The GENICA project – a prospective cohort of heart failure patients with a comprehensive ambulatory approach aiming better outcomes: study protocol

Carla Sofia de Almeida Martins, João Abranches Figueiredo Simões de Carvalho, Manuel Vaz da Silva and Luís Martins

Abstract

Introduction: Heart failure (HF) is a syndrome increasing worldwide, and literature shows that the hospitalizations are associated with greater mortality rates. A patient-centered method combined with optimized medical treatment and palliative care may improve HF outcomes, and some advocate a multifaceted approach to achieve a perfect management of chronic HF (CHF).

Objective: The objective of this study was to present the study protocol of GENICA project which aims to optimize the ambulatory approach of CHF patients, and reduce their re-hospitalization, emergency readmission, and global death rate.

Design: Prospective cohort including patients referred to HF consultation and collecting sociodemographic, clinical, and analytical variables among others. The outcomes will be mortality, re-hospitalization, and emergency readmission rates. The association between the independent variables and outcomes will be assessed by logistic regression. Comparison between GENICA patients and controls will be made by $\chi^2$ test. Significance at $p$ level of less than 0.05.

Results: GENICA will offer a wide range of longitudinal data with evidence that will influence future healthcare of CHF patients at an ambulatory basis.

Discussion: GENICA will provide practical evidence of real HF patient’s profile and develop workable decision algorithms, which will influence future ambulatory care of CHF. HF patients will be safer at home and will keep stability for longer periods, consuming less health resources and slow the progression of the disease. Being a matched cohort, GENICA benefits from an accuracy similar to that of randomized controlled trials, without the need to perform a rigorous allocation of the intervention. Being prospective there’s no problem about response bias.

Conclusion: CHF should be approached with a multidisciplinary and multifaceted strategy privileging the outpatient setting, including home monitoring, and GENICA is the paramount protocol enabling this. GENICA may come to show health policy makers that the asset is not to divide and rule, but to converge strategies, therapies, and knowledge.

Keywords: ambulatory care, heart failure, monitoring devices, noninvasive monitoring, telemedicine, telemonitoring

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Background
Heart failure (HF) is a syndrome with increasing incidence/prevalence worldwide, and Portugal shows this same trend in parallel with the increase in cardiovascular risk factors. Interestingly, however, HF has motivated huge technological innovations (innovative drugs, new medical devices . . .) in last decades. So, maybe we are still not managing/controlling all the complexity of this syndrome, and it is imperative to adopt a standardized, evidence-based approach, and prognostic risk stratification is essential to guide decision health policies. Yet, the potential benefit of a comprehensive approach should be weighed against the patient’s possible discomfort and escalation of associated costs.

At our hospital center, we had previously an HF consultation guided specifically to transitional care, with no post-discharge management. In fact, from 2008 till 2016 we have assisted to a rise of our in-hospital mortality from 12.9% to 15.2% probably reflecting the investment in acute care of HF at expense of home monitoring and chronic ambulatory management. The mortality rate is strictly related to readmission rate, and this rate results from an inexistence of a durable stabilization of chronic HF in ambulatory settings.

Literature shows that in HF patients the hospitalizations are associated with greater mortality rates, which should motivate the healthcare professionals to reduce that hospitalization rate, studying and modifying potential predicting variables unknown so far, among others. Actually, a patient-centered method combined with optimized medical treatment and palliative care improves certain HF outcomes, and some authors advocate a multifaceted approach to achieve a perfect management of chronic HF (CHF). Others advocate that this approach could benefit from telemedicine, and it has been theorized that remote monitoring could optimize the management of CHF. Some studies showed that the follow-up of HF patients, by structured phone calls and noninvasive home telemonitoring, reduces mortality and hospital admission rates.

On the other hand, the patient’s therapeutic adherence and health professionals’ compliance with international guidelines may not be the most appropriate. As patients with HF get older and polymedicated, the less they will be able to self-care and manage multiple treatments, and observational studies have shown that the probability of following guidelines is lower the older the patient. In addition, the international guidelines are based on clinical trials (CT) with participant’s average age around 65 years, and the consolidated data from the very elderly patient and with multiple comorbidities, our common patient from the HF consultation, are scarce.

Furthermore, selected traditional predicting factors lose their prognostic relevance among the elderly, and there are evidences that a few of them seem to provide some degree of protection to the HF patient, such as body mass index, serum cholesterol, and blood pressure, a situation called reverse epidemiology. Thus, it is imperative to determine prognostic predictive scores adapted to this reality. There are publications describing many HF scoring systems (some as decision algorithms) to apply in different points of the follow-up, but mostly are scores that cannot be used in clinical practice because they are too complex, not very user-friendly or based on data that are difficult to obtain or expensive.

From the aforementioned, we have implemented the GENICA project, a multidisciplinary HF consultation with a comprehensive and multifaceted profile to a systematic ambulatory approach of CHF patients. This project, based on its database, will provide a wide range of information that, on one hand, will design the profile of the real HF patient, and, on the other hand, will allow the development and validation of decision algorithms effectively useful for clinical practice.

Materials and methods

Design
Prospective matched 10-year cohort study (named GENICA), in which the control group will be the HF patients followed by other internists or cardiologists (both not included in the GENICA protocol), at the same Hospital Center, matched for the baseline characteristics (disease status and patient characteristics). The matching will be based on their propensity score as we are dealing with a large number of covariates, and the matching ratio will be 1:1.

GENICA stands for Grupo de Estudos Normalizando a abordagem da Insuficiência Cardíaca em Ambulatório, that means study group
standardizing the HF approach in an outpatient setting. On purpose, this acronym GENICA intends to refer to the adjective *genica* that is an informal Portuguese term that means energetic or vigorous way of acting and speaking. Precisely the characteristics that are lacking in most HF patients. The GENICA protocol encompasses a comprehensive strategy to give back some of that ‘genica’ to the CHF patients.

**Aims of GENICA project**

1. Optimize the ambulatory approach of chronic HF patients, aiming to reduce their re-hospitalization and emergency room (ER) readmission rates, as well as their global death rates. In addition, we aim to improve their functional capacity and quality of life.

2. Build a database which we intend to potentialize and turn into a national registry of CHF patients followed at an ambulatory basis. With this, we will obtain demographic, economic, social and clinical data from CHF patients at real-life, which are quite different from that of CT, mainly being older and with more comorbidities. Achieving such a comprehensive database, particularly if at a national basis, will enable proper comparisons of treatments and approaches in the future, improving health policies.

3. Development of a decision algorithm, including a risk score – the GENICA score – to predict major outcomes (death, re-hospitalization, and readmission to ER) in patients with CHF, and upgrade their ambulatory management.

4. Development of a noninvasive monitoring device (named MONITORIA) to support the optimization of some CHF patients (those with higher risk) at home.

5. Development of a mobile app to help monitor CHF patients at home, to use either with or without the MONITORIA device. This app will include the GENICA score and the decision algorithm presented at point 3, but also will incorporate artificial intelligence to potentialize its role in the ambulatory management of CHF patients.

6. Explore the impact of covid-19 pandemics in the management of CHF patients, as well as in the HF outcomes, aiming to highlight the importance of such an approach as that of GENICA.

**Setting of the study.** We implemented the GENICA project at CHF patients followed at a specialized consultation (performed by internists) at our center, which is a community hospital center. We aim to recruit all the patients referred to our consultation since they fit the inclusion criteria. The inclusion and exclusion criteria are listed in Table 1. Data will be collected by two of the investigators (which are also clinicians performing that specialized consultation) during the scheduled visits and registered at the database (using the software Access) built specifically for this project.

**GENICA team and its HF’s multidisciplinary approach**

The GENICA team includes five internal medicine specialists, two internal medicine residents, one cardiologist, a physiatrist, a psychiatrist, a social assistant, a nutritionist, two nurses specialized in cardiovascular area, and a palliative care specialist. At the first observation, the internists/internal medicine residents will fully evaluate patients and screen the need to refer them to the psychiatrist (anytime patients have not enough coping strategies to deal with the disease or show some evidence of reactive depression), to the social worker (when patients have no family support and have financial insufficiency, which may lead to problems about treatment compliance and follow-up), to the nutritionist (in situations of obesity or malnutrition) and to the palliative care physician (either when patients fulfill the criteria for advanced HF or anytime they are symptomatic despite optimized medical treatment). The cardiologist will manage the performance of electrocardiograms (ECGs), echocardiograms, and cardiac magnetic resonances and will be the bridge to the cardiothoracic surgeons or interventional cardiology, whenever appropriate. He also will give treatment support and guidance of patients with ischemic heart disease and valvular disease, in parallel to the internist in charge for those patients. After cardiovascular risk stratification and HF study, the patients will be referred to the physiatrist to begin a rehabilitation program according to their functional capacity and disease stage. The nurses will manage the appointments and treatments at the day hospital and will give support in terms of patient and family education.
Study population and recruitment process

We aim to recruit all the patients referred to our HF consultation, since they meet the inclusion criteria. Therefore, our sample will be a convenience sample and we estimate to have near 2000 patients at the end of recruitment process (30 June 2027). The control group will be recruited from referral records of our hospital center, every month, matching them to the GENICA patients recruited that month. The controls will be HF patients referred to general internist or cardiologist of the same hospital, but not acting under the GENICA protocol.

Follow-up

After referral, and provided they meet the inclusion criteria, patients will be observed in the subsequent 15 to 30 days. This first consultation will function to clarify the diagnosis of HF, stratify the HF and cardiovascular risk, and implement an action plan for further approach. The subsequent consultations (performed each 1 month, 3 months, or 6 months according to the decision algorithm) will function to improve management of the ambulatory care of CHF patients, which is the core of the project. Between the scheduled consultations, patients will be supported by structured telephone calls, performed by the physician in charge (see in the Appendix 1 the form to fill during the calls). This support will be upgraded with the monitoring app, which will function as bidirectional way of communication between the physician and the patient, and potentialized by the noninvasive monitoring device, when obtainable. Anytime the patients exacerbate and the situation is impossible to manage by telephone, the team will observe and care them in a day-hospital basis, this is, an open consultation without scheduling. Besides these structured telephone calls, patients will be able to call whenever they need to a 24 h/day phone number, which will be handled by one of the physicians performing the HF consultations. After recruitment, all patient should be followed for a minimum of 3 months to 3 years.

Table 1. Inclusion / exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| • HF diagnosed as “de novo” by the attending physician at the index hospitalization (which motivated the referral to our consultation). | • Acute HF. |
| • CHF patients with reduced LV ejection fraction, referred either by the family doctor, clinicians from other specialties at the hospital center, or from the hospitalization. | • Congenital HF. |
| • CHF patients with preserved or intermediate LV ejection fraction [referred also by the family doctor, other specialties or hospitalization], since they have had at least two hospitalizations and exacerbations motivating ED utilization during the previous year. | • Institutionalization at nursing or foster homes. |
| • Patients with 18 years old or more. | • Patients at continuity care units of medium and longer durations. |
| • Patients able to read, understand, and sign the informed consent. In cases in which this will not be possible, there must be a family member responsible for the patient, who must exercise this function, and who will legally represent the patient. | • Patients under palliative care for other reasons rather than HF. |
| • Patients with 18 years old or more. | • Cancer, with active disease, not candidates to curative treatment and/or under palliative care. |
| • Patients able to read, understand, and sign the informed consent. In cases in which this will not be possible, there must be a family member responsible for the patient, who must exercise this function, and who will legally represent the patient. | • Bedridden patients. |
| • Patients with known diagnosis of dementia, mental retardation, or psychiatric disorders affecting their judgment and ability to follow recommendations. | • Patients with known diagnosis of dementia, mental retardation, or psychiatric disorders affecting their judgment and ability to follow recommendations. |
| • Homeless and indigent patients. | • Homeless and indigent patients. |

CHF, chronic heart failure; ED, emergency department; HF, heart failure; LV, left ventricle.
Data collection and registry
As stated above, data will be collected and registered at the database by the two investigators who also are internists in charge of the HF consultation (CM and JA), avoiding collecting data from their own patients, to reduce bias. Data from patients referred to internists and cardiologists other than those performing in the scope of the GENICA project will be collected by two of the investigators (CM and JA) by consulting medical records and by telephone calls in case of missing data. All data will be handled in accordance with current legislation, at present the GDPR (General Data Protection Regulation) since 25 May 2018 and the Portuguese law No. 58/2019 of 8 August. Data will be secured using dedicated data management software and recorded in encrypted form to ensure anonymity. After the last participant’s final follow-up, all data will be stored for a minimum of 10 years.

Variables
In the scope of GENICA project, we will collect and record a large number of independent variables and covariables in parallel with the outcome variables in study, as depicted in Table 2.

Measurements
All sociodemographic and clinical variables will be collected during the anamnesis and physical examination performed during the HF consultations (including those at day-hospital basis) and the telephone calls. The blood pressure measurements will be made with the patient in the sitting position, with the cuff at left arm. The mean of three measurements will be considered. The comorbidities will be collected during clinical evaluations of follow-up, and the Charlson Comorbidity Index will be derived from these medical records, as it was previously shown that this way it is superior to the same index derived from administrative data. The quality-of-life scores will be obtained through adaptations of both SF36 and ‘Minesota Living With HF’. Analytical variables will be measured using Sysmex® XE-5000 equipment for hematology, ARCHITECT®ci8200, Abbott for biochemistry, Capillarys 2 Sebia for serum protein electrophoresis, Werfen’s ACL TOP® 700 for coagulation, and AUTION MAX® and SEDIMAX® for urine analysis. Venous blood and urine samples will be collected at admission and then once per year unless exacerbations/complications occur. The ECG variables will be measured by 12-leads ECG using BTL-08 MT plus ECG equipment. The chest X-ray variables will be measured using Philips’s machinery. The echocardiography variables will be measured using GE Vivid 9 ultrasound machine. The ECG, chest X-ray, and echocardiography will be taken at admission and then once per year. And the CMR (cardiac magnetic resonance) variables will be measured using a 3 Tesla magnetic resonance imaging equipment. The CMR will be performed only at admission.

Statistical analysis
Null hypothesis. The follow-up of CHF patients by GENICA protocol equals the usual care in terms of the studied outcomes.

Investigational hypothesis. The GENICA protocol is superior to the usual care in terms of the studied outcomes. The null hypothesis will be tested at the 5% level of significance.

To assess for normality, we will run the Kolmogorov–Smirnov test, to appropriately use parametric or non-parametric analysis. Quantitative (numerical) variables will be summarized as mean and standard deviation or median and interquartile range as appropriate. Categorical variables will be summarized as relative and absolute frequencies. Whenever pertinent, graphical representation of continuous variables will be made by histograms and box plot and categorical by bar graphs.

Baseline characteristics will be compared by t test for parametric continuous variables and by Fisher exact test (4 groups) or $\chi^2$ test (>4 groups) for categorical variables. The association between the independent variables and mortality, hospitalization, or readmission at emergency department (ED) outcomes will be assessed by logistic regression and between those variables and left ventricle ejection fraction will be assessed by multivariable linear regression, whenever appropriate. Multiple comparisons will be assessed using the Bonferroni correction or similar when appropriate. When comparing the group of patients followed by the GENICA protocol to the control group in terms of the outcomes in study, we will perform a $\chi^2$ test.
**Table 2. Variables collected and recorded for analysis.**

| Definitions                                                                 | Heart failure, chronic and acute: defined according to the European Society of Cardiology (ESC) guidelines. Decompensated heart failure: insidious appearance of symptoms/signs of pulmonary vascular congestion in a patient with chronic HF. Compensated heart failure: absence of symptoms/signs of pulmonary vascular congestion in a patient with chronic HF. Advanced an end-stage or terminal heart failure: defined according to AbouEzzeddine and Redfield.18 Homeless: miserable person without home. Comorbidities: Comorbid diseases present at the time of observation. |
|---|---|
| Sociodemographic variables | Age (date of birth and age in years), gender (male/female), marital status, education, professional status, profession, residence, household, migration status, ethnicity, income (average net monthly income of the patient and of the household). Self-care skills. |
| Clinical variables | Risk factors for HF (hypertension, diabetes mellitus, obesity/overweight, hyperlipidemia, hyperuricemia, ethanolic abuse, smoking, hyperhomocysteinemia, thyroid disease, use of cardiotoxic drugs, use of illicit drugs, radiation exposure, previous viral or bacterial infection, vitamin B and/or D deficit, anemia, previous blood transfusion), sun exposure (in average hours per day), perception level of stress, daily physical exercise (yes/no, time spent and distance covered in the exercise), daily alimentary diet, comorbidities, previous history of myocardial infarction, previous history of cardiac catheterization, pacemaker, chronic medication, functional class of HF, exacerbations of HF in the previous year, hospitalizations in the previous year, Charlson index, HF signs and symptoms, systolic arterial pressure, diastolic arterial pressure, heart rate, pulse characteristics, respiratory rate, peripheral oxygen saturation (oximetry), body weight, stature, ankle-arm index, data from cardiac auscultation, data from pulmonary auscultation, abdominal examination, limb and peripheral circulation examination, capillary fill time (seconds). Quality of life score. Exacerbations between clinical evaluations. Pertinent family history (sudden death in relatives under 50 years old, history of HF and myocardial infarction). |
| Analytical variables | Peripheral blood tests: Hemoglobin, hematocrit, leukocyte count, platelets, iron, transferrin, ferritin, transferrin saturation, urea, creatinine, glomerular filtration rate, uric acid, sodium, potassium, chloride, glucose, glycated hemoglobin, alanine and aspartate transaminases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, international normalized ratio, dimers, albumin, vitamin D3, vitamins B1, B6, and B12, homocysteine, free T4, thyroid-stimulating hormone [TSH], parathyroid hormone [PTH]. Urinalysis: qualitative analysis of urine and analysis of the urine sediment. Creatinine and albumin. |
| Variables derived from ECG | Rhythm, heart rate, QRS axis, QRS duration, hypertrophies [auricular/ventricular], atrial anomaly, electric conduction abnormalities, T wave alternans, ventricular repolarization anomalies. Other punctual alterations. |
| Variables derived from chest X-ray | Cardiothoracic index, signs of pulmonary vascular congestion, signs of alveolar/interstitial edema, ecstasy of intrathoracic great vessels, signs of primary lung disorders. |
| Variables derived from echocardiography | Heart chambers dimensions, ventricular wall thickness, valve status [morphological and functional evaluation], mobility alterations, systolic ventricular function, diastolic ventricular function, estimated pulmonary systolic arterial pressure, left ventricle ejection fraction, telediastolic volumes, inferior vena cava collapse, pericardial anomalies, masses. |
| Variables derived from cardiac magnetic resonance imaging (CMRI) | Heart chambers dimensions, telediastolic and telesystolic ventricular volumes, left ventricle ejection fraction, right ventricle ejection fraction, ventricular mass, myocardial edema, signs of myocardial inflammation, ventricular sphericity index, right ventricle telediastolic volume index [RVEDVI], delayed enhancement after gadolinium injection. |
| Variables for economical analysis | Monthly average costs with chronic medication, monthly average costs in dislocations from home to hospital, monthly average costs in hospital appointments. Costs per hospitalization. Costs per each emergency department episode of care. |
| Outcome variables | All-cause mortality, mortality for cardiac causes. Re-hospitalization rate [all-cause and cardiac-cause], readmission rate at the emergency department [all-cause and cardiac-cause]. Left ventricle ejection fraction. Quality of life score obtained using the MLHFQ (Minnesota Living with Heart Failure Questionnaire). |

ECG, electrocardiography; HF, heart failure; QRS, QRS complex that represents the depolarization of ventricles.
For repeated measures, we will use mixed effects models. Cox proportional hazard models will be used to evaluate the association between the association between independent variables and the outcomes over time, while adjusting for confounders/covariates.

**Missing data.** Cases with missing data will be dropped from the analysis.

**Sensitivity and subgroup analysis.** We will calculate the E-value for the estimates and for the limit of the 95% confidence interval closest to the null, as appropriate.

**Bias.** Besides matching, we will use the Cox proportional hazards regression model to further remove confounding and adjust for imbalances between the groups (the GENICA cohort versus controls). To prevent bias related to loss of follow-up, we plan to provide sufficient resources to achieve the maximum follow-up rate possible. Two of the investigators (CM and JA) are also internists performing the HF consultation, which may lead to bias. This will be minimized by the rule of not collecting data from their own patients and by having one of the investigators who do not perform the consultation, conducting the statistical analysis.

All the statistical analysis will be performed using the statistical software SPSS package version 27.

**Ethics**

The study protocol was approved by our institutional review board (registration number 17/2017 approved on 04-10-2017). Informed written consent will be obtained from the participants at first consultation, by the physician in charge.

**Discussion**

HF is a critical public health problem, with increasing prevalence, complex treatments, and high mortality, so a systematic and comprehensive analysis is necessary to provide optimized and personalized therapy.

Albeit providing the best evidence, randomized controlled trials face important ethical and logistical constraints, and have been criticized by some for focusing on highly selected populations. Hence, it is also important to carry out observational prospective studies with robust design, to complement the current knowledge on this theme.

Population-based prevention and promotion, through changes in lifestyle and environment, is indeed the most cost-effective and sustainable way of controlling cardiovascular and other major non-communicable diseases. In the current global situation, the GENICA project with its comprehensive and multidisciplinary method may come to show health policy makers that, in this case, the asset is not to divide and rule, but rather to converge strategies, therapies, and knowledge.

**Strengths and limitations of this study**

GENICA will provide a wide range of longitudinal data across sociodemographic, physical health, and quality-of-life outcomes, providing evidence for incidence and risk of death, re-hospitalization and recurrence to the ED. GENICA will provide high levels of evidence that will influence future healthcare of CHF patients at an ambulatory basis. Being a matched cohort, it benefits from an accuracy similar to that of randomized controlled trials, without the need to perform a rigorous allocation of the intervention. As this is a prospective cohort, there is no problem about response bias, but still may happen losses from follow-up.

**Conclusion**

CHF is a complex syndrome which should be approached with a multidisciplinary and multi-faceted strategy privileging the outpatient setting, including home monitoring. Therefore, the GENICA project will provide critical data enabling optimization of current HF management at ambulatory and improvement of the outcomes of these patients.

**Authors’ note**

The project GENICA is part of a thesis of CM within the scope of her Doctoral Program in Clinical Investigation and in Health Services.

**Declarations**

**Ethics approval and consent to participate**

We have submitted this protocol to the ethics committee of our institution and it was approved as declared in the annexed document. The par-
participants will sign their informed consent to participate as stated at Helsinki’s declaration.

Consent for publication
Not applicable.

Author contributions
Carla Sofia de Almeida Martins: Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

João Abranches Figueiredo Simões de Carvalho: Investigation.

Manuel Vaz da Silva: Formal analysis; Supervision; Validation; Writing – review & editing.

Luis Martins: Supervision; Validation.

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Competing interests
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Availability of data and materials
The data sets that will be generated, used, and analyzed during the current study will be available from the corresponding author on reasonable request.

ORCID iD
Carla Sofia de Almeida Martins https://orcid.org/0000-0001-7231-2968

Supplemental material
Supplemental material for this article is available online.

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### Appendix 1

**Telephone evaluation questionnaire of participants in the GENICA project**

| Identification of the patient | No. of entry at the Clinical trial | No. of the process at hospital | No. of consultation | No. of NHS patient |
|------------------------------|-----------------------------------|-------------------------------|--------------------|-------------------|
| Date:___/___/____            | Title of the study                |
| Current status of the patient: | Alive: date of death:___/___/___ | Dead: date of death:___/___/___ |
| Symptomatic assessment questionnaire | Dyspnea___ during rest/exercise, orthopnea___, paroxysmal nocturnal dyspnea___, chest pain___, dizziness___, history of syncope___, palpitations___, nocturnal cough___, nocturia /nicturia___, appetite___, feeling of flushing___, other symptoms___ |
| Objective questionnaire for family members | Mental confusion___, depressed mood___, easy irritability___, interaction in day-to-day activities___ |
| Complications | Since last evaluation have the patient’s symptoms worsened? |
| Need to use the emergency service? ______ How many times? ______ |
| Need for hospitalization? ______ How many times? ______ |
| Questions about illness or treatment? | | |
| Stress perception | |
| Diet | |
| How do you see your future? | |
| Feel supported by your doctor | |
| What do need else? | |