Dr. Julio Núñez Villota
• Introduction
• Hypothesis
• Results
• Conclusions
Most medical treatments have been designed for the “average patient”. This ‘one-size-fits-all-approach,’ assumes treatments are successful for most of patients.

Real clinical practice has shown this is not true.
**Precision medicine: our goal**

- Standard (Imprecise) Medicine
  - Same approach to heterogeneous clinical presentation and variable clinical outcomes
  - One-fits-it-all treatment
  - Morbidity and mortality remain high

- Precision Medicine
  - Greater understanding of individual variations in disease pathology
  - More precise disease and patient classification
  - Targeted and tailored therapeutics
Heart failure: a big problem

Pirámide de Kaiser en la Comunidad Valenciana año 2015
Insuficiencia Cardiaca: la Pirámide de Kaiser “Invertida”
n=62,500

Crónico de alta complejidad
n=36,542 (42,5%)

Crónico de moderada complejidad
n=26,776 (42,8%)

Crónico de baja complejidad
n=8,283 (13,3%)

Sano o con proceso agudo
n=899 (1,4%)

Gestión de la enfermedad

Alta complejidad Gestión del caso Manejo estrecho y coordinado

Gestión clínica y farmacéutica

Cáncer mama
Cáncer ovario
ICC
Cáncer pulmón

Cáncer vejiga
Cáncer próstata
ICC
Cáncer pulmón

Navarro J, et al. Rev ES Cardiol 2017
SEC. RECALCAR 2014
**Table 3.1**  Definition of heart failure with preserved (HFP EF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFP EF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRITERIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Symptoms ± Signs¹</td>
<td>Symptoms ± Signs¹</td>
<td>Symptoms ± Signs¹</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>1. Elevated levels of natriuretic peptides²; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
<td>1. Elevated levels of natriuretic peptides²; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
</tr>
</tbody>
</table>
HFrEF is not an exception

**Different phenotypes**

- Toxics
- Ischemic heart disease
- Hypertension
- Idiopathic
- Genetic

**Heart Failure**

- Right ventricular failure/
  Pulmonary hypertension
- Inflammation
- Iron deficiency
- Renal dysfunction
- Diabetes

**Heterogeneous phenotypes and clinical course**
Fluid overload

CONGESTION / FLUID OVERLOAD

- MYOCARDIAL STRETCH
- MYOCYTE INJURY
- MATRIX REMODELING
- INFLAMMATION
- RENAL DYSFUNCTION
- NEUROHUMORAL ACTIVATION
- OXIDATIVE STRESS
Fluid overload

Signs and symptoms in 4,537 residents of Worcester, Massachusetts, USA, hospitalized for acute HF between 1995 and 2000 (shaded area represents percentage of patients presenting with symptom)

Edema (swelling) of the ankles and feet
**Fluid overload assessment**

<table>
<thead>
<tr>
<th>Hallazgos</th>
<th>Sensibilidad</th>
<th>Especificidad</th>
<th>VPP</th>
<th>VPN</th>
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</thead>
<tbody>
<tr>
<td>Síntomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPN</td>
<td>0,41</td>
<td>0,84</td>
<td>2,6</td>
<td>0,70</td>
</tr>
<tr>
<td>Ortopnea</td>
<td>0,50</td>
<td>0,77</td>
<td>2,2</td>
<td>0,65</td>
</tr>
<tr>
<td>Edema</td>
<td>0,51</td>
<td>0,76</td>
<td>2,1</td>
<td>0,64</td>
</tr>
<tr>
<td>Disnea con el ejercicio</td>
<td>0,51</td>
<td>0,76</td>
<td>2,1</td>
<td>0,64</td>
</tr>
<tr>
<td>Fatiga y ganancia de peso</td>
<td>0,31</td>
<td>0,70</td>
<td>1,0</td>
<td>0,99</td>
</tr>
<tr>
<td>Tos</td>
<td>0,36</td>
<td>0,61</td>
<td>0,93</td>
<td>1,0</td>
</tr>
<tr>
<td>Examen físico</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tercer ruido</td>
<td>0,13</td>
<td>0,99</td>
<td>11</td>
<td>0,88</td>
</tr>
<tr>
<td>Reflejo hepatogénico</td>
<td>0,24</td>
<td>0,96</td>
<td>6,4</td>
<td>0,79</td>
</tr>
<tr>
<td>Ingergación yugular</td>
<td>0,39</td>
<td>0,92</td>
<td>5,1</td>
<td>0,66</td>
</tr>
<tr>
<td>Crepitantes</td>
<td>0,66</td>
<td>0,78</td>
<td>2,8</td>
<td>0,51</td>
</tr>
<tr>
<td>Soplo</td>
<td>0,27</td>
<td>0,90</td>
<td>2,6</td>
<td>0,81</td>
</tr>
<tr>
<td>Edema en piernas</td>
<td>0,50</td>
<td>0,78</td>
<td>2,3</td>
<td>0,64</td>
</tr>
<tr>
<td>PAS &lt; 100 mmhg</td>
<td>0,06</td>
<td>0,97</td>
<td>2,0</td>
<td>0,97</td>
</tr>
<tr>
<td>Cuarto ruido</td>
<td>0,05</td>
<td>0,97</td>
<td>1,6</td>
<td>0,98</td>
</tr>
<tr>
<td>PAS &gt; 150 mmhg</td>
<td>0,28</td>
<td>0,73</td>
<td>1,0</td>
<td>0,99</td>
</tr>
<tr>
<td>Sibilancias</td>
<td>0,22</td>
<td>0,58</td>
<td>0,52</td>
<td>1,3</td>
</tr>
<tr>
<td>Ascitis</td>
<td>0,01</td>
<td>0,97</td>
<td>0,33</td>
<td>1,0</td>
</tr>
</tbody>
</table>

Abreviaturas: VPP, valor predictivo positivo; VPN, valor predictivo negativo; DPN, disnea paroxística nocturna; PAS, presión arterial sistólica

- No detecta el 20% de las cardiomegalías por ecocardiografía
- Derrame pleural:
  - 67% sensibilidad
  - 70% especificidad
- Peores sensibilidad y especificidad en Rx torax portátil

“Los síntomas, signos, Rx torax y peptidos natriuréticos ofrecen una rentabilidad diagnóstica limitada para la identificación y cuantificación de la sobrecarga de fluidos”

CA125. Chemical structure

Glycoprotein synthesized by serous epithelial cells of extremely complex structure and high molecular weight

CA 125 and its relation to cardiac function

Herbert Nägele, MD, Marlies Bahlo, PhD, Rainer Klapdor, MD, Dorothea Schaeperkoetter, MD, and Wilfried Rödiger, MD, Hamburg, Germany

Figure 4

Pulmonary capillary wedge pressure and CA 125

CA125 serum levels
pre- and post HTx (n=25), mean -

Single logarithmic regression analysis of pulmonary capillary wedge pressure (PCP) and log CA 125 serum levels \( r = 0.37, \ P < .01, 71 \) consecutive patients with heart failure with a total of 157 determinations at different time points.

**CA125. Pathophysiology**

<table>
<thead>
<tr>
<th></th>
<th>Coeficiente β</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derrame pleural</strong></td>
<td>0.698</td>
<td>&lt;0.001</td>
<td>57.8%</td>
</tr>
<tr>
<td><strong>Edemas periféricos</strong></td>
<td>0.335</td>
<td>&lt;0.001</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

**Derrame pleural**

- **Grupo control**: n=181
- **Pacientes con IC**: n=529

- Coeficiente β = 0.698
- p = <0.001
- R² = 57.8%

**Edemas periféricos**

- Coeficiente β = 0.335
- p = <0.001
- R² = 12.9%

---

CA125 and prognosis

n=1111 patients with AHF

Modelo multivariado ajustado por: edad, sexo, ingreso previo por ICA, categoría de ICA (ADHF vs. otras), PAS al ingreso, FC al ingreso, FA, derrame pleural, FEVI<50%, creatinina sérica, Na≤130 mEq/L, BNP y tratamiento con ARAII y betabloqueantes.

CA125 Longitudinal measurements

- At a median follow-up of 2.61 years (IQR=1.2-5.3), 498 patients died (52.5%).
- Study sample representative of daily clinical practice (age 71 ± 11 years, 48.3% females, 41.8% ischemic etiology and 51% of LVEF<50%)

Núñez et al. Eur Heart J Acute Cardiovasc Care. 2016 May 19
Logistic issues

Standarized measurements
Widely available
Cheap
Long half-life (7-12 days)

Hypothesis

A CA125 guided-therapy in patients recently discharged for acute heart failure will decrease the risk of clinical adverse outcomes
ASUNTO: Orden SAS2377/2010, de 7 de septiembre, por la que se aprueba la convocatoria correspondiente al año 2010 de concesión de ayudas para el fomento de la investigación clínica independiente.

REMITENTE:
Jefe de Área de la Unidad de Subvenciones para la Investigación
Dirección General de Farmacia y Productos Sanitarios

DESTINATARIO:
Consejo de Apoyo a la Investigación Biomédica en Red
Sinesio Delgado 6
28029 Madrid

CC: Julio Núñez Villota

TÍTULO: EC16.108 Terapia guiada mediante los valores plasmáticos del antígeno carboidrático 125 tras un ingreso hospitalario por insuficiencia cardiaca aguda. Estudio randomizado y controlado.

Como continuación de la resolución del Ministerio de Sanidad y Política Social por la que se ha aprobado la relación definitiva de resultados de la convocatoria 2010 de acuerdo con lo establecido por la Orden SAS2377/2010, de 7 de septiembre, por la que se aprueba la convocatoria correspondiente al año 2010 de concesión de ayudas para el fomento de la investigación clínica independiente, le comunicamos lo siguiente:

- El plazo de ejecución de las ayudas es de un año de duración y comprenderá desde el 1 de enero de 2011 al 31 de diciembre de 2011.

- Las partidas presupuestarias concedidas para este proyecto son las siguientes:
Prognostic Effect of Carbohydrate Antigen 125-guided Therapy in Patients Discharged for Acute Heart Failure (CHANCE-HF)
A Randomized Study

Julio Núñez¹, Pau Llàcer², Vicente Bertomeu-González³, María José Bosch⁴, Pilar Merlos⁵, Sergio García-Blas¹, Vicente Montagud⁶, Vicente Bodí¹, Vicente Bertomeu-Martínez³, Valle Pedrosa⁶, Andrea Mendizábal⁴, Alberto Cordero⁸, Jorge Gallego⁴, Patricia Palau⁴, Gema Miñana¹, Enrique Santas¹, Salvador Morell⁶, Francisco J. Chorro¹, Juan Sanchis¹, Lorenzo Fácula⁶ for the CHANCE-HF Investigators.

¹ Hospital Clínico Universitario. INCLIVA. Universitat de Valencia. Valencia-Spain
² Servicio de Medicina Interna, Hospital de Manises. Valencia-Spain
³ Servicio de Cardiología, Hospital de San Juan. Alicante-Spain.
⁴ Servicio de Medicina Interna, Hospital de la Plana. Castellón-Spain
⁵ Servicio de Cardiología, Hospital de Manises. Valencia-Spain
⁶ Servicio de Cardiología, Hospital General Universitario de Valencia. Valencia-Spain

ClinicalTrials.gov Identifier: NCT02008110
CHANCE-HF

Design

Investigator-initiated, open-label, multicenter, randomized, controlled, prospective 2-arm trial that investigates whether a CA125-guided management strategy aimed to keep CA125≤35 U/ml would be superior to standard of care (SOC) in terms of 1-year clinical adverse events in patients recently discharged for AHF.

Objetives

Primary outcome:
- Composite of all-cause mortality plus acute heart failure related rehospitalization

Secondary outcomes:
- Composite of total mortality plus readmission for any cause
- Mortality and days alive outside of the hospital
- Rehospitalizations.
- Number of episodes of worsening HF not requiring hospitalization

All endpoints were evaluated as time to first event and longitudinally

ClinicalTrials.gov Identifier: NCT02008110

Núñez, et al. JACC HF 2016
### Inclusion criteria

- Age 18 years or older
- At least 1 episode of AHF in the last 180 days
- Demonstrates functional NYHA status of class ≥II at the moment of enrollment
- Objective evidence, either during the index admission or at least 180 days before enrollment, of a structural or functional abnormality of the heart at rest, defined as: NT-proBNP >1000 pg/ml or BNP >100 pg/ml or echocardiographic abnormalities congruent with HF diagnosis such as: systolic LV dysfunction (LVEF <50%); LV hypertrophy (defined as septum or LV posterior wall thickness ≥12 mm or LV mass index >104 g/m² in women or 116 g/m² in men); E/e’ ratio >15 or; significant valvular heart disease (moderate to severe)
- A plasma CA125 value >35 U/ml in a recent test evaluation (at least 30 days before enrollment, and preferably assessed before hospital discharge)
- Patient must be capable of understanding and signing an informed consent form

### Exclusion criteria

- Plasma CA125 ≤35 U/ml
- Life expectancy <12 months due to other diseases different from HF
- Having undergone a cardiac transplantation, coronary revascularization procedure (PCI and/or CABG) or cardiac valve replacement in the past 3 months
- Angina pectoris higher than class II (CCS Classification)
- Pregnancy at the moment of enrollment
- Valvular heart disease already scheduled for surgical intervention
- Severe chronic obstructive and/or restrictive pulmonary disease, requiring continuous oxygen administration
- Serum creatinine level >3 mg/dl or chronic renal insufficiency on dialysis treatment
- Patients receiving resynchronization therapy during the index admission
- Significant concurrent medical diseases including cancer or a history of cancer within 5 years of entering the screening period, endometriosis, cirrhosis, acute coronary syndrome within 6 months, uncontrolled hypertension, history of HIV infection, or a significant active infection
- Participating in another randomized study

### Randomization visit

- Consider use of statins in all patients, especially at low doses.
- Maintain LDD if clinical stability. Consider increasing LDD if symptoms and signs of congestion persist.

### Visits 1, 2, 3 and additional

#### CA125 returns to normal values (≤ 35 U/ml)
- Consider reducing LDD, especially in patients receiving high diuretic doses (FED ≥120 mg/day) and in those with evidence of worsening renal function.
- Encourage the initiation, if not prescribed, or the continuation of statin treatment if well tolerated.

#### CA125 decreases but remains high (>35 U/ml)
- Consider maintaining LDD or increase dose if FED <80 mg/day is currently prescribed.
- Reevaluate clinical status and CA125 in an additional prompt visit (2-8 weeks).
- Consider increasing statin dose.
- Consider up-titrating beta-blockers and/or ACEI and/or ARB doses to maximum doses recommended
- Consider adding aldosterone antagonist if previously not administered.

#### CA125 increases along the course of the trial
- Consider increasing LDD and/or adding HCTZ 12.5-50 mg/day or clorthalidone 12.5-50 mg/day and/or aldosterone antagonist 12.5-50 mg/day.
- Consider optional prompt visits (1-4 weeks).
- Consider ambulatory administration of intravenous furosemide and/or ultrafiltration techniques.
- Maximize the statin treatment if possible.
- Consider intravenous iron if iron deficiency is present.

LDD: loop diuretic dose; CA125: antigen carbohydrate 125; FED: furosemide equivalent dose; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; HCTZ: hydrochlorothiazide.
583 Assessed for Eligibility

203 Excluded
  165 Did not meet inclusion criteria
  11 Refused to participate
  5 Died after screening
  13 Acute coronary syndrome
  9 Pneumonia

380 Randomized

187 Assigned to CA125-guided therapy
  181 Received Intervention as Assigned
  6 Did Not Receive Assigned Intervention
    3 Cancer
    1 COPD requiring continuous O2 adm
    1 Acute coronary syndrome
    1 Consent withdrawal

193 Assigned to standard of care
  191 Received Intervention as Assigned
  2 Did Not Receive Assigned Intervention
    1 Cancer
    1 Consent withdrawal

187 Included in Analysis

193 Included in Analysis

0 Lost to Follow-up

ClinicalTrials.gov Identifier: NCT02008110
### Demographics and medical history

<table>
<thead>
<tr>
<th>Variables</th>
<th>CA125-guided therapy (n=187)</th>
<th>Standard of care (n=193)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>74 ± 11</td>
<td>73 ± 11</td>
<td>0.41</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>107 (57.2)</td>
<td>105 (54.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td>75.2 ± 17.3</td>
<td>75.7 ± 18.1</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypertension*, n (%)</td>
<td>167 (89.3)</td>
<td>158 (81.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>Diabetes Mellitus*, n (%)</td>
<td>100 (53.5)</td>
<td>82 (42.5)</td>
<td>0.040</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>110 (58.8)</td>
<td>114 (59.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>61 (32.6)</td>
<td>61 (31.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>16 (8.6)</td>
<td>16 (8.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>22 (11.8)</td>
<td>17 (8.8)</td>
<td>0.40</td>
</tr>
<tr>
<td>Prior history of valvular heart disease, n (%)</td>
<td>63 (33.7)</td>
<td>73 (37.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Chronic renal disease, n (%)</td>
<td>71 (38.0)</td>
<td>59 (30.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>32 (17.1)</td>
<td>24 (12.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>19 (10.2)</td>
<td>17 (8.8)</td>
<td>0.73</td>
</tr>
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</table>

### Physical examination

<table>
<thead>
<tr>
<th>Variables</th>
<th>CA125-guided therapy (n=187)</th>
<th>Standard of care (n=193)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>79 ± 19</td>
<td>80 ± 19</td>
<td>0.52</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>127 ± 25</td>
<td>122 ± 22</td>
<td>0.06</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>69 ± 14</td>
<td>69 ± 14</td>
<td>0.80</td>
</tr>
</tbody>
</table>

### Electrocardiogram and echocardiography

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Standard of care (n=193)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration†, msec</td>
<td>100 (80, 130)</td>
<td>100 (80, 120)</td>
<td>0.59</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>45.75 ± 16.75</td>
<td>44.74 ± 17.24</td>
<td>0.56</td>
</tr>
<tr>
<td>LVEF ≥50%, n (%)</td>
<td>73 (39.2)</td>
<td>78 (41.3)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

### Laboratory results

<table>
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<tr>
<th>Variables</th>
<th>CA125-guided therapy (n=187)</th>
<th>Standard of care (n=193)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.2 ± 1.9</td>
<td>12.4 ± 2.0</td>
<td>0.52</td>
</tr>
<tr>
<td>BUN†, mg/dL</td>
<td>60 (42, 83)</td>
<td>55 (42, 80)</td>
<td>0.20</td>
</tr>
<tr>
<td>Creatinine†, mg/dL</td>
<td>1.20 (0.93, 1.51)</td>
<td>1.13 (0.94, 1.50)</td>
<td>0.56</td>
</tr>
<tr>
<td>CA125†, U/mL (n = 61)</td>
<td>103 (64, 174)</td>
<td>86 (55, 160)</td>
<td>0.12</td>
</tr>
<tr>
<td>BNP†, pg/mL (n = 61)</td>
<td>582 (321, 1010)</td>
<td>662 (448, 1154)</td>
<td>0.334</td>
</tr>
<tr>
<td>NT-proBNP†, pg/mL (n = 319)</td>
<td>4570 (2251, 9849)</td>
<td>3773 (1947, 8192)</td>
<td>0.182</td>
</tr>
</tbody>
</table>
CHANCE-HF

Results

Loop diuretic doses

Number of ambulatory visits

*p = 0.003

Núñez, et al. JACC HF 2016

ClinicalTrials.gov Identifier:
NCT02008110
**Loop diuretics**

<table>
<thead>
<tr>
<th></th>
<th>CA125-guided therapy (n=187)</th>
<th>Standard of care (n=193)</th>
<th>IRR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization, n (%)</td>
<td>186 (99.5)</td>
<td>191 (99.0)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>End of the trial, n (%)</td>
<td>186 (99.5)</td>
<td>191 (99.0)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>FED at discharge, mg/24 hours (mean)</td>
<td>94.4 ± 51.6</td>
<td>96.6 ± 56.5</td>
<td>0.693</td>
<td></td>
</tr>
<tr>
<td>FED at the end of the trial, mg/24h (mean)</td>
<td>108.1 ± 90.0</td>
<td>97.1 ± 70.0</td>
<td>0.182</td>
<td></td>
</tr>
</tbody>
</table>

**ClinicalTrials.gov Identifier:** [NCT02008110](https://clinicaltrials.gov/ct2/show/NCT02008110)

Núñez, et al. JACC HF 2016
**CHANCE-HF**

**Results**

**Treatments**

- **Iron iv**: 25.4% CA125-guided, 13.9% SOC, $p=0.019$
- **Statins**: 82.4% CA125-guided, 53.4% SOC, $p<0.001$
- **Aldosterone antagonists up-titration**: 0.16 person-years CA125-guided, 0.08 person-years SOC, $p=0.031$

**ClinicalTrials.gov Identifier**: NCT02008110

Núñez, et al. JACC HF 2016
Evidence-based treatments

CHANCE-HF
Results

ClinicalTrials.gov Identifier: NCT02008110

Núñez, et al. JACC HF 2016
**CHANCE-HF**

**Results**

### Time to first event

**All-cause death/AHF readmission**

- **Cumulative rates of events**
  - SOC: [Graph showing cumulative events]
  - CA125-strategy: [Graph showing cumulative events]

- **Peto-Peto test:** $p=0.036$
- **RMST difference:** 0.08 years; 95% CI: 0.02-0.15; $p=0.017$

<table>
<thead>
<tr>
<th>Number at risk (events)</th>
<th>SOC</th>
<th>CA125-strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>193 (54)</td>
<td>139 (4)</td>
</tr>
<tr>
<td></td>
<td>133 (11)</td>
<td>122 (13)</td>
</tr>
<tr>
<td></td>
<td>109 (13)</td>
<td>109 (13)</td>
</tr>
</tbody>
</table>

### Time to first event

**All-cause death/any readmission**

- **Cumulative rates of events**
  - SOC: [Graph showing cumulative events]
  - CA125-strategy: [Graph showing cumulative events]

- **Peto-Peto test:** $p=0.135$
- **RMST difference:** 0.054 years (-0.018-0.125); $p=0.142$

<table>
<thead>
<tr>
<th>Number at risk (events)</th>
<th>SOC</th>
<th>CA125-strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>193 (54)</td>
<td>139 (4)</td>
</tr>
<tr>
<td></td>
<td>133 (12)</td>
<td>121 (13)</td>
</tr>
<tr>
<td></td>
<td>107 (14)</td>
<td>109 (13)</td>
</tr>
<tr>
<td></td>
<td>96 (11)</td>
<td>96 (11)</td>
</tr>
</tbody>
</table>

### Longitudinal events

**Repeated AHF readmission**

- **Mean number of recurrences**
  - SOC: [Graph showing mean number of recurrences]
  - CA125-strategy: [Graph showing mean number of recurrences]

- **$p=0.008$**

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>SOC</th>
<th>CA125-strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8</td>
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</tr>
<tr>
<td>1</td>
<td></td>
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</table>

**ClinicalTrials.gov Identifier:**

NCT02008110

Núñez, et al. JACC HF 2016
### CHANCE-HF

#### Results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients (n)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Omnibus p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 75 years</td>
<td>167</td>
<td>0.78 (0.45, 1.35)</td>
<td>0.565</td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>213</td>
<td>0.65 (0.44, 0.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>168</td>
<td>0.69 (0.43, 1.13)</td>
<td>0.762</td>
</tr>
<tr>
<td>Male</td>
<td>212</td>
<td>0.76 (0.49, 1.18)</td>
<td></td>
</tr>
<tr>
<td><strong>CAD etiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>258</td>
<td>0.62 (0.41, 0.95)</td>
<td>0.238</td>
</tr>
<tr>
<td>Yes</td>
<td>122</td>
<td>0.95 (0.57, 1.61)</td>
<td></td>
</tr>
<tr>
<td><strong>LV ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50%</td>
<td>224</td>
<td>0.87 (0.56, 1.35)</td>
<td>0.236</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>151</td>
<td>0.60 (0.36, 1.00)</td>
<td></td>
</tr>
<tr>
<td><strong>CA125</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 95 U/ml</td>
<td>190</td>
<td>0.56 (0.35, 0.89)</td>
<td>0.222</td>
</tr>
<tr>
<td>&gt; 95 U/ml</td>
<td>190</td>
<td>0.83 (0.52, 1.33)</td>
<td></td>
</tr>
<tr>
<td><strong>Natriuretic peptides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>190</td>
<td>0.60 (0.37, 0.99)</td>
<td>0.305</td>
</tr>
<tr>
<td>Above median</td>
<td>190</td>
<td>0.82 (0.53, 1.27)</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 ml/min/1.73m²</td>
<td>177</td>
<td>0.64 (0.37, 1.09)</td>
<td>0.543</td>
</tr>
<tr>
<td>&lt;60 ml/min/1.73m²</td>
<td>202</td>
<td>0.77 (0.51, 1.16)</td>
<td></td>
</tr>
</tbody>
</table>

"Decrease in risk"  "Increase in risk"
Conclusions

The CA125 strategy was superior to the SOC in terms of reducing the risk of the composite of 1-year death or AHF readmission. This effect was mainly driven by significantly reducing the rate of rehospitalizations.
Carbohydrate Antigen 125-Guided Therapy in Acute Heart Failure

CHANCE-HF: A Randomized Study

Julián Núñez, MD, 1,2,3 Pau Llacer, MD, 2 Vicente Bertomeu-González, MD, 1 María José Bosch, MD, 4 Pilar Medios, MD, 6 Sergio García-Blas, MD, 7 Vicente Montagud, MD, 1 Vicent Bodí, MD, 6 Vicente Bertomeu-Martínez, MD, 2 Valle Pedrosa, MD, 5 Andrea Mendiñabel, MD, 3 Alberto Condore, MD, 7 Jorge Gállego, MD, 7 Patricia Palau, MD, 4 Gemma Muñana, MD, 6 Enrique Santos, MD, 6 Salvador Morell, MD, 1 Ángel Llurba, MD, 7 Francisco J. Górho, MD, 2 Juan Sanchís, MD, 2 Lorenzo Fàbila, MD, 4 for the CHANCE-HF Investigators

ABSTRACT

OBJECTIVES The study sought to evaluate the prognostic effect of carbohydrate antigen 125 (CA125)-guided therapy (CA125 strategy) versus standard of care (SOC) after a hospitalization for acute heart failure (AHF).

BACKGROUND CA125 has emerged as a surrogate of fluid overload and inflammatory status in AHF. After an episode of AHF admission, elevated values of this marker at baseline as well as its longitudinal profile relate to adverse outcomes, making it a potential tool for treatment guiding.

METHODS In a prospective multicenter randomized trial, 380 patients discharged for AHF and high CA125 were randomly assigned to the CA125 strategy (n = 187) or SOC (n = 193). The aim in the CA125 strategy was to reduce CA125 to <35 U/mL by up or down diuretic dose, enforcing the use of statins, and tightening patient monitoring. The primary endpoint was 1-year composite of death or AHF readmission. Treatment strategies were compared as a time to first event and longitudinally.

RESULTS Patients allocated to the CA125 strategy were more frequently visited, and treated with ambulatory intravenous loop diuretics and statins. Likewise, doses of oral loop diuretics and aldosterone receptor blockers were more frequently modified. The CA125 strategy resulted in a significant reduction of the primary endpoint, whether evaluated as time to first event (66 events vs. 84 events; p = 0.017) or as recurrent events (85 events vs. 165 events; incidence rate ratio: 0.49; 95% confidence interval: 0.28 to 0.82; p = 0.008). The effect was driven by significantly reducing rehospitalizations but not mortality.

CONCLUSIONS The CA125 strategy was superior to the SOC in terms of reducing the risk of the composite of 1-year death or AHF readmission. This effect was mainly driven by significantly reducing the rate of rehospitalizations. (Carbohydrate Antigen 125-guided Therapy in Heart Failure; NCT02008110) J Am Coll Cardiol HF 2016;11:833-843 © 2016 by the American College of Cardiology Foundation.
Can Carbohydrate Antigen-125 Be a New Biomarker to Guide Heart Failure Treatment?

The CHANCE-HF Trial

Antonio D’Alessio, MD; Ernesto Uncini, MD; Marco Merca, MD

B iomarkers are among the most intensely studied areas in heart failure (HF). They are critical both for the identification of subjects at risk for HF in the general population and, to a much larger extent, in symptom-guided patients for the diagnosis and prognostic evaluation of HF (1-5). Because each biomarker is related to different pathophysiologic mechanisms (fibrosis, inflammation, oxidative stress, organ damage, renal function, and so on), it has been hypothesized that biomarkers may be used to tailor HF treatment depending on its major cause (6-10). Changes in biomarkers after treatment have been used to assess vagal therapy, with, however, different results with respect to the effects of treatment (11). In addition, because some biomarkers, such as natriuretic peptides, are both related to patients’ clinical conditions and sensitive to treatment, their measurement has been proposed to guide treatment of HF (12).

This hypothesis has been tested in multiple clinical trials to date, whose sizes, however, were too small to produce firm results in most cases. However, favorable results have been shown in meta-analyses and a properly powered randomized controlled trial is ongoing (13-16).

Carbohydrate antigen-125 (CA125) is secreted from ovarian cancer and lymphoma cells in a process stimulated by inflammatory activity (17-19). In patients with HF, CA125 is secreted by normal cells in response to congestion, increased central venous pressure, and inflammation (20-26). The first observation of an increase in CA125 plasma levels in patients with HF was published in 1999, by Spiegel et al. (26). They found marked elevations of CA125 levels in patients with HF, with significant correlations with clinical severity and filling pressures (25). Four years later, we reported serum CA125 levels in a larger group of patients with HF due to left ventricular systolic dysfunction and a wide spectrum of HF severity. We found a significant relationship among CA125, HF severity, and short-term prognostic risk. Further studies have confirmed the value of CA125 in patients with HF (27,28). Interestingly, serum levels of CA125 were shown to change after treatment, suggesting its potential utility for patient follow-up and assessment of the efficacy of therapeutic interventions (29).

THE CHANCE-HF TRIAL

In the scope of the CHANCE-HF (Carbohydrate Antigen-125-Guided Therapy in Acute Heart Failure) trial, the first prospective, multicenter, randomized, controlled trial aimed at the assessment of the effects of treatment on the basis of serial measurements of CA125 plasma levels in patients with HF, the trial was conducted in 310 patients admitted to the hospital for
CA125-guided therapy reduces AHF rehospitalizations

Carbohydrate antigen 125 (CA125)-guided treatment of acute heart failure (AHF) reduces the rate of rehospitalizations compared with standard of care (SOC). This finding was reported by the CHANCE-HF investigators and published in JACC: Heart Failure.

The majority of patients with AHF show symptoms and signs of fluid overload. In the past decade, CA125 has emerged as a potential surrogate of fluid overload and inflammation in the setting of AHF. CHANCE-HF was an investigator-initiated, multicentre, prospective, randomized, controlled trial designed to assess the efficacy of CA125 as a biomarker for guiding therapy in patients recently discharged for AHF.

In total, 380 patients discharged for AHF were enrolled into the trial; 187 were assigned to receive CA125-guided therapy, and 193 were assigned to SOC. The CA125 strategy involved a prespecified algorithm designed to maintain the levels of CA125 at 35 U/ml or less by increasing the number of monitoring visits, enforcing statin use, and by diuretic dose optimization. The primary outcome end point was 1-year composite of death or AHF readmission.

Patients in the CA125 treatment group received more visits and were more frequently treated with ambulatory intravenous loop diuretics and statins. CA125-guided therapy reduced the primary end point outcome compared with SOC, whether assessed as time to first event (66 versus 86 events; P = 0.017) or as recurrent events (85 versus 165 events; P = 0.008). Notably, the reduction in the primary end point was driven only by reduced AHF readmission, and not by a reduction in mortality.

In light of these positive findings, Julio Núñez, lead investigator of CHANCE-HF, explains that CA125 might be a useful clinical tool to tailor monitoring frequency, statin therapy, and diuretic treatment in patients with a recent episode of AHF. “The fact that plasma levels of this biomarker respond to the intensity of diuretic use opens the potential use of this biomarker as a guiding therapy not only during the transition phase, but also during hospitalization,” adds Núñez. Christian Mueller, Professor at University Hospital Basel, Switzerland, who was not involved in the study, welcomes these favourable findings, but reminds clinicians that, at this point in time, the new data have important implications for research, but no immediate consequences for routine clinical practice.

Karina Huysh
Using Biomarkers to Guide Heart Failure Therapy

Allan S. Jaffe¹ and James L. Januzzi, Jr.²

Table 1. Candidate “next” biomarkers for guiding chronic HF therapy.³

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Known mechanism(s)?</th>
<th>Defined cutoff?</th>
<th>Therapies identified to reduce risk?</th>
<th>Suitable for serial measurement?</th>
<th>Time window for resampling identified?</th>
<th>Acceptable assays available?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Soluble ST2</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Growth differentiation factor-15</td>
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<td>++</td>
<td>+/-</td>
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</tbody>
</table>

³ Markers are graded on a scale from - to ++. References are available in the online Supplemental Data File.
Agradecimientos

A mis mentores....
A mis compañeros...
A mi familia...

„The best physician for a patient with HF would be one with excellent training, extensive experience, and superb judgment with regard to all aspects of the disease. He or she would not necessarily follow guidelines slavishly."

J.N. Cohn, Circ Heart Fail 2008;1:87-88