Presentación Premio Real Academia de Medicina de la Comunidad Valenciana 2016

Prognostic Effect of Carbohydrate Antigen 125-guided Therapy in Patients Discharged for Acute Heart Failure (CHANCE-HF)
A Randomized Study

Dr. Julio Núñez Villota

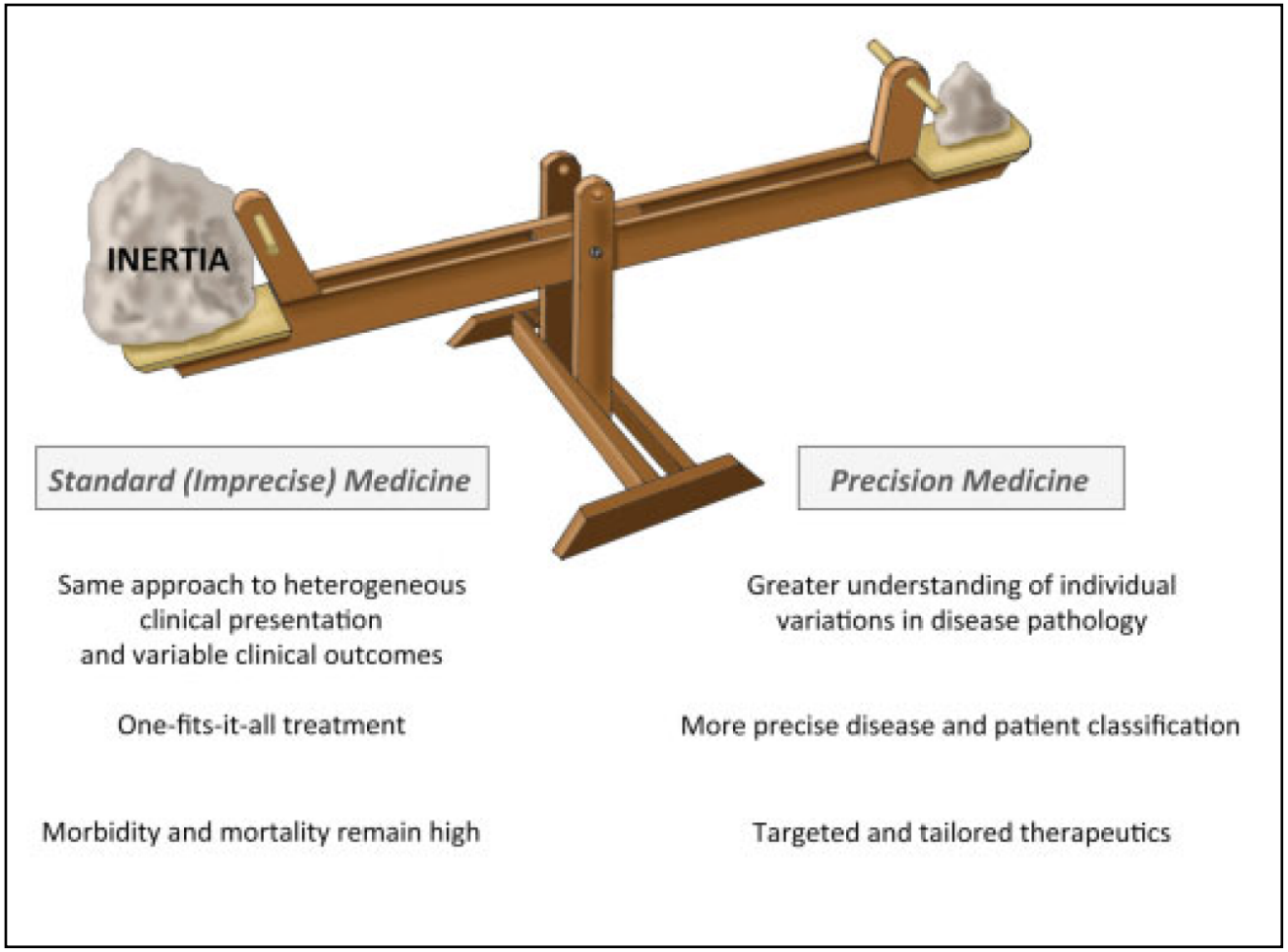
- Introduction
- Hypothesis
- Results
- Conclusions

Precision medicine: our goal

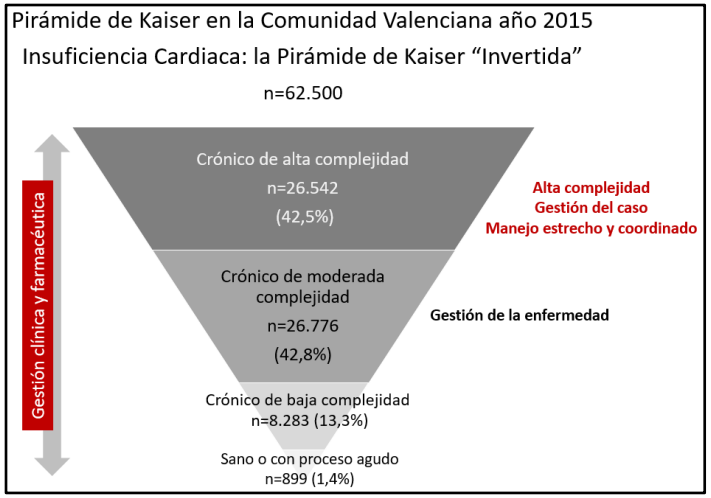
*Most medical treatments have been designed for the "average patient". This **'one-size-fits-all-approach**,' assumes treatments are successful for most of patients*

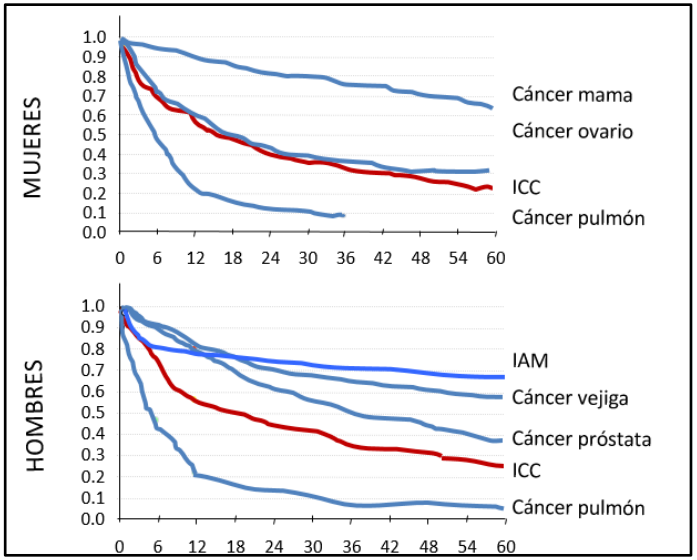
Real clinical practice has shown this is not true

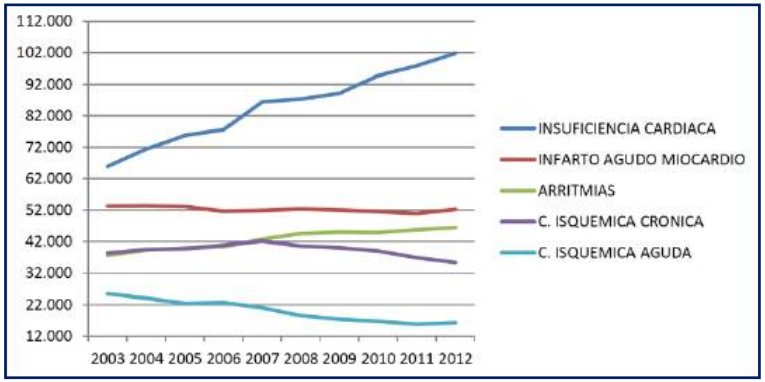
Precision medicine: our goal



Heart failure: a big problem





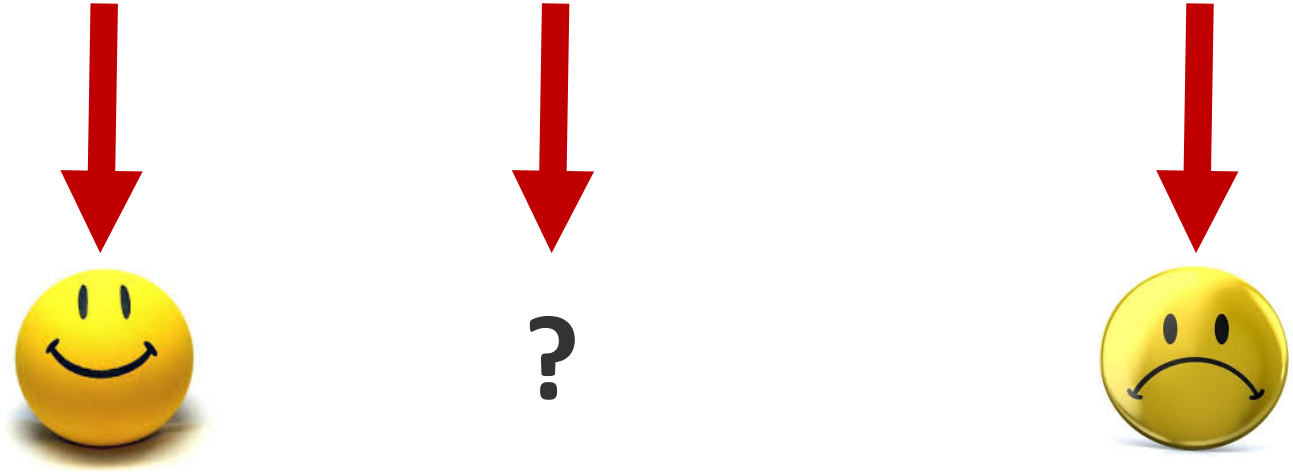


Navarro J, et al. Rev ES Cardiol 2017
SEC. RECALCAR 2014
Rev Esp Cardiol 2013; 66:649-656

HFrEF | HFmrEF | HFpEF

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

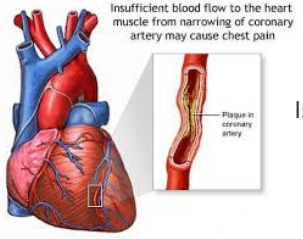
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 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).



ESC HF Guidelines European Journal of Heart Failure (2016)

HFrEF is not and exception
Different phenotypes

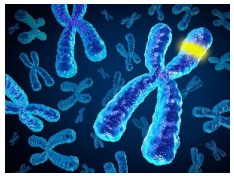
Toxics



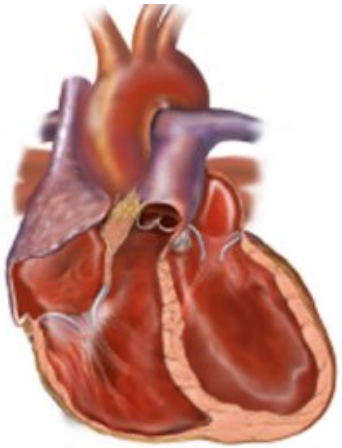
Ischemic heart disease

Hypertension

Idiopathic



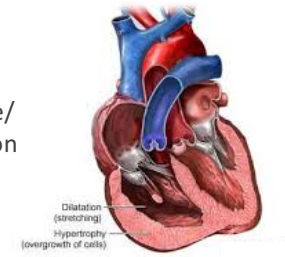
Genetic



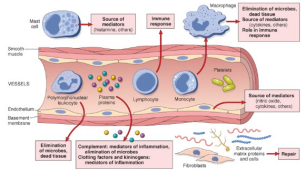
Heart Failure

Heterogeneous phenotypes and clinical course

Right ventricular failure/
Pulmonary hypertension

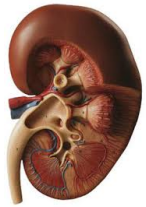


Inflammation



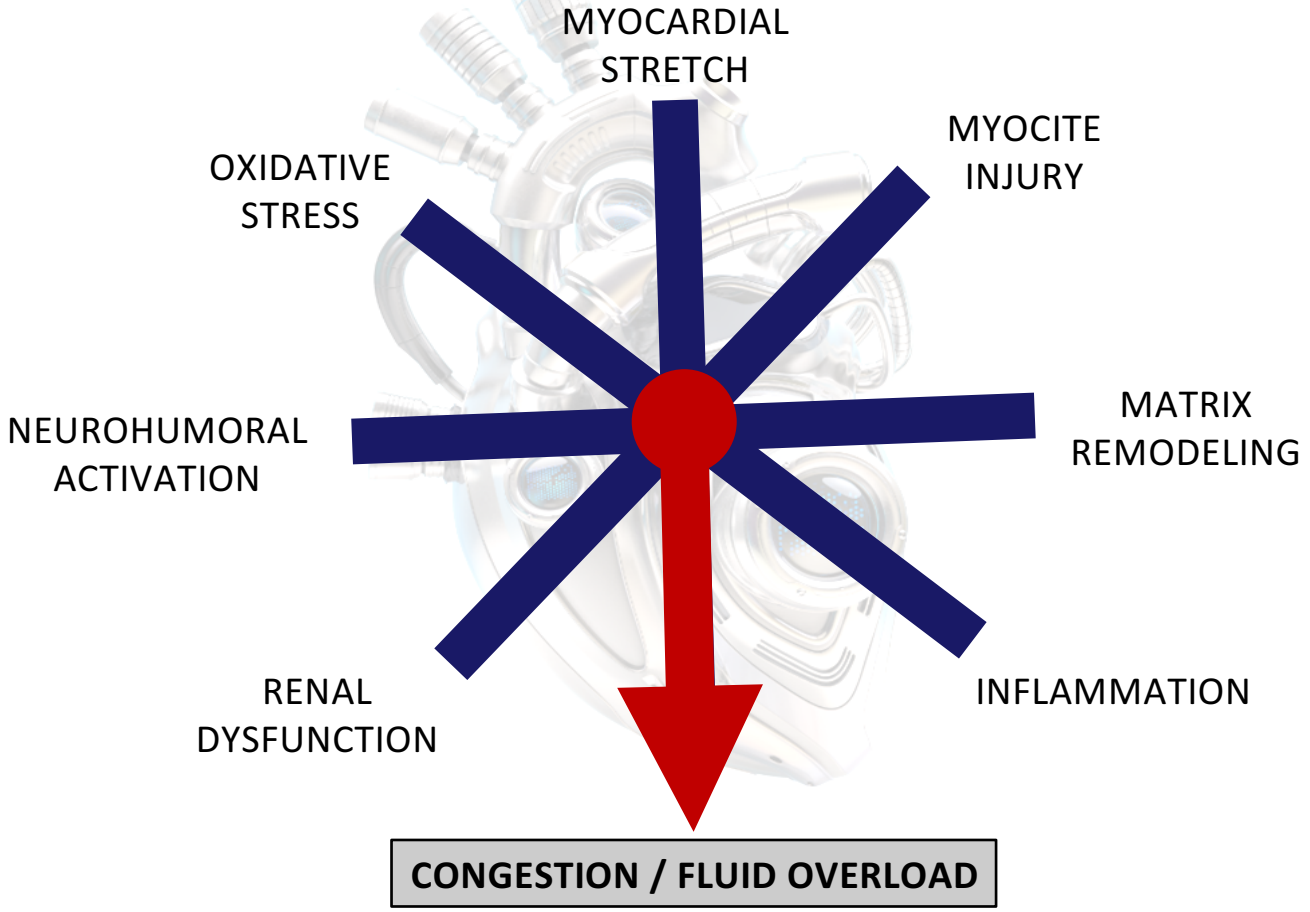
Iron deficiency

Renal dysfunction



Diabetes

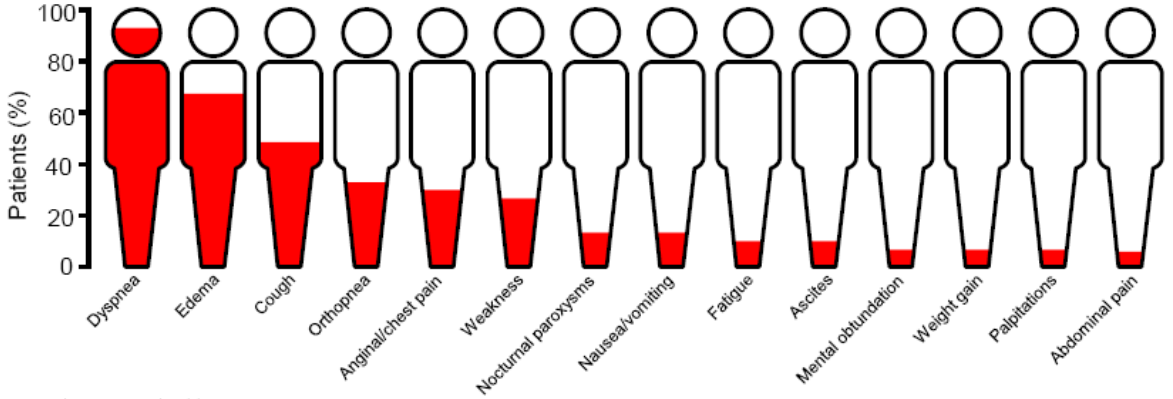
Fluid overload



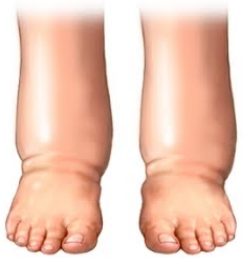
Braunwald et al. JCHF. 2013;1:1-20

Fluid overload

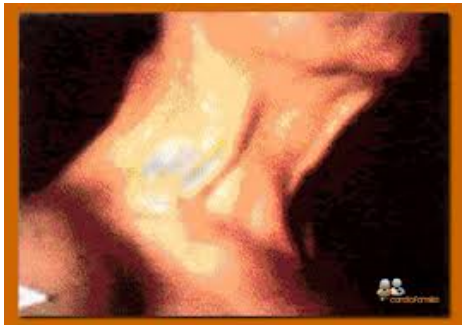
Signs and symptoms in 4,537 residents of Worcester, Massachusetts, USA, hospitalized for acute HF between 1995 and 2000 (shaded area represents percentage of patients presenting with symptom)



HF=heart failure; USA=United States of America
Goldberg et al. Clin Cardiol 2010;33:e73–80



Edema (swelling) of the ankles and feet



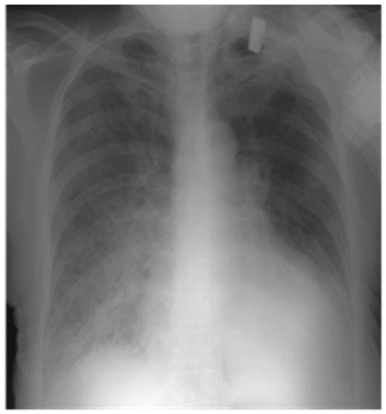
Fluid overload assesment

Resumen de la precisión del diagnóstico de los hallazgos en la exploración física e historia clínica de la sobrecarga hídrica en un departamento de emergencias en pacientes con disnea

Hallazgos	Sensibilidad	Especificidad	VPP	VPN
Síntomas				
DPN	0,41	0,84	2,6	0,70
Ortopnea	0,50	0,77	2,2	0,65
Edema	0,51	0,76	2,1	0,64
Disnea con el ejercicio	0,84	0,34	1,3	0,48
Fatiga y ganancia de peso	0,31	0,70	1,0	0,99
Tos	0,36	0,61	0,93	1,0
Examen físico				
Tercer ruido	0,13	0,99	11	0,88
Reflujo hepatoyugular	0,24	0,96	6,4	0,79
Ingurgitación yugular	0,39	0,92	5,1	0,66
Crepitantes	0,66	0,78	2,8	0,51
Soplo	0,27	0,90	2,6	0,81
Edema en piernas	0,50	0,78	2,3	0,64
PAS < 100 mmhg	0,06	0,97	2,0	0,97
Cuarto ruido	0,05	0,97	1,6	0,98
PAS > 150 mmhg	0,28	0,73	1,0	0,99
Sibilancias	0,22	0,58	0,52	1,3
Ascitis	0,01	0,97	0,33	1,0

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

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

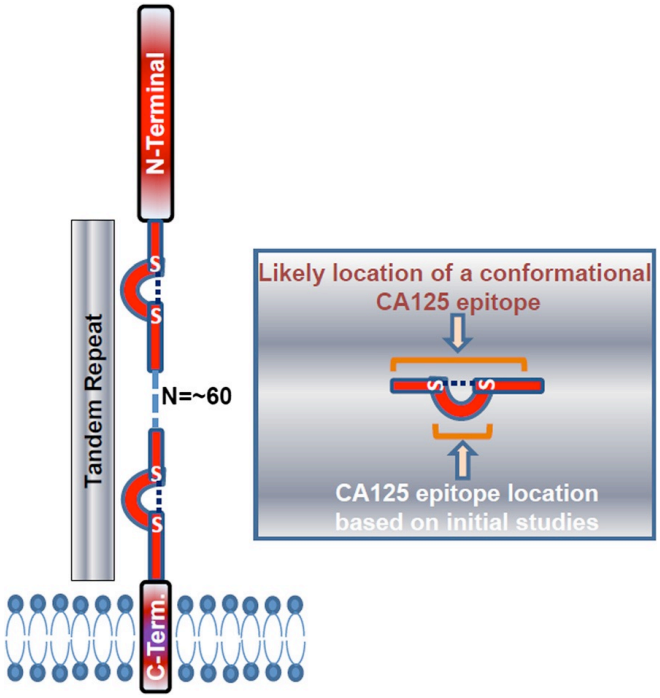


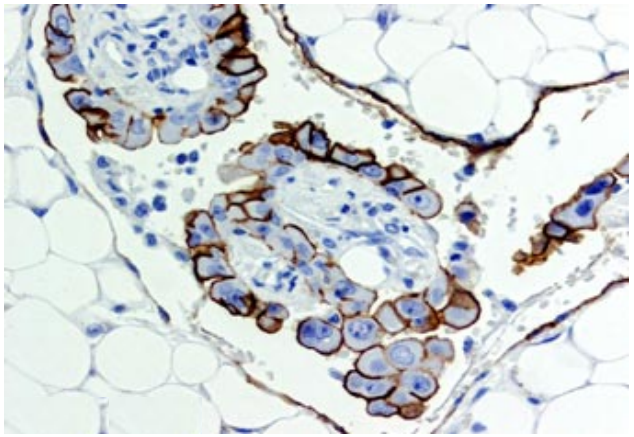
"Los síntomas, signos, Rx torax y peptidos natriuréticos ofrecen una rentabilidad diagnóstica limitada para la identificación y cuantificación de la sobrecarga de fluidos"

Peacock WF, et al. Contrib nephrol 2010; 164:128-42
Gheorghiade M, et al. Eur J Hear Fail. 2010;12:423-33
Verbrugge F, et al. J Am Coll Cardiol. 2015;65:480-92

CA125. Chemical structure

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





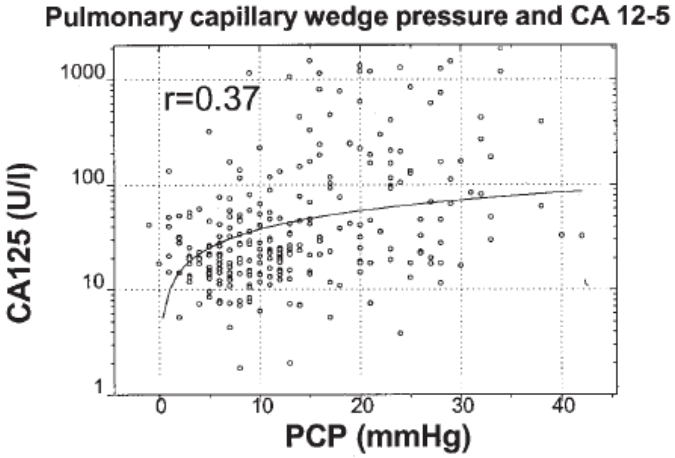
Davis HM, et al. Cancer Res. 1986
O'Brien TJ, et al. Int J Biol Markers. 1998

CA125. Pathophysiology

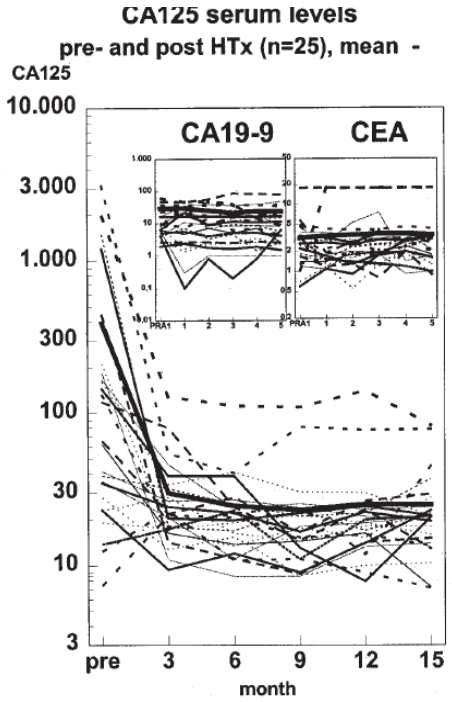
CA 125 and its relation to cardiac function

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

Figure 4



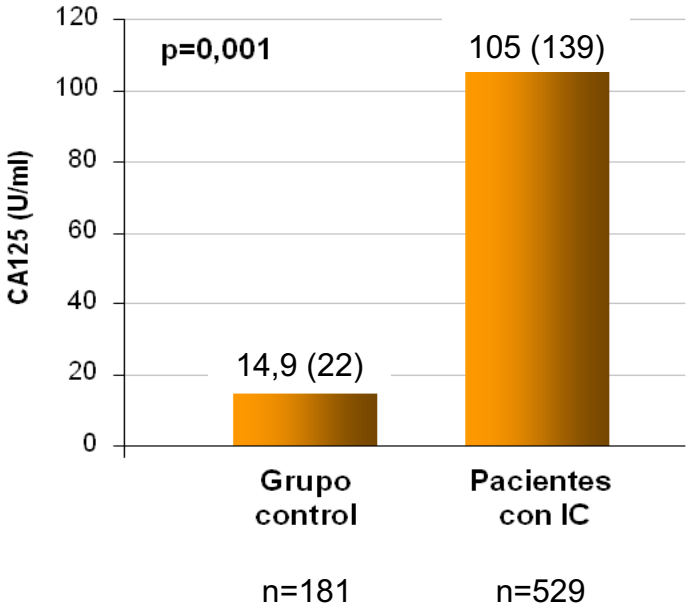
Single logarithmic regression analysis of pulmonary capillary wedge pressure (*PCP*) and log CA 125 serum levels ($r = 0.37$, $P < .01$, 71 consecutive patients with heart failure with a total of 157 determinations at different time points).



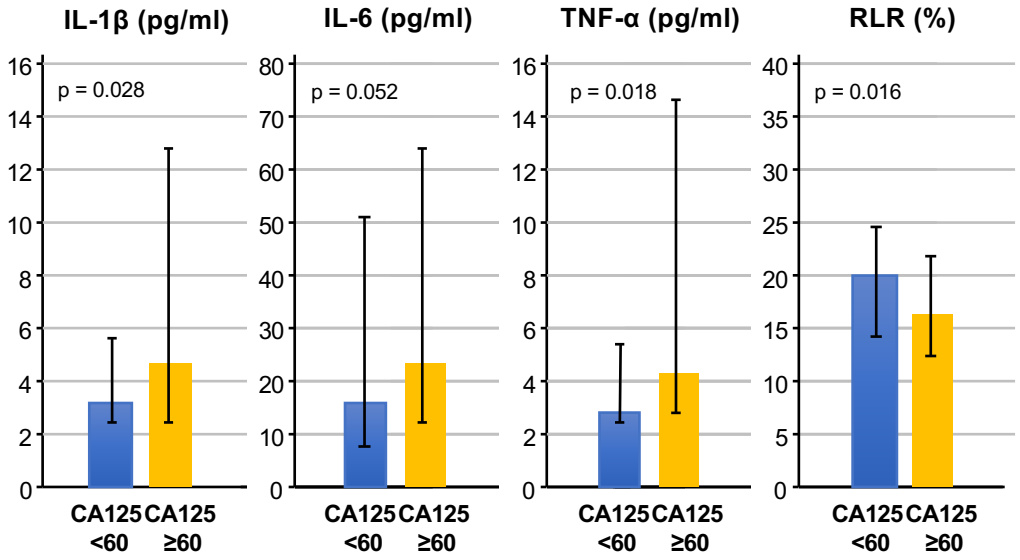
Time course of CA 125 serum levels before and after HTx (25 patients with heart failure requiring transplantation). Small graph shows no overall change in CA 199 or CEA in the same patients. $P < .001$ before versus all postoperative values of CA 125. Patient characteristics are shown in Table II.

Nägele H, et al. Am Heart J. 1999;137:1044-9.
Nägele H, et al. Anticancer Res. 1999;19:2531-4.

CA125. Pathophysiology



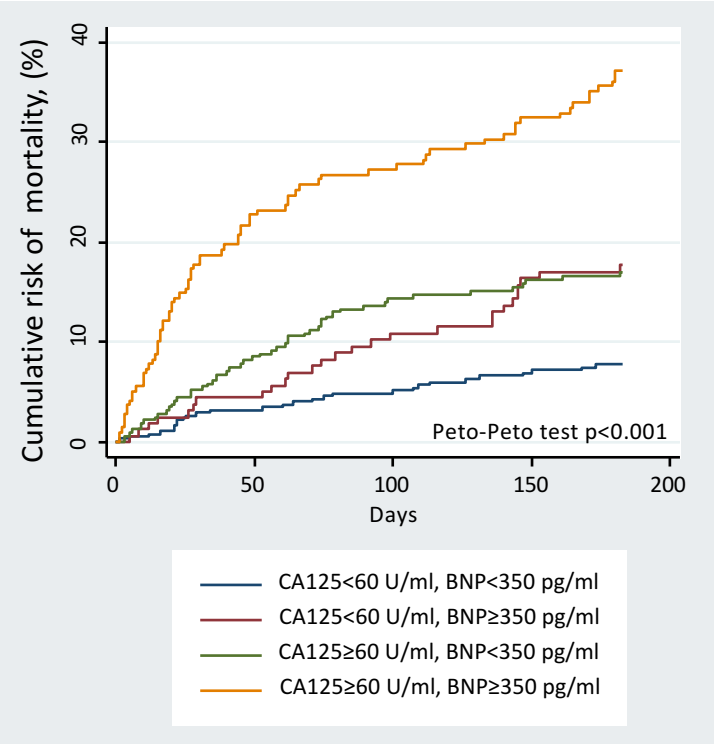
	Coeficiente β	p	R^2
Derrame pleural	0,698	<0,001	57,8%
Edemas periféricos	0,335	<0,001	12,9%

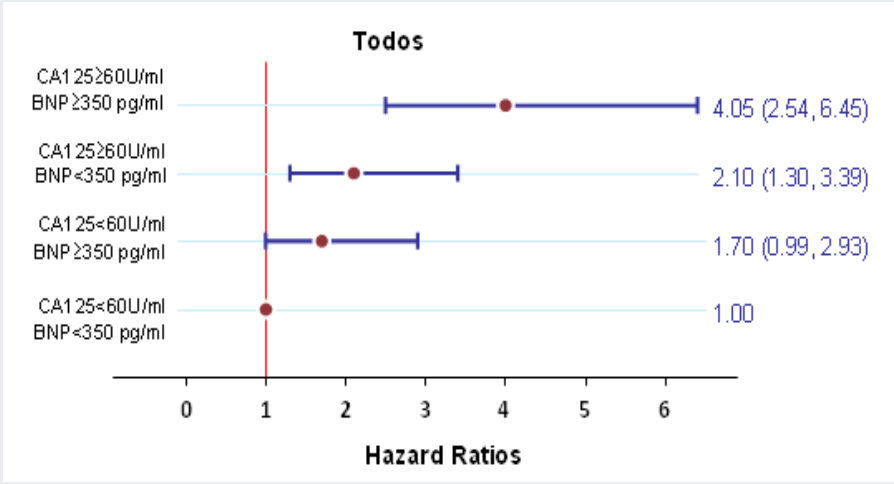


Núñez J, et al. Heart. 2007;93:716–721.
Núñez J, et al. Eur Heart J. 2010;31:1752-63.
Miñana G, et al. Int J Cardiol. 2010;145:547-8

CA125 and prognosis

n=1111 patients with AHF

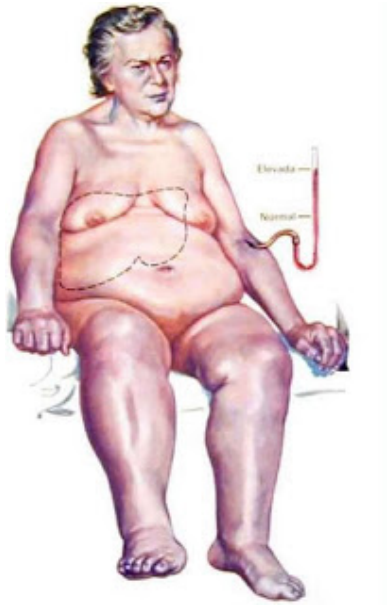




Modelo multivariado ajustado por: edad, sexo, ingreso previo por ICA, categoría de ICA (ADHF vs. otras), PAS al ingreso, FC al ingreso, FA, derrame pleural, FEVI<50%, creatinina sérica, Na≤130 mEq/L, BNP y tratamiento con ARAII y betabloqueantes.

Nuñez J, et al. Eur Heart J. 2010;31:1752-63

CA125 and monitoring



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%)

n=946

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

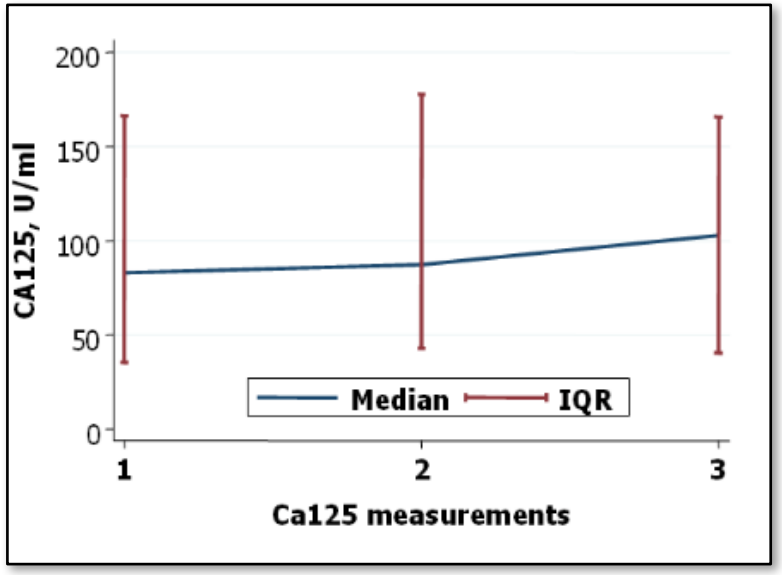
Logistic issues

Standarized measurements

Widely available

Cheap

Long half-life (7-12 days)



Nuñez J, et al. Eur Heart J. 2010;31:1752-63

Hypothesis

A CA125 guided-therapy in patients recently discharged for acute heart failure will decrease the risk of clinical adverse outcomes

INCLIVA
Instituto de Investigación Sanitaria

CHANCE-HF

MINISTERIO DE SANIDAD, POLITICA SOCIAL E IGUALDAD

Dirección General de Farmacia y Productos Sanitarios

FECHA: 31 de enero de 2011

ASUNTO: Orden SAS/2377/2010, 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 AREA DE LA UNIDAD DE SUBVENCIONES PARA LA INVESTIGACION

DIRECCION GENERAL DE FARMACIA Y PRODUCTOS SANITARIOS

DESTINATARIO: Consorcio de Apoyo a la Investigación Biomédica en Red

Sinesio Delgado 6

28029 Madrid

CC: **Julio Núñez Villota**

TÍTULO: EC10-108 Terapia guiada mediante los valores plasmáticos del antígeno carbohidrato 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 SAS/2377/2010, 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 Núñez[1], Pau Llàcer[2], Vicente Bertomeu-González[3], Maria José Bosch[4], Pilar Merlos[5], Sergio García-Blas[1], Vicente Montagud[6], Vicente Bodí[1], Vicente Bertomeu-Martínez[3], Valle Pedrosa[6], Andrea Mendizábal[4], Alberto Cordero[3], Jorge Gallego[4]. Patricia Palau[4], Gema Miñana[1], Enrique Santas[1], Salvador Morell[6], Francisco J. Chorro[1], Juan Sanchis[1], Lorenzo Fácila[6]
for the CHANCE-HF Investigators.

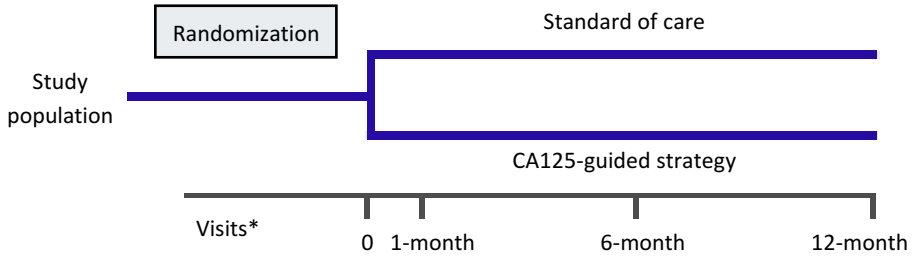
1 Hospital Clínico Universitario. INCLIVA. Universitat de Valencia. Valencia-Spain
2 Servicio de Medicina Interna, Hospital de Manises. Valencia-Spain
3 Servicio de Cardiología, Hospital de San Juan. Alicante-Spain.
4 Servicio de Medicina Interna, Hospital de la Plana. Castellón-Spain
5 Servicio de Cardiología,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

CHANCE-HF

Inclusión and exclusion criteria

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/m^2 in women or 116 g/m^2 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

AHF: acute heart failure; NYHA: New York Heart Association; NT-proBNP: amino-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide; HF: heart failure; LV: left ventricle; LVEF: left ventricular ejection fraction; CA125: antigen carbohydrate 125; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; HIV: human immunodeficiency virus.

ClinicalTrials.gov Identifier:
NCT02008110

Núñez, et al. JACC HF 2016

CHANCE-HF

Protocol

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.

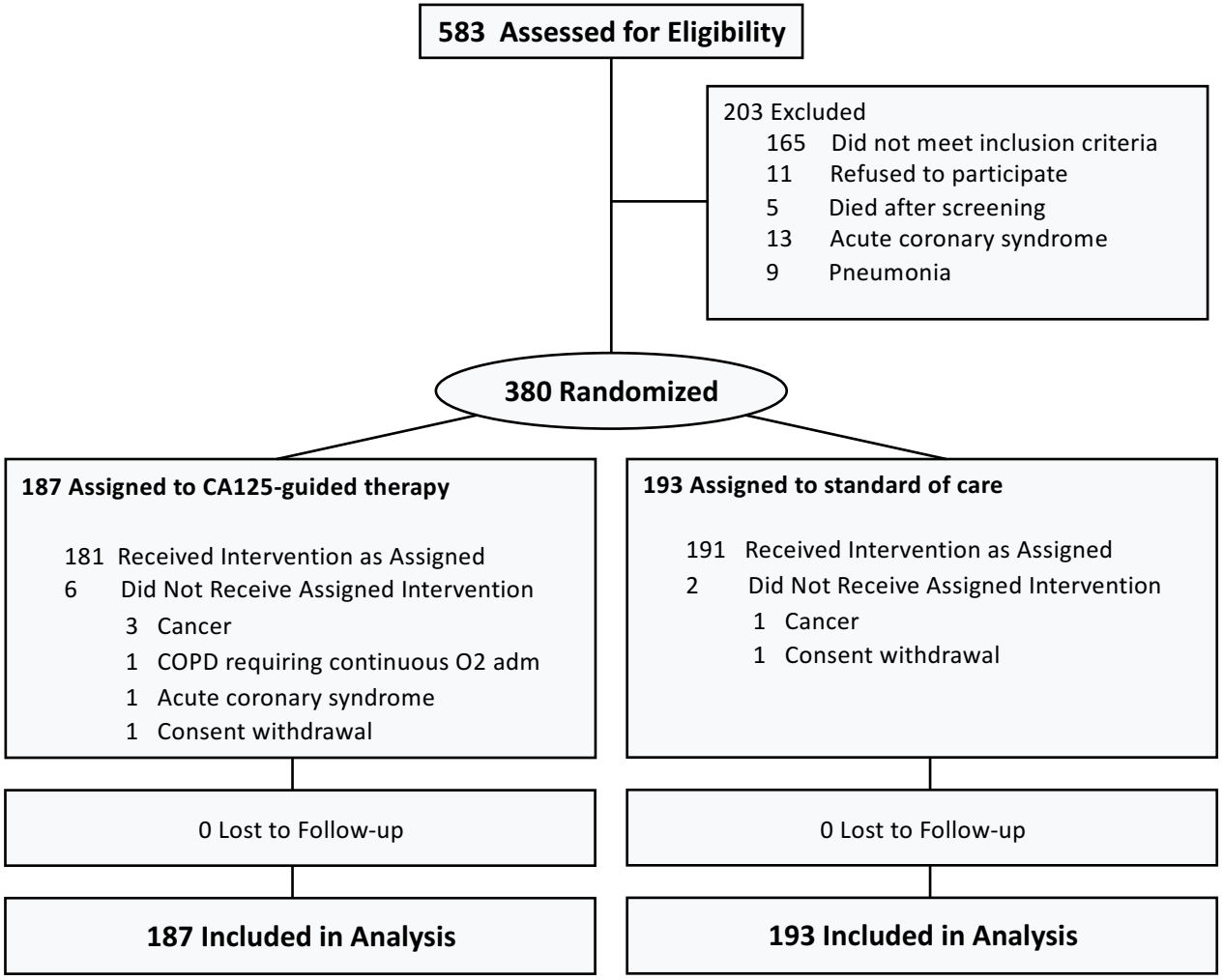
LDD: loop diuretic dose; CA125: antigen carbohydrate 125; FED: furosemide equivalent dose; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; HCTZ: hydrochlorothiazide.

ClinicalTrials.gov Identifier:
NCT02008110

Núñez, et al. JACC HF 2016

CHANCE-HF

Flow chart



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NCT02008110

Núñez, et al. JACC HF 2016

CHANCE-HF

Baseline characteristics

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

Variables	CA125-guided therapy (n=187)	Standard of care (n=193)	P-value
Physical examination			
Heart rate, bpm	79 ± 19	80 ± 19	0.52
SBP, mmHg	127 ± 25	122 ± 22	0.06
DBP, mmHg	69 ± 14	69 ± 14	0.80
Electrocardiogram and echocardiography			
QRS duration†, msec	100 (80, 130)	100 (80, 120)	0.59
LVEF, %	45.75 ± 16.75	44.74 ± 17.24	0.56
LVEF ≥50%, n (%)	73 (39.2)	78 (41.3)	0.75
Laboratory results			
Hemoglobin, g/dL	12.2 ± 1.9	12.4 ± 2.0	0.52
BUN†, mg/dL	60 (42, 83)	55 (42, 80)	0.20
Creatinine†, mg/dL	1.20 (0.93, 1.51)	1.13 (0.94, 1.50)	0.56
CA125†, U/mL	103 (64, 174)	86 (55, 160)	0.12
BNP†, pg/mL (n = 61)	582 (321, 1010)	662 (448, 1154)	0.334
NT-proBNP†, pg/mL (n = 319)	4570 (2251, 9849)	3773 (1947, 8192)	0.182

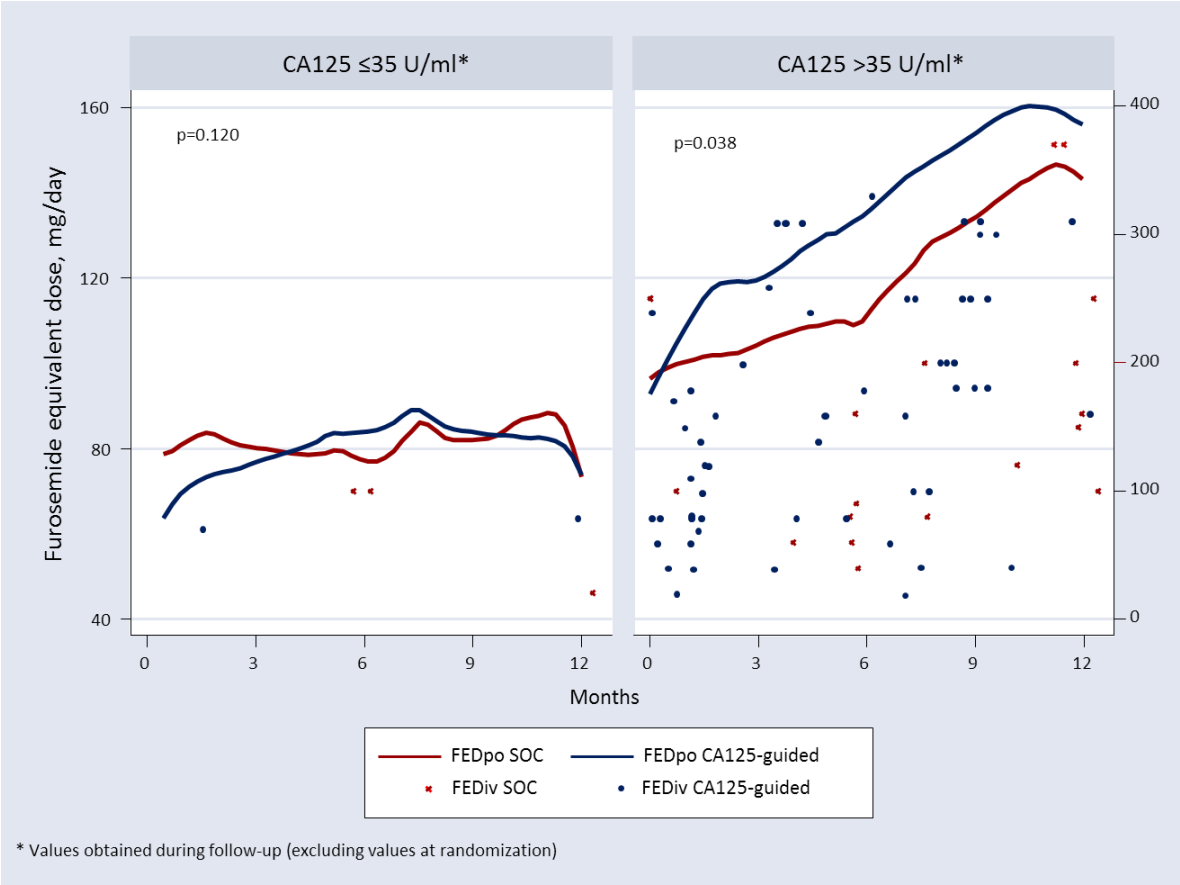
ClinicalTrials.gov Identifier: NCT02008110

Núñez, et al. JACC HF 2016

CHANCE-HF

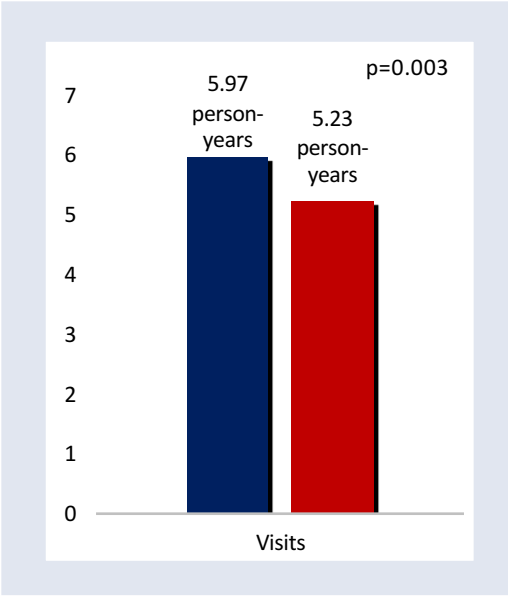
Results

Loop diuretic doses



* Values obtained during follow-up (excluding values at randomization)

Number of ambulatory visits



ClinicalTrials.gov Identifier:
NCT02008110

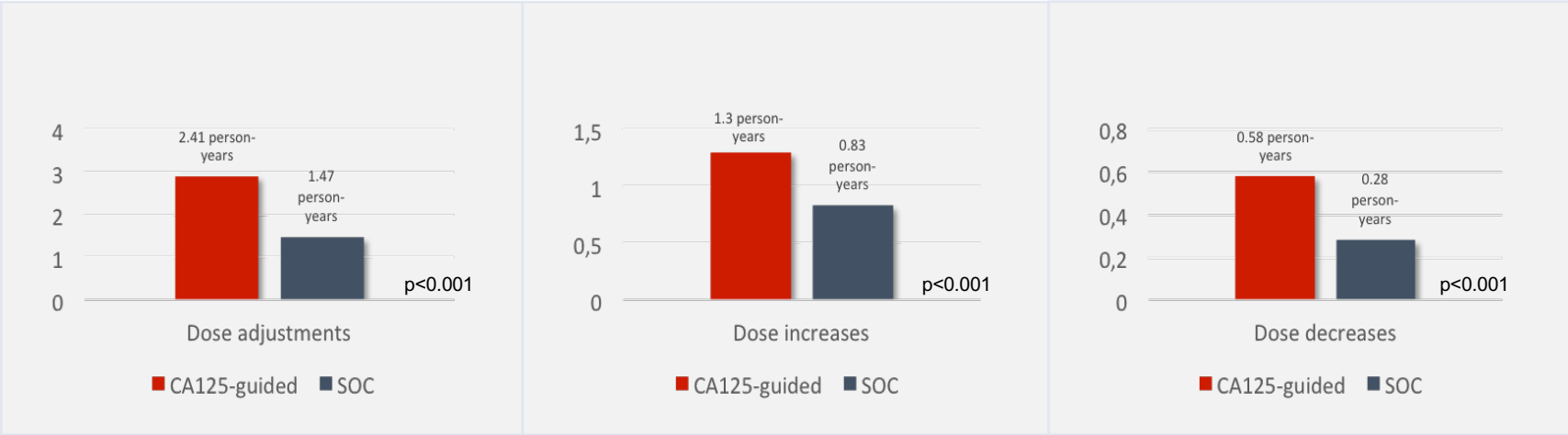
Núñez, et al. JACC HF 2016

CHANCE-HF

Results

Loop diuretics

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



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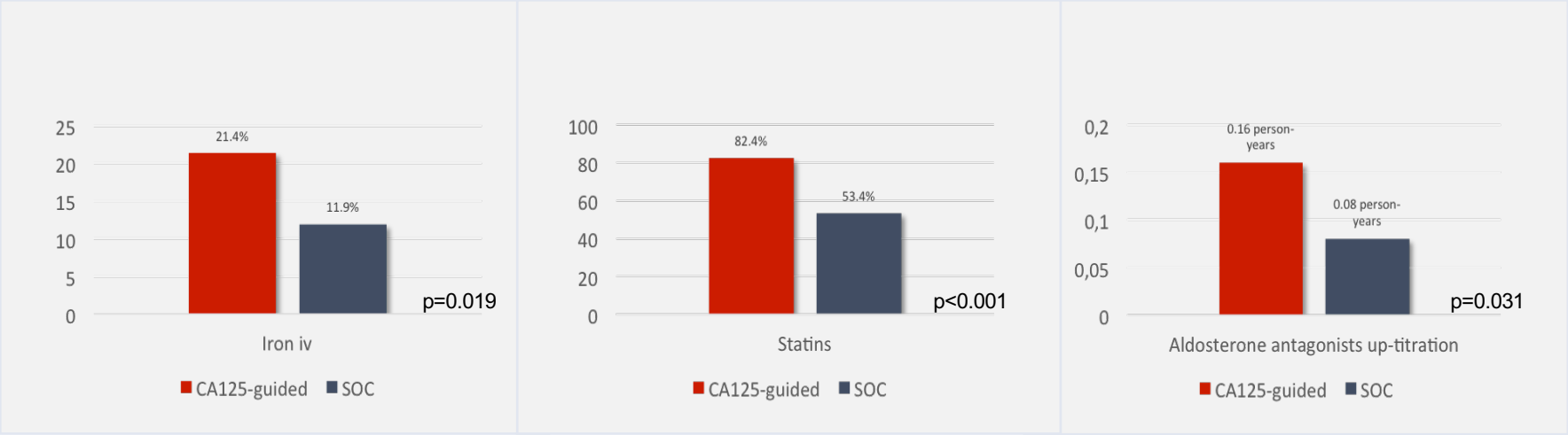
Results

Treatments



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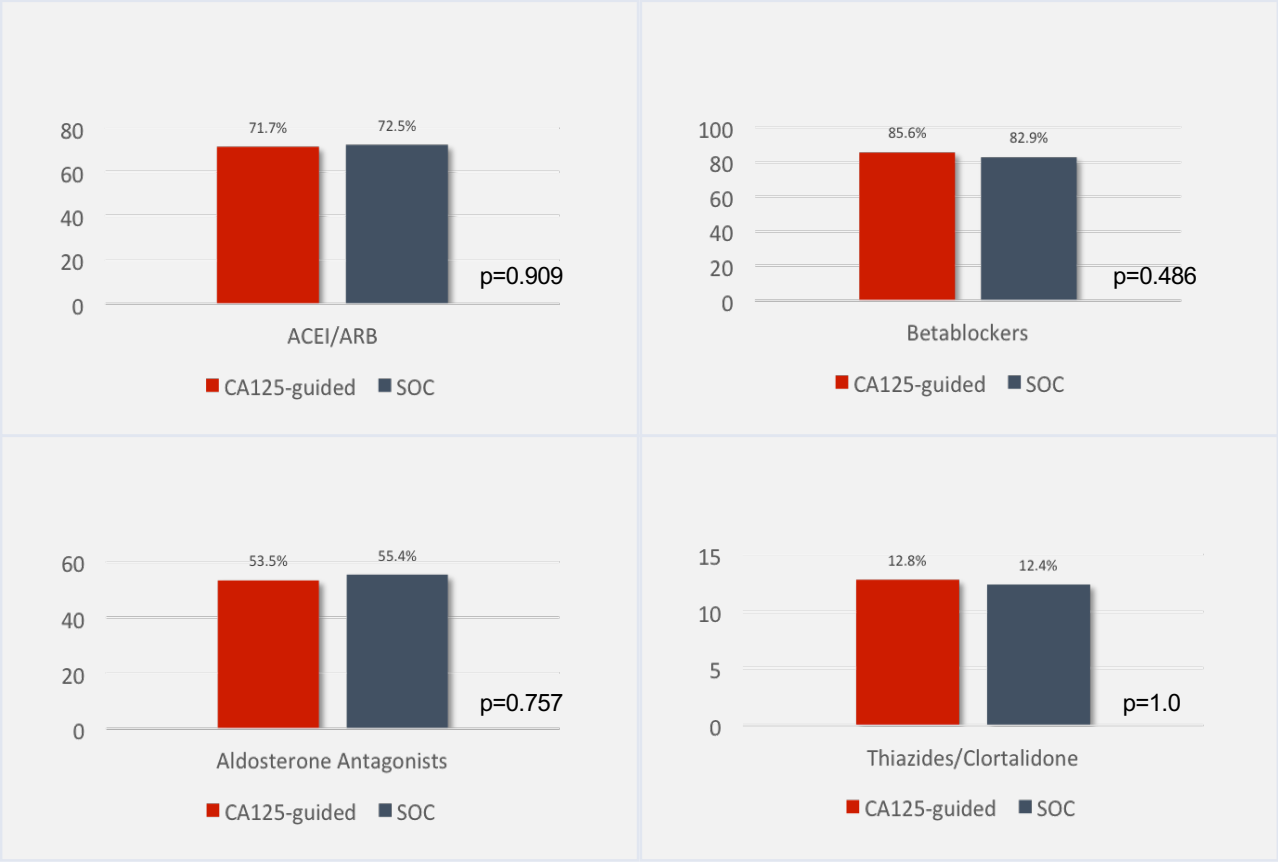
Results

Evidence-based treatments



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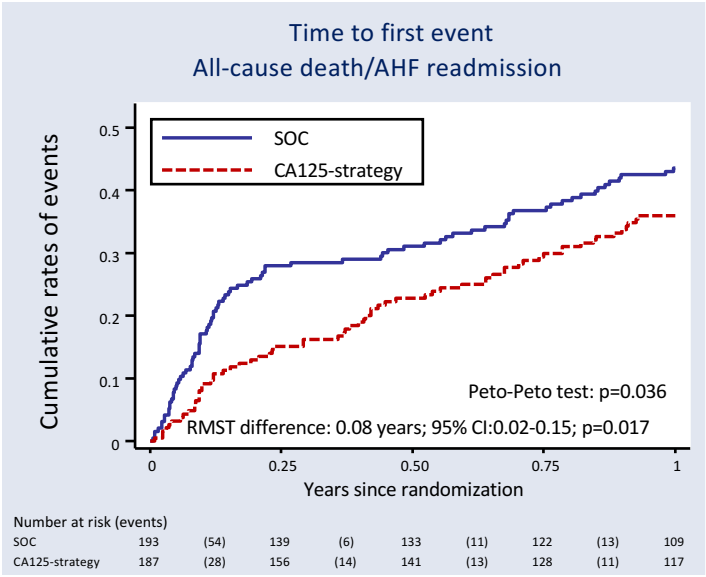

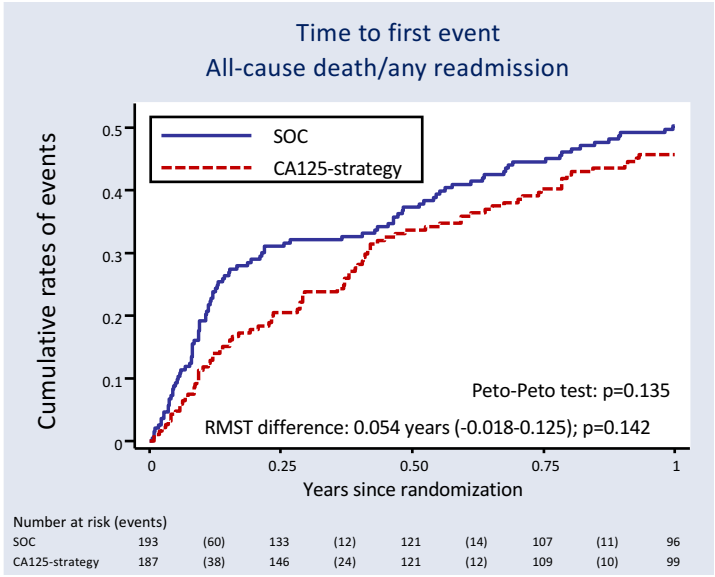

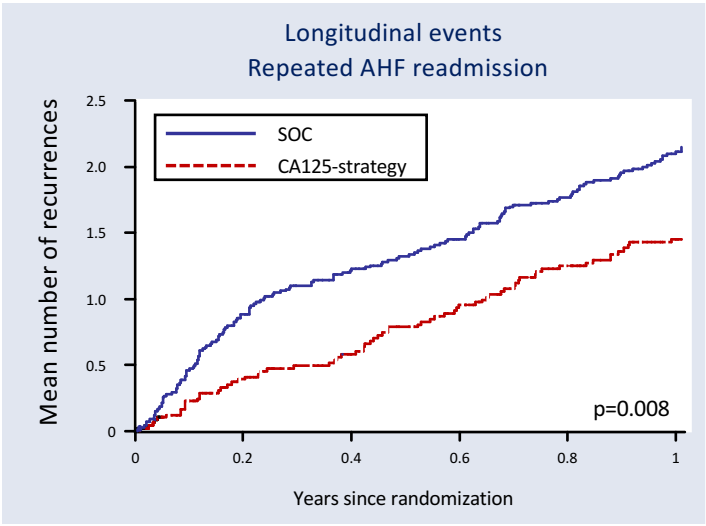

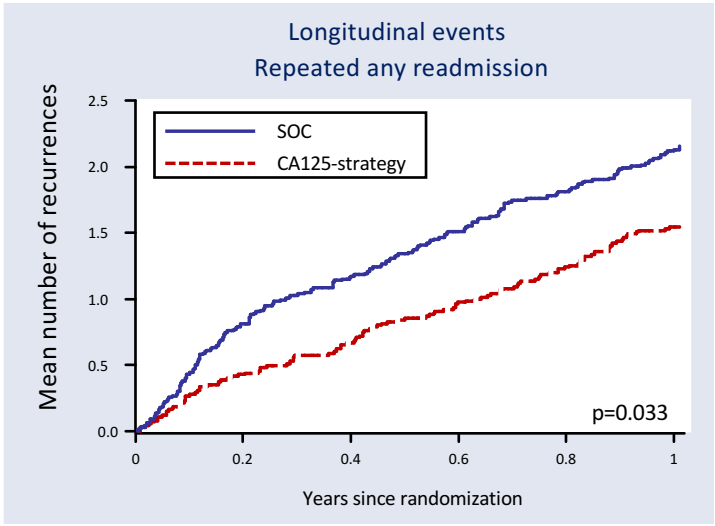

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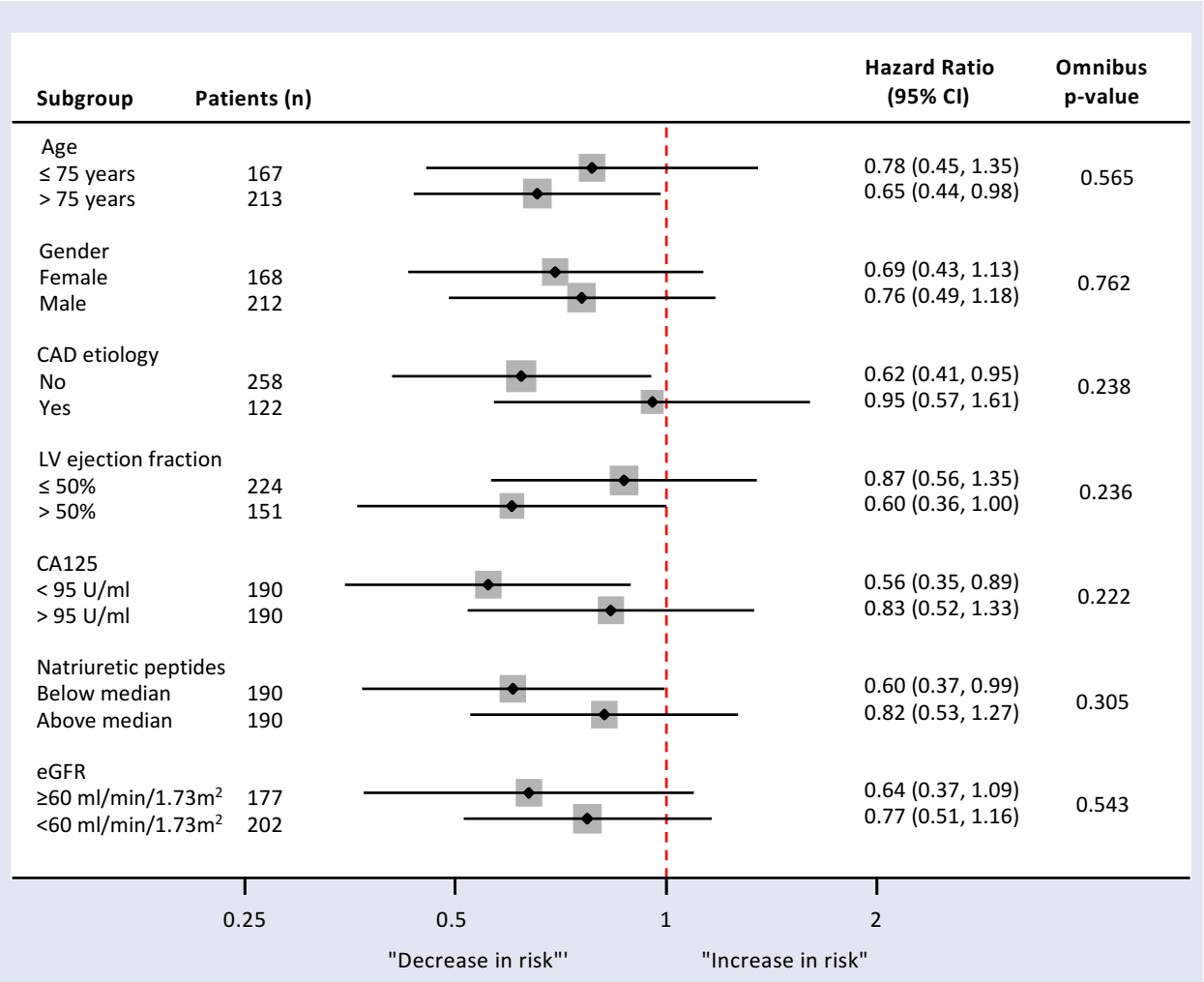
CHANCE-HF

Results



ClinicalTrials.gov Identifier:
NCT02008110

Núñez, et al. JACC HF 2016

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

Julio Núñez, MD,[a] Pau Llàcer, MD,[b] Vicente Bertomeu-González, MD,[c] Maria José Bosch, MD,[d] Pilar Merlos, MD,[e] Sergio García-Blas, MD,[a] Vicente Montagud, MD,[f] Vicent Bodí, MD,[a] Vicente Bertomeu-Martínez, MD,[c] Valle Pedrosa, MD,[e] Andrea Mendizábal, MD,[b] Alberto Cordero, MD,[c] Jorge Gallego, MD,[d] Patricia Palau, MD,[d] Gema Miñana, MD,[a] Enrique Santas, MD,[a] Salvador Morell, MD,[f] Angel Llàcer, MD,[a] Francisco J. Chorro, MD,[a] Juan Sanchis, MD,[a] Lorenzo Fácila, MD,[f] 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;■:■–■)

JACC Heart Fail. 2016;4:833-843

Can Carbohydrate Antigen-125 Be a New Biomarker to Guide Heart Failure Treatment?

The CHANCE-HF Trial*

Antonio D'Aloia, MD,[a] Enrico Vizzardi, MD,[a,b] Marco Metra, MD[a,b]

Biomarkers are among the most intensively studied areas in heart failure (HF). They are studied both for the identification of subjects at risk for HF in the general population (1,2) and, to a much larger extent, in symptomatic patients for the diagnosis and prognostic evaluation of HF (3-5). Because each biomarker is related to different pathophysiological 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 (3,6-8). Changes in biomarkers after treatment have been used to assess response to therapy, with, however, different results with respect to the relation with the effects of treatment (9-13). 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. This hypothesis has been tested in multiple clinical trials to date, whose sizes, however, were too small to produce final results in most of cases. However, favorable results have been shown in meta-analyses and a properly powered randomized controlled trial is ongoing (14-16).

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the [a]Cardiology, Cardio-Thoracic Department, Civil Hospitals, Brescia, Italy; and the [b]Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy. Dr. Metra has received consulting honoraria from Amgen, Bayer, Novartis, Servier, and Relypsa. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

CARBOHYDRATE ANTIGEN-125

Carbohydrate antigen-125 (CA125) is secreted from ovarian cancer and lymphomatous cells in a process stimulated by inflammatory activation (17,18). In patients with HF, CA125 is secreted by serosal cells in response to congestion, increased central venous pressure, and inflammation (19-21). The first observation of an increase in CA125 plasma levels in patients with HF was published in 1999, by Nagele et al. (19). They found marked elevations of CA125 levels in patients with HF, with significant correlations with clinical severity and filling pressures (7). 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 prognosis (8). Further studies have confirmed the value of CA125 in patients with HF (22,23). 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 (21,24).

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THE CHANCE-HF TRIAL

In this issue of *JACC: Heart Failure*, Nunez et al. (25) report the results 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 380 patients admitted to the hospital for

JACC Heart Fail. 2016;4:833-843

Difusión

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HEART FAILURE

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 treatment 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 visitations 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 depletive 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 tool 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 Huynh

ORIGINAL ARTICLE Núñez, J. *et al.* Carbohydrate antigen 125–guided therapy in acute heart failure: CHANCE-HF: a randomized study. *JACC Heart Fail.* http://dx.doi.org/ 10.1016/j.jchf.2016.06.007 (2016)
FURTHER READING ter Maaten J. M. *et al.* Diuretic response in acute heart failure — pathophysiology, evaluation, and therapy. *Nat. Rev. Cardiol.* **12**, 184–192 (2015)

> "CA125 emerges as a useful clinical tool … in patients with a recent episode of AHF"

Vicky summersby/NPG

Clinical Chemistry 63:5
954–957 (2017)

Opinion

Using Biomarkers to Guide Heart Failure Therapy

Allan S. Jaffe[1*] and James L. Januzzi, Jr.[2]

Table 1. Candidate "next" biomarkers for guiding chronic HF therapy.[a]

Biomarker	Known mechanism(s)?	Defined cutoff?	Therapies identified to reduce risk?	Suitable for serial measurement?	Time window for resampling identified?	Acceptable assays available?
Troponin	++	++	+	++	+/–	++
Soluble ST2	+	++	+	++	++	++
Growth differentiation factor-15	+/–	++	+/–	+	+/–	++
Galectin-3	+/–	++	–	+/–	+/–	++
Carbohydrate antigen-125	+/–	+	+	+	+	++
C-terminal pro-vasopressin	+/–	–	–	+/–	–	++
Midregional pro-adrenomedullin	+/–	–	–	Unknown	+/–	++
Neprilysin	+	–	–	Unknown	–	+/–
Orexin A	+	–	–	Unknown	No	+/–

[a] 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