th January each year, divided by the total number of patients under follow up on the December 31st of each year from the JMDC and Optum denominator files. - Prevalance will be presented as a crude measure as well as age and gender standardised to account for any changes in age distrubtion across the study period per 1000 persons with 95% confidence interval. Adjustment for Japanese CHF prevalence using MDV To adjust for the lack of JMDC data ≥ 75 age category, MDV database will be used to calculate the prevalence ratio of ≥ 75 /prevalence ratio 75+/-74, then calculate weighted/predicted prevalence in 75+ in JMDC to borrow the ratio from MDV prevalence ratio 75+/-74, then calculate weighted/predicted prevalence in 75+ in JMDC. For secondary analysis age stratification by using 10-year age bands up to age 99 (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-84, 84-89, 90-99). For JMDC analysis, 75 and above will not be calculated since there are no data in this age group) The standardized prevalence by age group and overall population is obtained by direct standardization method using Japanese and US population census data. Prevalence estimates will be calculated annually and cross-year from January 2009 to December 2013 to show the consistence of published results and prove the validity of primary analysis results based on the 2014 to 2019 estimates. Crude and standardized prevalence will be calculated by the similar method from US Optum data from 2014 to 2019 Sensitivity Analysis using hospital ratio of MDV Prevalence of HF = Total number of Japan HF patients in Japan acute hospitals/ All Japan population; Total number of Japan HF patients in acute hospitals = MDV total HF patients/ the weight of (MDV hospitals/total Japan acute hospitals) -> Total number of HF patients in Japan acute hospital The progressively increasing MDV representation of all DPC acute hospital beds in Japan (from 15.91% in 2015 to 28.88% in 2019). <table><tr><th>Year</th><th>MDV</th><th>DPC</th><th>Percentage in DPC</th><th>General hospital beds in Japan</th><th>Percentage in Total</th></tr><tr><td>2015</td><td>77019</td><td>484081</td><td>15.91%</td><td></td><td></td></tr><tr><td>2016</td><td>99 952</td><td>495227</td><td>20 .18%</td><td></td><td></td></tr><tr><td>2017</td><td>115553</td><td>483747</td><td>23 .89%</td><td></td><td></td></tr><tr><td>2018</td><td>133572</td><td>488563</td><td>27.34%</td><td>890712</td><td>15.00%</td></tr><tr><td>2019</td><td>139307</td><td>482361</td><td>28.88%</td><td></td><td></td></tr><tr><td>General</td><td></td><td></td><td></td><td>887468</td><td></td></tr></table>						Year	MDV	DPC	Percentage in DPC	General hospital beds in Japan	Percentage in Total	2015	77019	484081	15.91%			2016	99 952	495227	20 .18%			2017	115553	483747	23 .89%			2018	133572	488563	27.34%	890712	15.00%	2019	139307	482361	28.88%			General				887468	
	Year	MDV	DPC	Percentage in DPC	General hospital beds in Japan	Percentage in Total																																										
	2015	77019	484081	15.91%																																												
	2016	99 952	495227	20 .18%																																												
	2017	115553	483747	23 .89%																																												
	2018	133572	488563	27.34%	890712	15.00%																																										
	2019	139307	482361	28.88%																																												
	General				887468																																											
	Secondary outcome: incidence HF incidence (rate) will be defined as the number of incident cases observed during follow up divided by the total number of person years of follow up in the study period as obtained from the JMDC and Optum patient registry files. The estimates will be presented in per 1000 patient –year of follow-up with its 95% confidence interval. Exploratory outcome: Predicted HFrEF(EF<45) or HFpEF and HFmrEF(EF>40%) cases in HF cohort																																															

	HF subtype definition is always a challenge topic, considering cardiovascular test measure results (ejection fraction or echo diagrams) are difficult to collect in most of sedentary data, especially claims databases. In 2018, one predictive modelling publication by Rishi J. Desai provided a potential method to predict HF subtypes by using Medicare linked EMR data. Based on the US claims data, positive predictive value (PPV) for rEF was 73% while the PPV for pEF was 84%. In their most efficient predictive model for HFrEF (EF<45%) vs. HFpEF (≥45%), 35 baseline covariates were included in the multivariate binary analysis. The model performance C-statistics was 0.86. The maximum accuracy was 0.83, with the cut-off at probability of 0.4678. The baseline co-variables included in the model were: age, gender, systolic HF diagnosis (dx), diastolic HF dx, left HF unspecified dx, index dx during outpatient visit, # of hospitalization of HF, implantable cardio-defibrillator, ACE inhibitor, mineralocorticoid receptor antagonist, beta blocker, digoxin, loop diuretics, nitrates, thiazide diuretics, atrial fibrillation dx, anemia dx, coronary artery bypass graft, cardiomyopathy dx, COPD dx, depression hypertensive nephropathy dx, hyper-lipidemia dx, hypertension dx, MI dx, obesity dx, other dysrhythmias dx, psychosis dx, rheumatic heart disease dx, sleep apnea dx, heart valvular disorder.
--	---

Limitations:	Limitations: 1. Lack of data above age 75 in JMDC will lead to under-estimation of the incidence and prevalence estimates since age is highly correlated with CHF occurrence. 2. Incidence and Prevalence estimates may be imprecise due to mis-classification of CHF diagnosis due to choice of ICD 9, 10 codes to define the disease. 3. Generalizability of the results may be compromised by selection bias of population under study in the database 4. With the limited data, the HF subtypes have been attempted defined based on the predictive model results. The predicted cases can't be further verified because of lacking of EF data. Desai's predictive model has satisfactory PPV and sensitivity only for pEF cases, thus reliability for rEF cases is considered to be limited. 5. Direct comparison of the population identified as HFrEF/pEF subtypes have different EF cut offs (40% vs. 45%) and needs caution in interpretation. 6. Misclassification bias of pEF and rEF using the predictive modeling by Desai. The reported PPV of rEF was 73% and pEF was 84% with higher reliability for pEF, but rEF prediction is only fair. Sensitivity for rEF identification of the model was low (29%), most likely leaving many false negative cases. In general; {Claims} data are generated for billing purposes and may not be representative, may have misclassification of important outcomes, or in defining population, and may misclassify certain exposures. Algorithms validated for HFrEF may misclassify some patients but sensitivity analyses can be done to assess those effects. Laboratory values may not be available within. Coding conventions may also be inconsistent across the same claims database. {EHR} can rely heavily on physician notes, which may result in misinterpretations or misclassifications. Fields may be reported inaccurately. Details from prescription and procedure notes may also be inconsistent across the same administrative levels (within systems). Generic medications may be paid for out of pocket and not appear in either database. Analyses assessing 'Compliance' to treatment guidelines may be flawed because of comorbidities or other medications of patients, especially those unavailable in database which the clinician is aware of.
Milestones:	Data Collection Start: 3Q 2020 Data Collection End: 4Q 2020 Ethics Committee Approval: 4Q 2020 Interim results: 1Q 2021 Study report: 3Q 2021 Manuscript Submission 4Q 2021

5. AMENDMENTS AND UPDATES

Write <None> or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.

Number	Date	Section of study protocol	Amendment or update	Reason
1	<DD Month YYYY>	<Text>	<Text>	<Text>
2	<DD Month YYYY>	<Text>	<Text>	<Text>
<n>	<DD Month YYYY>	<Text>	<Text>	<Text>

6. MILESTONES

Planned dates for study milestones should be indicated in a table as indicated below. Milestones between <> are optional and should be included only if applicable. Start of data collection and End of data collection are defined in Module VIII of the Good Pharmacovigilance Practices (GVP); where the study uses data from existing electronic databases such as claims, prescriptions or health care records, “secondary use of data” applies to these definitions. Other important timelines can be added.

Milestone	Planned Date
IRB/IEC approval	December 18, 2020
Start of data collection	September 1 st , 2020
End of data collection	November 31 st , 2020
<Interim report 1>	April 30 th , 2021
<Registration in the EU PAS register>	March, 2021
Final report of study results:	November, 2021

7. RATIONALE AND BACKGROUND

Congestive heart failure can be defined as inability of the heart to keep up with the demands on it, with failure of the heart to pump blood with normal efficiency. When this occurs, the heart is unable to provide adequate blood flow to other organs, such as the brain, liver, and kidneys. Abbreviated as CHF, CHF can be due to failure of the right or left ventricle, or both. The symptoms can include shortness of breath, asthma due to the heart, pooling of blood (stasis), swelling, cyanosis and enlargement of the heart. CHF can be divided into three categories based on the ejection fraction measured; (1) HF with preserved ejection fraction $\geq 50\%$ (HFpEF), HF with moderately reduced EF of 40-49% (HFmrEF) and (2) HF with reduced ejection fraction $<40\%$ (HFrEF).¹

CHF is a major and growing public health problem in the developed countries. In the United States, approximately 6.2 million individuals have HF with prevalence estimates of 2.2% reported in 2016.² Japanese Circulation Society Treatment Guideline 2018 states that there are approximately 1.2 million Japanese CHF patients in Japan.³ However, this figure is based on a study conducted in 2002 reported by Okura et al, captures only the HFrEF population with EF $<50\%$, and evaluating the prevalence of patients who had echo cardiogram results in 15 hospitals located in Niitata City, thus the data is outdated and only reflective of HFrEF population, when prevalence estimates should reflect both HFrEF and HFpEF.⁵ In the US, prevalence estimates do not reflect the most recent data in the past few years, and the methods applied to estimate the prevalence in studies conducted in Japan and US are different with various study population in terms of age distribution, baseline comorbidities, etc. Additionally, there have been several studies comparing the patient characteristics between

Japan and Western countries which report lower prevalence of ischemic heart disease, obesity and COPD among Japanese heart failure patients (Sato et al, Attend Registry, *Circ J* 2013, Abraham et al, Optimize HF Registry, *J of Am Col Cardiology* 2008).

The primary objective of this study is to estimate the prevalence of Japan and US CHF patients using the same methodology using large population based claims and EMR databases accumulated in the two countries. The secondary objective is to compare the characteristics of heart failure population and treatment pattern of Japan and USA.

Heart Failure with Reduced Ejection Fraction and Preserved Ejection Fraction (HFrEF, HFpEF)

In 2018, Desai developed an algorithm to classify HFrEF patients into EF classes using predictors that were derived from linear and logistic regression models with the least absolute squares shrinkage operator and Bayesian information criteria to select relevant predictor variables. In the testing sample, the most efficient model resulted in 83% of patients being correctly classified (95% CI: 82%-84%) with a positive predictive value of 0.73 (95% CI: 0.68 – 0.78) and 0.84 (95% CI: 0.83 – 0.86) for reduced and preserved EF, respectively. There has been no publication to apply this algorithm using a Japanese claims data to date. An exploratory objective of this study will be to assess the ratio of HFrEF to HFpEF using a Japanese claims data to see if they would be similar to previously published data from Japanese heart failure registries such as J-CARE (Tsuchihata-Makaya et al, *Circ J* 2009).

8. RESEARCH QUESTION AND OBJECTIVES

This protocol represents the course of action that would generally be taken to identify CHF population from administrative claims in Japan and USA.

Primary objective:

- To assess the crude, age (≤ 44 , 45-64, ≥ 65) and gender stratified prevalence (annual and cross year) of CHF in Japan from January 1, 2014 to November 30, 2019; in United States from January 1, 2014 to December 31, 2019 for US data.

Secondary objectives are:

- To assess the incidence rate of CHF in Japan from January 1, 2014 to November 30 and in United States from January 1, 2014 to December 31, 2019.
- To describe the patient characteristics of incident and prevalent cases of CHF, (age, gender, co-morbidities in the one year look-back period prior to the incident CHF diagnosis) and the current use of CHF medication by type

Exploratory objective:

- To predict subtype of heart failure (rEF, <0.45 and pEF, >0.45) based Desai's predictive models

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, cohort study using existing data from either Japan or US administrative claims data sources (MDV, JMDC) or linked EMR/claims sources (Optum). The study implements an algorithmic approach within claims data sources to first identify prevalent and incident CHF population, then probabilistically identify HFrEF, mEF, pEF through the examination of variables that are typically populated within a claims data structure, using a published predictive algorithm by Desai et al.

9.2 DATA SOURCES

The study will utilize administrative claims to characterize eligible patients with CHF. The study will include all records related to inpatient and outpatient diagnosis, procedures, prescriptions and fees associated with diagnosis and procedure claims to address the research questions.

Study Period (time window)

The study period will be set from January 1st, 2014 and December 31st, 2019.

Data sources

Individual subsections in Section 10 of this document describe how to detect CHF in claims of MDV and JMDC and linked claims/EMR databases in Optum.

Japan Medical Data Center (JMDC)

JMDC database is a commercially available claims database in Japan. It is employment insurance based, and collected from over 7 million insured employees and their dependants across Japan. The limitation of the database is that the retired population is not well represented, with less individuals above age 65, and virtually no representation of those above 75 years of age.

Medical Data Vision Database (MDV)

MDV database contains hospital administrative claims data from more than 25 million uniquely identifiable in- and outpatients treated at more than 300 acute care hospitals within secondary medical care blocs around Japan. These hospitals used the Diagnosis Procedure Combination (DPC) case-mix classification system for inpatient reimbursement claims. The database contains pseudonymous information from health insurance claims for outpatients, administrative data for in- and out-patients, prescriptions, operations and medical procedures, hospitalization and results of laboratory tests from some of the participating hospitals. The age group ≥ 75 is much better represented in MDV at approximately 24% of patients compared to virtually 0% in JMDC, thus, it will be used to estimate the prevalence ≥ 75 in combination with JMDC

Optum Database

Commercially available claims and electronic medical record (EMR) database in the United States, holding approximately 180 million patients with claims records and 80 million patients with EMR data. Elderly population (age >65) consists of approximately 20% of the entire population, and considered to be well represented.

9.3 STUDY POPULATION

The population will include all known heart failure patients within the available data sets from 2014 – 2019. The starting population are any patients included in the Japan Medical Data Center, Medical Data Vision or Optum database with any claims record or insurance registration record during the period of January 1, 2014 to end of data period.

Prevalent CHF cases will be first identified, then incident cases based on identification of those without CHF diagnosis in the preceding 12 months to identify the numerator population in the prevalence and incidence calculation. The denominator in each calculation will be the population with at least one claims or one day insurance registration period during the year or period for which the prevalence and incident calculation will be made.

Inclusion criteria – Prevalent CHF case:

- A code indicating a confirmatory diagnosis of heart failure in JMDC, MDV or Optum database prior to December 31, 2019
- For JMDC and MDV, ICD 10 codes to identify heart failure cases will be: cardiac edema (I50.0), chronic congestive heart failure (I50.0), right heart failure (I50.0), insufficiency of left heart (I50.1), cardiac dyspnea (I50.1), acute cardiac failure (I50.9), cardiac failure (I50.9), chronic cardiac failure (I50.9), cardiogenic pulmonary

edema (I50.0), myocardial failure (I50.9), bi-ventricular failure (I50.9), right ventricular failure (I50.0).

- For Optum, at least 2 outpatient diagnosis or 1 inpatient diagnosis will be identified as confirmed cases. The following ICD 9-CM codes in addition to ICD 10 codes above) will be used to identify the CHF population of interest. Congestive heart failure: 428.0, 428.1, 428.2, 428.3, 428.4, 428.9, Heart failure with hypertensive heart disease: 402.01, 402.11, 402.91, Heart failure with hypertensive and renal disease: 404.01, 404.03, 404.11, 404.13, 404.91, 404.93

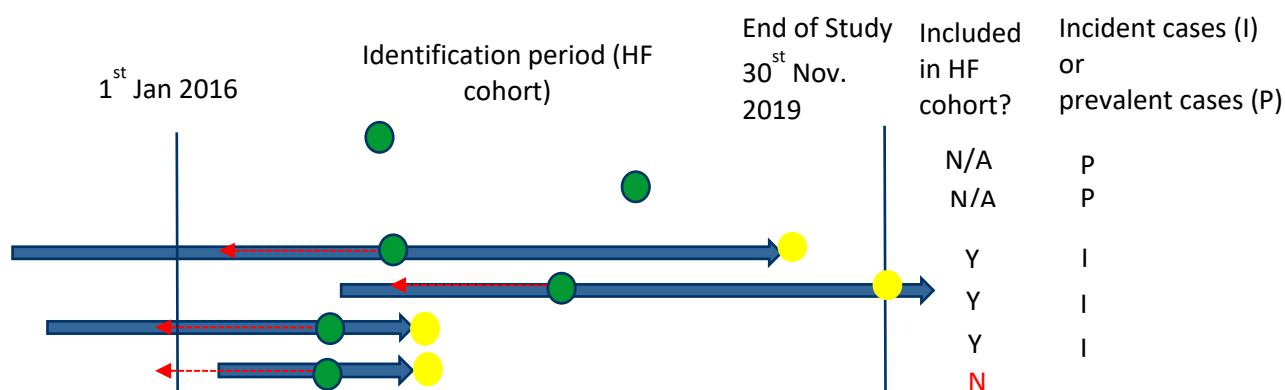
Inclusion criteria – Incident CHF case:

All above codes to identify CHF population will be used for JMDC, MDV and Optum; an incident case will be defined as having no diagnosis of CHF in the preceding 12 months of new CHF diagnosis. Thus, a patient must have at least 12 months of insurance registration data prior to the initial diagnosis date of CHF.

Exclusions:

- < 18 years at study entry
- Patients with missing or ambiguous age or gender information
- Patients with diagnosis code with doubt flag (suspect diagnosis)

Diagram: HF Prevalent or Incident cases in JMDC
HF cohort (for characterization study) only includes incident HF cases



● Index date: The first HF diagnosis date
 Exploratory objective: HFrEF and HFpEF population
 ← 1 year look back Follow-up End → Registration period in JMDC

A published algorithm (Desai, 2018) will be used to identify HF patients by subtypes (reduced (<0.40), moderately reduced (0.40-0.49), or preserved (≥0.50). Classifications into each HF subtype will be validated if possible, through comparisons to EMR-linked claims

records in Optum. Furthermore, the ratio will be compared with the previously published ratio from Japanese and US CHF registries for external validity (J-CARE, etc.).

9.4 COVARIATES

Covariates will include:

- **Age (years)**
- **Gender** (male/female)
- **Smoking status** (never, ex, current, missing) [as determined by all available codes prior to index].
- **BMI, proBNP** in one year prior to index date (proBNP is expected to be obtained in very few patients)
- **Previous (6 months prior to incident diagnosis) and Current CHF medication (6 months after incident diagnosis) usage** (diuretic, ACE inhibitor, ARB, sacubitril-valsartan (ENTRESTO), beta-blocker, mineralocorticoid receptor antagonist, digitalis, ivabradine). Current use is defined as having at least one prescription within 12 months after the index date]. Baseline medication of prevalent CHF case will be defined as presence of prescription claim within 6 months preceding the index diagnosis of Heart failure. The frequency (%) with at least one prescription of each type of medication will be described with 95% confidence interval.
- **Comorbid conditions** [all defined by ever presence of codes prior to index in JMDC and Optum]
 - Hypertension
 - Hyperlipidemia
 - T2DM
 - T1DM
 - Previous MI (ever and in 3 months prior to index)
 - Previous stroke (ever and in 3 months prior to index)
 - Cardiac procedure (ever and in 3 months prior to index)
 - Other covariates, such as : anemia, malignant cancer, valvular disease, ischemia heart disease
 - COPD
 - Atrial Fibrillation (AF)
 - CKD (as defined by code indicating CKD (ever) or two consecutive eGFRs < 60 in the year prior to index).
- Geographic region if available in Optum
- Heart Failure Severity (NYHA classification)
- Auxiliary covariates

Characteristic	Coding system		
	ICD-9	ICD-10	HCPCS/NDC
Heart failure type			
Right-sided	428.9	I50.810	
Left-sided	428.1	I50.1	
Biventricular	428.9	I50.82	
Congestive	428.0, 428.20, 428.21, 428.22, 428.23, 428.30, 428.42, 428.43	I50.20, I50.21, I50.22, I50.23, I50.30, I50.42, I50.43, I50.9	
Comorbidities (from Charlson Index)			
History of MI	412	I25.2	
History of Stroke	V12.54	Z86.73	
Chronic Kidney Disease	585.xx	N18.xx	
Hypertension	401-405	I10, I11.9, I12.0, I12.9, I13.0, I13.11, I13.2, I15.0, I15.8	
Type 2 diabetes	250	E11	
Insulin prescriptions	V58.67 (long-term/current)	Z79.4 (long-term/current)	J1815, J1817, 00002850101 (NDC)
Stage D Heart Failure		I50.84	

9.5 KEY OUTCOMES

The key study outcomes are as follows:

Primary outcome:

- To assess the crude, age (≤ 44 , 45-64, ≥ 65) and gender stratified prevalence (annual and cross year) of CHF in Japan from January 1, 2014 to December 31, 2019; in United States from January 1, 2014 to December 31, 2019 for US data.

Secondary outcomes:

- To assess the incidence rate of CHF in Japan from January 1, 2014 to November 30 and in United States from January 1, 2014 to December 31, 2019.
- To describe the patient characteristics of incident and prevalent cases of CHF, (age, gender, co-morbidities in the one year look-back period prior to the incident CHF diagnosis) and the current use of CHF medication by type

Exploratory outcome:

- To predict the ratio of subtype of HFrEF, HFmrEF and HFpEF based upon the latest publication of predictive models published by Desai et al.

All definitions, methodologies, and calculations pertaining to key outcomes and metrics will be described in the appropriate sections below.

9.6 MINIMUM SAMPLE SIZE

An initial feasibility analysis in JMDC suggests that there were 6.4 million individuals enrolled at least for 1 day between Jan 1st, 2014 to November 31, 2019. Each year, the total number of patients enrolled remain around 3 to 4 million. With the estimated prevalence

1.5%, one sample proportion power analysis indicates the power is above 0.9 for overall population each and every year between the years 2014 to 2019. For the elderly group (age between 70 to 80) in JMDC with higher prevalence (~5%) from feasibility analysis, sample size is around 30,000 per year, and the power is more than 0.9. Similar analyses have been conducted for reference data from 2009 to 2013, the results also show we have sufficient sample size with statistical power of more than 0.9 in our analyses.

For Optum, with even large denominator population as 39.8 million from 2014 to 2019, and around 12 million enrollees each year. When looking at each age group with sample size of at least 1 million and published prevalence as 2.2%, the statistical power is close to 0.99 at overall, annual population.

In JMDC, it is estimated that more than 70,000 HF patients are studied in descriptive analysis. Similarly, in Optum analyses, the estimated HF patients are around 750,000, from 2014 to 2019, which is an adequate sample size to provide accurate information on HF population.

Below, we report the prevalence with confidence interval (CI) estimated in feasibility study.

There were 6,208, 941 enrollees in the JMDC database during the period of Jan 1, 2016 to May 31, 2019. Assuming the prevalence rate ranges from 2/1000 to 14 /1000, the expected prevalence with 95% confidence interval will be:

<i>Population Size</i>	<i>Prevalence per 1000 persons with CHF</i>	<i>95% CI</i>	
		<i>Lower</i>	<i>Upper</i>
6,000,000	2	1.96	2.04
6,000,000	4	3.95	4.05
6,000,000	6	5.94	6.06
6,000,000	8	7.93	8.07
6,000,000	10	9.92	10.00
6,000,000	12	11.91	12.08
6,000,000	14	13.91	14.09

There were 371,721 enrollees in JMDC in 60-70 year old age group during the period between January 2016 and May 2019. Assuming 300,000 enrollees, ranging the prevalence from 10 to 50 per 1000 persons will give the following 95% CI's.

<i>Population Size</i>	<i>Prevalence per 1000 persons with CHF</i>	<i>95% CI</i>	
		<i>Lower</i>	<i>Upper</i>
300,000	10	9.92	10.08
300,000	15	14.90	15.10
300,000	20	19.89	20.11
300,000	25	24.88	25.12
300,000	30	29.86	30.14
300,000	35	34.85	35.15

300,000	40	39.84	40.16
300,000	45	44.83	45.17
300,000	50	49.83	50.17

There were 40,326 enrollees in JMDC in the 70-80 year old age group during the period between Jan 2016 to May 2019. Assuming 40,000 enrollees, ranging the prevalence from 50 to 200 per 1000 persons will give the following 95% CI's.

Population Size	Prevalence per 1000 persons with CHF	95% CI	
		Lower	Upper
30,000	50	49.83	50.17
30,000	75	74.79	75.21
30,000	100	99.76	100.24
30,000	125	124.74	125.26
30,000	150	149.71	150.29
30,000	175	174.70	175.30
30,000	200	199.68	200.32

Sample Size of Prevalence Estimates by Optum

Population Size	Prevalence per 1000 persons with CHF	95% CI	
		Lower	Upper
32,000,000	10	9.97	10.03
32,000,000	15	14.96	15.04
32,000,000	20	19.95	20.05
32,000,000	25	24.95	25.05
32,000,000	30	29.94	30.06
32,000,000	35	34.94	35.06
32,000,000	40	39.93	40.07
32,000,000	45	44.93	45.07
32,000,000	50	49.92	50.08

10. DATA ANALYSIS

10.1 CLAIMS-BASED CHF PREVALENCE

Primary outcome: prevalence

- Yearly prevalence over the study period will be calculated as the number of HF patients under follow up on the 30th January each year, divided by the total number of

patients under follow up on the December 31st of each year from the JMDC and Optum denominator files.

- Prevalence will be presented as a crude measure as well as age and gender standardised to account for any changes in age distribution across the study period per 1000 persons with 95% confidence interval.

Adjustment for Japanese CHF prevalence using MDV

To adjust for the lack of JMDC data ≥ 75 age category, MDV database will be used to calculate the prevalence ratio of ≥ 75 /prevalence ratio 75+/0-74, then calculate weighted/predicted prevalence in 75+ in JMDC to borrow the ratio from MDV prevalence ratio 75+/0-74, then calculate weighted/predicted prevalence in 75+ in JMDC. For secondary analysis age stratification by using 10-year age bands up to age 99 (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-84, 84-89, 90-99). For JMDC analysis, 75 and above will not be calculated since there are no data in this age group) The standardized prevalence by age group and overall population is obtained by direct standardization method using Japanese and US population census data as described below.

Prevalence estimates will be calculated annually and cross-year from January 2009 to December 2013 to show the consistence of published results and prove the validity of primary analysis results based on the 2014 to 2019 estimates. Crude and standardized prevalence will be calculated by the similar method from US Optum data from 2014 to 2019

Age and Sex Standardization based on Census Data in Japan/USA

Age and sex stratified prevalence data for each country will be adjusted to the most recent census data available to estimate the total number of prevalent patients in Japan, USA and UK.

Japanese age and sex stratified census data will be obtained from the Census Bureau of Statistics data available for 2015 and 2018 (table 2-5: population by age excel file)

<http://www.stat.go.jp/english/data/nenkan/69nenkan/1431-02.html>

The US age and sex stratified data will be obtained from the US Census Bureau data for 2018

<https://www.census.gov/data/tables/2018/demo/age-and-sex/2018-age-sex-composition.html>

Sensitivity Analysis using hospital ratio of MDV

Prevalence of HF = Total number of Japan HF patients in Japan **acute** hospitals/ All Japan population;

Total number of Japan HF patients in acute hospitals = MDV total HF patients/ the weight of (MDV hospitals/total Japan acute hospitals) -> Total number of HF patients in Japan **acute** hospital

The progressively increasing MDV representation of all DPC acute hospital beds in Japan (from 15.91% in 2015 to 28.88% in 2019).

Year	MDV	DPC	Percentage in DPC	General hospital beds in Japan	Percentage in Total
2015	77019	484081	15.91%		
2016	99 952	495227	20.18%		
2017	115553	483747	23.89%		
2018	133572	488563	27.34%	890712	15.00%
2019	139307	482361	28.88%		
General				887468	

Secondary outcome 1: incidence

HF incidence (rate) will be defined as the number of incident cases observed during follow up divided by the total number of person years of follow up in the study period as obtained from the JMDC and Optum patient registry files. The estimates will be presented in per 1000 patient –year of follow-up with its 95% confidence interval.

Secondary outcome 2: treatment pattern and patient characteristics

HF incident cases will be identified as above for descriptive analysis on their age, gender, BMI, smoking status, etc. (co-variables listed in previous section). Categorical variables will be described with number and proportion (%). Continuous variables will be described in means, median and 95% confidence interval. Treatment pattern will be described as previous medication usage in the 6 months period prior to incident HF diagnosis date, as well as the current medication usage in the 6 months period after the incident HF diagnosis date. The number and percentage of those with use of classes of medication identified as co-variables in the previous section in each time period will be shown in a tabulated format.

Medication classes (including, but not limited to): Beta blockers, ACE inhibitors, Angiotensin receptor blockers, Combination medications (e.g. Entresto – sacubitril/valsartan), Aldosterone antagonists, Digoxin, Hydralazine and nitrates, Diuretics, Farxiga (dapagliflozin)

Exploratory outcome: Predicted HFrEF (EF<45%) or HFpEF and HFmrEF (EF>40%) cases in HF cohort

HF subtype definition is always a challenge topic, considering cardiovascular test measure results (ejection fraction or echo diagrams) are difficult to collect in most of sedentary data, especially claims databases.

In 2018, one predictive modelling publication by Rishi J. Desai provided a potential method to predict HF subtypes by using Medicare linked EMR data. Based on the US claims data, positive predictive value (PPV) for rEF was 73% while the PPV for pEF was 84%. In their most efficient predictive model for HFrEF (EF<45%) vs. HFpEF (>=45%), 35 baseline covariates were included in the multivariate binary analysis. The model performance C-statistics was 0.86. The maximum accuracy was 0.83, with the cut-off at probability of 0.4678. The baseline co-variables included in the model were: age, gender, systolic HF diagnosis (dx), diastolic HF dx, left HF unspecified dx, index dx during outpatient visit, # of hospitalization of HF, implantable cardio-defibrillator, ACE inhibitor, mineralocorticoid

receptor antagonist, beta blocker, digoxin, loop diuretics, nitrates, thiazide diuretics, atrial fibrillation dx, anemia dx, coronary artery bypass graft, cardiomyopathy dx, COPD dx, depression hypertensive nephropathy dx, hyper-lipidemia dx, hypertension dx, MI dx, obesity dx, other dysrhythmias dx, psychosis dx, rheumatic heart disease dx, sleep apnea dx, heart valvular disorder.

Table 1 – Prediction thresholds for maximizing overall accuracy or sensitivity + specificity in Swedish Registry study

	Maximize accuracy	Maximize sensitivity + specificity
EF ≥40%: Simple model[§]		
Threshold	0.51	0.44
Overall accuracy	65.50%	63.20%
Sensitivity (accurate HFpEF + HFmrEF prediction)	50.20%	38.20%
Specificity (accurate HFrEF prediction)	77.60%	83.10%
§ = model with demographics, comorbidities and treatments (i.e. excluding NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR)		

Table 2 - Simplified logistic model (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) for EF ≥40%

	OR (95% CI)	p-value
Intercept	1.44 (1.31; 1.59)	< 0.001
Age (> 75 years vs. < 75 years)	1.32 (1.26; 1.38)	< 0.001
Sex (Female vs. Male)	1.99 (1.91; 2.08)	< 0.001
Ischemic heart disease (Yes vs. No)	0.78 (0.75; 0.81)	< 0.001
Anemia (Yes vs. No)	1.23 (1.17; 1.28)	< 0.001
Atrial fibrillation (Yes vs. No)	1.52 (1.45; 1.59)	< 0.001
COPD (Yes vs. No)	1.23 (1.16; 1.30)	< 0.001
Diabetes (Yes vs. No)	1.06 (1.01; 1.12)	0.015
Hypertension (Yes vs. No)	1.70 (1.62; 1.77)	< 0.001
Valvular disease (Yes vs. No)	1.13 (1.08; 1.19)	< 0.001
Malignant cancer (Yes vs. No)	1.09 (1.02; 1.16)	0.007

Device therapy (Yes vs. No)	0.34 (0.30; 0.39)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.46 (0.43; 0.49)	< 0.001
Beta-blocker use (Yes vs. No)	0.55 (0.52; 0.59)	< 0.001
MRA use (Yes vs. No)	0.69 (0.66; 0.72)	< 0.001
Digoxin use (Yes vs. No)	0.82 (0.78; 0.87)	< 0.001
Diuretic use (Yes vs. No)	0.74 (0.70; 0.78)	< 0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist

In our study, after collecting all needed baseline comorbidities in HF cohort by Japan or US claims data, the probability of HFrEF and HFpEF will be calculated by using the simplified predictive model estimates in Alicia Uijl's study.

While there are no HF subtype predictive studies published with Japanese databases, the same method will be used in both Japan and US.

10.2 SENSITIVITY ANALYSIS: HOSPITALIZED HF PREVALENCE BASED ON MDV HOSPITAL BEDS VS. ALL JAPANESE ACUTE HOSPITAL BEDS

MDV provides the number of DPC hospitals the company from which it collects its DPC claims data. MDV also has provided the number of total beds at the contracting DPC hospitals. Using these numbers, one can calculate the estimated number of HF patients hospitalized or being treated as an in- or out-patient. Several assumptions are made here. First, for hospitalized patients, most will occupy a bed at an acute DPC hospital, thus the ratio of acute hospitals contained in MDV to the total number of DPC acute hospitals in Japan roughly correlates with the HF patients admitted to MDV hospitals to the entire Japanese HF hospitalization. This assumption will also be tested using the ratio of total number of hospital beds in MDV and total number of hospital beds in Japan.

Calculation of Prevalence of hospitalized HF = Total number of hospitalized HF patients in Japan in acute DPC hospitals/ All Japan population;

Method 1 (using acute DPC hospital bed representation of MDV)

Total number of Japan HF patients in acute hospitals = MDV total HF patients/ the weight of (MDV hospitals/total Japan acute hospitals) -> Total number of HF patients in Japan **acute** hospitals

Method 2 (using DPC hospital beds represented in MDV) Prevalence

Total number of Japanese HF patients in Japan = MDV total HF patients/ the weight of MDV hospital beds vs. all DPC hospital beds in Japan.

There are three assumptions to get approximate hospitalized HF patients count in Japan

1. Most, if not all, HF patients will go to acute hospitals for initial diagnosis and treatment->All Japan acute hospital data captures all HF data
2. The proportion of beds in MDV/Number of Japan total beds the proportion of patients in MDV/Number of Japan total HF patients
3. HF patients have same probability to use any MDV hospital beds as the probability to use any hospital beds in Japan acute hospitals-> the proportion of HF patients in MDV hospital stays same as in Japan acute hospitals;

The progressively increasing MDV representation of all DPC acute hospital beds in Japan (from 15.91% in 2015 to 28.88% in 2019).

Year	MDV	DPC	Percentage in DPC	General hospital beds in Japan	Percentage in Total

2015	77019	484081	15.91%		
2016	99 952	495227	20.18%		
2017	115553	483747	23.89%		
2018	133572	488563	27.34%	890712	15.00%
2019	139307	482361	28.88%		
General				887468	

If only EMR data are available, HFrEF should be determined by the following hierarchy: 1) If EF is directly available as a quantitative variable (either continuous or categorical), HFrEF should be defined using that variable, 2) alternatively, if HFrEF is only available through physicians' notes, natural language processing (NLP) of the notes fields could be used to either identify the ejection fraction itself or at least identify keywords that are indicative of the presence of HFrEF.

If the EMR contains sufficient variables to execute the algorithm described in this document, then the algorithm should be executed and HFrEF cases should be validated against HFrEF patients as identified through the natural language processing we just described. The performance of both processes (algorithmic selection and natural language processing) in an EMR database is preferred especially if the notes sections do not identify the patient's ejection fraction for all patients.

Predictors of rEF may include, but are not limited to: age, sex, medications used, comorbidities (e.g. MI and valve disorders) [Zhang 2017]. All patients who are categorized by the Desai algorithm as having rEF will be classified as such for the purposes of capturing treatment patterns among rEF patients.

10.3 EXTERNAL VALIDITY FOR HFrEF ALGORITHM

To assess external validity of predictive algorithm by Desai et al, the calculated ratio of HFrEF, HFmEF and HFpEF results using JMDC, MDV and Optum will be compared against previously published HF registries from Japan and USA.

10.4 QUALITY CONTROL

Results of programmed algorithm and subsequent descriptive statistical analysis may be reviewed according to quality assurance protocols in place within the team/units/countries in which an analysis takes place. An appropriate senior reviewer would likely provide final approval for any pertinent deliverables.

10.5 DATA MANAGEMENT

Data management arrangements are dependent on the country and location in which this protocol is applied. Any personnel whose intention it is to apply this protocol should understand local regulations and how the data are collected and coded before undertaking an analysis/implementation of the methods found herein.

Data use and management may be further governed through an agreement by the data provider (e.g. IBM, Optum, CMS, CPRD).

10.6 LIMITATIONS OF THE RESEARCH METHODS

1. Lack of data above age 75 in JMDC will lead to under-estimation of the incidence and prevalence estimates since age is highly correlated with CHF occurrence.
2. Incidence and Prevalence estimates may be imprecise due to mis-classification of CHF diagnosis due to choice of ICD 9, 10 codes to define the disease.
3. Generalizability of the results may be compromised by selection bias of population under study in the database
4. With the limited data, the HF subtypes have been attempted defined based on the predictive model results. The predicted cases can't be further verified because of lacking of EF data. Desai's predictive model has satisfactory PPV and sensitivity only for pEF cases, thus reliability for rEF cases is considered to be limited.
5. Direct comparison of the population identified as HFrEF/pEF subtypes have different EF cut offs (40% vs. 45%) and needs caution in interpretation.
6. Misclassification bias of pEF and rEF using the predictive modeling by Desai. The reported PPV of rEF was 73% and pEF was 84% with higher reliability for pEF, but rEF prediction is only fair. Sensitivity for rEF identification of the model was low (29%), most likely leaving many false negative cases.
7.]Claims-based data are generated for billing purposes, not for research. These databases often provide large sample sizes that can be tracked over extended periods of time. They rely on professional ICD coding, which can be subject to coding errors (including upcoding and coding due to screening for conditions) as well as missed diagnoses [Tyree 2006].

11. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

Ethics committee approval for this study was obtained on December 18, 2020.

11.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

As all data used for analytical purposes would be de-identified, it is anticipated that any study of claims, EMR, or a linked database for the purposes of detecting HFrEF and describe its corresponding patient population would be exempt from a full review. However, caution should be taken to avoid stratifying results to the extent that any tabulations of a computation's results would display a count of less than 20 in a single cell.

11.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

14. REFERENCES

14.1 PUBLISHED REFERENCES

1. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2016;18:891–975
2. [AHA Heart Disease and Stroke Statistics – 2019 update; age≥20 years](#). AHA, 2016.

3. Japanese Circulation Society Congestive Heart Failure Guideline; http://j-circ.or.jp/guideline/pdf/JCS2017_tsutsui_h.pdf, accessed on March 10, 2020
4. Okura Y, Ramadan MM, Ohno Y, et al. Impending epidemic: future projection of heart failure in Japan to the year 2055. *Circ J* 2008; 72: 489-491.
5. Desai RJ, Lin KJ, Paterno E, et al. Development and Preliminary Validation of a Medicare Claims-Based Model to Predict Left Ventricular Ejection Fraction Class in Patients With Heart Failure. *Circ Cardiovasc Qual Outcomes*. 2018;11(12):e004700. doi:10.1161/CIRCOUTCOMES.118.004700

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write <None> if there is no document or list documents in a table as indicated below.

Number	Document Reference Number	Date	Title
1	<Number>	<dd mmm yyyy>	<Text>
2	<Number>	<dd mmm yyyy>	<Text>
<n>	<Number>	<dd mmm yyyy>	<Text>

ANNEX 2. COMPONENTS OF DESAI 2018 ALGORITHM

Table 1: List of ICD-9 and ICD-10 codes used to identify heart failure patients (modified from Desai, 2018)

ICD-9	ICD-10	Description
428.xx	I501, I5020, I5022, I5023, I5030, I5031, I5032, I5033, I5041, I5042, I5043, I509	Heart failure
398.91	I0981	Rheumatic heart failure (congestive)
402.01	I110	Malignant hypertensive heart disease with heart failure
402.11	I110	Benign hypertensive heart disease with heart failure
402.91	I110	Unspecified hypertensive heart disease with heart failure
404.01	I130	Malignant hypertensive heart and renal disease with heart failure
404.03	I132	Malignant hypertensive and renal disease with heart failure and renal failure
404.11	I130	Benign hypertensive heart and renal disease with heart failure
404.13	I132	Benign hypertensive heart and renal disease with heart failure and renal failure
404.91	I130	Unspecified hypertensive heart and renal disease with heart failure
404.93	I132	Unspecified hypertensive heart and renal disease with heart failure and renal failure

Table 2: Operational definitions for the variables included in the EF class prediction algorithm

Number	Variable	ICD-9 codes used in Desai's algorithm	Possible ICD-10 recodes
1	Cardiomyopathy	425.x	I43, I421-427
2	Diastolic heart failure	428.3x (not co-occurring with 428.2x)	I5030-I5033
3	Left heart failure	428.1x (not co-occurring with more specific systolic or diastolic HF codes of 428.2x or 428.3x)	I501
4	Systolic heart failure	428.2x (not co-occurring with 428.3x)	I5020-I5023
5	Myocardial infarction	410.xx	I2109, I2111, I2119, I2129, I213, I214
6	Unspecified heart failure	398.91 or 402.xx or 404.xx (not co-occurring with the more specific systolic, diastolic, or left HF codes or 428.2x, 428.ex, or 428.1x)	I0981, I110, I119, I1310, I1311, I132

7	Number of hospitalizations for CHF	Numeric count of number of hospitalization episodes with HF as the primary diagnosis.	
8	Male gender	Binary, coded as 1 if Male and 0 if female	
9	Implantable cardioverter defibrillator	V45.02 (ICD-9 diagnosis code) or 37.94-37.98 (ICD-9 procedure codes)	Z95810
10	Ace inhibitor	Any dispensed prescription for an ACE-inhibitor	
11	Index diagnosis recorded during an outpatient visit	Indicator for the place of HF diagnosis at the index date, 1 for outpatient and 0 for inpatient	
12	Mineralocorticoid receptor antagonist	Any dispensed prescription for mineralocorticoid receptor antagonist	
13	Anemia	280.xx	D500, D501, D508, D509
		281.xx	D510, D511, D513, D518, D520, D21, D528, D529, D530, D531, D532, D538, D539
		282.xx	D550, D551, D558, D569, D5740, D57419, D580, D581
		283.xx	D590, D591, D593, D594, D595, D596, D598
		284.xx	D600, D601, D608, D611, D612, D61810, D61811, D61818, D6189, D619

		285.xx	D630, D631, D638, D640, D641, D642, D643, D644, D6481, D649
14	Valve disorder	394.x	I050, I051, I051, I058
		395.x	I060, I061, I062, I068, I069
		396.x	I080, I088, I089
		397.x	I071 I072, I078 I091, I0989
		398.9x V42.2 V43.3	I099, I0981, I0989
		OR	
		ICD-9 procedure code 35.1x	
		35.2x	
		OR	
		one of the following CPT codes: 33660-33665	
		33400-33403	
		33420-33430	
		33460	
		33463-33468	
		33475	
		33496	
		0257T	
		0258T	
		0259T	
		0262T	

15	Digoxin	Any dispensed prescription for digoxin	
16	Thiazide diuretic	Any dispensed prescription for mineralocorticoid thiazide diuretics	
17	Obesity	278	E6601, E662, E663, E669, E670, E671, E673, E678
		278.01	E6601
		V85.3x V85.4x	Z683
		CPT codes	
		'43842', '43843', '43846', '43847', '43848', 'G0443', 'G0447'	
		Prescriptions of orlistat, sibutramine, phentermine, benzphetamine, phendimetrazine, diethylpropion	
18	Nitrate	Any dispensed prescription for nitrate	
19	Other dysrhythmias	427.0 x	I471
		427.1 x	I472
		427.2 x	I479
		427.4x	I4901, I4902
		427.6x	I4940, I491, I493, I4949
		427.8 x	I495, R001, I498
		427.9 x	I499
		785.0x	R000
20	Hypertension	401.xx-405.xx	I10, I119, I110, I120, I129 I1310, I1311, I132, I50, I58
21	Beta blocker	Any dispensed prescription for beta blockers	

22	Loop diuretic	Any dispensed prescription for loop diuretics	
23	Rheumatic heart disease	393-398.x	I092, I050, I051, I058, I060, I061, I068, I071, I072, I078 I069, I080, I088, I089, I090, I0981, I0989, I091
24	Psychosis	290.8x, 290.9x, 295.xx, 297.xx, 298.xx, 299.xx	F0390, F2089, F22, F23, F28, F323, F333, F4489, F840, F843, F845, F848
25	Coronary artery bypass graft	ICD-9 procedure codes: 36.1x 36.2x	
		CPT4:	
		33510 – 33536	
		33545	
		33572	
26	COPD	491.xx 492.xx 496.xx 493.2x	J44
27	Sleep apnea	327.2x	G4730-G4737, G4739
		780.51	G4730
		780.53	G4730
		780.57	G4730
28	Hypertensive nephropathy	403.xx, 404.xx	I120, I129, I130, I1310, I1311, I132,
29	Depression	293.83	F0630
		296.2 x	F320-F325, F329

		296.3 x	F330-F333, F3341, F3342, F339
		296.9	F39, F348
		298.0x	F323, F333
		300.4x	F341
		309.1x	F4321
		309.28	F4323
		311.xx	F329
30	Hypotension	458.xx	I951-I953, I9581, I9589
31	Stable angina	413.xx	I201, I208, I209
32	Age	Numeric variable for exact age	
33	Atrial fibrillation	427.3x	I4891, I4892
34	Hyperlipidemia	272.xx	E7521, E7522, E75249, E770, E771, E7889, E789, E8889, E780-E786, E881
* Codes are ICD-9 diagnosis codes that are determined based on medical claims (inpatient or outpatient) unless otherwise specified			

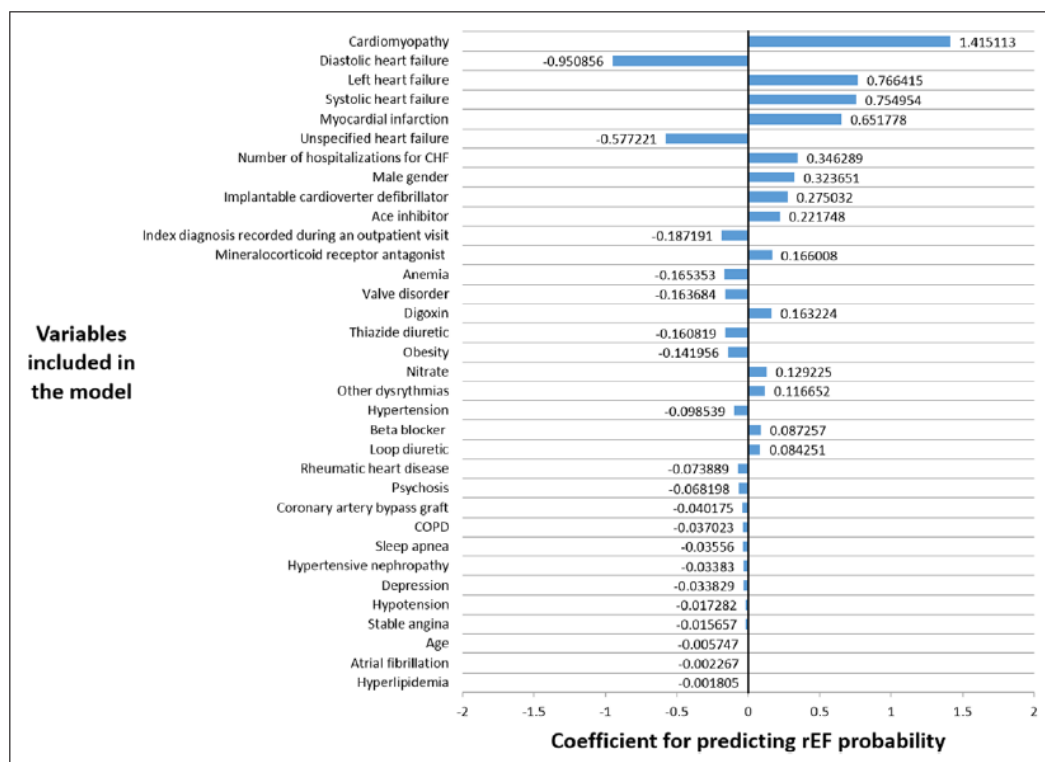


Figure 2. Selected variables along with the coefficients predicting reduced ejection fraction (rEF) heart failure probability. This list corresponds to the variables included in the full binary logistic model (model 3 from Table 1) that was selected out of the 8 candidate models. The intercept value was -1.37219 (not plotted). Codes for implementing this model are available at <http://www.drugapi.org/dope-downloads/>. ACE indicates angiotensin-converting enzyme; CHF, chronic heart failure; and COPD, chronic obstructive pulmonary disease.

Figure 2 from Desai 2018

ANNEX 3. comorbidities and concomitant medications

Comorbidities of heart failure/HFrEF and potential concomitant medications			
Condition	ICD-9	ICD-10	Potential Medications
Anemia	280.xx, 281.xx, 282.xx, 283.xx, 284.xx, 285.xx	D500, D501, D508, D509, D510, D511, D513, D518, D520, D21, D528, D529, D530, D531, D532, D538, D539, D550, D551, D558, D569, D5740, D57419, D580, D581, D590, D591, D593, D594, D595, D596, D598, D600, D601, D608, D611, D612, D61810, D61811, D61818, D6189, D619, D630, D631, D638, D640, D641, D642, D643, D644, D6481, D649	Erythropoiesis-Stimulating Agents (Esas), Iron Supplements (Ferrous Sulfate), Vitamin B Supplements
Anxiety	300; 300.01, 300.02, 300.09	F41.0, F41.1, F41.8, F41.9	Benzodiazepines, Buspirone, Antidepressants, Beta-Blockers
Atrial fibrillation	427.31	I48.21, I48.91	Blood Thinners, Beta Blockers, Calcium Channel Blockers, , Digoxin
Cardiac thrombus	444.9	I23.6, I51.3, I74.9	Thrombolytics
CKD	585.xx	N18.xx	Blood Pressure Medication, Statins
COPD	491.20, 491.21, 491.22, 493.20, 493.21, 493.22, 496	J44.xx	Short-Acting Bronchodilators, Corticosteroids, Methylxantines, Long-Acting Bronchodilators, Combination Drugs, Roflumilast, Mucoactive Drugs
Dilated cardiomyopathy	425.xx	I42.0	Ace Inhibitors, Antiotensis li Recceptor Blockers, Beta Blockers, Biuretics, Digoxin, Blood-Thinning Medications
Embolism (pulmonary)	415.11, 415.12, 415.13, 415.19	I26.9x	Anticoagulants, Thrombolytics
Embolism (other)	4449	I74.9	Anticoagulants, Thrombolytics
Gastroesophageal reflux disease	53081	K21.9	Cimetidine (Tagamet), Famotidine (Pepcid), Nizatidine, Dexlansoprazole (Dexilant), Esomeprazole (Nexium), Lansoprazole (Prevacid), Omeprazole (Prilosec, Zegerid), Pantoprazole (Protonix), Rabeprazole (Achiphex)

Hypertension	401-405	I10, I11.9, I12.0, I12.9, I13.0, I13.11, I13.2, I15.0, I15.8	Diuretics, Beta-Blockers, Ace Inhibitors, Arbs, Calcium Channel Blockers, Alpha-Blockers, Alpha-Beta-Blockers, Central Agonists, Vasodilators, Aldosterone Receptor Antagonists, Direct Renin Inhibitors
Major depression	29631, 29632, 29633, 29634, 29635, 29636, 29630	F33	Selective Serotonin Reuptake Inhibitors (Ssri), Serotonin-Norepinephrine Reuptake Inhibitors (Snris), Tricyclic Antidepressants, Norepinephrine And Dopamine Reuptake Inhibitors (Ndri), Monoamine Oxidase Inhibitors (Maois)
Myocardial infarction	412	I25.2	Beta Blockers, Ace Inhibitors, Statins, Antiplatelet Therapy, Aldosterone Blocker, Antianginal, Magnesium, Non_Nsaids: (Acetaminophen, Tramadol)
Obstructive sleep apnea	327.23	G47.33	Acetazolamide, Medroxyprogesterone, Fluoxetine, Protiptyline, Modafinil, Armodafinil
Stroke (History)	V12.54	Z86.73	Blood Thinners, Blood Pressure Lowering Medications (See Hypertension), Cholesterol Absorption Inhibitors (Ezetimibe), Fibrates (Fibric Acid Derivatives), Niacin, Resins, Statins (See Website For Ckd), , , Tpa (Tissue Plasminogen Activator)
Stroke (Incident)	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x	I50*	Blood Pressure Lowering Medications (See Hypertension), Blood Thinners, Cholesterol Absorption Inhibitors (Ezetimibe), Fibrates (Fibric Acid Derivatives), Niacin, Resins, Statins (See Website For Ckd), TPA (Tissue Plasminogen Activator)
Type 2 Diabetes	250	E11	Insulin, Metformin, Sulfonylureas, Meglitinides, Thiazolidinediones, Ddp-4 Inhibitors, Glp-1 Receptor Agonists, SglT2 Inhibitors
Valvular heart disease			Beta-Blockers, Calcium Channel Blockers, Digoxin, Diuretics, Vasodilators
Aortic valvular disease	424.1	I35.0-I35.9	
Mitral valvular disease	424.0	I34.0-I34.9	

ANNEX 4. COMMONLY PERFORMED TESTS ON HFREF PATIENTS

Commonly performed tests for CHF patients.		
Test	CPT	Includes (if not self-explanatory)
BLOOD TESTS		
Panels		
B12 and folates	82607, 82746	
Chemistry (basic metabolic panel)	80053	Alanine aminotransferase (ALT/SGPT); albumin:globulin (A:G) ratio; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, total; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide, total; chloride, serum; creatinine, serum; eGFR calculation; globulin, total; glucose, serum; potassium, serum; protein, total, serum; sodium, serum
Coagulation profile	85730, 85384, 85610, 85670	
Complete blood count	85025, 85027, 85007	Hematocrit; hemoglobin; mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); red cell distribution width (RDW); percentage and absolute differential counts; platelet count (RBC); red cell count; white blood cell count (WBC)
Enzyme markers Creatine kinase (CK), Total Troponin		CPK-1, CPK-2, CPK-3, Troponin
	82250	Creatine Phosphokinase, Total (CPK-1, CPK-2, CPK-3)
	84484	
Hepatic (liver) function	80076	Alanine aminotransferase (ALT/SGPT); albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, direct; bilirubin, total; protein, total, serum
Lipid panel	80061	Cholesterol, total; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol (calculation); triglycerides; very low-density lipoprotein (VLDL) cholesterol (calculation)

Renal function panel	80069	Albumin, serum; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide, total; chloride, serum; creatinine, serum; glucose, serum; phosphorus, serum; potassium, serum; sodium, serum
Thyroid panel	84436, 84443, 84479	Free thyroxine index; T3 uptake (THBR); thyroid-stimulating hormone (TSH); thyroxine (T4)
Individual tests		
DHEA-sulfate serum test	82627	
C-reactive protein	86140	
Glucose	82947, 82948, 82962	
B-type natriuretic peptide	83880	
N-terminal pro-BNP	83880	
Glomerular Filtration Rate (GFR)	82565	Creatinine, serum; eGFR calculation
HbA1c	83036	
OTHER TESTS		
Cardiac catheterization	93530	
Echocardiogram	93306	
Electrocardiogram (EKG or ECG)	93010	
Multigated Acquisition Scan (MUGA scan)	78472, 78473, 78494, 78496	
Nuclear stress test	93015, 93016, 93017, 93018	
Magnetic resonance imaging (MRI)	75557-75564	

ANNEX 5. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

A copy of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

“Study start” means “Start of data collection”

“Study progress” means “Progress report(s)”

“Study completion” means “End of data collection”

“Reporting” means “Final report of the study results”

ANNEX 6. ADDITIONAL INFORMATION

Additional annexes may be included if necessary.

ANNEX 7. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	NIS involving BI product(s)	NIS not involving BI product(s)	
		Global NIS	Local NIS
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

* After review by Global TM for function

*Include this Annex if signatures of external investigators are required **and/or** for studies that will not be stored in the DMS for submission documents. For non-interventional studies approval signatures must be obtained from the individuals as noted in section 5.1.3 “Manage NIS Protocol” in the corresponding SOP 001-MCS-90-118. If the study is a PASS, additional approvals are necessary; refer to SOP 001-MCS-90-140 “Post Authorization Safety Studies”.*

Study Title:

Study Number:

Protocol Version:

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Position: NIS lead Name/Date: Yasuhisa Ono Signature: _____

Position: Global TM Epi Name/Date: Qing Qiao Signature: _____

Position: RWE CoE Name/Date: Ling Zhang Signature: _____

Position: GPV SC Name/Date: Signature: _____

Position: Japan Local
Medical Director Name/Date: Signature: _____

Position: Japan Local
Market Access Head Name/Date: Signature: _____