Gender Specific Registry in Subjects hospitalized with Heart Failure in Santiago

(**Registro GENESIS-** Registro **Gén**ero **E**specifico en **S**ujetos hospitalizados con **I**nsuficiencia Cardíaca en **S**antiago)

Study Protocol and Statistical Analysis Plan

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1.- Rationale

Chronic Heart failure (HF) is associated with high morbidity, mortality, reduced quality of life, and increasing health-care costs across the world. [1]
Even though the improvement in HF treatments in the last decades has been substantial, the prognosis remains low, with high rates of hospital readmissions and five years observed survival of around 50%. [2] In fact, the risk of death is directly related to the

duration and frequency of HF hospitalizations. Solomon et al. reported that patients in the first month after discharge presented an estimated 6-fold excess risk in mortality, declining in the next years free of hospitalizations. [3] On the other hand, an extended HF hospitalization is also considered a predictor of death.

In Chile, Diaz-Toro et al. have reported that around 1% of hospital discharges were attributable to HF, when analyzing the Chilean Ministry of Health's hospital discharge database during 2014. Also they shown a 9,2% of hospital lethality attributable to HF. These numbers are comparable to the ones reported in the US and other Latin American countries.[4] Also, this study underlined that the length of stay over seven days associated with a higher hospital mortality (OR 1.13; 95%CI:1.01-1.29 =p:0.04). With the aging of the Chilean population, along with the burden of cardiovascular and metabolic risk factors shown in our last National Survey 2016, the prevalence of HF is expected to increase dramatically in the coming years. [5]

Conflicting data about sex-related differences in the HF patient regarding presentation, management, and prognosis have been reported. Some studies have shown a worse prognosis in women, primarily secondary to underutilization of recommended medical treatments, while others have shown a better prognosis with less in-hospital mortality. [6] In Chile, the only published data comes from Diaz- Toro et al., reporting a slightly higher incidence of HF hospitalization in men than in women, but higher in-hospital mortality in women (9,7 versus 8,6 %).[4] There was no analysis of the HF phenotype and treatment, and, as the statistics came from an administrative database, underreporting was highly probable.

The only HF registry in Chile has been the ICARO registry (**I**nsuficiencia **C**Ardíaca: **R**egistro y **O**rganización). It was performed from 2002 to 2013. This was a national prospective registry coordinated by the HF Department of the Chilean Society of Cardiology.[7] According to the ICARO registry, HF with reduced ejection fraction (HFrEF) was the predominant phenotype of HF in Chile. However, only 54 % of the participants had an available echocardiogram. Unfortunately, volume or tissue doppler analysis were not reported. [8] On the other hand, there was no information about blood biomarkers, mostly NT-terminal pro-brain natriuretic peptide (NT-pro BNP) levels. The ICARO project ceased recruitment in 2013. Therefore the real prevalence of HF and its distinct phenotypes is challenging to figure out in 2021 when HF with preserved ejection fraction (HFpEF) has been better characterized and better imaging tools are available to diagnose these syndromes.

Different registries had been published in patients with either chronic or acute HF describing the clinical history and the treatment strategies available. As examples, the literature stands out "To GET with the Guidelines Registry Heart Failure (GWTG-HF)" in the US and the "Euro Heart Failure Survey" in Europe. [9-10] Both examples have helped these regions set up new data to establish public health policies. Also, some experiences had been done in Latin America with international collaboration. [11]

Currently, the sex prevalence of different HF phenotypes as described nowadays (reduced, preserved and mildly reduced ejection fraction (HFmr EF)) is lacking [12]. In the same line, there is no information of characterization of the predominant risk factors associated with decompensated HF, and hospital readmissions in Chilean women and men. Finally, there is no recent data about the prescribed treatments during hospitalization and discharge in our country.

The Fundación de la Sociedad Chilena de Cardiología y Cirugía Cardiovascular (SOCHICAR) has been worried about the gaps of knowledge in prevention, treatment and access in Cardiovascular (CV) health in women. For this reason, the Fundación SOCHICAR has been working in promoting cardiovascular health in women, through educational campaigns to the community as well as supporting academic projects in that area. [13-14]

As is known, in the last decade in Chile there has been an important increase in obesity and diabetes prevalence, specially in women. [15] It would be expected that this would be reflected in a higher incidence of HF in Chilean women, however there are no published data about HF prevalence in women in our country. As the Lancet women and cardiovascular disease Commision reported CV disease in women remains under-recognised.[16] Therefore, the Fundación SOCHICAR decide to follow the Commision´s recommendations of promoting sex specific research and programmes. Our Fundación sought to obtain data that can improve health care for this population, and also cooperate to Chilean public health policies.

Therefore, the main purpose of this registry is to assess the sex-related differences in HF presentation, management, and prognosis in patients admitted to a hospital with a diagnosis of HF in a representative sample of patients from the Metropolitan Region, Chile.

2.- The Objectives and Hypotheses

The Primary Aim

The registry will determine the epidemiologic and clinical characteristics of patients hospitalized with a HF diagnosis, by sex specific analysis.

The outcome measure will be the prevalence of HF phenotype (preserved or reduced) and etiology (ie.ischemic, non ischemic, hypertensive)
The hypothesis is that HF pEF and non ischemic etiology are more prevalent in Chilean women vs men.

Secondary objectives:

1- To evaluate socioeconomic and educational level in the study population (patients hospitalized with HF) by a sex specific analysis.

The outcome measure will be family income and years of education.
The hypothesis is that women with HF have less educational level and a lower socioeconomic status compared to men with HF.

2- To assess the prevalence of comorbidities and clinical conditions associated with HF by a sex-specific analysis
The comorbidities that will be analysed wil be: diabetes, elderly, chronic renal failure (4-5 CKD phase), anemia, hiperkalemia, obesity and COPD.
The hypothesis is that the prevalences of comorbidities and clinical conditions are different in women and men with HF: ie, there is more prevalence of obesity in Chilean women with HF than in men.

3-To determine the main decompensating risk factors in HF patients by sex-specific analysis
The prevalence of decompensating risk factors that wil be assessed will be: medication and diet non-adherence, atrial fibrillation, infections, acute renal failure and acute coronary syndromes
The hypothesis is that the decompensating risk factors in Chilean hospitalized HF patients are different in women and men. Medication and diet non-adherence will be lower in men than in women

Exploratory objectives:

1- To determine the presence of depressive symptoms and depression in hospitalized HF patients by a pre-specified sex analysis.
The outcome measure will be assessed with the PHQ-9 questionnaire (mild-to-moderate depressive symptoms (10 to 19 points) and major depression (≥ 20 points)[17-18]
The hypothesis is that HF hospitalized women present with more depressive symptoms than men.

2- To determine if frailty prevalence is different in hospitalized HF patients by a sex pre-specified analysis.
The outcome measure will be evaluated by the Short Frailty score[19]
The hypothesis is that women with HF are more frail than men.

3- Methods

3.1 Study design and participants

Observational and prospective registry led by the Fundación SOCHICAR, that will be held at hospitals of different communes in urban Santiago. This project will incorporate two hospitals in a period of one year.

The hospital selection will be based on the purpose of having the most clinical information of the patient regarding his/her cardiac condition. Both participating centers must have coronary units, cardiac surgery, and interventional cardiology. Also, both hospitals must have medical teams with expertise in cardiac imaging, and have access to a local laboratory that performs biomarkers (i.e. NT pro-BNP, usTroponin).
The registry consists of a descriptive cross-sectional survey. Thereby, this study is a one-time assessment, with no visit schedule.

Ethics consideration

The registry must be approved by the Ethics committee of each clinical center, or in case of not having one, by the Metropolitan Region Ethics Committee respective of each area. Each patient must be informed about the study's rationale and his/ her potential willingness of participation. Written informed consent will be obtained from all participants before data collection.

3.2 Study population: approximately 500 patients hospitalized in the two recruiting centers during one year (January 2022 – December 2022) who comply with all the elegible criteria and without exclusion criteria.

3.2.1 Inclusion criteria

Patients will be eligible to participate if they are ≥ 18 years old, agree to participate and sign informed consent, and have been admitted to the hospital with a: 1) diagnosis of acute HF as the leading cause of admission, and in which a CV therapy is needed and prescribed (ie. diuretic, vasodilator, inotropic, device), or if a: 2) diagnosis of chronic HF is established during the patient hospitalization based on clinical, biochemical and/or imaging studies, and in which cardiovascular therapy is needed and prescribed (ie. diuretic, vasodilator, inotropic, device) during the hospitalization.

Patients will be eligible to participate if they are

- ≥ 18 years old
- Signed informed consent
- Admitted to the hospital with a :
  - 1) diagnosis of acute HF as the leading cause of admission, and in which a CV therapy is needed and prescribed (ie. diuretic, vasodilator, inotropic, device), or
  - 2) diagnosis of chronic HF is established during the patient hospitalization based on clinical, biochemical and/or imaging studies, and in which

cardiovascular therapy is needed and prescribed (ie. diuretic, vasodilator, inotropic, device) during the hospitalization.

The definition of Heart Failure will be according to the last 2021 European Society of Cardiology (ESC) Guidelines. HF is a clinical syndrome characterized by cardinal symptons that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, that results in elevated intracardiac pressures and /or inadequate cardiac output at rest or during exercise. A practical definition of HF will be shortness of breath and/or fatigue and /or ankle swelling, and/or jugular venous distention and /or rales at the lung examination, with an ejection fraction by echocardiography $\leq$ 40% (HF with Reduced ejection fraction- HFrEF) and /or greater than 40% (41 to 49 % represents HF with midly reduced ejection fraction-HFmrEF and $\geq$50 % Preserved Ejection Fraction-HFpEF); this last one associated with pro BNP > 125 pg/ml in sinusal rhythm. 15

The outcome measure will be the prevalence (% of the study population) according to the HF phenotype (preserved, mildly reduced or reduced). The working definition of HF phenotypes will be in accordance to 2021 ESC guidelines of HF, based on the followimg criteria: a. clinical (shortness of breath and/or fatigue and /or ankle swelling, and/or jugular venous distention and /or rales at the lung examination),b. echocardiography: measurement of ejection fraction by transthoracic echocardiogram: HF with Reduced ejection fraction- HFrEF-(< 40%), HF with midly reduced ejection fraction-HFmrEF- ($\geq$40 to 49 %) and Preserved Ejection Fraction-HFpEF- ($\geq$50%), this last one associated with NT pro BNP $\geq$ 125 pg/ml in sinus rhythm.

The outcome measure will be the prevalence of HF etiology (ischemic, non ischemic, and hypertensive). With regard to ischemic etiology, the study definition will be based on a definite diagnosis of ischemic heart disease (epicardial coronary artery stenosis greater than 50%, and /or previous myocardial infarction, and/or previous revascularization (CABG or PCI) or a positive imaging stress test, such as echo, nuclear, or cardiac magnetic resonance (CMR) . Hypertensive cardiomyopathy will be defined for HF with reduced , mild reduced or preserved eyection fraction only if long standing hypertension (at least 20 years) , and with cardiac structural changes suitable with hypertensive etiology: presence of diastolic dysfunction, and /or LV hypertrophy.

3.2.2 Exclusion criteria

Patient will be ineligible to participate if: a Covid 19 infection and/ or SARS-Cov 2 pneumonia is confirmed, or if the patient presents a psychiatric decompensated disorder and/or a cognitive impairment which preclude assessment of this survey. (Table 1)

Patient will be ineligible to participate if:

- The patient presents a Covid 19 acute infection and/ or SARS-Cov 2 pneumonia is confirmed
- The patient presents a psychiatric decompensated disorder and/or a cognitive impairment which preclude assessment of this survey.

3.3 Data source

The data will be obtained from the medical files, and will be collected prospectively by a center coordinator using a tablet electronic survey. The survey will be created using a Google form questionnaire, easy to fill in and register.
The confidentiality of the patient will be protect, using patients´ identification based on their initials (first name - first last name - second last name) plus an odd or even sequential number according to the belonging hospital (ie: María José Salas Gómez MSG1).
The registry will include: demographic, CV risk factors, medical history, comorbidities, blood biochemical parameters, diagnostic imaging determinants, treatment, and outcomes data.
The information about PHQ 9 questionnaire will be answered confidentially by the patient in the tablet

3.4 Study assessment

The registry consists of a descriptive cross-sectional survey. Thereby, this study is a one-time assessment, with no visit schedule

3.5 Study limitations

The main study limitations will be the failure to recruit 500 patients in the one-year period. Also the recruitment could be delayed by the current pandemic of Covid 19, due to prioritization of hospitalization in intensive care-unit beds of that patients. Another limitation is the Ethical Committee approval which depends on the meeting schedules, one per month, in each hospital.

With respect to data limitations, we will be conditioned by the information available in the medical file, and the laboratory and imaging exams requested by the head and

referral physicians. Also, we will depend on the cognitive status of the patient to fill out the information requested by the different questionnaires that must be fulfilled.

STATISTICAL METHODS

3.6 Sample size and statistical power; precision assessment

The sample size was estimated considering the data reported in one of the largest trials that have addressed sex differences in heart failure (HF-Action Trial by Sex, Am Heart J. 2009 Oct; 158(40): S16–S23.) [20]. This trial shows that the prevalence of Heart Failure of ischemic cause (one of the main objectives of our trial) was 59% in males and 32% in females.

The calculation of the sample size was carried out to find significant differences between the prevalence of heart failure from ischemic etiology in female patients consecutively hospitalized compared to male, based on Chi-square test for comparison of proportions, considering a significance of 95% and power of 90 %. Therefore, we will included in our study aproximately 500 patients knowing that to get a significance of 95 % and a power of 90% we must recruit at least 156 patients (52 females and 104 males) considering 2:1 male-to-female proportion. In order to perform a stratified analysis, we estimated that the lowest sample size for each center should be 78 patients.(with 2:1 male -to - female proportion)

3.7 Statistical considerations

Data management:

The data completeness and accuracy will be addressed through out-of-range alerts and control of nonreported data. The nurse coordinator will verify the completeness and accuracy of the information and send the respective queries on a daily basis.

Missing data will be addressed according to covariate. Given the observational data collection of the registry, few data could be missing. These data will be addressed according the kind of covariate. In general, a multiple imputation strategy will be performed.

All the data will be electronically registered in an Excel file. Privileges will be conferred according the role of the personnel on the study. The Principal Investigators will have access to all data.

Statistical Analyses: All the important covariates will be recorded. Specifically, information on patients' characteristics, demographics, basal functional capacity, complete blood test analyses, EKG, echocardiography, and relevant clinical information will be registered at baseline according to the protocol of each center. For analyses purposes, Prevalence of HF phenotype (i.e. HFpEF, HFmrRF and HFrEF) and etiology (ie. Ischemic and non ischemic) will be considered as primary outcomes.

All the variables will be tested for normality using Shapiro-Wilk test. We will compare percentages of phenotypes (i.e. HFpEF, HFmrHF, and HFrEF) and etiology (ie. Ischemic and non ischemic)according to gender, using Chi-square test. Moreover, T-test statistics will be used according the variable.

The demographic variables that will be incorporated are:

- Age
- Sex
- Educational Level: years of education < 8, > 8 and/or < 12, >12 years
- Married, single, divorced, widowed
- Race and Ethnic origin
- Insurance status
- Family income: ≤ $ 326.000 pesos (basic income) or less U$ 500
  $ 326.000 -$ 652.000
  $ 652.000 - $ 1.000.000
  $ 1.000.000 -$2.000.000
  $ ≥ 2.000.000- <3.000.000
  $ ≥ 3.000.000
- Employed, non employed, retired

The medical history that will be asked are:

- Anemia
- Smoking
- Diabetes
- Obesity
- Depression
- Hyperlipidemia
- Hypertension
- Atrial fibrillation /atrial flutter
- Ventricular arrhythmias
- Coronary disease
- Ischemic heart disease /Previous myocardial infarction (MI)
- Chronic obstructive pulmonary disease (COPD) / asthma
- Cerebrovascular disease: Ischemic Stroke /Haemorrhagic stroke /transient ischaemic attack (TIA)
- Peripheral vascular disease
- Renal insufficiency (MRDR: less 60 ml /min /m2)
- Dialysis (peritoneo/ Hemodialysis)
- Preeclampsia / Gestational Diabetes / Premature delivery
- Premature or late menarche
- Premature of late menopause

- Hyperkalemia
- Previous hospitalization
- Malignancies
- Autoimmune Diseases (i.e. Erythematous Systemic Lupus, Rheumatoid Arthritis, Chron Disease, Vasculitis , etc)
- Genetic and Metabolic Disease (i.e. Fabry Disease, Muscular Dystrophies)

HF Characteristics.

- **Preserved**
- **Mildly Reduced**
- **Reduced**

HF cause: ischemic, non ischemic and hypertensive.

Decompensating HF clinical factors.

- Medication and diet non-adherence
- Atrial fibrillation /flutter
- Arrhythmias (other than AF) including bradyarrhythmias
- Infections
- Acute renal failure
- Acute coronary syndrome
- Anemia
- Pulmonary thromboembolism
- Others: specified

Precipitating clinical factors.

- Respiratory (pneumonia and others)
- Arrhythmias
- Medication non-compliance
- Diet non-compliance
- Uncontrolled Hypertension
- Renal Failure
- Myocardial Ischemia (ACS)

Questionnaires:

- **Quality of life** Kansas City Cardiomyopathy Questionnaire. [21]
- **Depression**: PHQ-9: Patient Health Quesionnaire 9 (Depression scale) [17-18]
- **HFpEF approach**: The new H_2FPEF score (Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension [pulmonary artery systolic pressure > 35 mmHg], Elder age > 60 years, and elevated Filling pressures [E/e´>9]) score in patients hospitalized with HFpEF [22]

- **Frailty Score:** The Frail Score[19]

Laboratory Determinations:

- Nt-pro BNP
- Hemoglobin levels
- White blood count
- Creatinine
- Blood urea nitrogen (BUN)
- Plasma Electrolytes
- Troponin US
- Albumin
- Lipid profile
- Thyroid stimulating hormone (TSH)
- Hemoglobin A 1 C (if appropriate)
- Ferritin and Iron levels

Imaging Determinations

1- Ecocardiography:

- Ejection Fraction
- Left Atrial volume
- Left ventricular dimensions (Systolic, Diastolic) and /or volumes.
- LV segmentary motility (septal, anterior, inferior, posterior, lateral): akinesia,hypokinesia, diskinesia(Yes/No for each one),
- Presence of LV thrombus
- Pulmonary systolic arterial pressure
- Mitral E/e´ratio
- Global Longitudinal Strain
- Valvular Regurgitations
- Valvular Stenosis
- Tricuspid Annular Plane Systolic Excursion (TAPSE)

2-Thoracic RX

- Pulmonary congestion
- Left Ventricular enlargement
- Right Ventricular enlargement
- Pleural effusion

3- Magnetic cardiac resonance

- Late Gadoliniun enhancement
- Left ventricular Volumen and Ejection Fraction
- Right ventricular Volumen and Ejection Fraction

- Infiltrative cardiomyopathy pattern
- Constrictive Pericarditis
- Thrombus
- Hypertrofic cardiomyopathy

4- Coronary angiogram

- Coronary stenosis ≥ 50 % : one vessel, two vessels or three vessels
- Coronary stenosis ≥ 70 % :
- Coronary Oclussion
- Ventriculography (Yes or No) : eyection fraction and motility description.

Treatment

1- Pharmacological: names and daily doses

- B -blockers(total daily dose): bisoprolol, metroprolol,carvedilol, nebivolol , others
- Angiotensin converting enzyme (ACE) inhibitors (total daily dose) : enalapril, ramipril, captopril, perindopril, lisinopril, others/ Angiotensin 2 Receptors blockers (total daily dose): losartan, valsartan, telmisartan, candesartan, Olmesartan, others
- Angiotensin receptor/neprilysin inhibitor (ARNI)(total daily dose): Sacubitril / Valsartan
- Mineralocorticoid antagonist receptors (total daily dose): spironolactone /eplerenone/finerenone
- Sodium glucose cotransporter 2 (SGLT 2) Inhibitors (total daily dose): dapagliflozin, empagliflozin.
- Diuretics (total daily dose): furosemide (Intravenous /oral) metolazone, hydrochlorothiazide,chlortalidone, indapamide, others
- Vericiguat
- Ivabradine
- Digoxin
- Calcium Channel Blockers: amlodipine, others
- Nitrites: Intravenous nitroglycerine/ Isosorbide dinitrate / Isosorbide mononitrate
- Other vasodilators: hydralazine
- Statins: atorvastatin, rosuvastatin, simvastatin, others
- Ezetimibe
- Anti diabetic drugs: metformin, glibenclamide, glipizide, insulin, DPP4 (sitaglipitine, saxagliptine, linagliptine, vildagliptine) GLP1 analogues (semaglutide, liraglutide, dulaglutide, others)
- Anticoagulants: vitamin K antagonists (VKA), direct oral anticoagulants (OACs): apixaban, rivaroxaban, dabigatran.
- Platelet inhibitors: aspirin, clopidogrel, ticagrelor.
- Intravenous Iron Therapy
- Intravenous Inotropic therapy: dobutamine, milrinone, levosimendan.

2. Non pharmacological

- Cardiovascular Rehabilitation (Yes /No)
- Devices: Pacemaker / Cardiac resincronization Therapy/ (ICD) implantable cadioverter-defibrillator.

Final comments

The sponsor will have no role in the design of the study (registry) nor the data collection, analysis, interpretation of the data, and in the decision of submission to a journal.

We expected that this pilot project could motivate other Chilean clinical centers to participate in this registry in the future. We also have the ambition to continue this project in the future through the generation of funds by creating educational tools directed to health professionals and patients, as done by the "To Get with the Guidelines HF Registry" in the US.
This program is coordinated by a non-profit institution, Fundación SOCHICAR

References

1. McCullough PA, Philbin EF, Spertus JA et al. Confirmation of a heart failure epidemic: findings from the resource utilization among congestive heart failure (REACH) study. J Am Coll Cardiol 2002; 39 :60-69

2. Braunwald E. Heart failure. J Am Coll Cardiol HF 2013;1:1-20

3. Solomon SD, Dobson J, Pocock S, Skali H, Mc Murray J, Granger C, et al. Influence of fatal Hospitalization for Heart Failure on Subsequent Mortality in Patients with Chronic Heart Failure. Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Circulation 2007; 116:1482-17

4. Díaz-Toro F, Nazzal C, Verdejo H. Incidencia y letalidad intrahospitalaria por insuficiencia cardiaca en Chile: ¿Existen diferencias por sexo? Rev Med Chile 2017 ; 145:703-709

5. Margozzini P, Passi A. Encuesta Nacional de Salud, ENS 2016-2017: un aporte a la planificación sanitaria y políticas públicas en Chile. ARS Medica 2018; 43:30-34. doi.org/10.11565/arsmed.v43i1.1354

6. Lainščak M, Milinković I, Polovina M, Crespo-Leiro MG, Lund LH, Anker SD et al; European Society of Cardiology Heart Failure Long-Term Registry Investigators Group. Sex- and age-related differences in the management and outcomes of chronic heart failure: an

analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry. Eur J Heart Fail. 2020 Jan;22(1):92-102. doi: 10.1002/ejhf.1645.

7. Castro P, Vukasovic JL, Garcés E, Sepúlveda L, Ferrada M, Alvarado S; Insuficiencia Cardíaca: Registro y Organización. Insuficiencia cardíaca en hospitales chilenos: resultados del Registro Nacional de Insuficiencia Cardíaca, Grupo ICARO [Cardiac failure in Chilean hospitals: results of the National Registry of Heart Failure, ICARO]. Rev Med Chil. 2004 Jun;132(6):655-62. Spanish. doi: 10.4067/s0034-98872004000600001.

8. Vukasovic R JL, Castro G P, Sepúlveda M L, Nazzal N C, Garcés F E, Concepción Ch R, et al. Características de la insuficiencia cardíaca en pacientes con fracción de eyección preservada: resultados del registro Nacional de insuficiencia Cardíaca, grupo ICARO [Characteristics of heart failure with preserved ejection fraction: results of the Chilean national registry of heart failure, ICARO]. Rev Med Chil. 2006 May;134(5):539-48. Spanish. doi: 10.4067/s0034-98872006000500001

9. Kapoor JR, Kappor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez A et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced borderline, and preserved ejection fraction. J Am Coll Cardiol HF 2016;4:464-472

10. Jonsson A, Edner M, Alehagen Um Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure . European Journal of Heart Failure 2010; 12:25-31

11. Layerle B, Chafes D, Estragó V, Alvarez P, Pereda M, Spera E et al.Heart Failure Pilot Survey by the Uruguayan – European Survey Group (GUERNICA). Rev Urug Cardiol 2012; 27:286-303

12. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M,et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368. Erratum in: Eur Heart J. 2021 Oct 14;: PMID: 34447992.

13. Varleta P, Acevedo M, Casas-Cordero C, Berríos A, Navarrete C Low Cardiovascular Disease Awareness in Chilean Women: Insights from the ESCI Project. C. Glob Heart. 2020 Aug 12;15(1):55.

14. Acevedo M, Varleta P, Casas-Cordero C, Berríos A, Navarrete C, López R Prevalence and determinants of ideal cardiovascular health in a latin women cohort: a cross-sectional study. The Lancet Health Regional Americas 2001 Vol 4. 100071. doi.org/10.1016/j.lana.2021.100071

15. https://www.minsal.cl/wp-content/uploads/2017/11/ENS-2016-17_PRIMEROS-RESULTADOS.pdf

16. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA,et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet. 2021;397:2385-2438.

17. Lichtman J, Bigger JT, Blumenthal J, Frasure-Smith N, Kaufmann P, Lespérance F et al.Depression and Coronary Heart Disease. Recommendations for Screening, Referral, and Treatment: A Science Advisory From the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. Circulation. 2008;118:1768–1775

18. Bhatt K, Kalogeropoulos A, Dunbar S, Butler J, Georgiopoulou V. Depression in heart failure: Can PHQ-9 help ? Int J Cardiol 2016; 221:246-250

19. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R,et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14:392-7

20. Lopez D, Flicker L, Dobson A. Validation of the FRAIL Scale in a Cohort of Older Australian Women. J Am Geriatr Soc. 2012; 60:171–173.

21. Piña IL, Kokkinos P, Kao A, Bittner V, Saval M, Clare B, Goldberg L, et al, HF-ACTION Investigators. Baseline differences in the HF-ACTION trial by sex. Am Heart J. 2009 Oct;158(4 Suppl):S16-23

22. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000; 35:1245-1255

23. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018 Aug 28;138(9):861-870.

Table 1- Eligibility criteria for GENESIS Registry

I-Inclusion criteria:

1. Patients ≥ 18 years old
2.a. All patients admitted to the hospital with a diagnosis of heart failure considered as the leading cause of entry and in which cardiovascular therapy is needed and prescribed (ie. diuretic, vasodilator, inotropic, device)
or
2.b. All patients admitted to the hospital in which a diagnosis of heart failure is established based on clinical, biochemical and/or imaging studies, and in which cardiovascular therapy is needed and prescribed (ie. diuretic, vasodilator, inotropic, device)
3. Patient agrees to participate and signs informed consent.

II- Exclusion criteria:

1. Covid 19 infection and/ or SARS-Cov 2 pneumonia during hospitalization
2. Psychiatric decompensated disorder and/or cognitive impairment which preclude assessment of this survey.