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ORIGINAL ARTICLE

Prognostic value of glycoprotein CA125 and their time-line changes in decompensated heart failure

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Abstract

Introduction and objectives: Glycoprotein carbohydrate antigen 125 (CA125) has been proposed as a new biomarker in heart failure (HF). Its potential prognostic role in chronic (CHF) and acute HF (AHF) is still underrecognized. **Methods:** Observational prospective study. The aims of this study were to analyze prognostic information (mortality at 1 and 12 months after discharge) yielded by serum CA125 in AHF and whether changes in concentrations from admission to discharge improved risk stratification. **Results:** Two hundred and four patients with AHF were included (median age 81 ± 4 years). Both CA125, at admission and discharge, were associated with short and long-term prognosis. CA125 at discharge had the greatest area under the curve (AUC) for predicting HF mortality (AUC = 0.735, 95% CI 0.54 - 0.93 p = 0.003). Moreover, CA125 above median on admission and discharge, increased the risk of long-term mortality in the multivariate study (Admission CA125: Exp[B] = 2.16; p = 0.032 and discharge CA125: Exp[B] = 3.15; p = 0.023). In addition, a rise of CA125 during admission (56% of patients) was associated with higher mortality at 12 months (p = 0.035), especially among patients with CA125 > 55UI/mL at admission. **Conclusions:** Concentrations of serum CA125 measured during acute decompensation of HF may help identify patients with poor prognosis after discharge. The lack of CA125 decrease during hospitalization, despite clinical improvement, is related to long-term poor outcomes.

Key words: CA125. Heart failure. Prognosis. Congestion. Biomarker.

Introduction

Heart failure (HF) is one of the most prevalent conditions in the developed world, with an incidence of 1-2%[1] of the total adult population, rising to 10% in those over the age of 85. HF mortality is estimated at 50% within 5 years of diagnosis[2,3], and it is greater during the initial months after an admission for acute HF (AHF). Despite the plethora of clinical and biochemical HF investigations available, accurate individual assessment of patient prognosis still remains a challenge.

The usefulness of biomarkers, such as brain natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP), in the differential diagnosis of acute and chronic dyspnoea[4], have been well documented. In addition, they are robust prognostic indicators in both

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acute[5] and chronic[6] HF. Biomarker-based HF management has been shown to be superior to standard care, particularly among younger patients[7,8].

Recently, serum carbohydrate antigen 125 (CA 125) has been proposed as an alternative biomarker for stratifying prognosis in HF. This high-molecular-weight glycoprotein is physiologically expressed on the surface of cells derived from coelomic epithelium, and classically considered an ovarian tumor marker[9-11].

Some studies have suggested a prognostic role for CA125 in acute and chronic HF[9,10]. In combination with NT-proBNP[10,11], it appears to improve risk prediction when compared to each of these biomarkers alone. In one clinical trial, CA125 guided-therapy was effective in reducing hospital admissions for HF as compared to standard of care[12].

CA125 secretion is increased in response to cytokine driven inflammation, interstitial fluid, oxidative stress, and mesothelial cell injury. It may be, therefore, considered as a surrogate marker for systemic congestion[9,13]. Recognition of systemic congestion in AHF is imperative as it identifies a group of patients at greater risk of death[14].

Little is known about the relationship between changes in serum CA125 concentrations from admission to discharge and prognosis in patients with HF. In this study, we sought to analyze short and long-term prognostic information (mortality at 1 and 12 months after discharge) yielded by baseline serum CA 125 in patients admitted for AHF. We also analyzed whether the changes in serum CA 125 from admission to discharge improved risk stratification in this group.

Methods

Patients

Between February 2013 and December 2014, 204 consecutive patients admitted for AHF to the Internal Medicine Department of a tertiary referral teaching hospital (Lozano Blesa University Hospital, Zaragoza, Spain) were prospectively enrolled.

Inclusion criteria were: (1) Patients admitted with the diagnosis of AHF, (presented with shortness of breath and fulfilled Framingham criteria[15]), (2) Over 18 years of age, (3) NT-proBNP over 300 pg/mL, and (4) clinical signs and chest radiograph appearances consistent with a diagnosis of HF. Both new-onset AHF and acute decompensation of chronic HF were included in the study.

Exclusion conditions were: (1) Patients unwilling to participate in the study, (2) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (eGFR was calculated by the four-variable Modification of Diet in Renal Disease equation [MDRD-4]: 186.3 × [Scr]–1.154 × [age] – 0.203 [× 0.742 if female], where Scr is serum creatinine), (3) patients in cardiogenic shock, (4) Inotropic drugs required on admission, (5) life expectancy < 3 months, (6) advanced dementia, and (7) allergy or intolerance to diuretics.

Left ventricular (LV) systolic dysfunction was considered when LV ejection fraction (LVEF) was < 50%.

Laboratory measurements

Blood tests were performed during the first 48 h after admission. These included urea, creatinine, and electrolytes, as well as NT-proBNP (Roche Diagnostics GmbH, Mannheim, Germany) and CA 125 (Roche Diagnostics GmbH, Mannheim, Germany). The normal cutoff reference laboratory value for CA125 is below 35 UI/mL. In addition, NT–pro-BNP and CA 125 were measured 48 h before discharge (unless the patient died or was discharged unexpectedly; which occurred in 15 patients) and in out-clinic at 1-month post discharge. Additional blood tests were performed during the hospital admission as per routine clinical care at the digression of the treating physician.

Follow-up

Patients were prospectively followed-up in a specialized HF out-patient clinic. The first visit was scheduled 1 month after discharge. All patients were clinically followed up for at least 12 months after discharge, and the occurrence of the clinical event (death) was registered. Both all-cause and HF mortality were analyzed between 1 month and 1 year after discharge was registered.

During the initial hospitalization period, the responsible treating physician was blinded to (and therefore not influenced by) the patient's CA125 results. Echocardiography was performed to all patients before hospital discharge, or before first out-clinic visit 1 month after discharge. In those patients requiring further hospitalization after initial enrolment, medical records were carefully reviewed to identify the reason for admission.

Statistical analysis

Descriptive statistics: frequency distribution of the qualitative variables was shown in each category.

Quantitative variables were tested for normal distribution by means of the Kolmogorov–Smirnov test. Regarding normality, indicators of central tendency (mean or median), and dispersion (standard deviation or interquartile range [IQR]) were elaborated. A two-tailed p-value 0.05 was considered as statistically significant.

Comparisons were performed by means of contrast hypothesis, comparing proportions of qualitative variables (Chi-square or Fisher exact test) or means comparison of quantitative variables (t Student or ANOVA). If the distribution was not adjusted to normalcy, U Mann–Whitney or Kruskal–Wallis tests were used for comparisons between groups. Wilcoxon and Friedman two-dimensional analysis were performed for paired data.

Mortality was evaluated regarding the change in CA125 levels from admission to discharge: Group A, patients with increase; and Group B those with decrease in CA125.

Analysis was completed using a linear regression model (for continuous variables) or a logistic regression model (for categorical variables). Areas under receiver-operating characteristic (ROC) curves were drawn to assess the utility of CA125 for predicting adverse events during 12-month follow-up. Event-free Kaplan–Meyer (K-M) method with long-rank test at 12-month follow-up was carried out to assess cumulative survival against CA125 concentration at admission and on discharge. Pairwise testing was performed for detecting differences between groups.

An additional study was performed segmenting patients into four groups regarding CA125 median on admission (over or below 55 UI/mL) and dichotomizing changes in CA125 concentrations during decompensation (absolute increase or decrease of CA125). Group 1: CA125 ≤ 55 UI/mL and CA125 decrease; Group 2: CA125 ≤ 55 UI/mL and CA125 increase; Group 3: CA125 > 55 UI/mL and CA125 decrease; and Group 4: CA125 > 55 UI/mL and CA125 increase.

A multivariate cox regression analysis was performed for overall and 12-month HF mortality. Multivariate adjusted hazard ratios for mortality were generated after correcting for identified baseline predictors of all-cause mortality. Candidate variables selected based upon clinical relevance and published literature included: age, gender, length of hospital stay, ejection fraction, plasma urea and creatinine, NT-proBNP, Cystatin C, and well-known risk factors (hypertension, ischemic cardiomyopathy, diabetes mellitus, chronic kidney disease, and anemia). Variables non-following normalcy were introduced in the multivariable regression by means of their natural logarithmic form (Ln).

Analysis was performed using the statistical software package SPSS, version 22.0 (IBM, Chicago, IL).

Ethics

All patients who agreed to participate in the study signed a written informed consent form. The study was approved by the Ethics Committee for Clinical Research of Aragon (CEICA), (CI PI13/0019).

Results

Two hundred and four patients were included, median age 81 years (IQR 76-85 years), 50.5% male (n = 103), with a median hospital stay of 8 days (IQR 7-14 days). Hypertensive cardiomyopathy (39.2%; n = 80) was most frequent HF etiology, followed by ischemic heart disease (IHD) (28.9%; n = 53) and valvular disease (mitral 9.3%; n = 19, aortic 7.2%; n = 15). Baseline NYHA functional class, before admission, was either II or III in 172 (83.7%; n = 171) patients, none of the patients were in class IV. On admission, 93% (n = 190) of patients were on a loop diuretic, 76.5% (n = 156) on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, 56.3% (n = 115) on beta-blockers and 33.7% (n = 69) on mineral receptor antagonists.

The most frequent comorbidities were arterial hypertension (85.1%; n = 174), atrial fibrillation (58.4%; n = 119), and type 2 diabetes mellitus (39.6%). One hundred and sixteen patients (57%) had HF with preserved ejection fraction (HFpEF, [namely EF > 50%]), and 77% (n = 157) had a systolic pulmonary artery pressure over 30 mmHg. Median and IQR of baseline NT-proBNP and CA125 values are shown in table 1. NT-proBNP and CA125 levels were correlated at admission ($r = 0.331$, $p < 0.000$), discharge ($r = 0.313$, $p < 0.000$), and at 1 month after discharge ($r = 0.258$, $p = 0.006$).

Baseline clinical characteristics of the study population according to serum CA125 concentrations (subdivided by median [55 UI/mL] and reference [35 UI/mL] cutoff values) are listed in table 2.

Prognosis at 1 and 12 months after discharge, stratified according to CA125 concentration on admission and discharge

At 1 month (1M), 19 patients (9.3%) had died; 10 (4.9%) of them during the index hospitalization; and 9 (4.2%) within the 1st month after discharge. CA125 at admission was higher among those who deceased

Table 1. Serial concentrations and correlation of NT-proBNP and CA125

	Admission (A)	Discharge (D)	p-value A-D	Discharge (D)	1-month post-discharge (Pd)	p-value (D-Pd)	Global p-value
NT-proBNP (pg/mL), median (IQR)	3,306 (5,388)	2,084 (3,036)	0.000	2,084 (3,036)	2,184 (2,671)	0.054	0.000
CA125 (UI/mL), median (IQR)	55 (88)	53 (107)	0.026	53 (107)	25 (45)	0.000	0.003

CA125: carbohydrate antigen 125; IQR: interquartile range; NT-proBNP: N-terminal pro-brain natriuretic peptide.

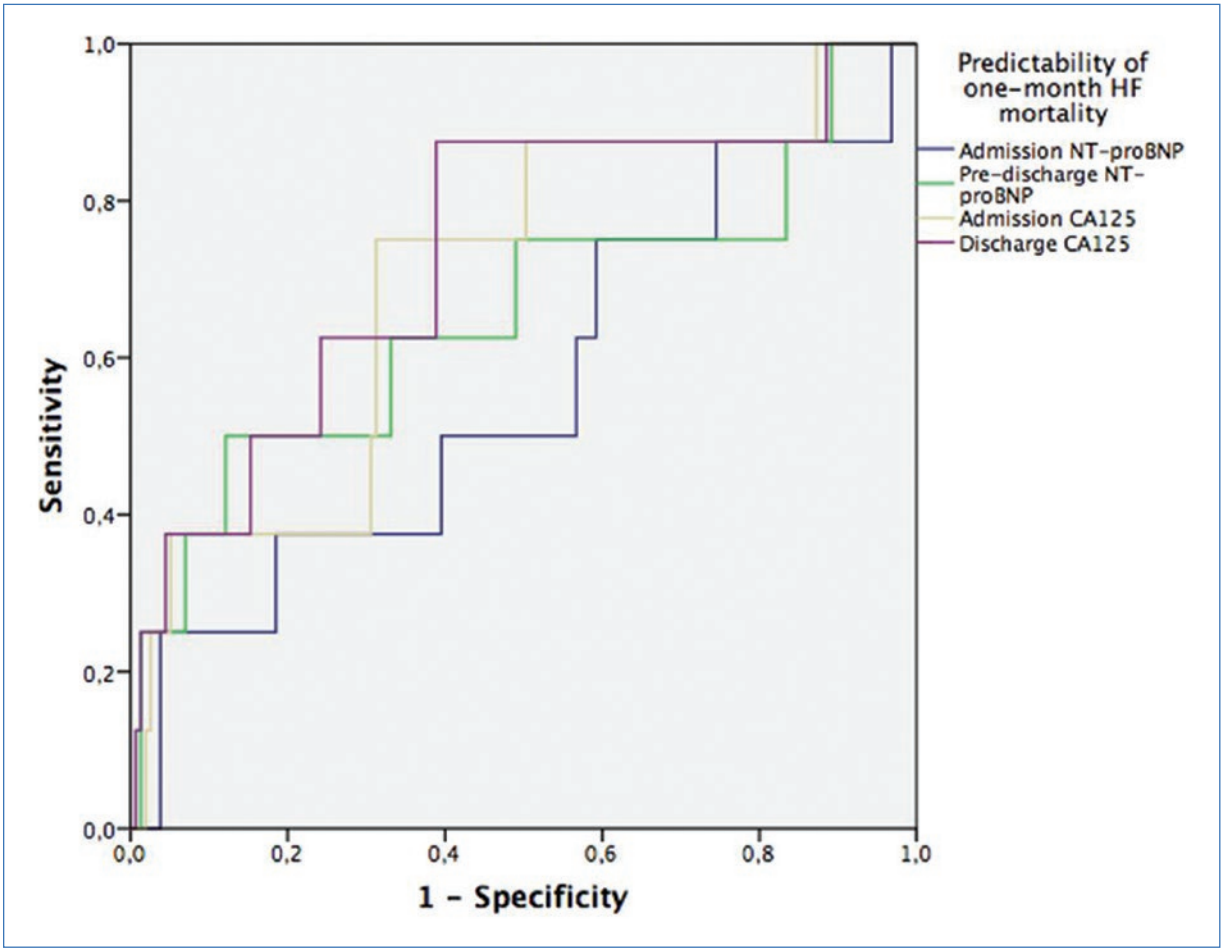

Figure 1. Receiver-operating characteristic curve for prediction of 1-month heart failure mortality defined by carbohydrate antigen 125 and amino-terminal fragment of natriuretic peptide type B.

during the 1st month (52 ± 87 vs. 93 ± 262, p = 0.014 for HF mortality and 52 ± 88 vs. 91 ± 254; p = 0.031 for all-cause mortality, respectively). Similar results were observed with CA125 concentrations at discharge (51 ± 99 vs. 147 ± 331 p = 0.025 for HF mortality and 50 ± 101 vs. 126 ± 302; p = 0.017 for all-cause mortality, respectively) (Table 3). Only three out of the 19 patients (15.8%) who died during 1st month had a concentration of CA125 at admission below normal cut-off. Two of these deaths were due to non-cardiovascular causes.

ROC analysis identified CA125 previous to discharge as the biomarker with the greatest area under the curve (AUC), for predicting HF mortality at 1M (AUC = 0.735, 95% confidence interval [95% CI] 0.54-0.93 p = 0.003) (Fig. 1). CA125 at admission also predicted adverse HF outcomes 1M post-discharge, but was less powerful

Table 2. Baseline characteristics of patients by CA125

	Global (n = 204)	CA125 < 35 UI/mL* (n = 73; 36%)	CA125 ≥ 35 UI/mL (n = 131; 64%)	p-value	CA125 < 55 UI/mL** (n = 102; 50%)	CA125 ≥ 55 UI/mL (n = 102; 50%)	p-value
Age, years	81 (9)	81.5 (12)	81 (9)	0.782	81 (10)	81 (9)	0.452
Men	98 (50)	33 (48)	63 (50)	0.731	44 (45)	54 (55)	0.153
Length of stay, days	8 (7)	8 (8)	9 (7)	0.439	8 (8)	9 (7)	0.577
Functional class NYHA III	45 (24)	11 /17)	34 (28)	0.132	18 (19)	27 (28)	0.145
Hypertension	165 (85)	60 (88)	104 (84)	0.413	86 (89)	79 (81)	0.159
IHD	71 (37)	26 (38)	44 (36)	0.705	36 (37)	35 (36)	0.882
Atrial fibrillation	119 (58.4)	33 (49)	81 (65)	0.023	55 (57)	59 (61)	0.560
CKD	51 (26)	16 (24)	33 (27)	0.639	22 (23)	29 (30)	0.254
Diabetes mellitus	78 (40)	30 (44)	48 (39)	0.466	39 (40)	39 (40)	1.000
COPD	37 (19)	12 (18)	24 (19)	0.772	21 (22)	16 (17)	0.361
Heart rate, bpm	81 (28)	79 (25)	85 (31)	0.091	80 (26)	86 (34)	0.180
SBP, mmHg	140 (43)	144 (46)	140 (35)	0.062	144 (46)	136 (35)	0.010
DBP, mmHg	74 (19)	74 (25)	74 (18)	0.875	75 (22)	74 (16)	0.259
LVEF, %	54 (24)	54 (21)	53 (27)	0.222	57 (21)	52 (27)	0.063
Cystatin C, mg/dL	1.45 (0.7)	1.44 (0.7)	1.45 (0.6)	0.954	1.45 (0.7)	1.41 (0.6)	0.393
NT-proBNP, pg/mL	3,306 (5,388)	2,069 (3,858)	4,107 (5,662)	0.000	2,434 (3,855)	4,391 (6,169)	0.000
Hematocrit, %	37.4 (8.5)	38 (11)	37 (7)	0.996	37.8 (7.5)	37.4 (7.1)	0.744
Distribution red cell width, %	15.7 (3)	15.5 (2.3)	15.9 (3.1)	0.124	16 (2.3)	16 (3.2)	0.285
Urea, g/L	0.6 (0.3)	0.5 (0.3)	0.6 (0.3)	0.213	0.5 (0.4)	0.6 (0.3)	0.213
Creatinine, mg/dL	1.1 (0.6)	1.1 (0.6)	1.2 (0.5)	0.598	1.1 (0.6)	1.2 (0.5)	0.549
Uric acid, mg/dL	7.8 (2.7)	7.7 (2.5)	7.9 (2.8)	0.307	7.6 (2.5)	8 (2.8)	0.153
Total proteins, g/L	6.4 (0.8)	6.5 (0.9)	6.4 (0.8)	0.192	6.5 (0.9)	6.3 (0.8)	0.026
Albumin, g/L	3.2 (0.5)	3.2 (0.4)	3.2 (0.6)	0.794	3.2 (0.5)	3.2 (0.6)	0.654
Total cholesterol, mg/dL	142 (40)	147 (44)	141 (40)	0.118	150 (43)	138 (39)	0.005
Triglycerides, mg/dL	88 (42)	93 (45)	86 (38)	0.036	92 (48)	84 (32)	0.014
GGT, UI/mL	43 (62)	31 (53)	47 (64)	0.012	37 (58)	46 (66)	0.184
Cardiorenal syndrome	43 (21)	15 (22)	27 (22)	0.982	48 (49)	53 (54)	0.475
Peripheral edema	156 (77)	49 (72)	99 (81)	0.182	70 (72)	80 (83)	0.062
Jugular distension	115 (56)	31 (46					

*Reference laboratory values cut-off (35 UI/mL).
** Median values (55 UI/mL).
Bpm: beats per minute; CA125: carbohydrate antigen 125; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRS: cardiorrenal syndrome; DBP: diastolic blood pressure; GGT: gamma-glutamyl transpeptidase; IHD: ischemic heart disease; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association functional class; SBP: systolic blood pressure.

Table 3. Admission and discharge concentrations of CA125 and mortality

		CA125 admission, median (IQR)	p-value		CA125 discharge, median (IQR)	p-value
1M HF mortality	No	52 (87)	0.014	No	51 (99)	0.025
	Yes	93 (262)		Yes	147 (331)	
1M all-cause mortality	No	52 (88)	0.031	No	50 (101)	0.017
	Yes	91 (254)		Yes	126 (302)	
12M HF mortality	No	49 (88)	0.011	No	47 (93)	0.005
	Yes	78 (120)		Yes	97 (173)	
12M all-cause mortality	No	49 (89)	0.014	No	47 (94)	0.011
	Yes	75 (102)		Yes	93 (180)	

1M: one month; 12M: twelve months; CA125: carbohydrate antigen 125; IQR: interquartile range, HF: heart failure.

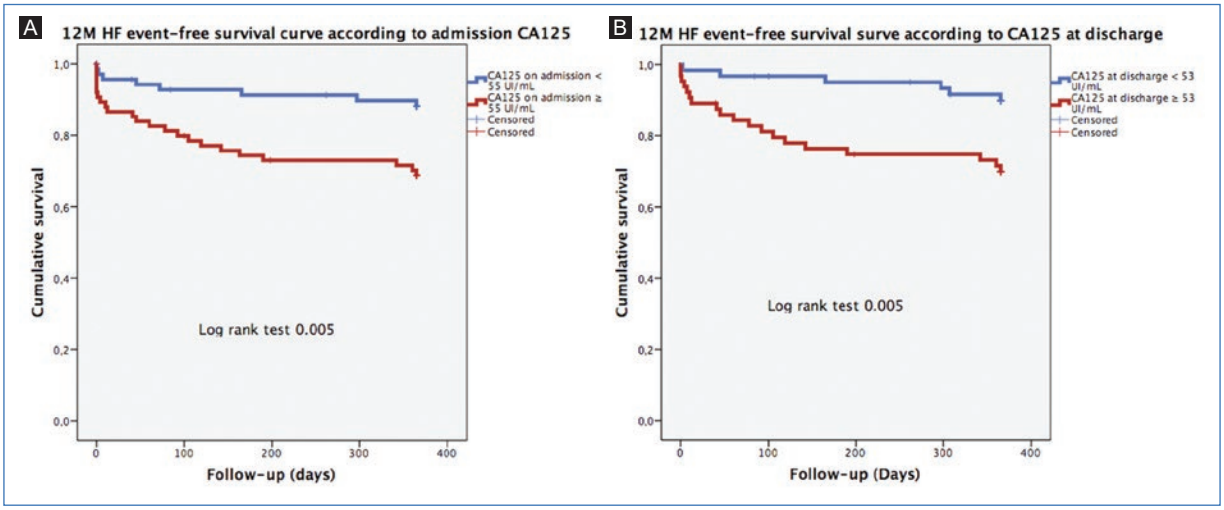

Figure 2. Kaplan–Meyer curves for 12-month heart failure (HF) mortality. A: 12-month HF event-free survival curve according to admission carbohydrate antigen 125 (CA125) concentration. B: 12-month HF event-free survival curve according to discharge CA125 30 concentration.

(AUC 0.703 CI 0.507-0.892 p = 0.031). As opposed, NT-proBNP AUC for predicting HF mortality was even lower (AUC 0.559 and 0.654 for admission and discharge NT-proBNP concentration, respectively).

Forty-six (22.5%) deaths were identified at 12M post-discharge, being 81% due to HF. Deceased patients had higher values of CA125 on admission and at discharge (p = 0.011 and p = 0.014 on admission; p = 0.005 and p = 0.011 at discharge, for HF and overall mortality, respectively (Table 3). Likewise, survival was significantly superior when CA125 concentrations (on admission and/or at discharge) were below the median, in terms of HF (Fig. 2) and all-cause mortality.

Median concentrations of CA125 1 month after discharge did not differed among patients who survived or died, respectively, at 12 months (23.7 UI/mL vs. 43.6 UI/mL; p = 0.137).

A concentration of CA125 above median at any point of HF decompensation predicted higher overall mortality on multivariable COX regression analysis (Table 4). The model was adjusted considering age, gender, length of hospital stay, NT-proBNP, Cystatin C, urea, creatinine, LVEF, and other well-known risk factors. CA125 above median, on admission and at discharge, increased the risk for all-cause and HF mortality (12M all-cause mortality: Admission Exp[B] = 2.16 p = 0.03; Discharge Exp[B] = 3.15 p =

Table 4. Multivariate COX regression analysis

Multivariate Cox regression model	12-month all-cause mortality			12-month HF mortality		
	p-value	Exp (B)	CI 95%	p-value	Exp (B)	CI 95%
Gender	0.47	1.36	0.59-3.16	0.30	1.61	0.66-3.91
Age, years	0.01	1.96	1.22-3.14	0.00	1.15	1.07-1.23
Length of stay, days	0.02	1.35	1.05-1.74	0.13	1.03	0.99-1.07
LVEF, %	0.63	0.92	0.65-1.30	0.05	0.24	0.06-1.01
Arterial hypertension	0.08	3.37	0.88-12.85	0.19	2.52	0.63-1.01
CKD	0.36	1.55	0.60-4.00	0.72	1.21	0.43-3.39
Atrial fibrillation	0.72	0.86	0.38-1.95	0.89	0.94	0.38-2.32
Diabetes mellitus	0.17	1.82	0.77-4.27	0.12	2.14	0.83-5.49
Anemia	0.29	1.68	0.64-4.43	0.20	1.98	0.70-5.58
IHD	0.72	1.18	0.48-2.86	0.77	1.15	0.44-3.03
NT-proBNP, pg/mL	0.00	1.47	1.21-1.78	0.00	2.15	1.28-3.63
Cystatin C, mg/dL	0.03	1.40	1.04-1.88	0.03	2.80	1.13-6.91
Urea, g/L	0.00	1.52	1.16-1.99	0.02	3.72	1.29-10.77
Creatinine, mg/dL	0.30	1.16	0.88-1.52	0.15	0.21	0.03-1.72
Hematocrit, %	0.08	0.74	0.52-1.04	0.09	0.86	0.63-1.64
Admission CA125 > median	0.03	2.16	1.97-4.37	0.01	3.15	1.34-7.41
Discharge CA125 > median	0.02	3.15	1.97-4.89	0.00	3.41	2.65-5.24

CA125: carbohydrate antigen 125; CI: confidence interval; CKD: chronic kidney disease; Exp (B): exponentiation of the B coefficient; HF: heart failure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide.

0.02; 12M HF mortality: Admission Exp[B] = 3.15 p = 0.01; Discharge Exp[B] = 3.41 p = 0.00) (Table 4).

Influence of time-line changes in CA125 concentrations during hospitalization in prognosis

Median concentrations of CA125 significantly differed between admission and discharge (p = 0.026). CA125 serum concentration during hospitalization decreased in 44% patients (group A), and increased in 56% (group B). Those patients who increased their CA125 concentrations despite clinical recovery had higher admission NT-proBNP and urea, as well as lower hematocrit, total proteins, and blood pressure (systolic and diastolic) (Table 5).

An increase in CA125 concentration between admission and discharge was associated with higher mortality at 12M; 11% versus 21.5%; K-M log rank test p = 0.029 for HF mortality (Fig. 3) and 15.1% versus 24.7%, p = 0.035 for all-cause mortality. Furthermore, increases in the concentration of CA125 higher than 20% were followed by a rise in mortality (2.8% to 20.8% for HF-mortality [p = 0.011], and from 8.3% to 23.8% for overall-mortality [p = 0.041]).

Moreover, patients with CA125 > 55 UI/mL on admission and further increase before discharge had the worst prognosis of all, with a rate of 12M HF-mortality of 30%: (Group 1 [CA125 < 55 UI/mL and decrease during hospitalization]: 9.3%; Group 2 [CA125 < 55 UI/mL and CA125 increase]: 11.9%; Group 3 [CA125 > 55 UI/mL and CA125 decrease]: 13.3%; and Group 4 [CA125 > 55 UI/mL and CA125 increase]: 30%). Global p-value was 0.026, with differences between group 1-4 and 2-4 within the pairwise testing.

Although timeline changes in CA125 between admission and, both, 1 and 12 months follow-up were observed, they lack of prognostic meaning in terms of all-cause mortality. Mortality was 11.9% versus 21.1% (p = 0.301), respectively, for patients with a decrease or increase of CA125 between admission and 1 month

Table 5. Clinical characteristics according CA125 changes during index hospitalization

	Group A: CA125 decrease during admission (n = 85; 44%)	Group B: CA125 increase during admission (n = 109; 56%)	p-value
Age, years	81 (3)	81 (9)	0.294
Male	39 (53.4)	45 (48.4)	0.519
Length of stay, days	8.5 (7)	9 (7)	0.294
Arterial hypertension	58 (80.6)	79 (85.9)	0.362
IHD	23 (31.7)	37 (40.2)	0.275
Atrial fibrillation	35 (48.6)	55 (59.8)	0.154
CKD	16 (22.2)	22 (23.9)	0.799
Diabetes mellitus	24 (33.3)	41 (44.6)	0.144
COPD	13 (18.1)	16 (17.4)	0.912
SBP, mmHg	143 (42)	132 (35)	0.005
DBP, mmHg	77 (24)	72 (16)	0.030
LVEF, %	51 (27)	55 (22)	0.402
Cystatin C, mg/dL	1.44 (0.61)	1.42 (0.66)	0.938
NT-proBNP, pg/mL	2,765 (4,174)	3,400 (5,346)	0.027
Hematocrit, %	40 (9)	37 (8)	0.037
Urea, g/L	0.5 (0.3)	0.6 (1.5)	0.020
Creatinine, mg/dL	1.1 (0.5)	1.1 (0.5)	0.861
Total proteins, g/dL	6.6 (0.8)	6.2 (0.8)	0.000

CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; IHD: ischemic heart disease; LVEF: left ventricle ejection fraction; NT-proBNP: amino-terminal fragment of natriuretic peptide type B; SBP: systolic blood pressure.

after discharge; and, as of 11.4% versus 20.8% (p = 0.251) between discharge and 1 month later.

Discussion

Our results confirm that a concentration of serum CA125 above the median is associated with poor short- and long-term prognosis in decompensated HF. Moreover, they also suggest that prognostic information yielded by CA125 during hospitalization for HF is independent from the time when samples are drawn. It is also suggestive that serial measurement during hospitalization may be of interest, since an increase in CA125 between admission and discharge identifies a group of patients with higher mortality during follow-up.

Serum CA125 may increase, in HF, as a result of the physical and mechanical stress associated with pleural, pericardial, or abdominal effusions. Local inflammatory triggers, the interleukin cascade[16], along with mechanical stress and fluid accumulation, upregulates CA125 synthesis[16,17]. However, some studies have suggested that patients without an acute fluid overload or effusions, but chronic elevation in LV filling pressures, may also increase their CA125 levels and this may be related to severe HF and cytokine stimulation[9,18,19].

Correlation between clinical (worse NYHA functional class and signs of fluid congestion), hemodynamic, echocardiographic parameters[9,20], and CA 125 serum concentration has been already shown. It could be expected that CA125 would decrease following clinical improvement, as a result of clinical fluid decongestion. However, our results show that in nearly 56% of the patients CA125 levels increase during hospitalization, despite a seemingly efficacious treatment allowing to discharge the patient. Furthermore, this group of patients had higher long-term mortality, reaching nearly 25% at the end of 1-year follow-up. Mortality rose up to 30%, among those patients who, in addition to an

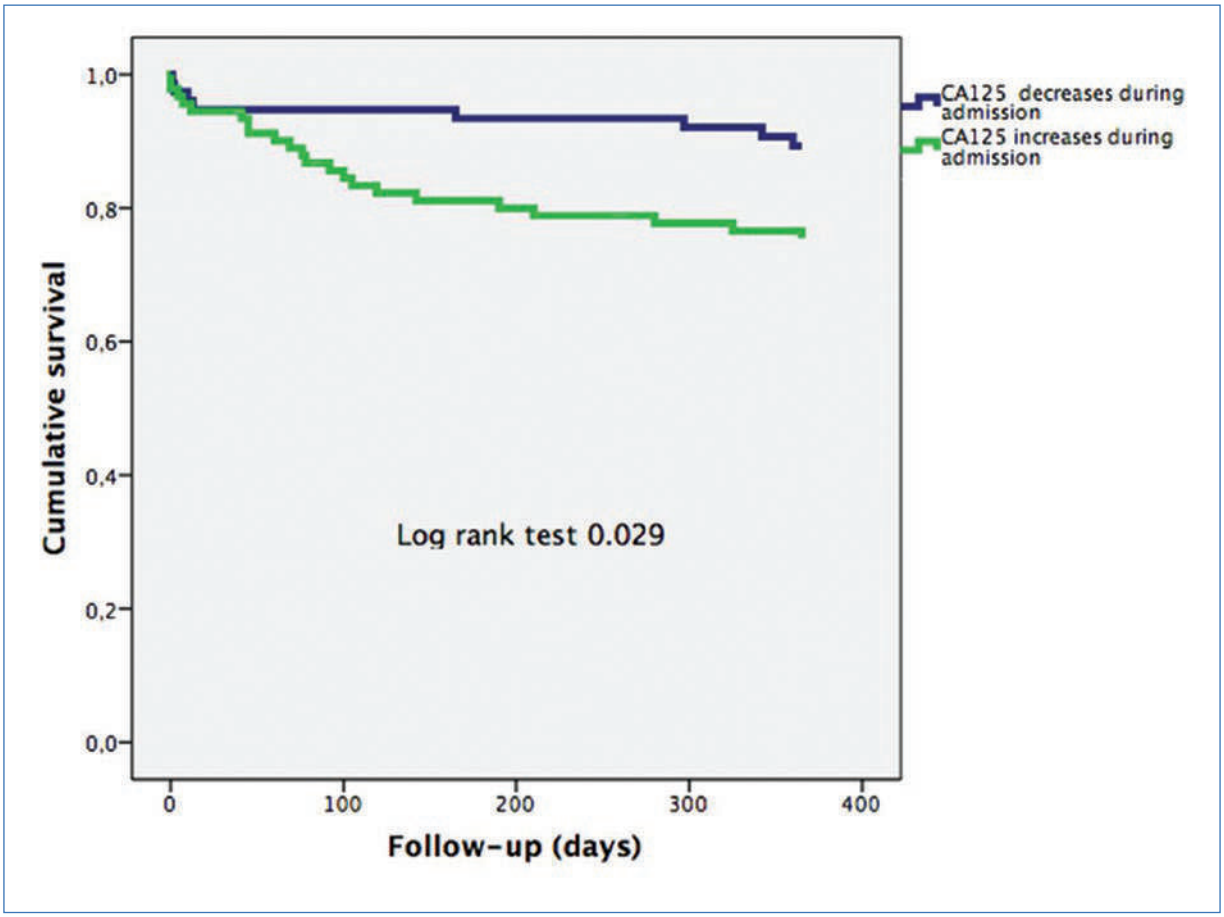

Figure 3. 12-month heart failure event-free survival curve according carbohydrate antigen 125 variations between admission and discharge.

increase in the concentrations of CA125 before discharge, had an admission CA125 above 55 UI/mL. Moreover, CA125 over the median during the acute period, measured at either admission or discharge, was associated with an increase in mortality risk that remained independent after multivariate study.

It is probable that a worse basal clinical situation, as reflected by lower systolic and diastolic blood pressure, anemia, and undernourishment (lower total proteins and albumin), as well as a higher degree of LV stress (higher admission NT-proBNP concentrations) may account for the rise in CA125 levels between admission and discharge. If this explanation is correct, CA125 would be a non-specific but rather sensitive and useful prognostic biomarker in AHF. Indeed, a meta-analysis conducted by Zhuang et al.[21] supported the strong relationship between CA 125 and HF, thus suggesting that CA 125 might be a cost-effective candidate to be considered as an additional biomarker for HF.

Serial measurements of CA125 have shown their utility in follow-up of HF[2,22,23]. The increase of CA125 during an AHF episode independently identifies patients with higher risk of complications after admission during follow-up[23]. In our study, we assessed, as well, the prognostic value of time-line changes of CA 125 in AHF. We found that an increase above 20% in serum concentration of CA125 between admission and discharge was associated with higher mortality rates.

Núñez et al.[22] measured CA125, along with NT-proBNP, in every medical visit after discharge for an AHF episode. Longitudinal trajectory of both biomarkers was useful to make prognostic predictions on a long-term basis. Patients with a sustained increase of both biomarkers had the worst prognosis. Our study shares the importance of categorical changes of CA125 compared to a single time measurement approach for predicting all-cause mortality. In our experience, however, CA125 levels measured after discharge, when the

patient is stabilized, does not add further prognostic information. Thus, suggest CA125 is a dynamic biomarker useful during the acute decompensation of HF.

In the meta-analysis by Llácer et al.[24], it was recommended serial measurements of CA125 during decompensation of HF, as a short-term prognostic biomarker. According to our results, if hospital stay lasts more than 5-7 days (median CA125 half-life), measuring the change in the concentration of CA125 between admission and discharge may help identify patients who required a closer follow-up. Additional testing, between discharge and 1-month later seems less useful.

Usually, patients are discharged when dyspnea and other signs of congestion had been relieved, according to the clinical judgment of the responsible physicians. It is suggestive to speculate that some of the patients were discharged with mild degrees of residual congestion, non-detected through physical examination. Residual congestion seems to be common in clinical practice and leads to worse prognosis[25,26]. We hypothesize that CA125 could help to identify patients with residual congestion, thus leading to a proper follow-up and probably better development.

Limitations

Our results are based in a single center cohort with a limited number of patients. The change in median concentrations of CA 125 between admission and discharge were modest. This makes the assignment of prognosis difficult to individual patients. Moreover, CA125 cutoff points are not standardized for HF.

Conclusion

Concentrations of serum CA125 measured during acute decompensated HF may help identify patients with poorer outcomes after discharge. A 20% increase of CA125 concentrations between admission and discharge, even if clinical improvement is present, is associated with long-term bad prognosis, especially among patients with admission CA125 over 55 UI/mL. Measurement of CA125 once the patient is stable does not provide additional prognostic information with respect to that yielded during decompensation.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Spanish Journal of Medicine

ORIGINAL ARTICLE

Basal-bolus insulin therapy fails to control glucocorticoid-induced hyperglycemia in patients with severe COPD exacerbation

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Abstract

Introduction and objectives: Patients with severe exacerbations of COPD often show hyperglycemia, which predicts adverse outcomes. We evaluated basal-bolus insulin therapy compared with sliding-scale insulin therapy as a treatment for glucocorticoid-induced hyperglycemia in patients with COPD exacerbations. **Methods:** A pre- and post-intervention study was conducted in the internal medicine department of a 280-bed hospital in Spain. During the intervention phase, we implemented the education and dissemination of inpatient insulin protocols with basal-bolus insulin therapy aimed at blood glucose values from 80 to 180 mg/dL. The primary endpoint was a composite of the need for mechanical ventilation, hospital readmission, or all-cause death at 30-day. Secondary endpoints included mean blood glucose during hospital admission, length of hospitalization, and hypoglycemia risk. **Results:** A total of 99 and 100 patients, pre- and post-intervention were evaluated, respectively. Patients' mean age was 75 years and 86% were male. A primary endpoint declined from 28 patients pre-intervention to 24 patients post-intervention (p = 0.54); mean in-hospital blood glucose concentration was 223.5 ± 66.6 and 216.8 ± 61.6 mg/dL (p = 0.73), and length of hospitalization was 6.9 ± 3.4 and 6.1 ± 5.0 days (p = 0.12), in the pre- and post-intervention group, respectively. There was a significant reduction in the proportion of patients with hypoglycemia from 12% to 6% in the pre- and post-intervention group, respectively (p = 0.03) **Conclusions:** Basal-bolus insulin therapy did not lead to reductions in the primary endpoint, mean in-hospital glucose, or length of hospitalization in COPD patients with glucocorticoid-induced hyperglycemia. Basal-bolus insulin therapy showed a lower risk of hypoglycemia.

Key words: Diabetes. Insulin. Length of stay. Mortality. Glucocorticoid. COPD.

Introduction

Approximately 80% of patients with COPD exacerbation admitted to the hospital show hyperglycemia[1]. Contributors of hyperglycemia in COPD exacerbations are the pre-existence of diabetes mellitus in 12-28%[2-4], the presence of stress hyperglycemia in 30%[5], and the frequent use of systemic glucocorticoids as the standard treatment for exacerbations[6].

Treatment with systemic glucocorticoids in COPD exacerbations has shown to improve clinical outcomes in terms of shorter hospital stay, lower rates of relapse, and increasing forced expiratory volume in one second. However, systemic glucocorticoids have a three-fold risk of inducing severe hyperglycemia compared to patients not receiving this medication[7]. Severe hyperglycemia is associated with an increase in nosocomial infections, risk of a hyperosmolar hyperglycemic

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syndrome, an increase in the length of stay, or mortality[8,9]. It has been estimated that for each 1 mmol/L (18 mg/dL) increment in glucose concentration, there is a 15% risk of an adverse outcome in terms of prolonged hospital stay or death[10].

The management of hyperglycemia-induced by systemic glucocorticoids is not well standardized. Non-insulin therapies such as metformin and dapagliflozin did not result in better control of glucose compared with placebo in clinical trials[11,12]. Insulin therapy has been the standard of care to control hyperglycemia-induced by glucocorticoids. The use of sliding scale insulin therapy, which means the administration of a pre-meal insulin dose based on the blood glucose level before each meal, has been the standard of care for many years[13,14].

Other insulin regimens have been recommended by experts but have not been enough tested in clinical trials of glucocorticoid-induced hyperglycemia[15]. Basal-bolus insulin therapy is now preferred as the best strategy for hospitalized patients with diabetes. Basal-bolus insulin therapy means the administration of long-acting form of insulin to maintain blood glucose levels stable through periods of fasting, and separate injections of shorter-acting insulin before each meal to prevent raises in blood glucose levels. However, there is scarce information about the efficacy of basal-bolus insulin therapy to control glucocorticoid-induced hyperglycemia during COPD exacerbations[16,17].

We carried out a pragmatic quasi-experimental study in which patients in a pre-intervention period treated with sliding-scale insulin therapy were compared with a post-intervention period where basal-bolus insulin therapy became the standard of care for hospitalized patients with hyperglycemia. Specifically, we aimed to assess the safety of each insulin therapy protocol and the benefits in terms of clinical outcomes.

Methods

Setting

Hospital Marina Baixa is a 280-bed center belonging to the National Health System providing care for 190,000 inhabitants on the East coast of Spain.

Type of study

We carried out a quasi-experimental before and after study.

Pre- and post-intervention study

The use of sliding scale insulin therapy was the standard of care at our institution until May 2008. In the pre-intervention study, we collected data from patients with COPD exacerbation and hyperglycemia admitted to our institution between April 2004 and May 2008. In May 2008, an educative program promoting the use of basal-bolus insulin therapy was presented and discussed with pulmonologists, cardiologists, hospitalists, and nurses. After disseminating the educative program, the use of basal-bolus insulin therapy became the standard of care.

An observational study carried out at our institution after the educative program, showed a reduction in mean blood glucose concentration of 24-42 mg/dL compared with the previous period, with no increase in hypoglycemia risk[16]. The educative program followed the recommendations endorsed by the American Diabetes Association for the management of hyperglycemia in hospitalized patients. The objectives for glucose control were values between 80 and 180 mg/dL, avoiding hypoglycemia.

The recommendations included: (1) stopping oral hypoglycemic agents, premixed insulins, and other injectable non-insulin antihyperglycemic drugs in all patients on admission; (2) bedside point-of-care measuring of capillary glucose at breakfast, lunch, and dinner or every 6-h if fasting; and (3) starting a basal-bolus-correction insulin regimen[17]. The estimated total daily dose of insulin was 0.3-0.5 units/kg/d. Insulin dosing was divided into 50% as basal insulin glargine, and 50% as short-acting aspart insulin. Aspart insulin was administered in three doses at breakfast, lunch, and dinner, or every 6-h as insulin correction dose if the patient was fasting. Adherence to basal-bolus insulin therapy was assessed by reviewing clinical records. The post-intervention study was carried out between January 2013 and July 2016. The post-intervention period was selected 5 years apart from the educative program to ascertain the widespread use of basal-bolus therapy in the hospital.

Patients

We selected for review the hospital records of patients with ICD-9-CM diagnosis code 491.21: Obstructive chronic bronchitis with (acute) exacerbation. We included patients if they were aged ≥15 years, had COPD diagnosed by physician assessment and/or spirometry, received systemic glucocorticoid therapy, and

were admitted to the hospital for an acute exacerbation. Furthermore, patients have to have type 1 or type 2 diabetes, and hyperglycemia greater than 140 mg/dL to enter the study.

The standard protocol for COPD exacerbation consisted of intravenous methylprednisolone given in a dose of 40 mg every 8 h for 3 days, followed by a progressive reduction in the dose. Patients were also treated during hospitalization with antimicrobials, inhaled beta-adrenergic, and inhaled anticholinergic agonists. Exclusion criteria were inpatients stay ≤ 48 h or the absence of at least 3 point-of-care glucose readings per day.

Assessments

We collected demographic variables, baseline treatments for diabetes mellitus and COPD, the severity of airway obstruction[18], the severity of COPD exacerbation measured by APACHE II score[19], arterial blood gases, admission values of glucose, creatinine, and glycated hemoglobin, bedside glucose readings, and 30-day endpoint.

The primary endpoint was a composite outcome of the need for invasive or non-invasive mechanical ventilation, all-cause emergency visits or readmission, and all-cause death within 1 month after discharge. The secondary end-points were in-hospital capillary glucose concentration, length of stay, and the proportion of patients suffering hypoglycemia (blood glucose < 70 mg/dL) during hospitalization. In the total population studied, we also examined the association between glucose concentration (divided by quartiles) and the proportion of primary endpoints and length of stay in each group.

Data were obtained from the electronic medical records of each patient.

Sample size

To estimate the sample size for the primary outcome, we used data from a Spanish study carried out in 2009-2010 in which the proportion of adverse outcome events in patients with COPD exacerbations at 30-day follow-up was 45%[20]. To detect a 22% reduction in the proportion of adverse outcomes, with an alpha error of 0.05, and at least 80% power, the sample size calculation obtained was 65 participants per group.

We also estimated the sample size needed to detect a 20 mg/dL reduction in blood glucose from a mean glucose value of 200 mg/dl (SD 50 mg/dL). For an alpha error of 0.05, and at least 80% power, the sample size calculation obtained was 99 participants per group.

Statistical analysis

Data are presented in absolute numbers and proportions for nominal variables. Mean ± standard deviation (SD) is used for continuous variables. Outcomes were analyzed with the use of a Student's t-test and the Pearson's Chi-square or Fisher's exact test for proportions. We calculated crude, and adjusted odds ratios for categorical endpoints.

In a logistic regression model, the outcome variable was each of the clinical endpoints, the controlling variables were age, duration of diabetes since diagnosis, the severity of airway obstruction, and the COPD exacerbation severity; the study variable was patient belonging to the pre- or post-intervention period.

We used the Chi-square test for trends to test the association between mean blood glucose concentrations divided by quartiles with the primary endpoint; and non-parametric tests for the association between mean glucose concentrations divided by quartiles and length of hospitalization. $p < 0.05$ were considered statistically significant. Data analysis was performed using SPSS/PC v. 15 as a statistical package (SPSS inc. Chicago, IL, USA).

Ethical and legal aspects

The study was approved by the Research Commission of our center. As it was a retrospective study, the informed consent of the patients was not requested. The treatment of personal data was governed by organic law 15/1999 and Royal Decree 1720/2007 for its protection.

Results

In the pre-intervention period, there were 348 patients with COPD exacerbation admitted to the hospital. We randomly selected 125 (36%) patients with hyperglycemia while receiving systemic glucocorticoid therapy. Ninety-nine (28%) patients with complete data enter the study. In the post-intervention period, there were 566 patients with COPD exacerbation admitted to the hospital. We randomly selected 150 (27%) patients with hyperglycemia while receiving systemic glucocorticoid therapy. One-hundred (18%) patients with complete data entered the study (Fig. 1).

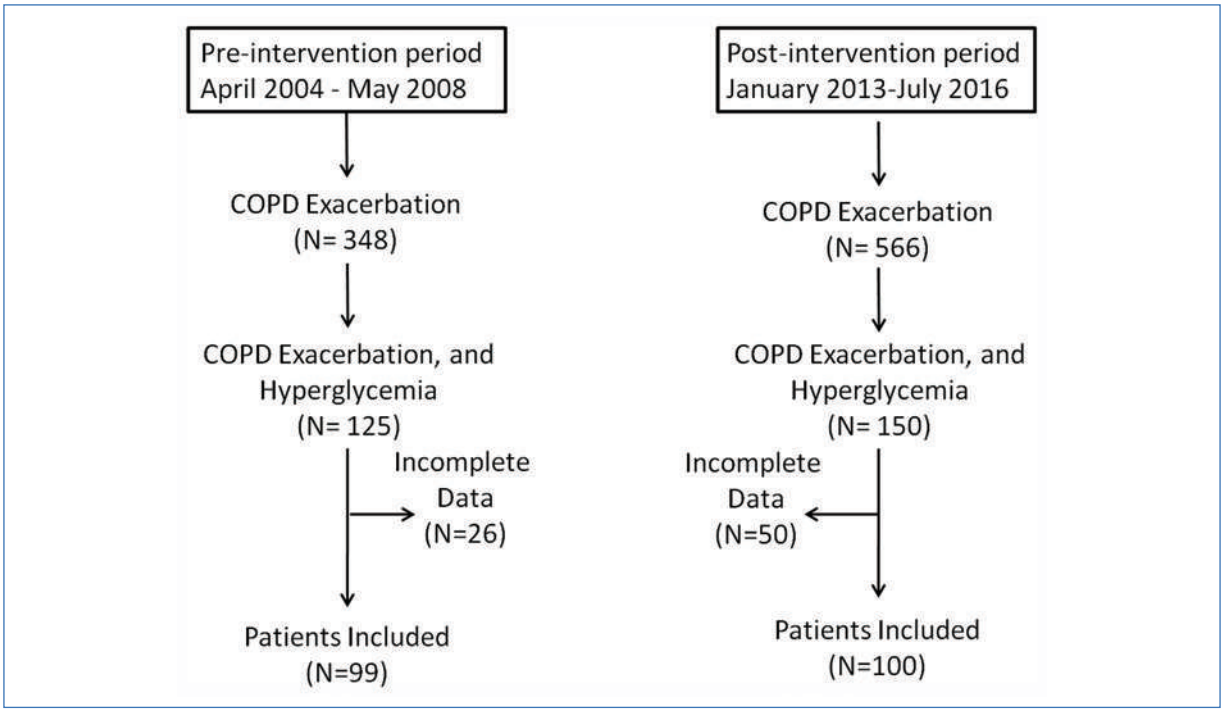

Figure 1. Flowchart of patients included in the study.

The baseline characteristics of the patients included in the study are shown in table 1. Compared with the post-intervention group, patients in the pre-intervention group were older, had less intense therapy for diabetes and COPD, had a more severe airway obstruction, and greater severity of COPD exacerbation according to APACHE II score calculated in the first 24-hour of admission. Fasting plasma glucose, creatinine, and glycated hemoglobin levels were similar between groups.

Primary endpoint

We observed a non-significant decline in primary composite endpoint in the post-intervention group compared with the pre-intervention group. Specifically, the 30-day need for mechanical ventilation, hospital readmission, or death occurred in 24 patients in the post-intervention group, and in 28 patients in the control group (crude odds ratio: 0.80; 95% confidence interval [CI]: 0.42-1.52; p = 0.497; adjusted odds ratio: 1.04; CI: 0.46-2.33; p = 0.540).

The analysis of each of the individual endpoints is shown in table 2. The need for mechanical ventilation during hospitalization, readmission at 30-day after discharge, and all-cause death were similar between groups. A lower proportion of patients in the intervention group than in the control group had hypoglycemia during hospitalization (6% vs.12%; adjusted odds ratio 0.26; CI: 0.08-0.89; p = 0.03).

Secondary endpoints

Mean in-hospital glucose concentration was 223.5 ± 66.6 and 216.8 ± 61.6 mg/dL in the pre- and post-intervention group, respectively (difference –6.7 mg/dL, 95% confidence intervals -11.6 to 24.6; p = 0.734). There were no significant differences in length of stay in the pre-intervention group (6.9 ± 3.4 days) compared with the post-intervention group (6.1 ± 5.0 days); difference between groups –0.08 days ([CI] -1.99 to 0.39; p = 0.120).

Association between mean glucose concentration during hospitalization and clinical outcomes

Both, pre- and post-intervention periods contributed data for this analysis. Mean glucose values during hospitalization were stratified by quartiles. We observed a trend for a greater proportion of adverse events (Fig. 2), and a similar length of stay (Fig. 3) in each of the mean glucose quartiles. Nevertheless, the associations did not reach statistical significance in either comparison.

Table 1. Baseline characteristics of the 199 patients according to the period of study

Characteristics	Pre-intervention group (n = 99)	Post-intervention group (n = 100)	p value
Age-year	76.4 ± 8.9	73.9 ± 8.9	0.048
Male sex	89 (90)	82 (82)	0.153
Body mass index, kg/m^2	29 ± 4.2	29 ± 5.7	0.980
Charlson comorbidity index	3.6 ± 1.7	3.4 ± 1.6	0.315
Duration of diabetes since diagnosis, years	7.5 ± 2.1	7.1 ± 1.3	0.138
Regular medications			
Inhaled beta-adrenergic agonist	90 (90)	86 (86)	0.398
Inhaled anticholinergic drug	59 (59)	80 (80)	0.004
Inhaled glucocorticoids	78 (78)	70 (70)	0.212
Systemic glucocorticoids	15 (15)	11 (11)	0.385
Diabetes therapy			0.001
None	5 (5)	5 (5)	
Oral anti-hyperglycemic drugs	54 (54)	36 (36)	
Oral anti-hyperglycemic drugs + insulin	36 (36)	38 (38)	
Insulin	4 (4)	21 (21)	
Severity of airway obstruction			0.001
Mild (FEV1 ≥ 80% predicted)	0 (0)	7 (10)	
Moderate (50% ≤ FEV1 < 80% predicted)	27 (39)	16 (24)	
Severe (30% ≤ FEV1 < 50% predicted)	41 (59)	33 (49)	
Very severe (FEV1 ≤ 30% predicted)	2 (3)	11 (16)	
Use of oxygen at home	32 (32)	23 (36)	0.654
Use of home non-invasive ventilation	4 (4)	13 (13)	0.023
Hospitalization for COPD in previous 1 year	57 (57)	43 (43)	0.041
APACHE II score	9.6 ± 3.3	8.5 ± 2.9	0.019
Arterial blood gases			
pH	7.39 ± 0.06	7.38 ± 0.06	0.522
pCO_2, mmHg	51.85 ± 14.43	47.46 ± 11.46	0.018
pO_2, mmHg	62.26 ± 18.66	70.73 ± 31.30	0.022
Biochemistry			
Glucose, mg/dL	191.4 ± 92.3	182.5 ± 68.20	0.435
Creatinine, mg/dL	1.1 ± 0.4	1.1 ± 0.8	0.927
Hemoglobin A1c, %	7.6 ± 2.1	7.8 ± 6.4	0.867

Continuous variables are presented as mean (±SD) and categorical variables are presented as frequencies (percentages).

Discussion

We carried out a pre- and post-intervention study to assess the efficacy and safety of a basal-bolus insulin strategy compared to sliding scale insulin therapy to control hyperglycemia in patients admitted with COPD exacerbation. We found no difference in the primary endpoint, a composite of the need for non-invasive or invasive mechanical ventilation, hospital readmission, or death between the intervention, and the control group after adjusting for confounders. However, we observed a 50% reduction in the proportion of patients with hypoglycemia in the post-intervention group compared with the pre-intervention group. The mean in-hospital glucose was 223.5 and 216.8 mg/dL in the pre- and post-intervention group, respectively. The in-between difference did not reach 18 mg/dL as suggested by Baker et al., as the threshold associated with a reduction in complications[10].

Other studies have also failed to prove the efficacy of a basal-bolus insulin protocol for controlling glucocorticoid-induced hyperglycemia in hospitalized patients[21,22]. A once-daily dose of prednisone given in the morning for COPD exacerbation produces a distinct circadian pattern of glucose elevation, which occurs

Table 2. Comparison of pre-specified clinical endpoints for categorical variables in patients with sliding-scale insulin therapy (pre-intervention group) and patients with basal-bolus insulin therapy (post-intervention group)

Endpoint	n (%)	Odds ratio [95% CI]	p value	Adjusted odds ratio* [95% CI]	p value
Composite outcome					
Pre-intervention	28 (28)	1		1	
Post-intervention	24 (24)	0.80 [0.42-1.52]	0.497	1.03 [0.46-2.33]	0.934
Need for mechanical ventilation					
Pre-intervention	5 (5)	1		1	0.469
Post-intervention	2 (2)	0.38 [0.05-2.00]	0.276	0.64 [0.19-2.15]	
Readmission					
Pre-intervention	26 (26)	1		1	0.754
Post-intervention	24 (24)	0.89 [0.46-1.69]	0.717	0.89 [0.43-1.84]	
Death					
Pre-intervention	7 (7)	1		1	
Post-intervention	1 (1)	0.13 [0.01-0.89]	0.034	0.08 [0.01-1.08]	0.086
Hypoglycemia, n (%)					
Pre-intervention	12 (12)	1		1	
Post-intervention	6 (6)	0.46 [0.13-0.96]	0.042	0.24 [0.06-0.97]	0.044

*Age, duration of diabetes since diagnosis, COPD severity (Airway obstruction severity), and COPD exacerbation severity (APACHE II score).

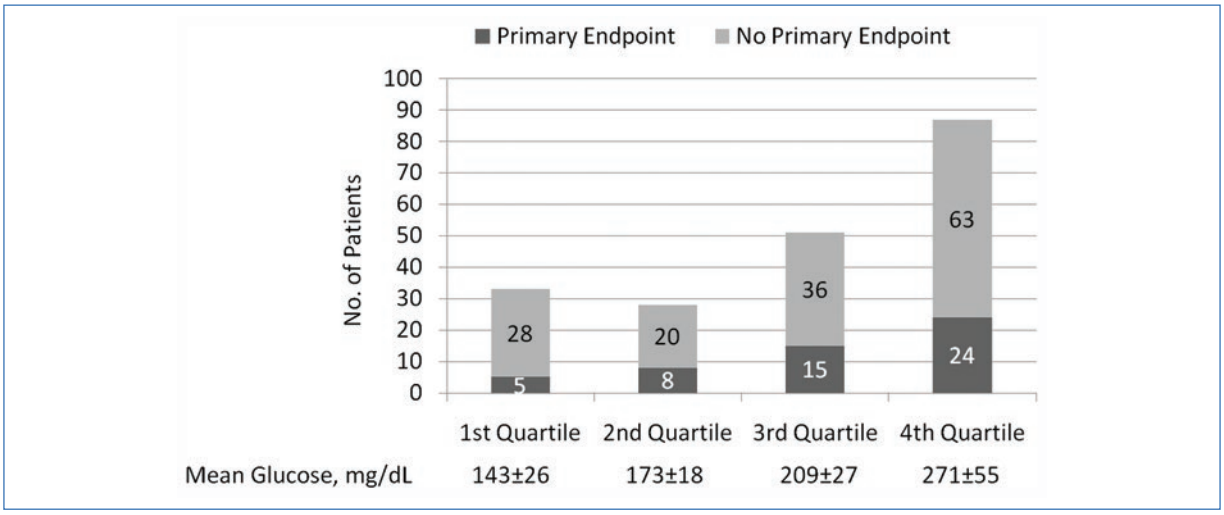

Figure 2. Proportion of patients with adverse outcomes (need for mechanical ventilation, readmission, or death) according to mean glucose values during hospitalization, stratified by quartiles (p for trend = 0.185).

predominantly in the afternoon and evening[23]. In those cases, treatment with a morning dose of isophane insulin could be a good choice since the pharmacokinetic pattern of isophane insulin matches the pattern of glucose elevation. Nevertheless, the use of additional short-acting insulin boluses is generally required to treat extreme glucose values. In a small clinical trial, the use of isophane insulin given at the same time or corticosteroid administration (daily, BID, or TID) in addition to outpatients' insulin regimen (basal-bolus, premixed, or basal only) was useful to reduce mean blood glucose. The mean glucose values were significantly lower in the isophane insulin group compared with the usual care (226 vs. 268 mg/dL, respectively)[24].

A small clinical trial has also proved the usefulness of adding correctional isophane insulin to control the hyperglycemia induced by prednisolone or methylprednisolone[25]. Another strategy tested was to increase the number of doses of prandial insulin to 5 doses

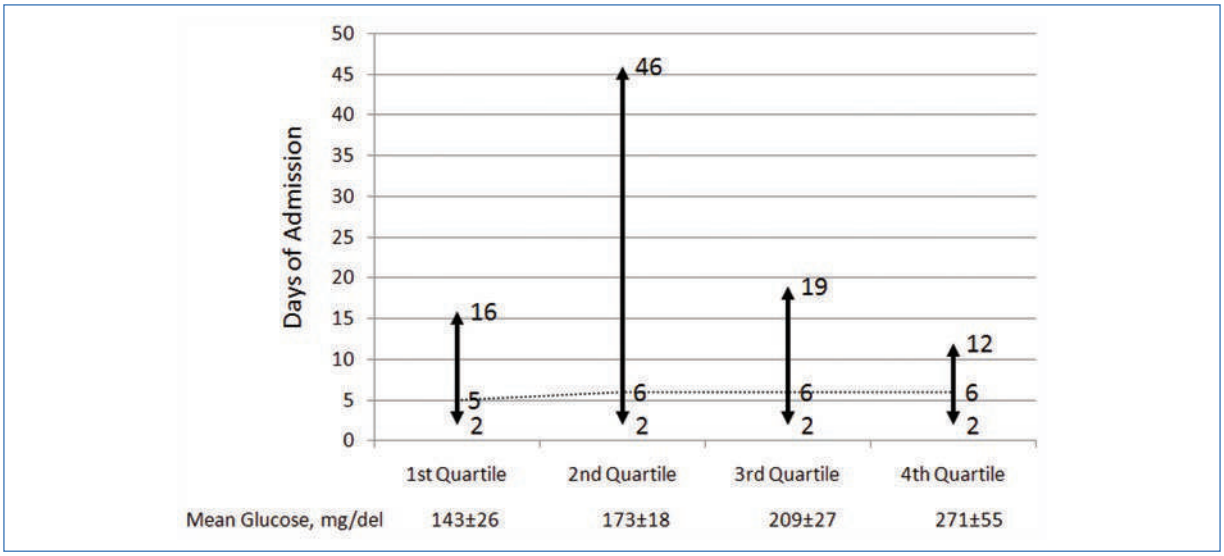

Figure 3. Length of stay (median [range]) according glucose values during hospitalization, stratified by quartiles (p = 0.899).

(breakfast, lunch, snack, dinner, and midnight) instead of three doses (breakfast, lunch, and dinner)[26]. This strategy achieved a 14.5 mg/dL reduction in the in-hospital mean glucose compared with the standard basal insulin therapy, but hospitalization days were similar in the two groups. There were no other major clinical outcomes assessed. For patients with hyperglycemia during dexamethasone therapy, the basal-bolus insulin regimen has proved in retrospective trials to offer advantages to insulin administered as sliding scale dosing[14].

Current guidelines recommend for hospitalized patients with blood glucose above 180 mg/dl to start insulin therapy at a dose of 0.3-0.5 units/kg[27]. However, patients on glucocorticoid treatment require a more intensive insulin regimen to compensate for increased peripheral insulin resistance. In patients with high dose glucocorticoids, the average daily dose of insulin needs often to be up-titrated to 1.2 units/kg[14]. The small reduction in mean in-hospital glucose values we observed in patients with basal-bolus insulin therapy compared with sliding scale insulin therapy could lie in an insufficient correction dose administered during glucocorticoid therapy.

A significant outcome to remark of our study was the reduction in the proportion of patients with hypoglycemia events in the post-intervention period. The absolute reduction was 6%, which translated into a 50% relative risk reduction. This difference was significant after in the multivariate analysis after controlling for potential confounders. However, the sample size of our study was not powered to assess the effect of hypoglycemia on mortality or length of stay. Other studies comparing basal-bolus insulin therapy with sliding scale insulin therapy did not find a significant reduction in the proportion of patients with hypoglycemia.

The published studies showed an incidence of hypoglycemia ranging between 0% and 3.2% in the basal-bolus therapy group compared with 0% to 3.4% in the sliding scale insulin group[21,22-25]. It should bear in mind that a sliding scale insulin regimen treats hyperglycemia after it has already occurred instead of preventing the occurrence of hyperglycemia. We also observed a reduction of deaths in the post-intervention period that could be linked to a reduction in hypoglycemia events, although this association could be speculative.

There was a reduction of adverse outcomes and in hospitalization days in patients with better glucose control. After dividing by quartiles the glucose values in both cohorts, those patients in the lower quartile showed a decline in relevant clinical outcomes and hospitalization days compared with patients in the higher quartile. Although the p-value for trend was not significant, this observation reinforces the importance to maintain in-hospital glucose values in the recommended targets.

Limitations of the study

Our study is subject to limitations. First, there was a significant lapse of time separating the pre-intervention

and post-intervention periods since the post-intervention period was selected when basal-bolus insulin therapy was fully-implanted in the hospital. The effect of this lapse of time may have introduced a temporal trend bias where advances or changes in clinical care, the nature of the disease, or patient population may account for observed changes between pre- and post-intervention periods. Specifically, patients in the pre-intervention period received less intense therapy for COPD and diabetes conditions than those in the post-intervention period.

We tried to compensate for these differences by multivariable analysis adjusting for confounders. Second, we did not collect the periods of fasting during hospitalization (requiring lower insulin doses), the type and dose of glucocorticoid used individually, nor the average insulin dosage per patient. During the study period, the hospital protocol for COPD exacerbation management remained stable. Moreover, since the study population was elderly patients with significant comorbidity, insulin therapy was very conservative in each group.

As for the strengths of our study, we remark the assessment of a sample size enough to detect significant differences in relevant clinical and laboratory outcomes. Furthermore, we addressed the different prognostic distribution by multivariate analysis. Despite the possible limitations, we think the results of our study carried out in real-world practice are generalizable to similar clinical settings.

Future directions

Hyperglycemia induced by glucocorticoid therapy is a common problem in patients hospitalized with severe diseases. There are no insulin protocols enough tested that resulted in improving clinical outcomes.

Recently, a systematic review concluded that there are no high-quality studies with well-defined diabetes mellitus phenotypes, settings, and treatment approaches to determine the optimal pharmacological intervention in patients with glucocorticoid-induced hyperglycemia[28]. Randomized controlled studies addressing patients' important outcomes are urgently needed.

Conclusion

The use of basal-bolus insulin therapy as a standard of care to control hyperglycemia induced by high-dose glucocorticoids needs to be re-evaluated. Our study shows that it is necessary to increase the frequency or the dosage of correctional short-acting insulin units. The use of isophane insulin as a correctional dose has not been properly evaluated and compared with basal-bolus insulin therapy.

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Conflicts of interest

Javier Ena has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies, including Novartis, Menarini, Ferrer, Janssen, Sanofi, and Novo Nordisk and has been a consultant for Novo Nordisk and Janssen.

Pablo Oteo has no competing interests to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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ORIGINAL ARTICLE

Is pulmonary embolism associated with pleural transudates, exudates, or both?

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Abstract

Introduction and objectives: Whether pleural effusions (PEs) secondary to pulmonary embolism can be exudative or transudative is controversial. This study aims to determine which type of effusion (exudate or transudate) is typically associated with pulmonary embolism, using Light's criteria as the discriminative gold standard. **Methods:** A retrospective analysis of all consecutive patients with pulmonary embolism subjected to a diagnostic thoracentesis over a 25-year period in a University Hospital was performed. Pleural fluid data were described in detail. **Results:** Seventy-one patients with pulmonary embolism-associated PEs comprised the study population. Pleural fluids were bloody in more than half the cases. The pleural fluid differential white blood cell count was variable; the predominant cells (> 50% of the total leukocytes) were lymphocytes in nearly two-thirds of the patients and neutrophils in about 30%. A proportion of eosinophils > 10% was observed in 7% of the cases. All fluids were exudates, meeting either 3 (78.2%), 2 (12.7%), or just 1 (9.1%) of the Light's criteria. **Conclusion:** The pleural fluid that accompanies pulmonary embolism is invariably an exudate.

Key words: Pleural effusion. Pulmonary embolism. Transudate. Exudate.

Introduction

Pulmonary embolism is a relatively infrequent cause of pleural effusions (PEs) but, at the same time, it is a disorder commonly overlooked during the work-up of undiagnosed effusions. In a series of 3077 patients with PEs who underwent thoracentesis, pulmonary embolism accounted for just 1.5% of the cases[1]. Paradoxically, PEs are observed in about one-third of patients with pulmonary embolism by chest radiograph, and half the cases when using computed tomography[2]. The fact that most of these PEs are small (and thus not amenable to thoracentesis) or discovered when the diagnosis of pulmonary embolism is already established (thus making unnecessary a diagnostic aspiration), explains the low prevalence of pulmonary embolism among the etiology of tapped PEs[3].

Whether pulmonary embolism may generate transudates or exudates has long been a point of discussion, largely due to the unawareness of the exact pathophysiology of fluid formation in this condition. The aim of the current study was to define the transudative or exudative nature of PEs secondary to pulmonary embolism, using Light's criteria as the reference standard[4], in the largest series published to date.

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Methods

We performed a retrospective analysis from a prospectively maintained database, which includes all consecutive patients with PEs who have undergone a diagnostic thoracentesis at the Arnau de Vilanova University Hospital (Lleida, Spain) for the past 25 years. Patients with a final diagnosis of PE secondary to pulmonary embolism were the focus of the current investigation. The study protocol was approved by the local ethics committee (CEIC No. 1965).

The diagnosis of pulmonary embolism was made radiographically by computed tomographic pulmonary angiography and, except in two patients with a history of hypersensitivity reaction to iodinated contrast agents who were diagnosed by using lower extremity compression ultrasonography with Doppler in the adequate clinical context. Attributing the PE to pulmonary embolism also required excluding other potential causes of fluid formation based on clinical data and pleural fluid analyses.

We recorded demographics, location, and size of PEs on chest radiographs, biochemistries of serum (i.e., protein, albumin, and lactate dehydrogenase [LDH]) and pleural fluid (i.e., total and differential cell count, protein, LDH, glucose, pH, adenosine deaminase and, if available, C-reactive protein, cholesterol, albumin, carcinoembryonic antigen [CEA], carbohydrate antigen 15-3 [CA 15-[3], and natriuretic peptides), time from symptom onset to thoracentesis, and elapsed time between the start of anticoagulation and pleural tapping.

Most thoracenteses were performed under ultrasound assistance. If the patient had been submitted to repeated thoracentesis, only the results of the first one were considered. All biochemical measurements of pleural fluid and serum were performed on selective, discrete multichannel analyzers using standard methodologies. Pleural fluid cell counts were carried out either manually in a Thoma counting chamber or using an automatic hematology analyzer. In our laboratory, the upper normal limit for serum LDH is 375 U/L. Malignancy cutoff points used for pleural fluid CEA and CA 15-3 were 45 ng/mL and 77 IU/mL, respectively[5]. Pleural fluid levels of brain natriuretic peptide (BNP) > 115 pg/mL[6] and of N-terminal pro-BNP > 1500 pg/mL[7] are generally associated with heart failure. A serum-pleural fluid albumin gradient (serum albumin minus pleural fluid albumin) > 1.2 g/dL or a serum-pleural fluid protein gradient > 3.1 g/dL has long been proposed to indicate a likely transudate in the setting of clinically suspected cardiac effusions that meet Light's criteria for exudate[8].

PEs were categorized as transudates or exudates using the criteria reported by Light et al.[4], wherein exudative PEs are identified by the presence of one or more of the following findings, whereas a transudate has none: (1) pleural fluid protein divided by serum protein > 0.5, (2) pleural fluid LDH divided by serum LDH > 0.6, and (3) pleural fluid LDH more than two-thirds (67%) of the upper normal limit for serum LDH (which in our study implies a pleural fluid LDH > 250 U/L).

Descriptive statistics were used to summarize patient characteristics and pleural fluid findings. Data are presented as numbers (proportions) or median (interquartile range [IQR]) as appropriate. Between-group comparisons were assessed by means of the Mann–Whitney U-test. $p < 0.05$ was considered statistically significant. Calculations were done using the SPSS version 24.0 statistical software.

Results

By November 2020, our database encompassed 5460 patients with PEs, of whom 71 (1.3%) had pulmonary embolism. Partial data of 26 of these patients were already reported in a previous own study with different primary outcomes[2].

The current study population comprised 45 (63.4%) men and 26 (36.6%) women, with a median age of 74 years (IQR 52-84 years, range 23-93 years). On chest radiographs, PEs were right sided (34, 48%), left sided (29, 41%), or bilateral (8, 11%), while occupying one-third or less of the hemithorax in 63 (88.7%) cases.

In the subgroup of patients in whom electronic records were available (n = 31), the median lag time between symptoms onset and diagnostic thoracentesis was 9 days (IQR 6-12 days). At the time of thoracentesis, 14 (45%) patients were receiving anticoagulant therapy and 12 (38.7%) were on diuretics.

Pleural fluid biochemical data are presented in table 1 and their interpretation, according to widely accepted cutoff values, is shown in table 2. Pleural fluid cultures and cytological examinations were performed in 46 and 59 patients, respectively, with negative results in all cases. The pleural fluid red blood cell count was higher than 10,000/μL, which usually corresponds with a bloody appearance, in 55.7% of the cases and surpassed 100,000/μL in 6 (8.6%). The differential white blood cell count revealed a predominance of lymphocytes (i.e., > 50% of the total leukocyte count) in about two-thirds of the cases, of neutrophils in nearly 30%, and pleural eosinophilia

Table 1. Pleural fluid findings in pulmonary embolism

Pleural fluid parameter	No. of patients	Value, median (quartiles)
Erythrocyte count, × µL	70	15,150 (3028-38,800)
Leukocytes, × µL	71	1639 (900-4000)
Polymorphonuclear cells, %	71	33 (17-59)
Eosinophils, %	71	15 (9-43)
Lymphocytes, %	71	63 (36-83)
Glucose, mg/dL	70	109 (92-129)
pH	65	7.47 (7.40-7.50)
Adenosine deaminase, U/L	70	15 (8-23)
Protein, g/dL	71	4.1 (3.3-4.8)
Pleural fluid to serum protein ratio	65	0.65 (0.59-0.72)
Serum to pleural fluid protein gradient, g/dL	65	2.2 (1.7-2.7)
LDH, U/L	70	428 (287-707)
Pleural fluid to serum LDH ratio	56	1.29 (0.85-2.64)
Cholesterol, mg/dL	29	70 (56-101)
Albumin, g/dL	22	2.3 (1.7-2.6)
Serum to pleural fluid albumin gradient, g/dL	21	1.0 (0.6-1.2)
C-reactive protein, mg/L	30	31 (17-71)
CEA, ng/mL	40	1.4 (0.9-2.2)
CA 15-3, IU/mL	35	14.6 (10.1-20.1)
BNP, pg/mL	12	83 (34-104)
NT-pro-BNP, pg/mL	25	564 (280-1778)

BNP: brain natriuretic peptide; CA 15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; LDH: lactate dehydrogenase; NT-pro-BNP: N-terminal pro-BNP.

(i.e., > 10% of eosinophils) in 7%. The discovery of predominantly neutrophilic or lymphocytic fluids was unrelated to symptom duration until the thoracentesis (median of 9 days when polymorphonuclear leukocytes predominated vs. 8.5 days for lymphocytic effusions, p = 0.451). No patient exhibited elevated adenosine deaminase levels, marked pleural fluid acidosis (i.e., pH < 7.20). or high concentrations of classical tumor markers. Raised natriuretic peptide levels were observed in some of the few pleural fluids in which they could be measured.

PEs from all 71 patients met Light's criteria for exudates. In particular, of 55 patients for whom all three Light's items were available, one criterion was fulfilled by 5 (9.1%) patients, two criteria by 7 (12.7%), and three criteria by 43 (78.2%). In addition, 85.7% and 92.3% of subjects had serum to pleural fluid albumin and protein gradients which were consistent with exudates, respectively.

Discussion

The present study supports the uniform exudative nature of all PEs secondary to pulmonary embolism. This challenge what has been traditionally taught, namely, that pulmonary embolism-associated PEs may be either an exudate or a transudate. In fact, the concept that pleural fluids in this condition might, although infrequently, have transudative characteristics is still reflected today in time-honored textbooks of Internal Medicine[9,10], and even recent reviews in top medical journals[11].

Confusion about the precise exudate-transudate classification of these PEs stems from a report dating back to 1976, in which 7 (27%) of 26 pleural fluids associated with pulmonary embolism were labeled as transudates[12]. However, the criteria used to define exudates (and therefore

Table 2. Pleural fluid characteristics according to widely accepted cutoff points

Pleural fluid parameter	No. of patients	No. (%)
Erythrocytes ≥ 10,000/μL	70	39 (55.7)
Neutrophils > 50%	71	21 (29.6)
Eosinophils > 10%	71	5 (7)
Lymphocytes > 50%	71	46 (64.8)
Glucose ≤ 60 mg/L	70	1 (1.4)
pH ≤ 7.20	65	0 (0)
Adenosine deaminase ≥ 35 U/L	70	0 (0)
Protein ≥ 3 g/dL	71	60 (84.5)
Pleural to serum protein ratio > 0.5	65	57 (87.7)
Serum to pleural fluid protein gradient ≤ 3.1 g/dL	65	60 (92.3)
LDH > 250 U/L	70	58 (82.8)
Pleural fluid to serum LDH ratio > 0.6	56	52 (92.8)
Cholesterol ≥ 45 mg/dL	29	27 (93)
Serum to pleural fluid albumin gradient ≤ 1.2 g/dL	21	18 (85.7)
CEA > 45 ng/mL	40	0 (0)
CA 15-3 > 77 IU/mL	35	0 (0)
BNP > 115 pg/mL	12	1 (8.3)
NT-pro-BNP > 1500 pg/mL	25	6 (24)

BNP: brain natriuretic peptide; CA 15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; LDH: lactate dehydrogenase; NT-pro-BNP: N-terminal pro-BNP.

transudates) were not those reported by Light 4 years earlier, which were not yet universally accepted, but rather the pleural fluid concentrations of proteins (> 3 g/dL) or LDH (> 200 U/L). Notably, pleural fluid LDH was only measured in 12 (46%) patients[12]. It should be stressed that the criteria reported by Light et al. 49 years ago[4] to separate exudates from transudates still prevail. This is because they are stringent and classifies virtually all exudates correctly (sensitivity 98%); even though they do misclassify about 25% of transudates as exudates, usually by a small margin[13]. Therefore, the application of alternative and less sensitive criteria for the identification of an exudate, as conducted in the study of Bynum and Wilson[12], and two subsequent ones[14,15], may miscategorize some cases. In fact, the sum of all studies, including the present one, where Light's criteria were applied demonstrates that all 142 patients with pulmonary embolism who were evaluated had pleural exudates (Table 3).

The terms transudate and exudate reflect the pathophysiological mechanism of pleural fluid formation. Transudates derive from imbalances in hydrostatic and oncotic forces over a structurally intact pleural surface, whereas exudates accumulate because of local factors affecting the pleura, such as increased capillary permeability and/or impaired lymphatic drainage resulting from many inflammatory and malignant causes. Since all pulmonary embolism associated PEs are exudates, it is presumed that increased permeability of pulmonary capillaries, probably related to the release of inflammatory mediators from the platelet-rich thrombi (e.g., vascular endothelial growth factor), is the most plausible mechanism by which pulmonary embolism produces PEs[19]. The right ventricular dysfunction that may accompany acute pulmonary embolism may account for the elevation of natriuretic peptides in the pleural fluid of some of these. Nearly 39% of patients were on diuretics at the time of thoracentesis, as now stated in Results.

This study is limited by its retrospective design and small sample size. However, thoracentesis is rarely attempted in the setting of a confirmed pulmonary embolism unless the PE is increasing in size and it is needed to exclude a hemothorax, or the patient is

Table 3. Studies that have evaluated the categorization of pulmonary embolism-associated effusions as transudates or exudates

Study	No. of patients	Criteria for exudates	No. (%) of exudative effusions
Bynum and Wilson, 1976[12]	26	PF protein > 3 g/dL or PF LDH > 200 U/L	19 (73)
Romero-Candeira et al., 2002[16]	60	Light's criteria	60 (100)
Erkan et al., 2004[17]	5	Light's criteria	5 (100)
Sandevski et al., 2012[14]	31	LDH fluid to serum ratio > 0.6	30 (97)
Choi et al., 2017[15]	13	Not specified	12 (92)
Panjwani et al., 2019[18]	6	Light's criteria	6 (100)
Current study, 2021*	71	Light's criteria	71 (100)
Total	142	Light's criteria	142 (100)

*This series includes data of 26 patients from a previous own publication[2].
LDH: lactate dehydrogenase; PF: pleural fluid.

persistently febrile and it is needed to exclude a pleural infection.

Conclusion

In summary, although pulmonary embolism associated PEs were previously sometimes thought to be transudates, the few exudate-transudate studies that have used Light's standard criteria[4] conclude that all are exudates.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Risk stratification scores for major bleeding in patients with venous thromboembolism

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Abstract

The standard treatment for venous thromboembolism (VTE) is anticoagulation. Drug selection and treatment duration will depend on the clinical presentation, the existence of provoking factors, bleeding risk, and the patient's preferences. Anticoagulation therapy is indicated for 3-6 months in all patients with acute VTE but may be extended, even indefinitely in some cases. The most severe side effect of anticoagulation is bleeding, with the highest risk occurring during the 1st week of therapy. Balancing the risk of bleeding and the risk of recurrence in patients with VTE remain a major issue. There are, currently, no simple and validated predictive scores to estimate the long-term bleeding risk in patients undergoing anticoagulant treatment and to safely select those patients with higher bleeding risk. Some authors have used risk factors to stratify the bleeding risk in patients with VTE. We review some of these scores, including the Kuijer score, the RIETE scores for 10 days and 3 months, the VTE-BLEED score, and the American College of Chest Physicians guidelines. They present different follow-up times and heterogeneous and contradictory results, without enough evidence and validation. Given the lack of evidence on the value of prognostic bleeding risk scores in patients with VTE, they should not yet be used as the main argument to interrupt anticoagulation after the first 3 months in patients with VTE. They may, however, be used to identify patients with low hemorrhagic risk in whom anticoagulation might be maintained indefinitely.

Key words: Venous thromboembolism. Bleeding. Mortality. Direct oral anticoagulants. Vitamin-K antagonists.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the main manifestations of venous thromboembolism (VTE). Most DVT cases occur in the lower limbs but can also develop in the upper limbs, splanchnic veins, cerebral veins, among others[1]. Both DVT and PE share similar risk factors, and, in most cases, PE occurs as a consequence of the lower extremity DVT[2]. PE is also the main cause of VTE-related mortality, being an important cause of preventable in-hospital mortality[3].

Clinical-administrative and hospital database studies show an annual incidence of VTE of 1-1.8/1000 inhabitants in Europe. However, incidence rates vary according to age, race, and gender, ranging from 1/100,000 in young people to 1/100 in individuals over 80 years-old. Men show a mildly higher incidence than women, but the female population display a higher incidence during the fertile years[3-5].

Blood hypercoagulable states, circulatory stasis, and the disruption of the endothelial wall are considered the pillars of the pathophysiology of VTE[6]. VTE presents a

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series of provoking risk factors, either persistent or transient, that sum or multiply to the total risk of VTE[1]. Knowledge of these risk factors has vastly increased in the last few decades; nevertheless, in more than a third of VTE cases, a risk factor is not identified, and these are thus classified as idiopathic or unprovoked[7]. Classifying an event as provoked or unprovoked has pronounced repercussions on its management since it is one of the main factors involved in the decision of maintaining long-term anticoagulation (longer than 3-6 months)[8]. Besides the above-mentioned environmental factors, there are other elements that may influence the development of VTE, including hereditary thrombophilias (heterozygous factor V Leiden and prothrombin mutations)[9] or acquired thrombophilias (e.g., antiphospholipid syndrome)[10]. Moreover, a strong association between VTE and cancer has been widely established. The relative risk of VTE is higher in patients with active cancer[11], and oncologic patients show a higher risk of mortality if they develop VTE[12,13].

Once the diagnosis of VTE has been established, anticoagulation must be initiated promptly. The anticoagulant of choice and duration of treatment will depend on the clinical presentation, the existence of provoking factors, the hemorrhagic risk, and the patient's preferences[14]. Classic anticoagulation treatments include parenteral drugs, such as unfractionated heparin, low-weight molecular heparin, and fondaparinux; and oral drugs, mainly Vitamin-K antagonists (VKA). In the last decade, new oral anticoagulants have been developed. They directly inhibit anticoagulation factors IIa (dabigatran) or Xa (rivaroxaban, edoxaban, and apixaban) and are thus named direct oral anticoagulants (DOACs)[15,16]. They are currently considered the gold standard over VKA when treating VTE, except for patients with cancer, pregnancy, antiphospholipid syndrome, or high-risk PE[6].

In patients with acute VTE, anticoagulation is recommended to prevent early mortality, symptomatic or fatal recurrence of VTE, and long-term complications, including post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension (CTPH). Standard anticoagulation treatment is divided into three phases: acute (first 5-10 days), long-term (10 days-3-6 months), and extended (longer than 3-6 months)[8,15,16].

VTE recurrence

Around 36% of VTE patients present a recurrence within the following 10 years after discontinuation of anticoagulant treatment for a first unprovoked VTE event[17]. Prevention of recurrences is the main justification of an extended therapy (longer than 3-6 months). The risk of recurrence after completion of anticoagulant therapy is linked to the presence of a provoking factor, being lower in VTE provoked by major transient factors (≤ 3% per year) than those provoked by permanent factors (10% or more per year) or unprovoked events[18-22]. Other predictors of recurrence are age, body mass index, male gender, active cancer, neurological diseases with paresis of the lower limbs, antiphospholipid syndrome, persistently elevated D-dimer and possibly, residual thrombosis[5].

Several predictive algorithms for recurrence of unprovoked or cancer-associated VTE have been developed, including the HERDOO2 (exclusively validated for unprovoked VTE in women)[23], the Vienna model[24], or the DASH model[25].

Bleeding risk in VTE and prognostic scores

The most severe side effect of anticoagulation is bleeding, which can be fatal[26]. The highest risk occurs during the first 7 days of treatment[27]. Early major bleeding in patients with PE can happen in 3-4% of the cases[28], whereas it occurs in 0.1% of patients with DVT[29]. However, the risk of bleeding depends on the anticoagulant therapy: compared to VKA, DOACs present a lower risk of major bleeding, fatal bleeding, intracranial bleeding, clinically relevant bleeding, and overall bleeding and do not increase the risk of gastrointestinal bleeding[30-32].

Anticoagulation therapy is indicated for 3 months in all patients with acute VTE[16,33]. Prevention of VTE recurrence and its associated morbidity and mortality outweighs the bleeding risk in most patients[34]. Nevertheless, patients may have an absolute contraindication for therapeutic doses, which must be avoided in the following circumstances: active intracranial bleeding, life-threatening bleeding, recent major surgery, and thrombocytopenia under 30,000/μL[35,36].

Optimal anticoagulation duration after a first unprovoked VTE event is controversial. Discontinuing therapy after the first 3-6 months requires a thoughtful evaluation of the risk of recurrence, and maintaining the treatment demands a careful assessment of major bleeding risk. Some clinical trials have shown the safety and efficacy of long-term aspirin treatment for the prevention of recurrent VTE[37]. Others have demonstrated superior efficacy of long-term anticoagulation with rivaroxaban

Table 1. Kuijer bleeding risk scores for the first 3 months of anticoagulant therapy in patients with venous thromboembolism[41]

Risk factors	Points
Age > 60 years	1.6
Female	1.3
Active cancer	2.2
Categories Low risk Intermediate risk High risk	 0 points 1-3 points > 3 points

versus aspirin (EINSTEIN CHOICE)[38] or apixaban versus placebo (AMPLIFY-EXT)[39].

There are currently no validated predictive scores to estimate the long-term bleeding risk in patients under anticoagulant treatment and to safely select those patients with a higher bleeding risk[17,40]. However, several risk factors used in clinical-analytical scores (age, gender, cancer, recent major hemorrhage, and among others) have been suggested to stratify the bleeding risk in patients with VTE. The Kuijer score, the RIETE scores for 10 days and 3 months, the VTE-BLEED score, and the American College of Chest Physicians (ACCP) guidelines score are some examples. They show variable follow-up times and heterogeneous results[15,27,34,41-47].

Kuijer score

A retrospective study by Kuijer et al.[41] in 1999 used hemorrhagic risk factors described in the literature (age, gender, and cancer) to develop a bleeding risk score for the first 3 months of anticoagulant therapy. The formula was: 1.6, 1.3, and 2.2 points for age > 60 years-old, sex female, and presence of cancer, respectively. Patients with a score ≥ 3 were classified as high bleeding risk, those between 1 and 3 points as intermediate risk, and those with 0 points as low risk. The score had external validation, and the C-statistic for major bleeding was 0.82 (0.66-0.98) (Table 1).

RIETE score

Ruiz-Giménez et al.[42] developed the RIETE score in 2008. Based on 314 bleeding events in almost 13,000 patients from the RIETE registry (Registro Informatizado de Enfermedad TromboEmbólica Venosa) treated with VKA during 3 months, the RIETE score identified six independent predictive variables which classified patients into three categories of risk for major bleeding. Variables were assigned either 2 (recent hemorrhage), 1.5 (creatinine > 1.2 mg/dL or anemia), or 1 (age over 75 years-old, cancer or PE) points. Patients with 0, 1-4, and > 4 points were categorized into low, intermediate, and high risk, respectively. The incidence of bleeding was 0.3% in the low-risk group, 2.6% in the intermediate risk group, and 7.3% in the high-risk group, and an internal evaluation was performed. Several studies have since evaluated the score[48-52], and the incidence within each risk group has thus raised, but the global predictive capacity is modest, especially on a long-term perspective. This score has not evaluated patients with unprovoked VTE or patients treated with dabigatran[34].

A prospective study conducted in 2015 compared two bleeding risk predictive scores for patients with VTE (Kuijer and RIETE scores) along with another three developed for patients with atrial fibrillation (AF) (HEMORR$_2$HAGES, Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR, Elderly, Drug or alcohol [HAS-BLED], and ATRIA). The predictive capacity of these scores for bleeding at 30 days in a population of patients with acute PE was poor (C-statistic 0.57-0.64), with no one being superior to others[50].

VTE-BLEED score

A prognostic score for major bleeding in patients with VTE under long-term anticoagulation (from day 30 to 6 months after the event) has recently been developed from a post hoc analysis of the RE-COVER trials (two randomized clinical trials comparing standard treatment with dabigatran)[27,43,44]. The score comprised six variables: active cancer (2 points), male with uncontrolled arterial hypertension (1 point), anemia (1.5 points), personal history of bleeding (1.5 points), age ≥ 60 years (1.5 points), and kidney failure (1.5 points). Patients with 0-1.5 points were labeled as low risk, and those with ≥ 2 points as high risk. The C-statistic was 0.75 (95% confidence interval [CI] 0.61-0.89) and 0.78 (95% CI 0.68-0.86) for dabigatran and warfarin, respectively, thus consolidating this score as a solid predictor of major bleeding risk during anticoagulation with these drugs (odds ratio [OR] 7.5)[50]. The scale was later validated in a *post hoc* analysis of the Hokusai-VTE randomized clinical trial (edoxaban vs. warfarin for the treatment of VTE)[53], the XALIA study, in patients with unprovoked VTE or those treated with rivaroxaban[54].

In 2019, the score was used in the Japanese registry COMMAND-VTE (COntemporary ManageMent AND outcomes in patients with VTE), with an average follow-up of 1.8 years, maintaining its predictive capacity[55]. Although one of the variables is cancer, the subgroup analysis in all studies shows that the predictive capacity is also acceptable in patients with unprovoked VTE[53,54]. It has shown predictive capacity for fatal and intracranial bleeding[56,57], and for major in-hospital bleeding[47,48,58-61].

"10-day RIETE" score

Another predictive score evaluated the risk of a compound of complications (mortality, recurrence of PE, major bleeding) in the 10 days following an episode of acute PE. It has been named "10-day RIETE" to easily differentiate it from the bleeding RIETE score, previously described. According to this score, patients without any of the following clinical or laboratory parameters had a low risk (under 1%) of complications: chronic heart failure, immobilization, recent major bleeding, cancer, arterial hypotension, tachycardia, hypoxemia, renal insufficiency, and platelets below 100.000/mm^3 or above 450.000/mm^3. The C-statistic was 0.77 (95% CI 0.75-0.78)[45]. The external validation was performed prospectively, showing a lower C-statistic (0.60), and no superiority to other predictive scores (Pulmonary Edema Predictive Scoring Index [PESI], PESIs, Ginebra)[46].

ACCP clinical guidelines

The ACCP guidelines in 2016 suggested the use of a table with 18 risk factors for bleeding risk in the decision to extend a long-term treatment: age over 65 or 75 years, history of bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, stroke, diabetes, anemia, antiplatelet therapy, uncontrolled anticoagulant therapy, comorbidities, reduced functional capacity, recent surgery, frequent falls, and alcohol abuse. These risk factors were sourced from the literature, and the individual risk for each factor could not be determined. The authors estimated that those patients without any risk factor were at low bleeding risk, whereas those patients with one risk factor would present moderate risk and those with multiple risk factors were at high risk.

Nevertheless, the actual bleeding risk depends on the severity of each factor (e.g., platelet count), the temporary relation to the anticoagulation period (e.g., time from the previous bleeding event) and whether the factor has been corrected. An annual update of the risk of major bleeding was recommended to allow for a comparison against the recurrence risk of VTE to help with the decision of discontinuing or maintaining the anticoagulation therapy after the first 3 months[15]. The global predictive capacity of this score has also been moderate[48,60,62,63]. However, the authors stated that the list should not be used as a quantitative risk score[40].

HAS-BLED score

The HAS-BLED score is probably the best validated predictor tool[34]. It was sourced from the Euro Heart Survey of patients with AF and provided a simple tool to evaluate the individual risk of bleeding after a year in patients with AF[64]. This score has been widely validated in patients with AF, in large cohorts, and varied subgroups[57,61]. It includes the variable "labile INR," which is not relevant in patients treated with DOACs, and lacks the variable "cancer," which is one of the most important variables to determine the bleeding risk in patients with VTE. The score was thus modified in different validating trials of patients with VTE, consistently showing a low risk of major bleeding in those classified as low risk by the score[47,61,62,65,66].

Table 2 summarizes the main prognostic scores for major bleeding in VTE.

Discussion

A major issue in the assessment of acute VTE treatment is balancing the risk of bleeding and the risk of VTE recurrence[67]. Bleeding risk is particularly high during the 1st month of anticoagulation and in patients undergoing fibrinolytic therapy. Moreover, temporarily interrupting anticoagulation during this period carries a worse prognosis than during the long-term period, since the risk of recurrence is higher[68]. In this sense, VTE management guidelines suggest including a bleeding risk assessment in the treatment decision. However, simple and validated tools are lacking[16,33].

The estimation of the bleeding risk has several goals: modifying the identified risk factors and thus reducing the global risk of bleeding; determining the most convenient anticoagulant drug for each patient; choosing the optimal anticoagulant dosage and the most favorable duration of treatment. Nonetheless, it is unlikely that these goals may all be achieved by the same bleeding risk stratification tool[34].

VTE recurrence-related mortality decreases over time after the first 3 months. However, bleeding-related mortality remains constant, even increasing after 3

Table 2. Prognostic scores for major bleeding in patients with VTE under anticoagulation

Scores	RIETE bleeding score[42]	VTE-BLEED[27,53,55]	*10-day* RIETE[45]	ACCP guidelines[15,33]	VTE-adapted HAS-BLED [48,61,63,66,67]
Variables	– Age > 75 years – Recent major bleeding – Cancer – Creatinine levels > 1.2 mg/dL – Anemia – Pulmonary embolism	– Age ≥ 60 years – Previous history of bleeding – Active cancer – Renal failure – Anemia – Uncontrolled arterial hypertension in male	– Chronic heart failure – Recent major bleeding – Cancer – Renal insufficiency – Platelet count – Immobilization – Arterial hypotension – Tachycardia – Hypoxemia	– Age > 65 years – Age > 75 years – Previous history of bleeding – Cancer – Metastatic cancer – Renal failure – Anemia – Thrombocytopenia – Reduced functionality – Frequent falls – Uncontrolled anticoagulation – Antiplatelet therapy – Liver failure – Previous history of stroke – Diabetes – Comorbidities – Recent surgery – Alcohol abuse	– Age > 65 years – Systolic blood pressure >160 mmHg or uncontrolled – Chronic kidney injury – Chronic liver disease – Stroke – Previous history of major bleeding or predisposition – Labile INR – Drugs predisposing to hemorrhage (antiplatelets, NSAIDs) – Alcohol consumption – Cancer[61]
Usefulness	Risk of fatal bleeding during the first 3 months	Risk of major bleeding from day 30 to 180	Risk of complications (mortality, recurrence of PE, major bleeding) during the first 10 days	Risk of major bleeding; decide whether or not interrupt anticoagulation after 3 months	Risk of major bleeding during the first 3[61] or 12[67] months in patients with VTE
C-statistic	0.77 (95% CI 0.72-0.83)	0.75 (95% CI 0.61-0.89) for dabigatran and 0.78 (95% CI 0.68-0.86) for warfarin.	0.77 (95% CI 0.75-0.78)	Not quantitative	0.57-0.67 (for VKA)[52]
Validation	External	External	External[46]	External	External[61,67]
Evaluated in patients under VKA	Yes	Yes	No	Yes	Yes
Evaluated in patients under DOACs	Yes	Yes	No	Yes	Yes
Prospective validation	No	No	No	No	No

DOAC: direct oral anticoagulant; ACCP: American College of Chest Physicians; VKA: vitamin-K antagonists; PE: pulmonary embolism; VTE: venous thromboembolism; AF: atrial fibrillation; RIETE: Registro Informatizado de Enfermedad TromboEmbólica venosa; CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs.
Adapted from Klok et al. 2020[84].

months of anticoagulation, which would be in line with a reduction of the anticoagulation intensity 3 months after the event[69]. Other therapies for PE also increase the bleeding risk, such as fibrinolysis[70]. The PEITHO clinical trial randomized anticoagulation alone versus anticoagulation plus fibrinolysis in hemodynamically stable patients with acute PE (intermediate-risk for mortality). Fibrinolysis prevented hemodynamic instability without reducing mortality, but significantly increased the risk of major bleeding (6.3% vs. 1.2%, $p < 0.001$) and stroke (2.4% vs. 0.2%, $p = 0.003$)[71].

Several risk factors, used in different clinical-analytic scores to stratify bleeding risk in acute VTE (e.g., Kuijer score[41], RIETE bleeding score[42], *10-day* RIETE score[45], VTE-BLEED score[27], and ACCP guidelines scale[15]), have been suggested: gender, age, cancer, or recent major bleeding. These scores present different follow-up times and heterogeneous and conflicting results, without enough evidence and validation[34] (Table 2). Most of them have been evaluated in studies with different definitions of major bleeding, and patients with diverse VTE etiologies, including provoked VTE events. Moreover, most trials included patients treated with warfarin, in whom the risk/benefit balance might be quite different from that of DOACs. Recently, a prospective study found no bleeding predictive scores to be useful in patients treated with DOACs, including Kuijer, RIETE, VTE-BLEED, HAS-BLED, and others[47].

Concerning the follow-up time of these studies validating prognostic scores, it varies from 3 to 12 months[15,27,41,42]. Only one evaluated the bleeding risk within the first 10 days, and not in a specific way, but as part of a compound of complications (mortality, recurrence of PE, and major bleeding)[45]. Studies comparing the precision of these scores have yielded disappointing results, with C-statistic values around 0.5-0.6, and little to no differences between scores. Most of these studies were retrospective or *post hoc* and did not include follow-up times beyond 3 months[48-50,63].

It should be taken into consideration that the reported discriminating values (e.g., C-statistic) are important when developing a predictive model, but the clinical application of these predictive models, measured through the absolute risk or the differential risk is, at least, as important if the model is used to make clinical decisions. Nevertheless, patients classified as high-risk by most scores did present a higher risk than those labeled as low risk, even though the statistical calibration was insufficient, thus suggesting a certain degree of clinical usefulness[34].

International AF guidelines recommend the application of bleeding risk assessment scores to identify modifiable risk factors, but not to withhold anticoagulation, due to its clinical benefit in all bleeding risk categories[72]. Given the lack of evidence on the value of prognostic bleeding risk scores in patients with VTE, they should not yet be used as a main argument to interrupt anticoagulation after the first 3 months in patients with VTE[34,57,65]. They should, however, be used to identify patients with low hemorrhagic risk in whom anticoagulation might be maintained indefinitely, for which the ACCP table and the VTE-BLEED score are the best currently available tools[34].

Prognostic bleeding biomarkers in VTE

The aforementioned scores include clinical variables, such as age, gender, cancer, recent bleeding, arterial hypertension, history of stroke, renal failure, diabetes, and antiaggregation, among others. However, only some laboratory markers have been included, such as altered prothrombin time, thrombocytopenia, anemia, and creatinine clearance levels below 30 mL/min. None of the suggested scores included biomarkers among their variables.

In a cohort of the RIETE registry, Nieto et al.[26] found that an altered prothrombin time (upper the normal limits) independently rises the risk of fatal hemorrhage at 3 months after the event (OR 2.09, 95% CI 1.34-3.26). In the same cohort, anemia also demonstrated to be an independent risk for fatal bleeding at 3 months (OR 1.54, 95% CI 1.07-2.22)[26]. In the VTE-BLEED score, anemia was one of the variables included in the predictive score, with a regression coefficient of 0.77[27]. A platelet count < 100.000/μL displayed an OR of 2.23 (95% CI 1.16-4.29) for fatal bleeding at 3 months[26]. In another study[45] performed in patients with PE from the RIETE registry, a compound of complications 10 days after the event (mortality, recurrence of PE, and major bleeding) were evaluated; an altered platelet count (< 100.000/μL or > 450.000/μL) showing an OR of 2.15 (95% CI 1.68-2.74).

In the study of Nieto et al.[45], a glomerular filtration under 30 mL/min showed an independent risk of fatal bleeding 3 months after the event, with an OR 2.27 (95% CI 1.49-3.44). In the VTE-BLEED score, a creatinine clearance rate between 30 and 60 mL/min produced, in the multivariate analysis, a regression coefficient of 0.66 ($p = 0.004$), thus being included in the risk assessment score for major bleeding between days 30 and 180 after the event[27]. In the study of Maestre

et al.[45], creatinine clearance rates between 30 and 60 and under 30 mL/min showed an OR 2.17 (95% CI 1.81-2.60) and 4.95 (95% CL 3.9-6.3), respectively. A glomerular filtration rate ≤ 60 mL/min/1.73 m^2 was associated with clinically relevant hemorrhages at 30 and 180 days in acute PE[71].

Nevertheless, beyond the already mentioned analytical parameters, there is scarce evidence of biomarkers showing predictive capacity of bleeding risk in patients with VTE. More specifically, there are currently no published data on biomarkers as bleeding risk predictors in patients with cancer-associated thrombosis[73]. A recent study showed that D-dimer levels were associated with early bleeding (OR 2.3, 95% CI 1.05-5), and adding a threshold of 5.750 ng/mL to the prognostic scores VTE-BLEED, RIETE, HAS-BLED, and HEMORR2HAGES improved their discriminatory capacity[58].

The association between inflammatory markers and hemorrhagic risk has been studied with less intensity than the mortality risk, and there is scarce evidence on C-reactive protein (CRP) and the bleeding risk in patients undergoing anticoagulation therapy. In patients with acute coronary syndrome, raised CRP, and interleukin-6 (IL-6) levels have been associated with hemorrhagic complications[74]. However, in patients with AF treated with anticoagulation, the HAS-BLED score showed no improvement when adding inflammatory biomarkers (CRP and IL-6) for the prediction of major bleeding[75]. In a recently published study, CPR levels were associated with bleeding complications within the first 30 days after the VTE event (OR 2.7, 95% CI 1.3-5.7), although their predictive capacity was modest (area under the receiver operating characteristic curve 0.65, 95% CI 0.54-0.75)[76]. Marchena-Yglesias et al.[77] found no association between CRP levels and bleeding events during a follow-up time of 12 months.

Conclusion

Multiple risk factors (e.g., gender, age, cancer, and recent major bleeding) have been used in several clinical-analytical risk assessment scores to stratify the bleeding risk in patients with acute VTE (Kuijer scale, RIETE at 3 months, RIETE at 10 days, VTE-BLEED score, and the ACCP guidelines table, among others), showing heterogeneous and conflicting results, without enough evidence or validation in specific studies[15,27,33,34,41-47].

There is a need to find early bleeding predictors for these patients. Given the lack of evidence on the validity of the prognostic bleeding scores in VTE populations, they should not yet be used as a main argument to stop the anticoagulant treatment. They can, however, be used to identify patients with the low hemorrhagic risk in which anticoagulation may be maintained indefinitely, being the ACCP guidelines and the VTE-BLEED score the best currently available tools for this purpose.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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REVIEW ARTICLE

Congestion in heart failure, a prominent role in pathophysiology, and a therapeutic goal

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Abstract

Systemic congestion plays a key role in the management of patients with heart failure (HF). Most of the patients admitted for acute decompensated heart failure show congestive signs and/or symptoms (clinical congestion). The medical community is being progressively aware of the active role of congestion in the pathophysiology of HF. Congestion can lead to organ damage, such as congestive kidney failure or endothelial dysfunction. When congestion remains after diuretic therapy (residual congestion), prognosis worsens. Even though, residual congestion is common among patients at discharge. Accordingly, the active search of remnant signs of congestion before discharge is nowadays a first-line therapeutic goal.

Key words: Heart failure. Residual congestion. Intraabdominal pressure. Cardiorenal syndrome. Impaired renal function. Clinical bedside ultrasound. CA125.

Introduction

Two popular characters of black novel and police TV series, Inspector Wallander (from Henning Mankell) and Lieutenant Columbus, always turn back on his own steps whenever they face a difficult problem to solve. They always succeed thanks to the careful revision of facts, the deep exam of the evidence at the crime scene, and a brilliant interpretation of the gathered data. Something similar is going on with congestion in heart failure (HF), a very old character, now revisited by some of the most relevant researchers in the world of cardiovascular diseases.

Systemic congestion plays a key role in the management of patients with heart failure[1]. Most of the patients admitted for acute decompensated heart failure (ADHF) show congestive signs and/or symptoms, a situation called clinical congestion[2,3]. Indeed, clinical congestion, along with natriuretic peptides and echocardiography, is the cornerstone in HF diagnosis[4] and guides the use of intravenous loop diuretics during admissions[3,5].

Although clinical congestion has been classically considered the last consequence of HF, the burden of evidence for an active role of congestion in the pathophysiology of HF is increasing[6-9]. Congestion can lead to organ damage, such as congestive kidney failure[10], but also endothelial dysfunction[11], and worsens prognosis when it remains after seemingly appropriate diuretic therapy, the so-called residual congestion[12].

The purpose of this review is to update the knowledge of the involvement of systemic venous congestion in HF, focusing on its role in pathophysiology, the prognostic significance of residual congestion, and finally,

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to give some insights on the fight against residual congestion, based on the latest evidence.

Pathophysiology of congestion in HF. Cause, consequence, or both?

Congestion, interstitium, and vascular endothelium

Under physiological conditions, one-third of the total body water volume is distributed between intravascular and extravascular space[13]. Starling forces and oncotic pressure rule the balance between these compartments. A decrease in blood volume is compensated by the passage of free fluid from the interstitium to the vascular bed, leading to the recovery of an effective circulating volume[14-16].

In HF, the decrease in cardiac output is compensated by the activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), leading to the redistribution of circulating volume and the reabsorption of water and sodium (Na^+) by the kidney[14]. Total body water increases because of Na^+ retention, then redistributed between intravascular and extravascular spaces (including the interstitial space) thanks to the semipermeable characteristics of the endothelium[17]. However, in the long term, this compensatory mechanism becomes dysfunctional. One of the mechanisms leading to the loss of the regulatory capacity of the interstitium is due to the damage in the molecular structure of the proteoglycans network[16,17]. The interstitium is made up of multiple elements that interact with one another, mainly glycosaminoglycans anchored to protein chains, collagen, and elastin[16,18]. These structures make up a structural network with a predominantly negative anionic charge, capable of attracting large amounts of Na^+ and thus managing to retain the fluid in the interstitial space, establishing a fine balance between the intra and extravascular spaces[18]. However, prolonged activation of the RAAS generates an excessive increase in Na^+ and water exceeding the capacity of the mucoproteins at the interstitial level, causing their rupture and the loss of their ability for self-regulation. Once broken, water and Na^+ flow into the intravascular space out of regulation, raising central venous pressure (CVP), and ultimately leading to hemodynamic congestionn[3,19,20], and clinical congestion when clinical findings are overt[20].

On the other hand, interstitial space is involved in the autoregulatory properties of vascular endothelium through nitric oxide (NO) production[18,21]. In HF, the high concentrations of Na^+ and the secondary hyperaldosteronism elicited by the activation of RAAS upregulates Na^+ channels of the endothelium, decreasing the production of NO, causing endothelial dysfunction. Therefore, according to this view, systemic congestion, understood as an increase in CPV, is even capable of causing endothelial inflammation[16,18]. One study[11] showed an increase in blood concentrations of interleukin-1 (IL-1), IL-6, angiotensin II, and several adhesins, following peripheral congestion elicited by compression of forearm veins. These results support the theory of congestion as a trigger for an inflammatory response.

The link between congestion and impairment of renal function

Both the kidneys and the heart are organs required to talk to each other in HF syndrome. Multiple pathophysiological mechanisms link both organs and explain the dysfunction caused by one on the other, and vice versa[22-25]. Conventionally, the impaired renal function associated with cardiac dysfunction has been explained through renal hypoperfusion, due to a fall in cardiac output and the initiation of the RAAS. However, in ADHF-systemic venous congestion, and therefore, the increase in CVP, seems to play an even more important role in kidney damage than renal hypoperfusion. The term “congestive renal failure” has been coined to define that interplay[25-27].

In a retrospective study using the right catheterization to measure CVP, the increase in CVP was directly related to the fall in glomerular filtration rate (GFR) and independently linked to a worse prognosis[27]. In another study carried out in a chronic HF rat model, an increase in CVP was followed by kidney damage, tubular dysfunction, and a rise in plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL)[28].

Nonetheless, although a link between the increase in CVP and renal dysfunction has been shown, the intimate mechanism through which congestion operates is far from known. Several mechanisms have been postulated to explain this intriguing relationship. First, the increase in CVP is transmitted to the abdominal compartment, and especially to the kidneys through renal veins, producing an increase in kidney interstitial pressure[27,28]. This mechanism is supported by the study of Iida et al.[29], a prospective study analyzing the Doppler pattern of renal vein and intrarenal venous flow in patients with ADHF. The authors found a direct relationship between intrarenal venous flow and right atrial

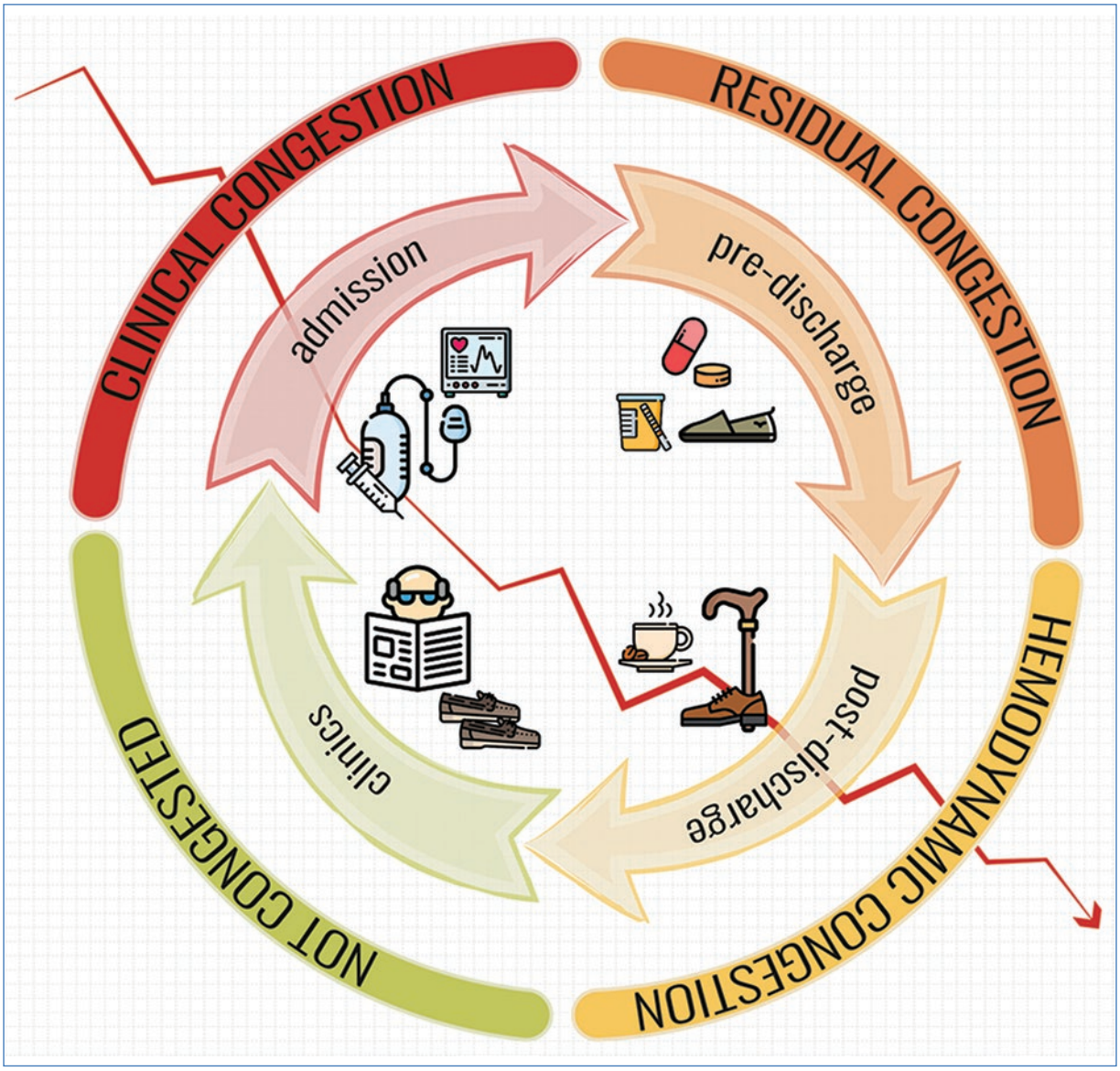

Figure 1. Congestion in heart failure. Patients admitted for decompensated heart failure show overt symptoms and signs of congestion. They need treatment with loop diuretics, usually by intravenous route (red arrow). Once stabilized, diuretics are given by mouth and several other classes of drugs are up titrated, as a transition to discharge (orange arrow). During early phase of admission, treatment is roughly guided by means of clinical changes through physical examination. Unfortunately, this is an inaccurate measurement of congestion. Indeed, a significant proportion of patients are discharged with subtle degrees of congestion –residual congestion–, so far demonstrable exclusively by haemodynamic measurements (yellow arrow). Patients with residual congestion have higher mortality rates. Hence, the accurate diagnosis of residual congestion and its proper treatment, to achieve an actual decongested state (green arrow) is a primary goal in heart failure. Additional strategies, complementary to physical examination and easy to implement in clinical setting, must be encouraged to eradicate residual congestion.

pressure, thus linking the increase in CVP with the increase in intrarenal venous pressure[29].

Similar results were observed in another study that included 205 patients with pulmonary hypertension[30]. Based on the Doppler pattern of renal veins, the authors calculated a novel *Renal Venous-Stasis Index* (RVSI), useful to improve risk stratification in patients with pulmonary hypertension. Nijst et al.[31] also studied the influence of CVP and renal congestion on diuretic response through a *venous impedance index* (VII). Their results showed that VII was positively correlated with a diuretic response in HF patients with reduced ejection fraction (HFrEF), independently of baseline renal function ($R^2 = 0.35$; $p \leq 0.001$)[31].

A second mechanism is an increase in intraabdominal pressure (IAP) along with the dysregulation of the splanchnic circulation[8]. Given that the abdominal compartment is a closed anatomical space, the increase in CVP leads to the passive congestion of abdominal organs, hence transmitting the rise of pressure to all of them[8]. Furthermore, the repetitive stimulation of the SNS would lead to dysregulation of blood volume storage in the splanchnic veins. The splanchnic bed is rich in alpha and beta-adrenergic receptors, which become dysfunctional in HF due to the overstimulation of SNS. Once a new adrenergic discharge is elicited by a new bout of HF decompensation, a large volume of blood suddenly shifts from the splanchnic bed to the general circulation leading to an acute congestive state[8].

The first studies on IAP and renal dynamics in HF were carried out in HFrEF patients admitted at the intensive care unit (ICU). Mullens et al.[32] found that the increase in IAP was proportionally related to the impairment of renal function. Another study by the same group showed an improvement in renal function when paracentesis was performed in patients with advanced HFrEF and the presence of congestive symptoms[33]. Recently, we carried out another study[34] in hospitalized patients with ADHF admitted at the Internal Medicine ward, showed that the baseline (admission) level of IAP was associated to poorer renal function and a worse diuretic response during the first 72 h of admission. Finally, Abu-Saleh et al.[6] analyzed the role of increased IAP in an ADHF rat model with reduced ejection fraction. Their findings confirmed that increased IAP had harmful effects on tubular renal function associated to a disturbance in hemodynamic kidney profile.

In conclusion, according to the latest published results[27,30,31,33-35], the relationships between systemic venous congestion, CVP, and IAP seem to play an important role in the pathophysiology of the so-called "congestive renal failure." Further studies are needed to refine the definition, diagnostic criteria, pathophysiology, and treatment of congestive renal failure.

The prognostic meaning of residual congestion

Most of the patients hospitalized for ADHF present, at admission, with congestive symptoms and/or signs[36]. The main goal for clinicians is to overcome congestion by means of intravenous (i.v.) loop diuretics[4,37-41]. Even though, there is a relevant percentage of patients discharged with remaining symptoms of congestion[2,12]. This situation is defined as *residual clinical congestion* (Fig. 1), which impacts negatively on prognosis after discharge[2].

Lala et al.[42] carried out a retrospective analysis of Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure[43] and Cardiorenal Rescue Study in Acute Decompensated Heart Failure[44] cohorts, creating a congestion score based on the presence of peripheral edema and orthopnea during hospitalization for ADHF. Their results showed that persistent congestive symptoms at discharge were associated with an increase of 60-day mortality or readmissions for HF[42]. These findings were similar to those obtained applying clinical congestion scales in PROTECT[45] (Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to assess Treatment Effect on congestion and Renal Function). The multivariable logistic analysis identified the rise in blood urea nitrogen (BUN), the increase in body mass index (BMI), and worse diuretic response (defined as Δ body weight in the first 72 h/40 mg i.v. furosemide or equivalent) as the best predictive factors for the persistence of clinical congestion at discharge or day 7[12].

Factors related to residual congestion

In short, residual clinical congestion places HF patients at a higher risk of complications and darkens their prognosis. Several factors potentially related to it are discussed below.

First, a physical examination is not reliable enough to accurately identify subtle signs of congestion[46-49]. The increase in end-diastolic pressure in the left ventricle and the rise in CVP are hallmarks of hemodynamic congestion[3,50]. Hemodynamic congestion can trigger pathophysiological mechanisms capable of interfering with internal homeostasis, especially at the kidneys[31]. Hemodynamic congestion[3] normally predates the clinical picture of ADHF. However, it cannot be detected by physical examination[47-49]. It is even more difficult to diagnose in obese[51], malnourished, or patients with previous admissions for HF[52].

Second, cardiorenal interaction[22,53,54], diuretic resistance[38,55,56], and diuretic response[57-59] are directly linked to decongestion. Chronic kidney disease (CKD) is a common comorbidity in ADHF patients. In fact, both share multiple risk factors[22]. About one-third of HF patients, experiment fluctuations in creatinine concentrations during admission, a situation which is called "worsening renal function" (WRF)[60,61]. However, WRF

do not always translate into a worsening prognosis (pseudo-WRF). Sometimes is just the expression of the forced diuresis induced by diuretics to relieve congestion, it is transient and is heralded by haemoconcentration[59]. Thus, WRF and pseudo-WRF can hinder titration of decongestive therapy[60,62].

On the other hand, the chronic use of oral loop diuretics (above 80 mg oral furosemide or equivalent), produces a chronic reduction in Na^+ and water urine excretion, leading to diuretic resistance[43,55,63]. The continued blockade of Na/K/2Cl co-transporter at the ascending portion of the loop of Henle favors hypertrophy of distal nephron, secondary hyperaldosteronism, and metabolic alkalosis[57,64-67]. This situation, together with high blood concentrations of nitrogen products such as urea[68-71], hypoalbuminemia[72,73], or decreased intestinal absorption of oral diuretics[74] due to intestinal wall congestion, generate, on a long-term basis, the claudication of depletive treatment, and the appearance of residual congestion. In fact, the presence of diuretic resistance is an independent risk factor of all-cause mortality or HF-readmissions in ADHF patients[57,66]. Both impaired renal function and diuretic resistance limit achieving an effective diuretic response and worsen the prognosis of HF-patients.

Testani et al.[75] analyzed diuretic response (defined as the total diuresis in 24 h/40 mg of furosemide i.v.), in a cohort of 1047 patients with HF[75]. Their results showed that patients with a lower diuretic response (lower than the median) had higher mortality. Another study[65], which analyzed diuretic response in HF-patients included in ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial), found an increase in mortality in patients with a worse diuretic response after the 1st 72 h of admission for ADHF[65].

Third, a standardized schedule of depletive treatment enabling an efficient and predictable decongestion in patients with ADHF is lacking. The use of i.v. loop diuretics is nowadays the standard of treatment during admission. Nonetheless, the drug, daily dose, frequency, and the route of administration are selected relying on findings from physical examination and clinical judgment. Both of these, often, may not reflect the actual congestive state of the patient[48], leading to non-adequate decongestive therapy. The DOSE[43] study compared two strategies of i.v. administration of loop diuretics: Continuous perfusion vs. intermittent injection. No significant differences in the reduction of congestive symptoms ($p = 0.47$) or the decrease in serum creatinine concentrations ($p = 0.45$) were observed. Even more, no differences were found either when comparing the use of high versus low doses of furosemide. These results underline the importance of shedding some light on the schedule of administration of diuretics during acute HF.

Finally, there are no good alternatives to diuretics to relieve congestion during ADHF. The EVEREST trial[76] analyzed the use of aquaretics (vaptans, inducing diuresis through inhibition of vasopressin receptors) versus placebo during ADHF in patients with HFrEF (< 40%). The study failed to demonstrate significant differences in the primary objectives (weight loss during the first 24 h of admission and readmission for HF 60 days after discharge). RELAX-HF2[77] trial analyzed the use of seralaxine, a vasodilator with proven actions on the cardiovascular system during pregnancy. The trial results did not show a beneficial effect for serelaxin as compared to placebo in the pre-specified end-points (all-cause mortality and HF-rehospitalizations).

In short, residual clinical congestion, when present, is a factor of poor prognosis in patients with HF. It is caused by multiple factors, such as WRF, diuretic resistance, or the lack of a clear guide for diuretic titration.

Fighting residual congestion

Diuretic treatment guided by estimation of congestion

Forced by the limitations of physical examination in quantifying the degree of congestion and, in consequence, to guide diuretic treatment[48], some new tools have emerged for estimating the magnitude of congestion. Many of them are feasible and potentially useful for guiding diuretic treatment.

The following section will focus on the use of clinical bedside ultrasound (US) and blood biomarkers of congestion.

Clinical bedside ultrasound

Clinical bedside US is based on the use of portable devices to assess the presence of an excess of fluid at alveolar or interstitial spaces of the lung. The excess of fluid translates to many typical US patterns. The radiological Kerley “b” lines[78] are shown as the so-called “comet-tail artifact” while filled alveolar spaces appear as “cannon-ball artifacts”. The diameter of the inferior vena cava (IVC) and its change during the inspiratory phase – diameter and collapse – are also known as indirect markers of increased CVP[79-82].

Ultrasonography technics applied to HF have been demonstrated to identify patients at a higher risk of all-cause mortality and HF-readmissions[83-85].

A recent clinical trial demonstrated that lung US can help clinicians to guide diuretic therapy. Rivas-Lasarte et al.[86], analyzed the usefulness of pulmonary US to guide i.v. diuretic treatment after an admission for ADHF in 123 patients, mostly with reduced LVEF (mean LVEF 39.4%). Patients were randomized to diuretic therapy guided by US versus conventional management (physical examination). In the cohort guided by lung US, a reduction over 50% of the primary composite endpoint (emergency room visits, HF-hospitalizations, and death from any cause) (HR 0.518 95% CI: 0.268-0.998, p = 0.049]) was observed. In addition, exercise tolerance increased in the US-guided group (6-min walking test 60 m vs. 37 m; p = 0.023).

Lung US has also been tested to guide diuretics in chronic HF. The CLUSTER-HF study[87] was an open, randomized clinical trial that included patients with chronic HF to receive diuretics guided by lung US vs. standard therapy, guided by physical examination[4]. The study was conducted in a unit specialized for HF. A total of 126 patients were included (mean age of 62.5 ± 10 years and a median LVEF 31%). Patients included in the "lung US guided therapy group" had a 45% reduction in the composite primary outcome (urgent HF visits, rehospitalizations, and death) of HR 0.55 (95% CI: 0.31–0.98, p = 0.044).

Marini et al.[88] obtained similar results to those described in CLUSTER-HF study[87], with a higher and significant reduction in NT-proBNP at three months of follow-up (p = 0.01) and an improvement in the quality of life (p = 0.02).

The use of lung US is currently being tested in the field of specialized HF nursing. The RISK-HF study[89] is an ongoing, prospective, multicenter study to evaluate the effectiveness of lung US to stratify risk and guide diuretic treatment in an HF specialized nurse clinic.

In conclusion, lung US has shown its usefulness to guide diuretic treatment. Therefore, it is becoming more and more implemented in HF units and probably the forthcoming new guidelines will include lung US in the management of HF.

Several studies have shown the usefulness of IVC US for risk stratification in HF. Both diameter and the degree of inspiratory collapse are predictors of mortality and HF-re-hospitalization[79,85-87,90]. However, the evidence concerning its value in the setting of ADHF is debatable, as pulmonary hypertension, often present in HF, can induce an overestimation of its usefulness. The CAVA-ADHF-DZHK-10[82] trial will analyze the usefulness of therapy guided by IVC morphology to achieve a maximum diameter ≤ 21 mm and the degree of collapse > 50%.

Blood biomarkers

The use of biomarkers in HF has been analyzed in depth, especially natriuretic peptides[4,24,57,91,92]. Despite natriuretic peptides are robust tools for diagnosis and medium and long-term risk stratification[91], their usefulness as markers for decongestion has yet to been proven[93,94]. The GUIDE-IT study[95] was carried-out in high-risk outpatients (LVEF <25%, NT-proBNP ≥ 2653 pg/mL, and previous admission for HF). GUIDE-IT compared outcomes between a group under intensive treatment strategy versus a standard one[4], based on NT-proBNP concentrations. Patients received intensive HF-therapy (neurohormonal blockade and diuretics) to achieve NT-proBNP concentrations < 1000 pg/mL. After completing 50% of the recruitment, an interim analysis showed no benefits, hence the study was stopped[95]. Although the goal of the study was not exclusively focused on diuretics, these results demonstrate that natriuretic peptides are not optimal tools to assess congestion and for guiding the treatment of out-patients with HF[93-95].

Carbohydrate antigen 125 (CA125) has emerged over the last decade as a reliable biomarker of congestion in HF[96]. CA125 was initially shown, along with NT-proBNP, to identify patients with acute HF at a higher risk of readmission[85,97,98]. Similar results have been recently validated in BIOSTAT-CHF[99], which showed a positive correlation between a rise in CA125 and the presence of clinical congestion. In addition, CA125 was an independent predictor of risk for the combined endpoint of all-cause mortality and/or HF-readmissions in patients with worsening heart failure (either in-hospital or at the office)[98].

Interestingly, CA125 may add some value for guiding decongestive treatment in ADHF. IMPROVE-HF was a clinical trial[100] aimed to show whether baseline CA125 concentrations could guide i.v. diuretic treatment as compared to the standard assessment of congestion[4]. Patients whose diuretic regime was guided by CA125, received higher doses of diuretics (p < 0.001), yielded larger volume of diuresis (p = 0.013), and showed preserved renal function 72 h after admission (p = 0.036). Furthermore, the risk for combined primary endpoint of death and/or HF-readmissions was lower among CA125-guided therapy patients (HR 0.46 [95]% CI:

0.21–1.03, p = 0.059]). Although these differences did not reach statistical significance for the primary end-point, this trial opened the door for the putative use of CA125 to guide intensification of diuretic therapy and thus fight residual congestion[100].

Another promising biomarker is bio-adrenomedullin (Bio-ADM)[101,102]. Concentrations of Bio-ADM at admission have been related to a higher rate of residual congestion (assessed by clinical congestion score) and higher oral loop diuretic doses at discharge, after hospitalization for ADHF. The concentration of Bio-ADM at baseline was, as well, related to higher 60-days HF re-hospitalizations (HR 4.02 95% CI: 2.23-7.26, p ≤ 0.001]). Unfortunately, Bio-ADM has not yet been tested for diuretic titration during ADHF.

Natriuresis, an alternative approach to titrate loop diuretics?

An efficient diuretic response is one of the cornerstones to improve prognosis during ADHF[63,65]. Along with diuretic resistance, it is one of the main factors in determining the degree of residual congestion[12] and eventually, clinical outcomes[12,61,65]. However, a diuretic response is not well defined in HF-guidelines[4], as patients may have different responses to the same diuretic regime. There are also different ways to calculate a diuretic response, being the most used the change in body weight[58,103], haemoconcentration[59], or even indirect measurement of plasma volume reduction[104-106].

Recently, urinary sodium concentrations from single spot urine collected after initial intravenous loop diuretic administration have become a parameter of great interest to define a diuretic response. Damman et al.[66], analyzed the value of urinary sodium excretion (UNa) in the first urine sample, collected after the first dose i.v. of furosemide during the first 6 h of admission. Authors found that lower UNa was linked to the male gender, younger mean age, the presence of impaired renal function, and previous use of oral loop diuretics[66]. In addition, UNa was identified as an independent risk marker for the primary endpoint of all-cause mortality (HR 3.81 95% CI: 1.92-7.57, p ≤ 0.001])[66].

Another study conducted by Luk et al.[107] analyzed the potential use of assessing urine Na concentrations in the first spot urine after starting i.v. loop diuretics in 103 ADHF patients. A cutoff < 60 mmol/L for UNa after the initial dose of furosemide at admission identified patients with lower systolic blood pressure and lower neurohormonal blockade background on admission[107]. In addition, the proportion of patients with Una < 60 mmol/L who later on developed WRF was higher (23.6% vs. 6.5%, p = 0.05), and length of hospital stay was longer (11 vs. 6, p < 0.006). This subgroup of patients had a worse prognosis with a two-fold increase in the risk for the primary endpoint (HR 2.40 95% CI: 1.02–5.66, p = 0.045]).

Finally, a sub-analysis of the ROSE-AHF[108] (Renal Optimization Strategies Evaluation AHF) study demonstrated the usefulness of urinary analysis, establishing, again, a threshold of UNa < 60 mmol/L to identify those patients with a worse prognosis. Nonetheless, these results did not reach statistical significance for the composite end-point of death and/or readmission for HF (HR 1.41 95% CI: 0.88–2.27).

In conclusion, the analysis of diuretic response seems to have potential utility to adjust diuretic treatment during decompensation. The European Society of Cardiology (ESC)[38] advises either to determine the urinary sodium concentration at 2 h or the total urine volume after the 1st 6 h of initiation of diuretic treatment, along with physical examination, clinical US, and biomarkers to guide serial adjustments of diuretic dosage, during early stages of ADHF[38].

New therapies to fight against congestion

The new sodium-glucose co-transporter-2 inhibitors (SGLT2i) anticipate a change in the management of congestion in HF-patients. These drugs, initially approved as an oral hypoglycemic treatment for type 2 diabetes mellitus (DM), have demonstrated other beneficial effects beyond glycemic control. They have shown a consistent effect in reducing cardiovascular risk, renal protection, and more recently improving prognosis in HF[109-112]. DECLARE-TIMI-58 clinical trial[111] compared dapagliflozin versus placebo in patients with type 2 DM, with or without a history of myocardial infarction, for the primary endpoints of MACE (CV death, MI, or ischemic stroke), and the composite endpoint of CV death or hospitalization for heart failure.

The results of this study were of great importance, especially in the field of HF. The study demonstrated a significant reduction in hospitalizations for HF (HR 0.81 95% CI: 0.65–1.00, p = 0.046]). These results were similar to those obtained in the EMPA-REG-OUTCOME and CANVAS clinical trials[113-115], which demonstrated the ability of empagliflozin to reduce death from all causes, MACE, and readmissions for HF.

As a result of these studies, two new clinical trials were designed specifically for HF-patients, DAPA-HF[112], and EMPEROR-HF[116]. They showed the usefulness of

dapagliflozin and empagliflozin, respectively, to reduce all-cause mortality and HF-readmissions in patients with HFrEF, regardless of the presence or absence of DM. These are impressive results since they are the first drugs class, after spironolactone[117] and sacubitril/valsartan[118], to demonstrate a clear improvement in the prognosis of patients with HFrEF[112,118].

A recent meta-analysis published by Zannad et al.[119] analyzed the results of DAPA-HF[112] and EMPEROR-HF[116] together. This work has shown a reduction of 13% for all-cause mortality (HR 0.87 [0.77–0.98]; p = 0.018), of 14% in cardiovascular deaths (HR 0.86 95% CI: 0.76–0.98, p = 0.027]) and around 25% in HF-readmissions (HR 0.75 95% CI: 0.68–0.84, p ≤ 0.0001]). Furthermore, these beneficial results remained when data are adjusted by age, gender, history of diabetes, use of angiotensin receptor neprilysin inhibitor (ARNI), or baseline glomerular filtration rate.

The mechanisms whereby SGLT2i are so beneficial in patients with HFrEF[112,116,119] are not fully understood, but they appear to have an influence on the pathophysiology of HF at multiple levels[120,121]. Regarding congestion, these drugs have been shown to have a beneficial and protective effect on the kidney, an organ of great importance in HF[111]. The ability to increase diuresis through glucosuria could be a new strategy to achieve decongestion in patients with ADHF, especially those with residual congestion[120]. The RECEDE-CHF trial[113] (Renal and Cardiovascular Effects of sodium–glucose cotransporter 2 [SGLT2] inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure) is a currently ongoing, controlled, double-blind, and randomized clinical trial.

This study aims to analyze whether the addition of SGLT2i to i.v. loop diuretics during ADHF can increase diuretic efficacy to improve decongestion during admission. The interim analysis[122] of this study in 23 patients with a mean age of 69.8 years and a mean diuretic dose of furosemide of 49.6 ± 31.3 mg every 24 h has shown that empagliflozin combined with loop diuretics, increases 24 h urinary volume, without increasing natriuresis. These preliminary results are promising in the war against residual congestion in HF.

Conclusions

Clinical congestion plays a crucial role in the pathophysiology of HF, it is capable of damaging other organs (especially the kidneys) and its persistence at discharge worsens prognosis. The use, in the clinical setting, of tools such as US and biomarkers, as CA125, could be useful to guide diuretic therapy and, therefore, should be encouraged. The development of new strategies and therapies, probably including the new class of SGLT2i drugs, could offer a great opportunity to combat residual congestion and improve the prognosis of patients with a devastating syndrome, as is HF.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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REVIEW ARTICLE

Malnutrition. An undervalued issue in patients with heart failure

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Abstract

Undernutrition is commonly found in patients with heart failure (HF), mainly in the most advanced stages of the disease. Inflammation plays a fundamental role in the development of malnutrition. Furthermore, advanced age, comorbidities, and frequent hospitalizations contribute to the worsening of nutritional status in these patients. Malnutrition may affect clinical outcomes in HF. It enhances the risk of complications, mortality, and hospitalizations. In HF patients, traditional parameters of malnutrition as low body mass index (BMI) and hypoalbuminemia are not reliable indicators of the nutritional status. BMI may be influenced by volume changes. Although nutritional screening is mandatory in all clinical and care settings, malnutrition is underdiagnosed in HF patients. Most of the nutritional screening tools have shown good prognostic value and provide a critical clue for stratifying patients with high mortality. Correction of malnutrition is a potentially modifiable risk factor and therapeutic target. Nevertheless, HF guidelines do not recommend a specific nutritional strategy. Deficiencies in micronutrients, such as thiamine and L-carnitine, are described to cause cardiomyopathy and the failing heart is deficient in several micronutrients. Low plasma levels of micronutrients have been associated with adverse clinical outcomes. There are some evidences that micronutrients supplementation such as thiamine or Coenzyme Q10 can improve clinical outcomes in HF patients. This review will address the role of malnutrition in HF patients including its prevalence, pathophysiology, diagnosis, and prognostic impact. Furthermore, the value of nutritional supplementation, including the most well studied micronutrients (i.e., thiamine, coenzyme Q10, Vitamin D, and L-carnitine) will be reviewed.

Key words: Heart failure. Nutritional deficiency. Malnutrition. Outcomes. Nutritional screening. Micronutrients.

Introduction

Malnutrition has become a challenge within day-to-day clinical practice, affecting the course of diseases and patients' prognosis. Both chronic diseases and acute clinical conditions may induce or intensify processes resulting in poor nutritional status[1]. Although in practice most people associate malnutrition with undernutrition, the strict scientific definition of malnutrition includes both the deficiency or excess (or imbalance) of energy, protein, and other nutrients. The European Society for Clinical Nutrition and Metabolism (ESPEN) defines as nutritional disorders: malnutrition (considered synonym of undernutrition), overweight, obesity, and micronutrient anormalities[2].

Heart failure (HF) is a highly prevalent, progressive systemic syndrome associated with substantial morbidity and mortality worldwide. Medical advances have improved HF survival; nevertheless, HF patients still have a poor long-term prognosis[3]. The majority of HF research to date has focused on pharmacology and devices. Nutritional intervention has received little

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attention, and the role of nutritional factors in the pathogenesis and treatment of HF remains underexplored and underappreciated[4,5]. Despite the fact that clinicians often make explicit dietary recommendations to patients with HF (e.g., low sodium and low cholesterol), it is remarkable that specific dietary recommendations are lacking in the guidelines of the European Society of Cardiology (ESC) 2016[6] and the American Heart Association 2017[7], with modest advices focusing on restriction of salt and fluid.

The association between malnutrition and HF is known from the times of Hippocrates[8]. Undernutrition is commonly found in patients with HF, mainly in hospitalized patients and in the most advanced stages of the disease, and is being related with an enhanced risk of complications and mortality[9].

On the other hand, micronutrient deficiencies, such as thiamine and L-carnitine, are described to cause cardiomyopathy[10]. These micronutrients, which are important in myocardial energy production, are deficient in some HF patients. At times, these deficiencies contribute to the progression of HF, and they have been considered potentially modifiable factors[11].

This review aims to summarize data from the literature on the malnutrition and micronutrients deficiencies in HF patients. It will address the epidemiology, pathophysiology, diagnosis, and prognosis of undernutrition in these patients. Furthermore, the prognostic impact of nutritional supplementation, including the most well-studied micronutrients (specifically, thiamine, coenzyme Q10 [CoQ0], Vitamin D, and L-carnitine), will be reviewed.

Epidemiology

The prevalence of HF-associated malnutrition depends on the characteristics of the population studied, including the timing of the patient evaluation (while outpatient, in hospital, or at discharge) and the patient's baseline condition and comorbidities. Furthermore, with no gold standard for assessing the nutritional status of HF patients, the prevalence of malnutrition varies according to the diagnostic criteria and screening instruments used to define malnutrition[1].

In a systematic review that included 17 studies, the prevalence of undernutrition in HF patients ranged from 16 to 90%[12]. This prevalence was different depending on the test used, varying between 16 and 90% by Mini Nutritional Assessment (MNA), 22 and 48% by Geriatric Nutritional Risk Index (NRI) (GNRI), and 23-90% by Nutritional NRI[12].

Furthermore, there are differences in the prevalence of malnutrition between subpopulations of HF patients. Undernutrition is very common in advanced HF patients (80%)[13,14] and in acute decompensated HF patients (73-90%)[15-18]. In stable HF patients, the prevalence of malnutrition is lower, ranging from 6.7 to 62.4%[19-25]. In other studies that included different types of HF patients, the prevalence of undernutrition was 15-69%[17,26-30].

Malnutrition has been more studied in HF patients with reduced left ventricular ejection fraction (LVEF). More recently, different studies have analyzed malnutrition in patients with HF with preserved ejection fraction (HFpEF)[31-33]. In a subanalysis of the Spironolactone for HFpEF (TOPCAT) trial, using the GNRI tool, approximately one-third of patients (36%) were at risk for malnutrition[34].

In Spain, it has been described in hospitalized HF patients a high prevalence of risk of malnutrition (59.5%), and malnutrition (13%) using the MNA tool[26]. In outpatients with HF it was found a lower prevalence of malnutrition (12.2-20.6%)[28].

Undernourished patients are older, with high comorbid burden[35,36], and reduced mobility[24]. This suggests that malnutrition is closely linked to the process of the frailty cycle. Malnutrition status is associated to high NYHA functional class[24,37], and higher brain natriuretic peptide (BNP) levels[1,15,37,38], suggesting that it is related to the severity of HF. The highest prevalence of malnutrition is found in patients who are underweight[24]. Nevertheless, it is also noteworthy that malnutrition has also been observed in overweight patients[24,28].

Cachexia, a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass[39] may occur in 5-15% of patients with HF, especially those with HFrEF, and more advanced disease status[40].

Pathophysiology

In general, malnutrition can result from starvation, from disease, with and without inflammation, or from advanced ageing, alone or in combination[2]. Patients with HF have a disease in which multiple factors can contribute to the development of malnutrition (Table 1). These factors include inadequate intake, malabsorption secondary to intestinal edema, high energy demand, neurohormonal derangements, and cytokine-induced hypercatabolism[10,41,42]. Furthermore, as HF mainly affects older people[43], advanced age is another important factor that can contribute to malnutrition.

Table 1. Factors related to malnutrition in heart failure patients

– Low nutritional intake (anorexia, unpalatable diets)
– Malabsorption secondary to intestinal edema
– Liver dysfunction
– Systemic inflammatory activation
– Anabolic hormone resistance (insuline, growth hormone)
– Comorbidities associated with heart failure
– Advanced age
– Hospitalization
– Prolonged immobilization and physical deconditioning

Inadequate nutrient intake may be due to unpalatable and restrictive diets[44]. Anorexia, which is described in 34% of HF patients[45], has been related to inflammation, the use of loop diuretics[45], and neurohormonal imbalance[40].

Neurohormonal disturbances underlie the altered balance between anabolism and catabolism. Anabolic hormone resistance (including insulin and growth hormone) has been observed in HF patients[46]. Ghrelin, a growth hormone-releasing peptide that stimulates appetite, has been observed to be negatively regulated in HF patients[47]. Furthermore, in these patients occur an autonomic dysfunctions with autonomic nervous system imbalances[48], as a lower inhibitory effect of noradrenaline on TNF-α production[42].

HF causes inflammation that affects the heart, skeletal muscle, and adipose tissue[42]. The increased levels of endotoxin in the portal blood and/or the hepatic damage may be related to production of excessive amounts of pro-inflammatory mediators that may trigger systemic inflammation when they enter the blood circulation[49]. The insidious inflammation with elevated pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin IL-1β, and triggers chronic pathological changes in the body, such as defective intestinal nutrient absorption and low body stores of proteins and energy, resulting in protein-energy malnutrition[35]. Furthermore, higher level of TNF can increase myocyte apoptosis[47].

Other factors that may contribute to malnutrition in these patients are prolonged immobilization and physical deconditioning[6]. Moreover, common comorbidities associated with HF (such as chronic kidney disease, depression, and frailty) may contribute to malnutrition[10].

Hospitalization *per se* is another risk factor for malnutrition that has been reported to be as high as 20-50% among hospitalized patients[50]. In fact, HF is the most common reason for hospitalization among older adults[40].

In relation to cachexia in HF patients, the causes are multifactorial. In addition to the above-mentioned factors, in these patients the systemic inflammatory activation, inmunesystem dysregulation, and neurohormonal derangements have a prominent role[51]. Patients with cardiac cachexia are found to have higher levels of inflammatory markers such as IL-6 and TNF-α, as well as higher concentrations of adiponectin[1]. HF patients with undernutrition enter a vicious cycle of inflammation, catabolic drive, and undernutrition, which further exacerbates HF[12].

Diagnosis

There is not universally accepted definition of malnutrition or a gold-standard methodology for nutritional assessment[52]. Various combinations of clinical, anthropometrical, biochemical, and immunological measures have been used for the diagnosis of undernutrition[53]. Given the lack of universally accepted diagnostic criteria, in 2017, the ESPEN established the importance of considering the "risk of malnutrition" in addition to malnutrition[2]. Furthermore, these guidelines stated that nutritional screening is always mandatory in all clinical and care settings, given that patients affected by acute and chronic diseases are at high risk of developing nutritional impairment[2]. To assess the risk of malnutrition, ESPEN[53] recommends using the following validated screening tools in the hospital, elderly care, and community settings: Nutritional Risk Screening 2002[54], MNA-Short Form (MNA-SF)[55] and Malnutrition Universal Screening Tool (MUST)[53,56]. These screening tools combine about the same variables, that is, body mass index (BMI), weight loss, signs of eating difficulties, and severity of on-going disease. Other tools, such as the Malnutrition Screening Tool (MST)[57], or the Short Nutritional Assessment Questionnaire[58], have been widely used in certain countries but less frequently worldwide.

On the other hand, the American Society for Parenteral and Enteral Nutrition (ASPEN) separates nutritional screening from nutritional assessment. "Nutrition screening" is defined as "a process to identify an individual who may be malnourished or at risk for malnutrition to determine if a detailed nutrition assessment is indicated." It includes the prognostic nutritional index (PNI)[59], the NRI[60], and the GNRI[61]. Nutritional assessment is defined

by ASPEN as "a comprehensive approach to diagnosing nutrition problems that use a combination of the following: medical, nutrition and medication histories; physical examination; anthropometric measurements; and laboratory data" and includes the Subjective Global Assessment (SGA)[62] and the MNA[63], a validated nutritional screening tool for the elderly population that is recommended for routine geriatric assessment. Despite the number of available tools, there is neither an international consensus on the "best tool" for the screening of malnutrition risk[50], nor an accepted approach to nutritional assessment in HF patients[52].

In HF patients, traditional parameters of malnutrition, as low BMI and hypoalbuminemia, are not reliable indicators of the nutritional status[64]. A low BMI has been widely used to determine malnutrition. In fact, one definition of malnutrition according to the ESPEN consensus is a reduced BMI < 18.5 kg/m[22]. Nevertheless, BMI is not actually sensitive to malnutrition. Volume changes can significantly affect BMI. Edema, and its treatment with diuretics, has an effect on weight and BMI. In fact, BMI does not reflect adequate energy intake in HF-patients and may mask malnutrition[1]. Notably, malnutrition may be present in overweight patients with HF[24,28]. Serum albumin levels can be affected by other reasons in HF patients, such as chronic inflammation, fluid overload, hepatic congestion, absorption disorders, and renal losses[64].

Most of the nutritional screening tools have been used in HF patients: NRI[19,21,65], SGA[66], MNA[13,14,16,20,26,66], MNA-SF[14,20,66], GNRI[17,22,24,27,34,38,61], CONtrolling NUTritional status (CONUT)[24,67], PNI[24,67], MUST, and MST[66]. NRI[59,68] combines serum albumin and the ratio of present to usual weight (percent usual body weight). Body weight may be influenced by congestion. Faced with the difficulty in identifying the usual body weight of HF patients, different authors have utilized modified formulas[15].

The CONUT and PNI scores only consider serum markers. CONUT uses serum albumin level, total cholesterol, and lymphocyte count[69]. It has the limitation that many patients with HF are treated with statin therapy, which causes decreased cholesterol levels. Consequently, the total cholesterol level may reflect either the effects of medication or the nutritional status. In a comparative study, the CONUT score suggested that many more patients were malnourished compared with GNRI or PNI, perhaps reflecting low plasma cholesterol resulting from statin therapy. Thus, CONUT score is perhaps not the ideal tool in HF patients[24]. PNI considers only albumin level and lymphocyte count. This score can identify fewer patients as malnourished compared with CONUT, and it may underestimate the overall prevalence of malnutrition[24]. Although CONUT and PNI may not correctly reflect the nutritional status in HF patients, both have a prognostic impact in these patients in different situations, including inpatients with decompensated acute HF[32,67], hospitalized patients after discharge[38], and outpatients followed in a community HF clinic[24].

GNRI was developed as an adaptation of NRI for geriatric patients and includes albumin and ideal weight[61]. This score uses a formula and it is necessary to calculate ideal body weight[61] because of the difficulty to obtain the real weight. The GNRI may be influenced by fluid status, which, in turn, may decrease serum albumin levels. Nevertheless, this score has shown to predict the long-term prognosis of elderly HFpEF patients[27,33,34].

MNA is a validated nutritional screening tool for the elderly[63]. It has been applied to HF patients in different settings: at hospital discharge[26], in outpatients[20], and in advanced HF[13]. MNA was an independent prognostic factor for mortality[12,52]. Sargento et al.[52], in an algorithm for choosing the most relevant instrument for assessing nutritional risk in elderly HF patients, consider the MNA an adequate instrument, especially in HFrEF. The shorter version, MNA-SF, is composed of only six questions and adequately predicts the full MNA under most conditions[55]. This tool is recommended for nutritional screening, especially among the elderly, by the ESPEN and other entities. MNA-SF has also been used in HF patients with good results[14,20,66]. Compared to MUST or MST, it was a better screening method for detecting malnutrition[66]. Thus, some authors consider that the evaluation of patients with HF should systematically include the MNA-SF[66].

Despite the numerous nutritional screening tools available and the recommendation to assess nutritional status in all HF patients, malnutrition is clearly underdiagnosed. It was reported in only 1.1% of 370.983 discharge reports of patients admitted with the diagnosis of HF, from all hospitals of the Spanish National Health System[70].

Cachexia is clinically defined as unintentional weight loss, with or without skeletal muscle wasting, of at least 5% of baseline weight during the previous year[39]. For the diagnosis, three of the following factors are also required: anorexia, fatigue, reduced muscle strength, reduced fat-free mass index, and abnormalities in blood biomarkers (hemoglobin < 12 g/dL, serum albumin < 3.2 g/dL, elevated IL-6, or increased C-reactive

protein)[51]. Nevertheless, other definitions have been proposed[44]. In contrast to cachexia, sarcopenia, and muscle wasting cannot be diagnosed simply by the use of weighing scales. Different diagnostic tools are available to detect muscle wasting, including dual-energy X-ray absorptiometry, computed tomography, magnetic resonance imaging, bioelectric impedance analysis, and ultrasound. However, they are infrequently utilized in daily practice[46]. Further validation of body composition measurement techniques in HF populations is required[44]. Furthermore, serological biomarkers represent a tool in the diagnosis of cardiac cachexia, including cytokines, myostatin, sarcomeric proteins (myosin, actin), or neurohormonal peptides[46,51]. Like malnutrition, cachexia is infrequently identified or diagnosed in HF patients[39].

Prognostic value

Undernutrition is known as one of the most critical determinants of poor clinical outcomes in HF patients[33]. Malnutrition in HF patients has been related with worse outcome, including higher mortality, hospitalizations, length of stay, complications, and a worse quality of life (QoL)[10,12,44].

Most studies that have analyzed the relationship between undernutrition and mortality in HF patients have shown that undernutrition was associated with a high risk of mortality[13,14,16-18,20,21,23,24,26-29,31,32,35,38,67,70]. The higher risk of mortality in undernourished patients with HF has been described in different scenarios, including outpatients[20,23,24,34,61,71], during hospitalization[13,14,31,33,35,70], and after hospitalization[15,32,33,37].

In Spain, an analysis of all patients discharged for HF between 2006 and 2008 showed that malnourished patients had a much higher risk of dying while in hospital (odds ratio [OR]: 1.83 95% confidence interval [CI]: 1.69-1.97) or of being readmitted within 30 days after discharge (OR: 1.39, 95%CI: 1.29-1.51)[70]. A recent study in USA that analyzed protein-energy malnutrition and outcomes of hospitalizations for HF patients showed that malnourished HF patients had a rate of mortality over twice higher (8.34% vs. 3.55%). They also had more complications, longer duration of admission, and higher hospital costs[35]. Other authors have also described a higher incidence of complications[30], and a longer hospital stay in HF patients with malnutrition[15,30].

Malnutrition evaluated by different tools has shown an independent relation with higher rehospitalization. A higher readmission rate has been related to malnutrition evaluated by NRI[15]. In a large, post-discharge HFpEF cohort, worse nutritional status evaluated by PNI and GNRI remained independent indicators for higher HF rehospitalization, but not by using the CONUT score[32]. Furthermore, patients with malnutrition evaluated by MNA-SF were at greater risk of hospitalization and a worse QoL[20].

Cachexia has a negative impact on prognosis and QoL in HF patients. It is associated with more severe symptoms and reduced functional capacity, more frequent hospitalization and decreased survival[51]. Mortality rates of patients with cachexia range from 20% to 40%/yr in chronic HF[40].

Malnutrition treatment

The first step in any patient with HF is to provide general nutritional advice and counseling. Nutritional recommendations, however, are rarely evidence-based and instead are based on expert opinion[47]. There is still no consensus on which dietary model should be adopted by this population. The Mediterranean dietary pattern (MedDiet) and Dietary Approaches to Stop Hypertension (DASH) are the most frequently studied dietary patterns to improve outcomes in patients with preexisting HF[72]. A systematic review of dietary patterns in secondary prevention of HF concluded that DASH diet contributes positively to secondary prevention, mainly in relation to cardiac function, functional capacity, oxidative stress, and mortality. The MedDiet had a correlation with inflammation, QoL and cardiac function, but just on cross-sectional studies[73]. More recently, Miró et al.[74] found that adherence to the MedDiet was associated with a lower rate of 1-year HF rehospitalization, but did not influence mortality, after an episode of acute HF. Of note, both the MedDiet and DASH diet are primarily composed of plant-based foods, suggesting that this dietary pattern might be beneficial in HF.

Regarding the correction of nutritional deficiencies in HF, there is surprisingly little human intervention research[75]. None of the existing HF guidelines offer detailed recommendations for the management of malnutrition or cardiac cachexia. ESC guidelines[6] recommend monitoring body weight and preventing malnutrition in HF patients. However, these guidelines do not make specific recommendations for patients who are at high nutritional risk or undernourished.

Nutritional support and physical activity are the main treatment options for clinicians to counteract the devastating consequences of wasting disorders in HF[47], in which lean mass abnormalities are common and

contribute to worse QoL and clinical outcomes[76]. Several studies have examined the effects of dietary protein and/or amino acid (AA) supplementation on skeletal muscle strength and performance. The administration of essential AA has shown a significant increase in body weight[77] and exercise tolerance[77,78]. In contrast, no benefit from the branched chain AA supplementation added to a resistance exercise program was found in another trial[79].

Other studies have combined protein or amino-acid supplementation with additional calories in the form of high-calorie and high-protein oral supplements to counteract this wasting process. A trial that analyzed the effect of an oral nutritional supplement with beta-hydroxy-beta-methylbutyrate in 652 malnourished patients hospitalized for HF and other pathologies, showed a significantly lower 90-day mortality in the intervention group versus control. Nevertheless, there was no significant difference in the composite primary endpoint of death or readmission post-discharge between groups[80].

Another trial in patients with HFrEF and cachexia evaluated the administration of high-calorie, high-protein supplement compared with placebo. The nutritional supplement was related with a significant benefit in body weight, QoL, 6-min walk test (6MWT) distance, and laboratory parameters[81].

In the PICNIC trial (Nutritional Intervention Program in Hospitalized Patients with HF who are Malnourished)[82], a total of 120 malnourished hospitalized patients due to acute HF were randomized to conventional HF treatment alone or combined with an individualized nutritional intervention. This study showed that a nutritional intervention in undernourished patients reduced the risk of all-cause death and the risk of readmission for worsening of HF[82].

Potential treatments for cachectic and sarcopenic patients, mentioned in the ESC guidelines of HF, are appetite stimulants, exercise training, and anabolic agents (including testosterone) in combination with the application of nutritional supplements and anticatabolic interventions[6], but the guidelines caution that none of these treatments have proven benefit and their safety is unknown[47].

Micronutrient deficiencies

The failing heart is an energy-compromised organ, characterized by "metabolic remodeling"[83]. Several micronutrients are essential cofactors of metabolic reactions and contribute to the efficiency and the appropriate utilization of energy[84]. Selective deficiencies of taurine, carnitine, and thiamine are established primary causes of dilated cardiomyopathy[85]. It has also been demonstrated that the failing heart is deficient in several micronutrients[86]. Although inadequate intake and low plasma levels of micronutrients have been associated with adverse clinical outcomes, evidence supporting therapeutic repletion is limited[44].

Thiamine

Thiamine is a water-soluble vitamin that is absorbed in the jejunum and renally excreted. It is an important cofactor in cellular energy production and it plays a key role in myocardial contractility. The adult human body has a limited thiamine reserve[65]. Thiamine deficiency (TD) can lead to congestive HF, known as "wet beriberi"[87]. TD is more prevalent in the HF population than in control subjects[65]. The prevalence of TD in HFrEF patients in a systematic review of 13 studies, ranged from 3% to 91%[65], with higher prevalence in hospital (5-91%) than in ambulatory settings (3-27%). These variations in prevalence of TD were possibly due to study location (ambulatory or hospitalized patients), variations in thiamine assay methods, disease severity, food habits, age, and comorbid conditions. Numerous factors have been linked with the risk of TD in these patients, including HF severity, comorbidities (renal dysfunction or diabetes), malnutrition, advanced age, frequent hospitalizations, and restrictive diets[87]. A recent study in ambulatory HF patients showed a low prevalence of TD (6%) suggesting that, unlike hospitalized patients, ambulatory patients may be at low risk for TD[88].

Thiamine intake may decrease in HF patients due to splanchnic congestion and early saciety[65]. In addition, HF patients have increased thiamine requirements as a result of chronic diuretic use which may promote renal wasting. The use of loop diuretics has been associated with TD in a dose-dependent manner, related to increased urinary thiamine excretion[89]. Likewise, it has been described that urinary thiamine losses are not specific to loop diuretic use, and it can occur with all diuretics[65]. Earlier studies linked TD to diuretic use, but more recent studies doubt on those findings[65,90]. A systematic review concluded that the evidence supporting a correlation between diuretics and TD comes from small, poor-quality studies, with different methods for measuring TD[65].

Various small randomized trials have shown evidence that thiamine supplementation may improve significantly LVEF compared against placebo[65,91,92].

Benefits of thiamine supplementation in HF patients include improvements in end-systolic volume and NYHA functional class[92]. A recent randomized trial in 69 ambulatory HF patients with reduced LVEF showed that oral thiamin supplementation for 6 months did not improved LVEF, QoL or exercise capacity, and despite the increase in thiamin concentrations[93]. It should be noted the lower prevalence of TD in ambulatory patients. Further trials are required to establish thiamine's role in patients with systolic HF. With the available data, some authors conclude that it is reasonable to evaluate hospitalized HF patients for TD or offer empirical treatment (i.e., relatively ease, safe, and inexpensive) if testing is unavailable or cost is a limitation[65,90].

CoQ10

CoQ10 or ubiquinone is a natural lipid-soluble antioxidant. It is a component of the respiratory chain in mitochondria. CoQ10 exerts three main biological roles in humans: contributes to mitochondrial energy production, stabilizes the cell membrane, and has an antioxidant effect[94]. About one-half of CoQ10 is provided by diet and the remainder is synthesized endogenously through the mevalonate pathway, which is blocked by statins[95]. Statins and beta-blockers have been proved to reduce CoQ10 plasmatic concentration[94].

In HF patients, lower CoQ10 levels are associated with increasing severity of HF symptoms and worse NYHA functional class[96]. In CORONA trial (Controlled Rosuvastatin Multinational Study), the HF patients with the lowest values of CoQ10 had significant lower LVEF and higher NT-proBNP levels[95].

Despite the association of worse HF-related clinical status with lower CoQ10 levels, the prognostic use of CoQ10 is controversial. In an observational study of 236 hospitalized HF patients, the serum CoQ10 concentration was an independent predictor of mortality[97]. However, there was no association between CoQ10 level and mortality or other outcomes in the CORONA trial[95].

There have been a large number of trials examining the effect of CoQ10 in HF conducted during the past 30 years[96,98]. Most of these studies reported the usefulness of CoQ10 in improving HF symptoms[99], LVEF[99,100], and left ventricular size[101]. Nevertheless, these studies are limited by the small number of patients enrolled and the heterogeneity of clinical endpoints[94]. In 2014, a Cochrane review of seven studies comparing CoQ10 versus placebo concluded that the existing data are derived from small, trials that concentrate on physiological measures, and their results are inconclusive[102]. Furthermore, in 2014 was published the first randomized, placebo controlled clinical trial (Q-SYMBIO), powered to show a mortality difference. This study concludes that treatment with CoQ10 in HF patients, in addition to standard therapy, is associated with a reduction in mortality, hospital stays and improved NYHA functional class. In addition, CoQ10 was safe and well tolerated[103].

Recently, many reviews[96,98,101,104] and new meta-analyses[105,106] on the efficacy of CoQ10 supplementation for HF patients have been published. Lei et al.[106], in a meta-analysis of 14 studies, reported that patients with HF who used CoQ10 had lower mortality and a higher exercise capacity improvement than the placebo-treated patients. There were no significant differences in the endpoints of LVEF and NYHA classification. Jafari et al.[105], in other meta-analysis concluded that evidence suggests that the CoQ10 supplement may be a useful tool for managing patients with HF. Therefore, different authors suggest that CoQ10 may be considered a safe therapeutic option for patients with HF[96,98,101,105].

Vitamin D

Vitamin D deficiency is one of the most common nutritional deficiencies in the world[107]. Multiple factors influence 25-hydroxyvitamin D levels, including nutrition, sunlight exposure, outdoor physical activity, and skin color. However, there is currently no consensus about defining optimal serum levels and dietary requirements.

In recent years, there has been growing evidence that Vitamin D deficiency is associated with the development and progression of chronic HF[108]. Vitamin D deficiency is highly prevalent in subjects suffering from HF[109]. Furthermore, lower levels of Vitamin D are associated with poorer prognosis. In many observational studies lower Vitamin D concentrations were independently associated with an increased risk for all-cause mortality and HF rehospitalization[109-111].

Although there is sufficient evidence that Vitamin D deficiency is associated with increased incidence and poor prognosis of HF, it remains unclear whether vitamin D supplementation can improve clinical prognosis in these patients. A meta-analysis of seven randomized controlled trials that investigated the effects of Vitamin D on cardiovascular outcomes concluded that, in HF patients, Vitamin D supplementation may decrease serum levels of parathyroid hormone and inflammatory

mediators, whereas it has no beneficial effects on improvement of LVEF and exercise tolerance[112].

The VINDICATE study (Effects of Vitamin D on cardiac function in patients with chronic HF) reported that 1 year of high–dose Vitamin D3 supplementation does not improve 6MWT distance, but has beneficial effects on LV structure and function[113]. More recently, in the EVITA study (effect of Vitamin D on all-cause mortality in HF), no difference in mortality or hospitalization was observed in 400 patients with advanced HF treated with Vitamin D or placebo for 3 years[114], whether Vitamin D supplementation will improve outcomes in HF patients is, as yet, unproven.

Carnitine

Levocarnitine (L-carnitine) is a non-essential AA that plays a critical role acting as a cofactor in fatty acid transport into mitochondria, acetyl-CoA production, and glucose metabolism[94,115]. Genetic carnitine deficiency results in a cardiomyopathy[116]. L-carnitine is either supplied in the diet or produced endogenously, although daily consumption exceeds endogenous production. L-carnitine deficiency in the failing heart has been well documented[115,117].

Several studies evaluating the role of L-carnitine in HF have shown an improvement in exercise capacity and LV volumes[94]. A double-blind placebo-controlled trial found an improvement in 3-year survival[118]. A meta-analysis of 17 clinical trials showed that L-carnitine was associated with improvement in LVEF, stroke volume, and cardiac output. Moreover, treatment with L-carnitine resulted in significant decrease in serum levels of BNP and NT-proBNP. However, there were no significant differences in all-cause mortality, 6MWT, and adverse events between L-carnitine and control groups[119]. Further research is required to more accurately assess the results of L-carnitine for treating HF patients.

Conclusions

Undernutrition is very common in HF patients. It is associated with worse outcomes, higher rate of hospitalization, and mortality. Although nutritional screening is mandatory in HF patients, malnutrition remains underdiagnosed. Numerous validated screening tools for malnutrition have shown good value in predicting prognosis of HF patients. There are nutritional interventions that can improve the outcomes of these patients.

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Conflicts of interest

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Ethical disclosures

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REVIEW ARTICLE

Legacy effect in diabetes mellitus: fact or fiction?

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Abstract

The "legacy effect or metabolic memory" describes the long-term health benefits of intensive glycemic control early in the course of the disorder in reducing long-term diabetic complications compared to standard glucose control. The association between poor glycemic control and high rates of chronic diabetic complications in patients with type 1 and type 2 diabetes mellitus is well established. Several randomized control trials of intensive diabetes therapy have reported a substantial reduction in both micro- and macro-vascular complications compared to conventional therapy. Several landmark diabetes studies such as the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have reported long-term reduction in the prevalence of micro- and macro-vascular complications that persist for decades after completion of these studies with intensive intervention compared to conventional diabetes therapy. Recent long-term follow-up of several multicenter studies has confirmed the beneficial effect on microvascular complications; however, has raised doubts regarding the benefits of the legacy effect in improving cardiovascular outcome and mortality in patients with type 2 diabetes. In this review, we discuss the epidemiologic evidence in favor and against the metabolic memory hypothesis in patients with type 1 and type 2 diabetes. In addition, we discuss potential underlying mechanisms that could play a role on the effects of glycemic exposure on vascular complications in patients with diabetes.

Key words: Legacy effect. Diabetes mellitus. Glycemic control. Vascular complication.

Evidence of a legacy effect of intensive glucose control: DCCT and UKPDS trials

The association between poor glycemic control and increased risk of long-term complications of diabetes is well established[1-4]. A large number of observational, prospective randomized control trials, and meta-analyses have shown that improvement of glycemic control with intensive therapy reduces the risk of microvascular complications in individuals with type 1 and type 2 diabetes[3,4].

The DCCT, a landmark study randomized 1,441 participants with type 1 diabetes to a "standard" (conventional) and to an "experimental" (intensive) treatment arm. The conventional group reflected diabetes care practices in the early 1980's and included one or two daily injections of single or mixed insulin, daily urine or capillary self-monitoring blood glucose (SMBG) testing, and diabetes education[1].

Treatment remained unchanged unless the quarterly obtained glycated hemoglobin (HbA1c) was > 13.1%. The intensive treatment group received multi-dose injections at least three injections of insulin per day or

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continuous subcutaneous insulin infusion (insulin pumps, CSII), with dose adjustment guided by four or more SMBG tests per day targeting premeal glucose concentrations between 70 and 120 mg/dL and postmeal glucose < 180 mg/dL, and a weekly 3:00 a.m. concentration > 65 mg/dL. The overall goal of intensive intervention was to achieve and maintain an HbA1c levels < 6.05%.

The DCCT ended in 1993, after a mean duration of follow-up of 6.5 years. Intensive treatment (median HbA1c, 7.3%) compared with conventional treatment (median HbA1c, 9.1%) reduced the progression of retinopathy by 76% in the primary prevention cohort and by 54% in the secondary intervention cohort5. For each 10% decrease in HbA1c concentration, such as from 9.0% to 8.1% or from 8.0% to 7.2%, there was a 39% decrease in the risk in microvascular complications[5]. The appearance and progression of diabetic nephropathy were assessed by yearly measurement of albumin excretion rate and creatinine clearance showed a similar beneficial effect on diabetic nephropathy with a reduction in the development of microalbuminuria by 39% and the development of clinical albuminuria (≥ 300 mg/dL) by 56%[6]. For each 10% decrease in HbA1c, there was a 25% decrease in the risk of microalbuminuria.

In addition, at 5 years, the prevalence of confirmed clinical neuropathy in those without this complication at study baseline was reduced by 69% and 57% in the primary and secondary cohorts, respectively[7]. The DCCT reported higher rates of hypoglycemic events in the intensive group[8], but no differences in cardiovascular events, quality of life assessment[9], or neurocognitive function between treatment groups[10].

At the end of the DCCT, patients were invited to participate in the long-term Epidemiology of Diabetes Interventions and Complications (EDIC) observational study aimed to determine the long-term effects on microvascular complications and cardiovascular events[11]. In this study, the diabetes care of all participants was transferred to their primary care providers, and patients were assessed annually for the development of complications. Ninety-six percent (n= 1394) of the surviving DCCT cohort elected to continue their participation in the observational follow-up study.

During the study period, differences in HbA1c observed in the DCCT dissipated rapidly during EDIC trial, and rose by ~0.8% in the intervention group and fell by ~1.0% in the control group[12]. By year 5 of EDIC, the HbA1c levels were no longer statistically different, and the mean levels over the past 20 years of EDIC remained ~8% in both groups. Despite similar HbA1c concentrations, after the first 4 years of EDIC, there was a significant separation in the incidence of complications with a dramatic 70% reduction in the risk of progression of retinopathy in favor of the intensive DCCT group[12].

A similar finding was noted in the progression of albuminuria and changes in glomerular filtration rate with longer-term follow-up[13]. By 2012 (EDIC, year 19), the risk of severe retinal outcomes, such as complication-related ocular surgeries, had been reduced by 48% with former DCCT intensive intervention versus control. In addition, there was a 50% reduction in incidence of albuminuria and severe renal dysfunction, defined as a reduction in glomerular filtration rate, in of ~50% in the former intensive group compared to the conventional group[14], as well as a reduction in the development of peripheral and autonomic neuropathy[15,16].

Furthermore, the DCCT/EDIC study at 17-year follow-up reported a lower risk of cardiovascular events by 42% and of non-fatal myocardial infarction, stroke, or deaths from cardiovascular disease by 57%[17] compared to the former conventional group. The durable effect of the earlier separation in glycemia during DCCT on microvascular complications during EDIC was referred to as “metabolic memory.”

The United Kingdom Prospective Diabetes Study (UKPDS) randomized recently diagnosed adult individuals with type 2 diabetes to an intensive policy with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin, or to conventional policy with diet.

The glucose target in the intensive group was fasting plasma glucose (FPG) < 6 mmol/L (108 mg/dL). In the conventional group, the treatment aim was the best achievable FPG with diet alone, with antidiabetic drugs added in the presence of hyperglycemic symptoms or FPG > 15 mmol/L (270 mg/dL). Three aggregate endpoints were used to assess differences between treatment groups on any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, and sudden death); and all-cause mortality[18].

Over 10 years, HbA1c was 7.0% (6.2–8.2%) in the intensive group compared with 7.9% (6.9–8.8%) in the conventional group, with no difference in HbA1c among treatment agents[3]. Compared with the conventional group, the intensive group had a significant reduction

for any diabetes-related endpoint (12%), with most of the risk reduction of 25% in microvascular endpoints[3,19]. There was a 21% reduction in diabetic retinopathy and a 33% risk reduction in diabetic kidney disease after 12 years of follow-up. However, no significant reduction in macrovascular disease was observed, with a reported 10% lower diabetes-related death and a 6% reduction in all-cause mortality[3,19].

Patients in the UKPDS trial were invited to participate in a post-trial monitoring to determine whether the improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes. In the post-trial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies[3]. The median post-trial follow-up was 8.5 and 8.8 years. During the long-term observational period, between-group differences in HbA1c levels were lost after the 1st year. In the sulfonylurea/insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%) and microvascular disease (24%), risk reductions for myocardial infarction (15%), and death from any cause (13%).

Among overweight subjects, metformin therapy was associated with a significant risk reduction for any diabetes-related end point (21%), myocardial infarction (33%), and death from any cause (27%). These results indicate that even after both groups returned to a similar HbA1c level during the 10-year follow-up, individuals in the original intensive therapy group continued to have a significantly lower risk of long-term diabetes complications.

The combined results of the DCCT/EDIC in patients with type 1 diabetes and UKPDS in patients with type 2 diabetes clearly shows a sustained legacy effect of an intensive glucose-control strategy that persists after 10-20 years of the initial intervention. These results indicate that intensive glucose control starting shortly after diagnosis is associated with a significantly decreased risk of microvascular and macrovascular diabetic complications.

Recent evidence on the legacy effect: ACCORD, ADVANCE, and VADT

Based on the encouraging results of the DCCT and UKPDS, several large multicenter clinical trials including the Action to Control Cardiovascular Risk in Diabetes [ACCORD][20], Action to in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE][21], and Veterans Affairs Diabetes Trial [VADT])[22] were conducted to test the hypothesis that normalization or near-normalization of glucose in patients with type 2 diabetes will reduce microvascular and macrovascular complications compared to moderate levels of blood glucose reduction.

The ACCORD trial randomized 10,251 participants with type 2 diabetes who were at high risk for cardiovascular disease to determine whether a targeting a normal HbA1c levels <6.0% would reduce serious cardiovascular events compared to standard therapy targeting a HbA1c level between 7% and 7.9%[20]. As compared with standard therapy, the use of intensive therapy for 3.7 years reduced the 5-year nonfatal myocardial infarction (hazard ratio [HR] 0.79; 95% confidence internal [CI] 0.66 to 0.95) but increased 5-year mortality (HR 1.21; 95% CI 1.02 to 1.44). There was a 21% higher rate of death from any cause in the intensive-therapy group compared to the standard-therapy group (1.42 vs. 1.16; 95% CI 1.02 to 1.44). The higher mortality led an independent data and safety monitoring board to terminate the intensive glucose-lowering regimen.

A subgroup of 2856 ACCORD participants was evaluated for the long-term effects of intensive intervention on the progression of diabetic retinopathy or diabetic retinopathy requiring laser photocoagulation or vitrectomy[23]. Among the participants, the baseline median HbA1c level was 8.0%. At 1-year, median levels were 6.4% among participants receiving intensive glycemia therapy, as compared with 7.5% among participants receiving standard therapy. After 4 years of follow-up, progression of diabetic retinopathy was seen in 7.3% of participants in the intensive control group, compared with 10.4% of in the standard therapy group (odds ratio [OR] 0.67; 95% CI 0.51-0.87; p = 0.003). The rates of moderate vision loss were 23.8% and 26.3% among patients receiving intensive and standard glycemia therapy, respectively (adjusted HR 0.88; 95% CI 0.77-1.01; p = 0.06)[23].

Participants were reexamined in the ACCORD Follow-On (ACCORDION) Eye Study 4 years after the ACCORD trial closeout[24]. Diabetic retinopathy progressed in 5.8% with intensive glycemic treatment versus 12.7% with standard therapy (OR 0.42, 95% CI 0.28-0.63, p < 0.0001)[24].

The long-term effects of intensive versus standard glucose control on kidney outcome in the ACCORD trial were recently reported by Mottl et al[25]. Mean follow-up for kidney-related outcomes was 7.7 years (median 5.7 years). The primary composite kidney outcome was incident macroalbuminuria (Urine albumin-to-Creatine ratio > 300 mg/g), creatinine doubling, self-reported need for dialysis, or death from any cause. Of the 3410 participants with the primary composite kidney

outcome, two-thirds had two or more components of the composite outcome. Randomization to the intensive glycemic control arm reduced the incidence of the composite kidney outcome (HR 0.92; 95% CI 0.86-0.98) but this effect was primarily driven by a reduction in macroalbuminuria (hazard ratio, 0.68; 95% CI, 0.59-0.77). This follow-up study indicates that intensive glycemic control results in kidney protection with a long-term impact in reduction in macroalbuminuria.

The ACCORD Memory in Diabetes (MIND) examined the effects of intensive versus standard glycemic control on cognitive function by Digit Symbol Substitution Test (DSST) score, at baseline and at 20 and 40 months and total brain volume by magnetic resonance imaging (MRI) at baseline and 40 months[26]. This study enrolled 2977 patients, 1378 assigned to receive intensive treatment, and 1416 assigned to receive standard treatment. There was no significant treatment difference in mean 40-month cognitive score (difference in mean 0.32, 95% CI 0.28-0.91; p = 0·2997). The intensive-treatment group had a greater mean total brain volume than the standard-treatment group (4.62, 2.0 to 7.3; p = 0.0007)[26].

Participants in the ACCORD MIND study received a fourth cognitive assessment and a third brain MRI at 80 months post-randomization and approximately 47 months after the intensive glycemia intervention was stopped[27]. There was no significant difference from baseline in cognitive function by DSST scores or in total brain volume between the two glycemic intervention groups. The ACCORD-MIND follow-up study indicated no long-term beneficial or adverse effects on cognitive or in brain MRI outcomes. These findings, together to the increased mortality in participants in the intensive treatment group, do not support the use of intensive therapy to reduce the adverse effects of diabetes on the brain and cognition.

The ADVANCE study randomized 11,140 patients with type 2 diabetes to either intensive glucose control with target HbA1c < 6.5% or standard control with the use of gliclazide plus other drugs[21]. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy). After a median of 5 years of follow-up, the mean HbA1c level was 6.5% in the intensive and 7.3% in the standard-control group. There were no significant effects of the type of glucose control on major macrovascular events (HR 0.94; 95% CI 0.84-1.06; p = 0.32), death from cardiovascular causes (HR 0.88; 95% CI 0.74-1.04; p = 0.12), or death from any cause (HR 0.93; 95% CI 0.83-1.06; p = 0.28). However, intensive control was associated with a significant reduction in renal events, including new or worsening nephropathy (HR 0.79; 95% CI 0.66-0.93; p = 0.006), new-onset microalbuminuria (HR 0.91; 95% CI 0.85-0.98; p = 0.02), the development of macroalbuminuria (2.9% vs. 4.1% with standard control; HR 0.70; 95% CI 0.57-0.85; p < 0.001), with a trend toward a reduction in the need for renal-replacement therapy or death from renal causes (0.4% vs. 0.6%; HR 0.64; 95% CI 0.38-1.08; p = 0.09)[21].

The 6-year post-trial follow-up study (ADVANCE-ON) reported no evidence that intensive glucose control during the trial led to long-term benefits with respect to mortality or macrovascular events[28]. In addition, there were no cumulative benefits with respect to major clinical microvascular events or severe diabetes-related eye disease (composite of end-stage renal disease, defined as requirement for renal-replacement therapy; death from renal disease; requirement for retinal photocoagulation; or diabetes-related blindness in either eye). There was a significant cumulative benefit with respect to end-stage renal disease (HR 0.54; 95% CI 0.34-0.85; p = 0.007), although relatively few events were recorded[28].

The VADT randomized 1791 patients with type 2 diabetes to receive either intensive or standard glucose control for a median follow-up of 5.6 years[22]. The goal in the intensive-therapy group was an absolute reduction of 1.5% points in the HbA1c level, as compared with the standard-therapy group.

The primary outcome was the first occurrence of a major cardiovascular event including a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. After a median follow-up was 5.6 years, the median HbA1c levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. There were no significant differences between the two groups in the primary outcome (HR in the intensive-therapy group 0.88; 95% CI 0.74-1.05; p = 0.14) or in any component of the primary outcome or in the rate of death from any cause (HR 1.07; 95% CI 0.81-1.42; p = 0.62). No differences were observed between the two groups for microvascular complications. Fundus photographs showed no significant differences in progression to proliferative diabetic retinopathy or in macular edema. The estimated glomerular filtration rate declined to 76 mL/min by year 6, with no difference between the two study groups[22].

VADT participants were followed after the conclusion of the original clinical trial for the incidence of

Table 1. Principal characteristics of DCCT, UKPDS, ACCORD, ADVANCE, and VADT Clinical Trials

	DCCT	UKPDS	ACCORD	ADVANCE	VADT
Number of participants	1441	3867	10,251	11,140	1791
Population	Type 1 diabetes	Type 2 diabetes recent diagnosis	Type 2 diabetes with ≥ 2 cardiovascular risk factors	Type 2 diabetes with ≥ 1 cardiovascular risk factor	Type 2 diabetes poorly controlled
Age (years)	27.7 ± 7.0	53.0 ± 8.5	62.2 ± 6.8	66.6 ± 6.0	60.5 ± 8.7
In-trial/Total follow-up (years)	6.5/30	10/17	3.5/9.0	5/10	5.6/9.8
Basal HbA1c (%)	> 8.5	7.2	8.1	7.5	9.4
HbA1c differences (%)	2.0	0.9	1.7	0.7	2.5

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; DCCT: Diabetes Control and Complications Trial; UKPDS: United Kingdom Prospective Diabetes Study; VADT: Veterans Affairs Diabetes Trial.

cardiovascular events, hospitalizations, and death[29]. During the observation period, the HbA1c difference declined to 0.2-0.3% points by 3 years after the trial ended. Over a period of 15 years of follow-up (active treatment plus post-trial observation), the risks of major cardiovascular events or death were not lower in the intensive-therapy group compared to the standard-therapy group (HR 0.91; 95% CI 0.78-1.06; p = 0.23)[29].

Principal characteristics of DCCT, UKPDS, ACCORD, ADVANCE, and VADT are shown in table 1.

Legacy effect with lipid-lowering therapy

Although there are not studies in diabetic population to support the existence of a legacy effect with lipid-lowering therapies, some clinical trials with high proportion of patients with diabetes and a meta-analysis reported that statins therapy can be associated with long-term benefits in reducing cardiovascular events.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) assigned patients ≥ 55 years with hypertension and moderate hypercholesterolemia to receive pravastatin 40 mg/day or usual care (n = 5,185) during a mean follow-up of 4.8 years. A 35% of patients had type 2 diabetes. A passive post-trial surveillance of 11.4 years did not find significant differences in mortality for pravastatin versus usual care (HR, 95% CI: 0.96, 0.89-1.03), or other secondary cardiovascular and renal outcomes. However, there was a significant treatment effect for coronary heart disease in Blacks (HR, 95% CI: 0.79, 0.64-0.98)[30].

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy Study reported mortality outcomes after 15.7 years of follow-up of the UK participants. The original ASCOT trial recruited subjects (median age 64 years, over 80% male) with hypertension and no previous history of coronary event. In the Lipid-Lowering Arm (LLA) of the ASCOT, subjects who had a total cholesterol 247 mg/dL or lower and no previous lipid-lowering treatment underwent further randomization to receive either atorvastatin 10 mg/day or placebo. In the LLA, patients assigned to atorvastatin had significantly fewer cardiovascular mortality (HR, 95% CI: 0.85, 0.72-0.99, p = 0.0395) than those assigned to placebo[31].

Three meta-analyses have assessed the evidence for post-trial effects of statin therapy on mortality among adult participants of placebo controlled randomized controlled trials[32-34]. A meta-analysis that examined 13 randomized clinical trials of lipid-lowering agents compared to placebo or usual care with follow-up after the randomized phase, a legacy effect was demonstrated with a 13% reduction in all-cause mortality (OR, 95% CI: 0.88, 0.83-0.93, p = 0.0000)[32].

Another meta-analysis, which included 10 lipid-lowering trials reported sustained benefits of statin therapy on all-cause and cardiovascular mortality, but the benefit decreases during long-term follow-up (relative risk [RR], 95% CI: 0.92, 0.87-0.97)[33]. In the more recent, meta-analysis of aggregate data from 8 trials with statin therapy (5 trials of primary prevention and 3 trials of secondary prevention) (Table 2), including 44,255 patients with a mean post-trial follow-up from 1.6 to 15.1 years, reported a reduction on all-cause mortality (p = 0.01), but not on cardiovascular mortality. The pooled post-trial analysis for the three primary prevention studies demonstrated a legacy effect both on cardiovascular mortality (HR, 95% CI: 0.87, 0.79-0.95) and on all-cause mortality (HR, 95% CI: 0.90, 0.85-0.96)[34].

Table 2. Characteristics of the randomized clinical trials included in the meta-analysis by Nayak et al.

Study	Target population	Number of participants	Mean follow-up (years)	Mean age (range, years)	Diabetes (%)	Duration of post-trial follow-up (years)	Statin
PRIMARY PREVENTION							
WOSCOPS	Men with high cholesterol and no history of myocardial infarction	6595	4.8	55 (45–64)	1	15.1	Pravastatin 40 mg
ALLHAT-LLT	Hypertension and high cholesterol	10,355	4.8	66 (55-NA)	35	11.4	Pravastatin 40 mg
ASCOT-LLA	Hypertension, no history of CHD, with other CVD risk factors	10,305	3.2	63 (40–79)	25	8.3	Atorvastatin 10 mg
SECONDARY PREVENTION							
LIPID	Myocardial infarction or hospitalization for unstable angina	9014	5.6	62 (31–75)	9	10.0	Pravastatin 40 mg
HPS	Coronary disease, other CVD, diabetes, or hypertension	20,536	5.0	64 (40-80)	29	5.7	Simvastatin 40 mg
PROSPER	Patients ≥ 70 years with history of CVD or high CVD risk	5804	3.2	75 (70–82)	11	5.4	Pravastatin 40 mg
4S	History of angina or myocardial infarction	4444	5.2	60 (35-70)	5	5.0	Simvastatin 20-40 mg
ALERT	Renal or combined renal-pancreas transplant recipients at high CVD risk	2102	5.1	50 (30-75)	19	1.6	Fluvastatin 40 mg

CHD: Coronary Heart Disease; CVD: Cardiovascular Disease.

In summary, these studies support a potential legacy effect of statin therapy, including diabetic patients, with long-term cardiovascular benefits persisting for up to 20 years after the original trials. Possible post-trial statin legacy effects on mortality appear to be driven mainly by the primary prevention studies. Although the mechanisms remain unproven, it is plausible that early treatment of subclinical atherosclerosis promotes plaque stabilization and confers lower event rates. The main limitation of these studies is that they are not based on individual data but on aggregate data of treatment with statins during the post-trial period, which favors potential confounders.

The ACCORDION-Lipid study, an observational follow-up from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[20] did not find superiority of statin-fibrate combined treatment compared to statins alone on cardiovascular outcomes and mortality after 5 years of active treatment in patients with type 2 diabetes. However, in the extended post-trial period, with a median follow-up of 4.9 years, fibrate treatment was associated with a legacy benefit of reduced all-cause mortality (adjusted HR 0.65, 95% CI 0.45-0.94; p = 0.02). These findings support re-evaluation of fibrates as an add-on strategy to statins to reduce cardiovascular risk in diabetic patients with dyslipidemia[35].

Legacy effect with blood pressure-lowering therapy

The evidence of a legacy effect of blood pressure-lowering therapy is more conflictive than with glucose and lipid-lowering treatments.

In the UKPDS post-trial follow-up, in sharp contrast to legacy effect observed with intensive glucose control, the benefits of tight blood-pressure control on both macrovascular and microvascular events were not sustained in patients with type 2 diabetes and hypertension[3]. The lack of long-term benefit of tight blood-pressure control during the trial could be explained by the fact that the HbA1c level was 0.8% higher in the UKPDS tight blood-pressure group than in the control group. It is possible that a glycemic legacy effect favoring the less-tight blood-pressure group might

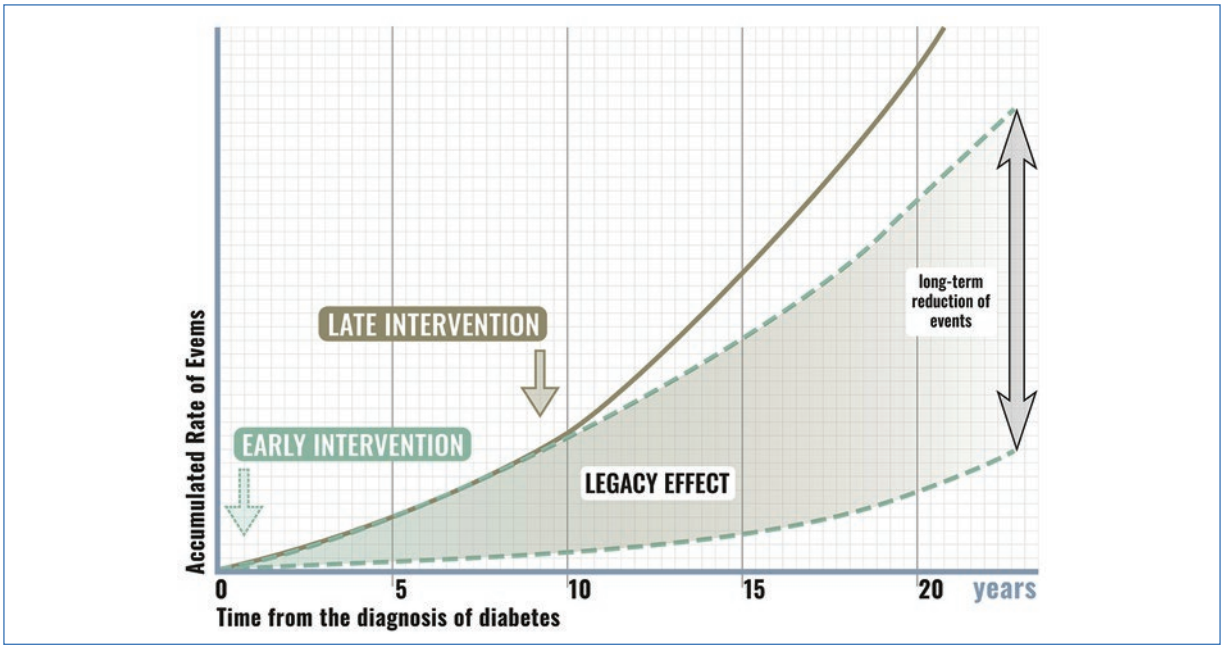

Figure 1. Critical importance of the timing to achieve a legacy effect in diabetes treatment.

have masked a potential long-term benefit of tight blood-pressure control during the trial[36].

In contrast with the UKPDS, in the 10 years follow-up of the ADVANCE-ON study, a long-term reduction in all-cause mortality and cardiovascular mortality was observed in patients assigned in the trial period to blood pressure-lowering therapy, but there was no evidence of legacy effect with long-term intensive glycemic control[28]. The observed gradual attenuation of benefits over time reinforces the importance of continuing antihypertensive treatment in patients with type 2 diabetes[36].

A meta-analysis of long-term follow-up of 18 clinical trials of blood pressure-lowering medication, with an average post-trial follow-up of 41 months and a variable proportion of patients with diabetes, reported a significant and sustained decrease in overall mortality during the open label follow-up[37]. A different meta-analysis of 13 blood pressure trials with a mean follow-up of 10 years showed a persistent, but attenuated reduction in all-cause mortality and cardiovascular mortality after discontinuation of randomized treatment, without differences in diabetes and non-diabetes trials[33].

In the ALLHAT trial, which recruited middle-aged adults in primary prevention, 44.3% of patients with diabetes reported a lack of legacy effect in mortality and major cardiovascular events during 14 years of follow-up[38].

In summary, despite the possible lack of blood pressure legacy, the overwhelming evidence of cardiovascular protection in patients with diabetes and hypertension, an adequate and maintained antihypertensive treatment early in the course of the disease, remains a cornerstone in the current approach to diabetes management[39]. In addition, the Steno-2 Study provided solid evidence on the long-term benefits from a multifactorial therapeutic approach in patients with type 2 diabetes and microalbuminuria. The post-trial benefits reported in the Steno-2 trial support a legacy effect of this multifactorial approach, although part of these benefits could be explained for the persistence of differences in the control of risk factors between groups[40].

Mechanisms for the legacy effect

Persistent hyperglycemia is a known risk factor for cardiovascular complications[41]. Although mechanisms of benefit are not well-established, a potential mechanism could be related to the memory of prior exposure of targets cells to persistent hyperglycemia observed in experimental models[42]. The benefits of glucose lowering include reduction in oxidative stress, accumulation of advanced glycated end products, endothelial dysfunction, and epigenetic factors[43,44]. All these factors could be plausible causes of structural and functional changes that would occur in the early metabolic environment but that would carry implications for the development and

progression of microvascular and macrovascular complications in the long term[45-47]. The mechanisms implicated in blood pressure benefits have been related to lower rates of atherosclerosis, reduction of infarction size, and attenuation of adverse left ventricular remodeling[37]. The beneficial effect of renin-angiotensin-aldosterone system inhibiting therapies on vascular inflammation and remodeling could also play a relevant role in cardiovascular protection[48]. In addition, lipid lowering benefits are associated with prevention and regression of atherosclerotic disease, and reduction in infarct size[41]. Furthermore, reductions in non-cardiovascular deaths, particularly due to infections and respiratory illnesses have been suggested as another important contributor to legacy effect in the ASCOT Trial[49].

Conclusion

Several observational and randomized controlled multicenter studies have shown a beneficial effect of improving short-term glycemic control in reducing the risk long-term complications in patients with type 1 and type 2 diabetes. There is strong evidence indicating a reduction in the prevalence of microvascular complications that persist for decades after completion of the studies with intensive intervention compared to conventional diabetes therapy. However, there is less evidence on the benefits of a legacy effect in reducing macrovascular complications and cardiovascular mortality, which could be limited to patients at the early stage of diabetes and without clinical cardiovascular disease (Fig. 1). In regard to legacy effect with lipid-lowering therapies, evidence suggests that statins therapy can be associated with short- and long-term benefits on cardiovascular outcomes. Finally, despite the possible lack of blood pressure legacy, an adequate and maintained antihypertensive treatment, possibly early in the course of the disease, remains a cornerstone in the current approach to diabetes management. Patients with diabetes could be benefited from an early and long-term multifactorial therapeutic approach.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

On the basis of sex and gender in healthcare

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Abstract

Sex and gender equality matters for health. Biological sex and gender constructs are major disease modifiers and exist across leading causes of death and morbidity globally. Greater awareness of how sex and gender impact main diseases may lead to new insights into how improvements in prevention, early diagnosis, treatment, and survival can be made. Future research should focus on improving outcomes for women, including a large proportion of women in trials and exploring different approaches in men and women. Governments and institutions must understand that there are strong ethical arguments supporting sex and gender equality in medicine. This review explores how sex and gender determine morbidity, mortality, access to healthcare, help-seeking behaviors, treatment response, and different clinicians' behaviors that could drive to unequal diagnosis and treatment according to sex/gender.

Key words: Gender. Sex. Bias. Healthcare.

Sex and gender inequality in healthcare

Sex and gender are important determinants of health inequalities and influence, not only in a particular burden of disease and healthcare needs but also in different treatments, adherence, and response to drugs[1,2]. Although sex and gender are often interchangeably used, they are not equivalent concepts: sex is a biological variable that defines species (including humans) as male or female (or intersex) according to their reproductive organs, based on their chromosomal assignment. In contrast, gender refers to the socially constructed norms that determine roles, relationships, and positional power for all people across their lifetime[2-4]. Both concepts are integrally related and influence health and wellbeing in different ways.

Gender and sex inequalities can occur across the life course, at all healthcare levels, and undermine health issues of both sexes, but especially that of women. Sex bias in healthcare can manifest as the assumption that males and females are the same when they have differences that need to be addressed.

Historically, women were excluded from clinical trials, and therefore, medical research has been centered on male physiology[2]. Consequently, preclinical drug research, diagnosis, treatment, and disease prevention originates from studies mostly done on male cells, male mice, and men. Results have been inferred and applied in women assuming that male and female cells and animals are biologically identical[5,6]. Integrating the practice of studying both sexes in preclinical research will improve our currently incomplete knowledge in this area[7,8].

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A simple way to evaluate gender bias is to identify if, for the same illness, same efforts made in both sexes by health providers. When both genders are not offered equal quality of treatment and care for the same medical complaints or when different manifestations of the disease are not considered based on sex, patients' outcomes can be expected to worsen.

This review discusses how biological sex and gender constructs determine morbidity, mortality, access to healthcare, help-seeking behaviors, treatment response, and different clinicians' conducts that could drive to unequal diagnosis and treatment according to sex/gender.

A search was performed in PubMed for papers published between November 2000 and November 2020, using "gender" or "sex" and the name of the disease of interest as search terms. The reference list of all related articles was screened to find other previously unidentified articles. Our review tries to select the significant studies published on this topic but is not a systematic review.

Sex and gender biases in diagnostic and therapeutic efforts

Diagnostic and therapeutic efforts biases are closely related: the probability of a patient suffering from a disease being adequately treated is low if, for any reason, the patient is excluded from the diagnostic process or if the relevant tests are not carried out or not accurately interpreted[9]. Both professionals, with their scientific knowledge and interpretation of the signs and symptoms, and patients, with their biological and gender-based conditions, are involved in the incidence of diagnostic and therapeutic biases.

Women demand medical assistance with a series of biological conditions, such as age, comorbidity, menstrual cycle, or menopause, but also with gender conditions such as social and family roles, cultural level, perception and interpretation of symptoms, and their severity. Physicians analyze these clinical manifestations based on their knowledge and previous experience, make a diagnostic effort using a more detailed anamnesis, an appropriate physical examination, and request certain complementary tests. As an example, variations in the way women depict myocardial ischemia symptoms can lead physicians to misdiagnose this condition as emotional distress[10].

A sex and gendered view in medicine also entails identifying diseases underestimated in men. Namely, depression, as gendered manifestations of depressive symptoms, may play a role in why some men do not seek mental health issues[11] or osteoporosis, which definition was developed from healthy young white women and generalized to men, leading to undiagnosed and undertreated osteoporosis in men[12].

There are several relevant dimensions to illustrate the gender bias related to the therapeutic effort. First, there are differences in drug consumption between men and women. The potential gender inequality in drug use and abuse could be explained by different adverse drug reactions, inaccurate research in clinical trials, and international institutions' decisions in the marketing of certain medical products.

Prescription also differs depending on sex and gender. There is greater tendency to prescribe pain relievers, regardless of pain, in women than in men[13]. Sometimes, blurred clinical presentations lower the thresholds for diagnosing psychiatric disorders resulting in antidepressant drugs being more frequently prescribed in women[14,15]. The opposite occurs in the prescription of aspirin, statins, and angiotensin-converting enzyme inhibitors in primary care, with a higher prevalence prescription in men[16].

Furthermore, adverse drug reactions are observed more frequently in women than in men, where determinants such as body weight, distribution volumes, sex hormone levels, activity of enzymes, and different routes of excretion can affect the drug metabolism[17,18].

Second, there is evidence of gender disparities in access to healthcare and health system responses that usually deprioritize women's health; in low and middle-income countries, there is even a greater need to ensure that limited resources are used efficiently and equally[2,19-21]. These disparities have many complex sources and require global actions. For example, women are less likely to undergo invasive procedures such as coronary angiography and coronary revascularization than men presenting with acute myocardial infarction (AMI)[22-26].

Finally, the gender gap in first medical contact and delay in diagnosis and treatment in some medical conditions has not been fully explained. Differences in admission route and times may be explained by greater diagnostic uncertainty among women who report non-specific or atypical symptoms more often than men, especially when suffering a myocardial infarction[27,28]. Unfortunately, women can unknowingly contribute to a biased delay in diagnosis and treatment because they often think of stroke and heart disease as "men's diseases" and therefore assume they are not likely to have either of these conditions[29]. Furthermore,

some physicians might not understand that women may experience symptoms differently than men; they can be less willing to engage female patients in shared decision making or believe women's symptoms have emotional causes rather than physical.

Representative diseases with sex and gender differences

Sex and gender are significant disease modifiers and exist across leading causes of death and morbidity globally[30]. Furthermore, the distribution of disease differs between women and men throughout their different life stages, highlighting the role of sex and age interaction[31].

Cardiovascular disease

Remarkable sex and gender differences have been reported in the cardiovascular field: risk factors, ischemic heart disease, heart failure, and stroke are good examples.

Cardiovascular risk factors differ by sex: systolic blood pressure and hypertension, smoking, and diabetes are associated with higher hazard ratios for AMI in women than in men[32,33].

Diabetes mellitus is the paradigm of these risk factors with different impact between sexes. It represents a "risk magnifier" for both micro and macro vessels' damage differently in women and men[34,35]. Several studies have reported that the risk of death from coronary heart disease associated with type 2 diabetes mellitus is up to 58% higher in women than in men[36]. The basis for diabetes increasing cardiovascular disease risk in women is related to interactions between biological characteristics as hormones and genetics related to sex (in the prediabetes period, women have an earlier, greater, and more prolonged deterioration in cardiovascular factors than men, that include central obesity and insulin resistance) and gender constructs (there is evidence that physicians take longer to diagnose diabetes in female patients and therapeutic goals are less frequently achieved)[30,33,37-39]. Recently, coronary artery calcium appears to predict coronary heart disease, cardiovascular disease, and all-cause mortality more strongly in women with diabetes than in men[40].

Coronary heart disease has traditionally been considered a men's disease. Despite the improvement in women's cardiovascular disease mortality in the last two decades, it remains understudied, underdiagnosed, and undertreated in women. Women often underestimate their risk compared with men and seek consultation later than men in the clinic to treat AMI. Even after women's awareness campaigns to increase women's consciousness of their risk of heart disease, there was no time reduction from symptoms onset to hospital presentation for myocardial infarction[41].

When compared with men, women often present pain between shoulders, nausea or vomiting, and shortness of breath rather than chest pain or diaphoresis, although both sexes show most often with chest pain[42,43]. They are underdiagnosed and are less likely to have a pre-hospital diagnosis of AMI[10]. Moreover, angina in women is associated with more adverse morbidity, mortality, and quality-of-life outcomes, despite women having less obstructive coronary artery disease and better left ventricular function[42].

In the GENESIS-PRAXY prospective study, mortality 1 year after an acute coronary event was more strongly associated with gender than with biological sex[44].

This disparity reflects the intersection between sex and gender. First, biological sex differences exist in the pathogenesis of ischemic heart disease. Whereas men are more likely to be affected by obstructive coronary artery disease of large vessels than women, coronary microvascular dysfunction leading to chronic myocardial ischemia without obstructive coronary artery disease has a higher prevalence in women than men[24,45]. Gender factors also play an essential role. Although the first scientific statement on AMI in women was published in 2016[46], they are less likely to receive aggressive invasive treatment and pharmacotherapies, leading to higher mortality[24-26,47-50].

Furthermore, women suffering from myocardial infarction treated by male emergency physicians have a higher mortality rate than those treated by female physicians. In addition, male physicians are more effective at treating female patients with AMI when working with female colleagues and when they have experience in treating female patients[51].

Regarding heart failure, there are significant sex-specific differences in the epidemiology, etiology, and use of evidence-based heart failure therapies and treatment response[52-54]. Heart failure incidence remains the same for both sexes, but the overall prognosis is improved for women. Women with heart failure are older than men, have multiple comorbidities such as diabetes mellitus and high blood pressure, and a higher proportion of preserved ejection fraction[54]. These differences are partially driven by sex hormones, as estrogens produce anti-inflammatory actions on endothelial and immune cells and promote cardioprotective effects in premenopausal women. Guidelines for the treatment of

heart failure are similar for women and men. However, evidence suggests that optimal survival in women occurs with lower doses of b-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors than in men[54,55]. In general, women appear to obtain the same clinical benefit from evidence-based heart failure drugs and device therapies, but these therapies' utilization rates remain low[54].

Cerebrovascular disease

Although age-specific stroke incidence and mortality rates are higher in men than in women, stroke affects a greater number of women because of their increased longevity and the fact that stroke event rates increase substantially in the oldest age groups. There is a natural protection of endogenous estrogens before menopause. Still, ischemic stroke rates begin to increase in middle-aged women, and stroke prevalence is higher in older women than older men[56-59].

Ischemic stroke is the most prevalent type of stroke (87%) in female patients[59]. The risk of subarachnoid hemorrhage is 45% higher in women than men, and risk factors, mainly smoking, have a stronger adverse effect in women than men[56,60]. How sex and gender affect intracerebral hemorrhage prevalence and outcomes has been less studied, although, as in ischemic stroke, age is a major confounder[61]. Women with stroke have worse functional outcomes and quality of life than men, even after adjusting for important sociodemographic variables, stroke severity, and disability[56,62].

Some stroke risk factors are common to both sexes, but each risk factor's frequency differs between the sexes. As shown in the international INTERSTROKE case-control study[63], hypertension, abdominal obesity, and adverse lipid profiles are the most impactful causes of stroke in women worldwide. Some risk factors are more prevalent in women, including diabetes, hypertension, and atrial fibrillation[64]. Female sex is one of the independent risk factors for stroke in atrial fibrillation included in the CHAD2DS2VASc score[58,65]. This increased thrombotic risk in women is multifactorial, involving hormonal changes after menopause, structural, endocrine, lifestyle, and social factors, and their interactions. It has been reported that even though women with atrial fibrillation may benefit from anticoagulation more than men because of their higher risk of stroke, they are less likely to receive anticoagulation. When they do, the quality of anticoagulation may be lower[66-70].

The PINNACLE Registry, a contemporary cohort of patients in the United States with atrial fibrillation and indication for anticoagulation, found that women were 9% al 33% less likely than men to receive oral anticoagulation at all levels of thromboembolic risk[71]. Therefore, it assessed gender differences in the use of oral anticoagulants.

Factors such as underestimation of the high thromboembolic risk of female patients, women rejecting more frequently oral anticoagulation because of fear of bleeding, lack of social support to go to hospitals, or greater fragility of women perceived by health professionals, have been pointed out as possible reasons to explain the differences in anticoagulation treatment between men and women. These results were similarly reproduced in a retrospective study of Medicare data[72], in which overall oral anticoagulant initiation was lower in black individuals and women. As a result, women remain undertreated. Moreover, many are older and frailer and seen as poor candidates for thrombolysis and thrombectomy, the only two effective therapies for the treatment of acute ischemic stroke. This practice is concerning, as emerging data suggest that women benefit more from this kind of intervention than men, with a better outcome after endovascular stroke therapy[73].

Venous thromboembolic disease

Few studies have analyzed sex and gender differences in venous thromboembolic disease. The results, although inconclusive, point to different characteristics, presentation, and outcomes in women and men: women tend to have more adverse effects and an increased risk of bleeding compared to men, suggesting the need for more careful monitoring of the intensity of anticoagulation in female patients[74-76]. Women with thrombosis and cancer also need a different approach and may require a more personalized anticoagulant treatment[77].

Cancer

Differences by sex and gender have also been studied in cancer patients. The lifetime probability of being diagnosed with an invasive cancer is slightly higher for men than for women[78]. The reasons for this excess risk in men are not fully understood but partly reflect differences in environmental exposures, endogenous hormones, and probably complex interactions between them[79]. Recent research suggests that sex differences in immune function and response may also play a role. Immunotherapy can improve overall survival in patients with advanced cancer. Still, the magnitude of its benefit

is significantly greater in men than in women, regardless of the type of tumor, the line of treatment, and the type of immunotherapy[80].

Colorectal cancer is an example of a disease that has both biological sex differences and socio-cultural gender components. As there are minimal sex differences in the data from routes to diagnosis to survival, the higher mortality of colorectal cancer in men appears to be a result of exogenous and endogenous factors pre-diagnosis that leads to higher incidence rates[81]. In lung cancer, there has also been a focal point on the impact of sex and gender. While biological and genetic differences could explain the disparity in incidence and mortality of lung cancers, the degree to which gender habits, genetics, and environmental exposure to carcinogenic agents participate remains unanswered[82].

All these findings warn of the need for different screening and diagnosis approaches based on sexual and gender factors to improve overall survival. In the future, cancer prevention and treatment will be improved by sex-specific and gender-specific approaches.

Miscellaneous

Other major chronic diseases with sex and gender disparities are chronic pulmonary disease, chronic liver disease, and dementia. The risk of chronic pulmonary disease in women has been associated with both gender and sex biology, and women are both more susceptible and more vulnerable than men[83]. The female lung is more susceptible to chronic pulmonary disease than the male lung. Women develop the disease symptoms at a younger age with less tobacco exposure than men[84]. The tobacco industry actively targets women, and its smoking advertising campaigns resulted in higher smoking rates in women[85]. Understanding the genetic, molecular, social, and behavioral mechanisms that underlie these differences requires further research.

Chronic liver disease is another example of sex and gender disparities: sex influences are cause-specific, with a higher risk of primary sclerosing cholangitis, chronic viral hepatitis, cirrhosis, and hepatocellular cancer for men and a higher risk of autoimmune hepatitis and primary biliary cholangitis for women[86,87].

Furthermore, the degree to which the resulting health conditions (obesity, type 2 diabetes, and cardiovascular disease) impact dementia risk varies by sex. Ratio of male to female prevalence differs depending on the subtype of dementia. Males are at greater risk of developing vascular dementia, whereas females are at greater risk of developing Alzheimer's disease dementia[88].

Coronavirus disease (COVID-19)

Finally, sex and gender disparities have been recently reported in the pandemic pneumonia (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The severity of COVID-19, as measured by hospitalization, admission to intensive care units, intubation for mechanical ventilation, and death, has been 1.5-2 times greater for men than for women around the world[30,89-91]. Sex appears to affect the immune response to pathogenic agents and susceptibility for some respiratory diseases. This different response in men and women may be related to the actions of sex hormones. Angiotensin-converting enzyme 2 acts as the receptor for SARS-CoV-2, and its expression is influenced by sex hormones[92,93].

Secondary effects include differences in social and economic consequences resulting from the pandemic, including the risk of domestic violence, economy, job insecurity, and increased domestic workload[94-96]. The COVID-19 pandemic has also underscored systemic assumptions about women physicians that may cause unintentional disadvantage, namely reducing professional work hours or limiting leadership opportunities to balance the increasing personal responsibilities[97].

Sex and gender imbalance in academic setting, leadership positions, and research in medicine

In recent years, evidence has been mounting that there is a lack of gender balance in Science, Medicine, and Global Health[1]. Academic and institutional rank in the field of medicine is no exception. Women are still underrepresented in areas such as leadership positions, journal authorship, clinical research, grants, assistant professorships, professional meetings, and speaker invitations, compared with their male peers, supposing a vicious disadvantage cycle for women[98,99].

The significant differences in leading medical positions and higher academic ranks held by men and women illustrate the "leaky pipeline phenomenon," consisting of a disproportionately low number of women achieving professional advancement throughout the higher educational levels[100,101]. Why are women less likely to hold institutional or national leadership positions? The reasons behind continued gender inequality in medicine are numerous and complex and extend from medical schools, hospitals, and clinics, to all aspects of society. Biological evidence is contradictory and inconclusive to explain women's underrepresentation in the top fields

of science. There is evidence of early sex differences in spatial and mathematical reasoning suggesting a biological background in some areas. However, the gap between average female and male math ability is narrowing in recent years, suggesting strong environmental influences[102].

These sex differences also show variation across nationalities, ethnicities, and other factors, indicating that males' ratio to females at the right tail can and does change, suggesting that sociocultural context constitutes the most powerful explanatory factor. Concerns exist over self-advancement retention of women and their willingness to assert themselves professionally[103,104]. Household, childcare responsibilities, and parents' commitments are often cited as significant barriers[105].

Gender bias in assessment and success funding rates is also well documented[106,107]. Lack of grants for female scientists prevents women's full participation and contributions in the scientific and medical spheres. The transition from graduate programs to assistant professorships shows a pipeline leakage in females as well. Women are a minority among senior academics in many European countries[108]. Similarly, women hold 25% of full professor positions and 37% associate professor positions in the United States[109].

Regarding medical conferences, the visibility of women as speakers at academic medical meetings is an essential part of gender equity and can have a broad impact on their careers. Panels represent opportunities for networking, mentorship, and career advancement. Female speakers at conferences increased from 24.6% in 2007 to 34.1% in 2017[110]. However, despite the rise in women's participation, females are still underrepresented overall, and without a substantial cohort of women, it is more difficult to weaken stereotypes about gender roles[111,112].

Academic research illustrates gender inequality as well. According to the 2018 United Nations Educational, Scientific, and Cultural Organization report, overall, women account for a minority of the world's researchers (< 30%)[113]. In addition, women continue to be underrepresented in clinical trials making a challenge to assess the real quality and efficacy of drug efficacy and guidelines in managing diseases[114,115]. Future research efforts should focus on increasing women's enrollment in trials to improve knowledge of sex-specific differences in treatment effects and clinical outcomes. Trials should disaggregate demographics and outcome data by sex and gender, reporting the methods used to obtain information on both[116].

Furthermore, the publication of articles is also critical to career advancement in academic medicine. The academic publishing system is gendered[117]. As such, journals and editors may contribute to the disadvantaged vicious circle for women. If women are less likely to have opportunities to publish, particularly as first and senior authors, their career growth can be impeded. When women are underrepresented as authors, they have fewer opportunities to contribute and influence their field[118].

Along these same lines, the Sex and Gender Equity in Research guidelines[119] have been designed to guide authors in preparing their manuscripts. Still, they are also useful for editors, as gatekeepers of science, to integrate sex and gender assessment into all manuscripts as part of the editorial process[2,114]. Recommendations for reporting in research articles include using the term *sex* when reporting biological factors and *gender* when writing gender identities or psychosocial or cultural factors[114]. Ideally, the increased interest in the importance of sex and gender from funders and editors for all research should result in improved reporting of these considerations[120,121].

Initiatives to support sex and gender equality in healthcare and specific medicine by gender and sex

Achieving sex and gender balance in Medicine is a central challenge and must become an essential goal of healthcare delivery policies. Multiple national and international organizational groups have presented useful strategies to bring sex and gender into the mainstream of modern medical research, practice, and education[30].

One interesting initiative is Gendered Innovations, which lumps together sex and gender analysis in research design not only in medicine but also in other disciplines, such as engineering and the environment[8,122]. The 2018 Global Health 50/50 report was a pioneer in this setting. The dossier provides an in-depth review of gender-related politics of more than 140 health-related prestigious organizations[4]. The World Health Organization and The United Nations consider investigating gender as a cause of health inequality one of their priorities and include it as a goal in the 2030 Agenda[123,124]. Recently, The Lancet Commission on Gender and Global Health has been created to mobilize individuals and institutions to redress the imbalance in the gender-health relationship[125].

Some of the recommendations to promote sex and gender equity in health include: proper sex and gender enrolment in clinical trials, specific research questions in studies with segregation of results by sex or gender, appropriate personalized sex-specific and gender-specific guidelines for primary and secondary prevention, standards for journal editors that favor studies that report results by sex and gender, and incorporation of sex-based physiology and pathology into the early stages of instruction of Nursing and Medical Schools[1,2,18,19,99].

Implementation of programs to favor diversity and parity in professional teams, with the possibility of reaching positions of responsibility in the scientific community and academia, is crucial[126]. Gender-transformative policies are needed to empower women to integrate their social, biological, and occupational roles and function to make essential contributions to the sustainable development of women's health. Women's contributions in healthcare and their crucial roles in the healthcare of families and communities are important drivers, although often underappreciated, of nations' wealth and health[19].

In recent years, one growing interest concept is precision or personalized medicine, which should start focusing on differences in gender and sex in medicine. Efforts to address sex and gender disparities should be directed toward better understanding the differences in baseline risk and care pathways to highlight areas that would benefit from the target, sex, and gender-specific interventions. Specific medicine by gender and sex should not be a different discipline. It should still be incorporated into all educational, medical resources, and formative clinical programs to support gender and sexual dimorphism influence in physiology and human health.

Governments and institutions must understand that there are strong ethical arguments supporting sex and gender equality in medicine. First, gender balance in medical research and clinical workforce can improve research quality and patient outcomes. Second, more gender diversity, particularly in corporate settings, can mean increased productivity, more significant innovation, and better decision-making. However, more importantly, achieving gender balance in medicine is the right thing to do.

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REVIEW ARTICLE

Hypertension and frailty in older people: A dangerous liaison

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Abstract

Hypertension is a common condition in older people. Comorbidity, together with aging, is commonly associated with frailty, which is a cause of a worse prognosis, more hospitalizations, increased dependency, and mortality. Despite being increasingly common conditions, data on the prevalence and influence of frailty in hypertensive older patients are lacking. This may be due to the multidimensional aspects of frailty and the differing tools used to evaluate it. Nevertheless, in clinical practice, it is common to see frail hypertensive patients but the specific characteristics of this group of patients, including multimorbidity and frailty and the lack of data from registries or randomized clinical trials, make the diagnosis and management of these patients more difficult than in those of other ages. This review focuses on what is known and on where future investigations should focus in this common but unclear situation.

Key words: Hypertension. Frailty. Multimorbidity.

Introduction

Hypertension (HT) has an increasing prevalence according to age, and therefore, it is a common disease in older people. In the CARLA (CARdiovascular disease – Living and Ageing in Halle) cohort[1], the prevalence of HT in people aged ≥ 75 years was 81.5% for men and 86.1% for women. One reason why elderly patients with HT are frequently seen in our clinics is the worldwide progressive increase in life expectancy.

In daily clinical practice, also, elderly people with HT and frailty are common. However, the specific characteristics of this particular segment of the population, including multimorbidity and frailty, and the lack of data, either from registries or from randomized clinical trials, make the diagnosis and management more difficult than people of other ages. This review aims to summarize what is already known in this field and what should be the goal in future studies.

HT in older people

As stated before, the prevalence of HT rises with age, especially isolated systolic HT. A recent systematic review[2] that included 135 population-based studies, which recruited 968,419 adults from 90 countries found that the estimated prevalence of HT in adults aged ≥ 70 years, was 73.6% for men and 77.5% for women (in high-income countries) and 65.6% for men and 74.7% for women (in low- and middle-income countries). Kearney et al. showed in an analysis of worldwide data of the global burden of HT that HT prevalence increases with age consistently in all world regions[3].

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However, not only isolated systolic HT is frequent in older people, Sinnott et al., in a cohort study, aimed to estimate the incidence and prevalence of resistant HT among a UK population treated for HT from 1995 to 2015, found that those aged more than 70 years were more likely to develop incident resistant HT[4] than those aged 65-69 years.

However, in older people, HT is, also, frequently associated with other risk factors, including dyslipidemia, obesity, and diabetes, which increase the cardiovascular risk, cardiovascular mortality, and all-cause mortality in patients with HT[5].

As a general term, as HT in the elderly, mixes younger old patients with the oldest old, another question to be considered is which should be the cutoff age, that should be used, to consider specific goals and treatment for HT in the elderly. Some authors and scientific society recommendations specify that the segment included in these recommendations should be specifically individuals aged ≥ 80 years. This age cutoff value is, of course, arbitrary but it may help us to identify a population that is expanding faster, and has a high incidence and prevalence of comorbidities, frailty, and loss of autonomy[6].

Although HT is very common in older people, current evidence on the efficacy and safety of blood pressure (BP)-lowering treatment in older patients with HT is far from being based on indisputable evidence. It is known that in the oldest old, BP-lowering drugs have been shown to reduce the risk of stroke, cardiovascular events, and total mortality, according to some trials, such as the HT in the Very Elderly Trial (HYVET) study[7]. Moreover, in the Systolic BP (SBP) Intervention Trial (SPRINT) which included including 28.3% of patients aged ≥ 75 years, a lower SBP target (corresponding to a SBP goal < 120 mmHg) resulted in lower rates of major cardiovascular events and any cause mortality. In the subgroup analysis, the authors found no differences between subjects aged < 75 years and those aged ≥ 75 years[8]. However, it is important to remember, also, that both low BP and orthostatic hypotension are associated with syncope, falls, and related injuries and fractures that are more frequent in frail patients[9]. Therefore, both the benefits and the risks of antihypertensive therapy should be considered before starting[6]. Therefore, these results could reflect the benefit of more intensive BP reduction in relatively healthy octogenarians, rather than the effect on frail hypertensive.

Definition and evaluation of frailty

Life expectancy has increased worldwide over the past century[10], reflecting changes in lifestyle and diet, as well as aging. However, older people have a greater likelihood of presenting multiple, and usually interacting, conditions[11]. This situation, known as multimorbidity, can lead to interactions between disorders and their treatments, affecting functionality, quality of life, and the risk of mortality. These interactions represent a greater risk than the sum of all individual effects expected from any disorder alone[5].

Together, aging, underlying physiological changes, chronic diseases, and multimorbidity result in the so-called "geriatric syndromes"[12], among which frailty is very common. Figure 1 shows the mechanisms leading to frailty. The prevalence of frailty in high-income countries is around 4% in persons aged 50-64 years and increases to 17% in people aged ≥ 65 years[13].

However, what does frailty mean? Frailty has been defined as a state of reduced ability to recover from stress resulting from an age-related decline in reserves. Frailty involves several domains: physical, psychological, social, and others. Its importance lies in the fact that it confers an increased risk of adverse health outcomes such as falls, fractures, post-operative complications, disability, institutionalization, and mortality[14]. Therefore, a careful evaluation of frailty in older people is a better predictor of survival and other outcomes, than disease or the extent of comorbidities[15].

How should we evaluate frailty? Frailty includes at least four domains: clinical, physical-functional, cognitive-psychological, and social[16]. In addition, the tools available for its evaluation usually examine a partial aspect of this complex situation. For instance, Fried[17] proposed the frailty phenotype with five components: weakness, slowness, exhaustion, low activity, and weight loss. However, this only focuses on physical frailty, while there is a possible floor effect in heart failure patients, and unintentional weight loss is difficult to assess in patients taking diuretics. Another useful tool is the Short Physical Performance Battery[18], which is a composite measure assessing walking speed, standing balance, and sit-to-stand performance. Again, it only focuses on physical frailty and has a possible floor effect in heart failure patients. Another tool is the Frailty Index of Accumulative Deficits (FI-CD), also known as Rockwood's approach[19], which assess frailty through the accumulation of health deficits across multiple domains including cognition, the activities of daily living,

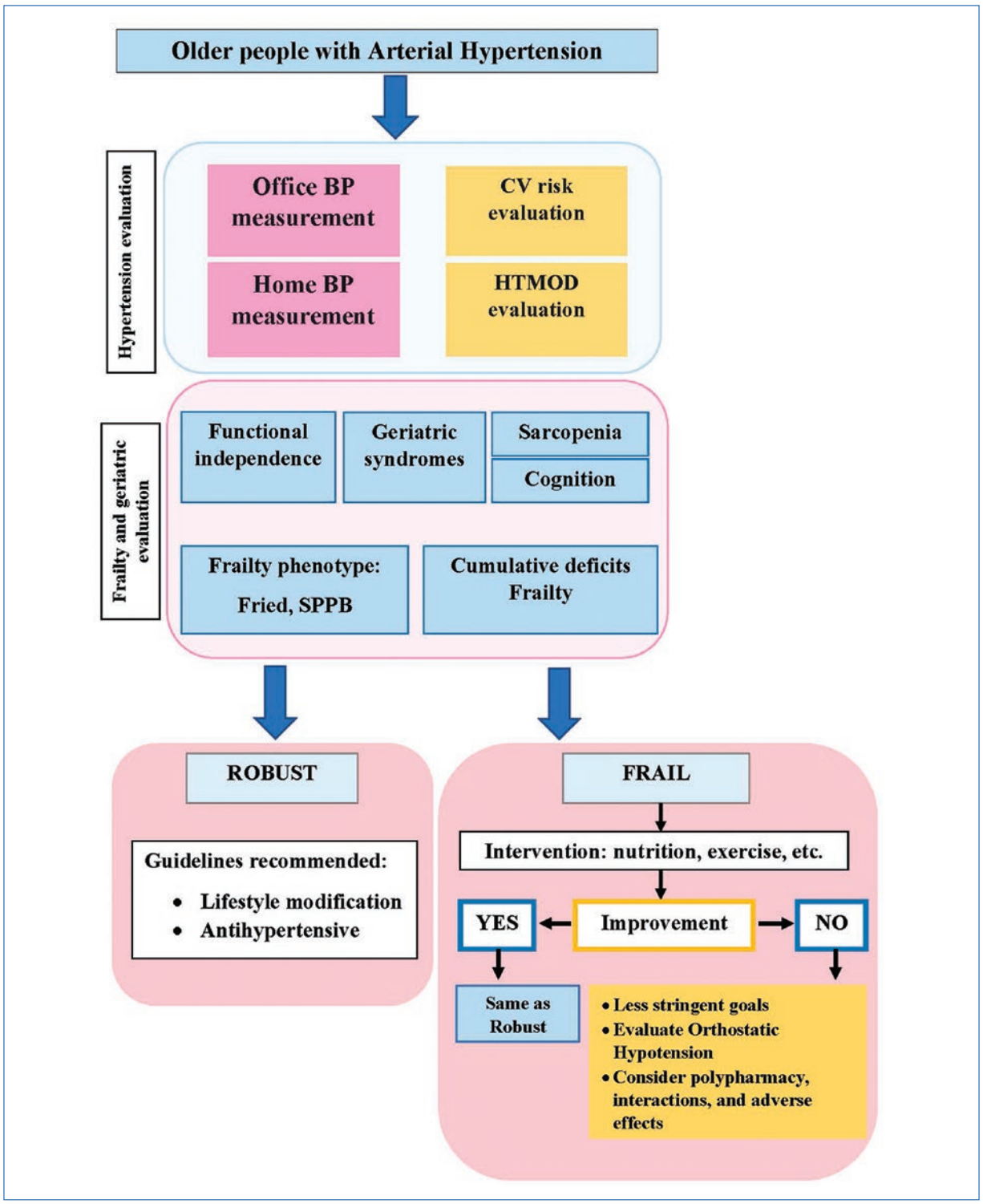

Figure 1. Management of hypertension in frail older adults. Our proposed management process of hypertension in frail older adults is a three-step pathway, starting with a careful evaluation of hypertension including home BP (either ABPM or home BP monitoring). We recommend also a comprehensive geriatric evaluation including tools to identify frailty. For those who are identified as frail, a recommended approach would be to start interventions directed to improve frailty, to identify those patients who had reversible frailty and treat them as the robust following guidelines. As for the frail hypertensive, less stringent goals are recommended and also to avoid secondary effects related to orthostatic hypotension as falls. We should also consider that these patients usually are under polypharmacy that facilitates adverse effects, low adherence to prescription, etc. BP: blood pressure; CV: cardiovascular; HTMOD: hypertension-mediated organ damage; SPPB: short physical performance battery.

comorbidity, deficits in social relations and social support, and abnormal laboratory results. The main problem is that, for routine use, it is time consuming.

HT and frailty

The association between HT and frailty syndrome, in older patients, is far from being clear for various reasons, including the definition of frailty and the tools used to measure it. This may originate a lack of information on the prevalence of HT in frail older patients. Likewise, there are no data on the relationship between HT and frailty. Therefore, whether a BP-lowering treatment could result in a net benefit for frail older patients must be balanced against the safety risks which, in these patients, could be associated with drug treatment, including orthostatic hypotension, falls, and polypharmacy.

Recent guidelines propose taking functional status into account when targeting BP in older people. Therefore, a better understanding and control of frailty risk factors could improve the prognosis of older adults with HT. However, there are relatively few studies on HT and frailty in older adults, especially studies focused on antihypertensive treatment. The goals, target values, and choice of antihypertensive treatment for frail older adults are still disputed[20].

There are little data on the prevalence of HT in frail older people. A cross-sectional study of 619 older outpatients by Aprahamian[21] found that HT was more prevalent in the pre-frail (72.5%) and frail (83%) groups than among controls (51.7%), measuring frailty through the FRAIL scale.

Kang[22] analyzed data from the 5th Korean National Health and Nutrition Examination Survey, including 4352 older adults (age ≥ 65 years). They measured frailty through a FI-CD based on 42 items. The prevalence of HT was higher in frail older people (67.8%) than pre-frail (60.8%) or robust older people (49.2%) ($p < 0.001$). Moreover, frail older people were more likely to be treated than pre-frail or robust older people ($p < 0.001$) but, interestingly, the proportion of patients whose BP was controlled (< 150/90 mmHg) was lower in frail older people ($p = 0.005$).

More recently, a meta-analysis[23] analyzed the relationship between HT and frailty. With respect to the incidence of frailty according to baseline HT, two studies found that baseline HT did not significantly predict the incidence of frailty, but one found that HT was significantly associated with an increased incidence of pre-frailty and frailty, although there was no adjustment by confounders. Another study found an association between HT and incident frailty in the univariate analysis, but this was not confirmed in the multivariate analysis. With respect to cross-sectional associations between frailty and HT, 13 studies found a significantly higher prevalence of frailty in patients with HT and 10 found no significant association. These data indicate that some subgroups of older patients with HT might be particularly fragile due to specific risk conditions and will require caution and strict monitoring during antihypertensive treatment.

With respect to relationship between BP values and mortality, the Milan Geriatrics 75+ Cohort Study[24] was a longitudinal geriatric outpatient cohort that investigated the relationship between BP and mortality in older adults by age, functional, and cognitive status: 1587 outpatients (age ≥ 75 years) were included. The results showed a U-shaped relationship between SBP and diastolic BP (DBP) and the mortality risk. However, although BP, the Mini-Mental State Examination and the Basic Activities of Daily Living were assessed at baseline, there was no specific assessment for frailty.

With respect to the efficacy of intensive BP lowering, an exploratory subgroup analysis from the SPRINT trial[25] stratified by baseline frailty, showed higher event rates with increasing frailty but significantly lower event rates in the intensive treatment group. The same results were found after stratifying by gait speed in favor of the intensive treatment group.

With respect to the safety of intensive BP lowering in frail individuals, the PARTAGE (Predictive Values of BP and Arterial Stiffness in Institutionalized Very Aged Population) study[26] assessed all-cause mortality according to SBP levels achieved (target SBP < 130 mmHg) and the number of antihypertensive drugs in older residents of nursing homes. There was a higher risk of mortality in frail octogenarians who had lower SBP but were on ≥ 2 antihypertensive agents compared with those on one or no medications.

Xue et al. in a cross-sectional study aimed to determine the association between frailty and atherosclerosis, showed that patients with frailty had a lower ankle-brachial index and a higher proportion of carotid intima-media thickening with values of at least 1 mm compared with those in the pre-frail and non-frail groups. The cardio-ankle vascular index score was higher in the frail group than that in the other two groups. Those findings remained even when adjusting for multiple factors[27].

Zhu et al., in a retrospective study, with elderly patients with essential HT undergoing 24 h ambulatory

BP monitoring (ABPM), found that overall magnitudes of BP variability were significantly greater in patients with frailty than those with pre-frailty and non-frailty and, therefore, concluded that longitudinal studies are needed to investigate the causality associations between HT and frailty[28].

Bastos-Barbosa et al. in a cross-sectional study found also that subjects with frailty syndrome had higher BP evaluated by ABPM and other cardiovascular risk factors such as lower high-density lipoprotein and more abdominal fat than non-frailty group[29].

Kabayama et al. found that a lower SBP level was associated with a higher prevalence of physical frailty on patients with age above 80 years on antihypertensive medication, with no association among those without antihypertensive medication[30].

Mol et al. found that orthostatic BP drop rate was associated with frailty and falls and may reflect the challenge to the baroreflex rather than drop magnitude[31].

In a prospective observational analysis using electronic health records (Clinical Practice Research Datalink, including 415,980 patients aged ≥ 75 years), Masoli et al. found that BP < 130/80 was associated with excess mortality, concluding that HT was not associated with increased mortality at ages above 85 or at ages 75-84 with moderate/severe frailty, perhaps due to complexities of coexisting morbidities[32].

Therefore, available evidence shows that low BP is associated with poor outcomes in older frail adults or those with poor functional status, due to increased risk of hypotension, serious fall injuries, and polypharmacy. In contrast, in non-frail older adults, low BP appears beneficial[33].

On the other hand, Bromfield et al. investigated the association of SBP, DBP, number of antihypertensive medication classes taken, and indicators of frailty with risk for serious fall injuries among 5236 participants aged ≥ 65 years taking antihypertensive medication at baseline, in the REGARDS study. They found that indicators of frailty, but not BP or number of antihypertensive medication classes, were associated with increased risk for serious fall injuries among older adults taking antihypertensive medication[34].

Trials and observational studies of BP lowering in older people

Very few trials have considered the treatment of very elderly people with HT. The only one that was directed specifically to this age strata were the HYVET trial, which was aimed at analyzing if the treatment of patients with HT who are 80 years of age or older is beneficial[7]. This trial has shown that antihypertensive treatment in persons 80 years of age or older is beneficial. Nevertheless, before applying the results, some aspect must be considered. There was only a little percentage of the HYVET patients close to or above 90 years of age and therefore this question remains unanswered in this age segment. On the other hand, the trial was prematurely interrupted, and therefore, the follow-up was rather short, and hence, the duration of benefit is not clear.

Another aspect to be considered is that HYVET excluded patients with clinical orthostatic hypotension and did not include very frail patients and that patients with multiple morbidities and clinically significant cognitive impairment.

Another question that has risen from observational studies is that the association between BP and mortality could vary according some measures usually associated to frailty as walking speed, cognitive function, and disability[35]. For instance, SBP is positively correlated to mortality in those with normal/high walking speed, but not in slower walkers, and in those that were not able to complete the walk test, SBP was negatively associated with the risk of death. As for those with cognitive dysfunction or disability, the Milan Geriatrics study has shown that those aged 75 years with impaired cognition or activity of daily living, higher SBP values were related to lower mortality[24].

Mossello et al.[36] found a more pronounced cognitive decline in treated old hypertensive patients having mild cognitive impairment or dementia in whom SBP was low (<128 mmHg). Such an effect was not observed in subjects with low SBP but without antihypertensive treatment.

It is important to remember that both low BP and orthostatic hypotension are associated with syncope, falls, and related injuries and fractures[37-39] Therefore, both the benefits (including preserving autonomy) and the risks of antihypertensive therapy should be considered before starting treatment in the very frail older population.

This population is the one at the highest risk of not only HT-related cardiovascular events but also hypotension-related events.

Pending questions

As the evidence shows, the evaluation and treatment of frail elderly people with HT is a very important, and still unsolved, question.

Before starting to evaluate and measure frailty, as mentioned above, a proper valuation of HT should be done. It includes the evaluation of HT-mediated organ damage and, of course, the type of BP measurement is also important, as it is known that ambulatory BP measurement is more reliable than office BP measurement with respect to outcomes. However, very few studies are based on ambulatory BP measurement.

Among those studies, a cross-sectional study by Bastos-Barbosa[40] in 77 frail, pre-frail, and non-frail older subjects (according to Fried criteria) found that on ambulatory BP measurement, frail patients had a higher SBP and DBP levels at 24 h and during sleep than the non-frail group.

As ambulatory physical activity is associated with daytime BP, lower physical activity in frail older people causes lower daytime BP, which often could result in non-dipper type of night-time BP. In the elderly, non-dipping/reverse dipping may also be related to other factors such as poor sleep, impaired renal function, and others[29,41,42]. These conditions are associated with frailty.

The new ambulatory BP measurement equipped with actigraphy could measure physical activity associated BP increases (Actisensitivity)[43-45]. Hyper-actisensitivity and inverse actisensitivity are considered abnormal pathological conditions. Inverse actisensitivity (negative association between physical activity and daytime BP) is associated with heart failure with a reduced ejection fraction. Responders may recover from inverse actisensitivity to adequate actisensitivity with medication.

Therefore, HT is significantly associated with frailty and is more prevalent in frail older patients. It also seems that intensive BP control could influence the development of frailty, but there is scarce information to support this hypothesis, and it should be explored in future prospective clinical trials. As for intensive BP lowering, it should not be forgotten that frail older patients may not tolerate BP lowering in the same way as robust elderly patients with HT.

With respect to measuring clinical BP or ambulatory BP and their concordance, it should be remembered that white coat HT (WCH) represents a large percentage of our patients. In the HYVET study[46], 50% of people aged > 80 years had WCH and the authors found that very old patients with WCH may benefit from treatment, but as explained above, there was no frailty evaluation in HYVET. In another study, Pierdomenico[47] assessed the prognostic value of masked uncontrolled HT (MUCH) and white coat uncontrolled HT (WCUCH), respectively, in older treated patients with HT. They found that those with MUCH (34%) had a significantly higher risk and those with WCUCH (30%) have a slightly, non-significantly higher risk. Nevertheless, frailty was not evaluated in either of these studies.

Another aspect to be considered in the relationship between frailty and HT is sarcopenia. Dutra et al. showed that SBP is significantly higher in subjects with sarcopenic obesity[48]. Individuals with sarcopenia were significantly more likely to present a high CV risk score in a recent analysis of the Korean National Health and Nutrition Examination Surveys database by Han et al.[49] Tamura et al. found also found a high prevalence of frailty, cognitive impairment, and sarcopenia in patients with cardiometabolic disease[50]. But unfortunately, the data on sarcopenia, frailty, and HT are scarce.

Conclusion

Older patients commonly have HT complicated with frailty. However, our knowledge of this common situation is far from satisfactory. HT is more frequent at advanced ages, where frailty is also more frequent, but there are no validated tools to measure frailty in those patients. In addition, knowledge of the repercussions of frailty on HT is very limited.

Taking this into account, and as current guidelines recommend, individualized treatment strategies are indicated, considering the benefits of appropriate BP control, as some studies have shown clinical benefits by reducing elevated BP in “healthy” older people aged > 80 years, but should frail older patients with multiple comorbidities and a reduced life expectancy be “overtreated” or rather, should the first goal to avoid harm and adverse effects in frail older patients? As part of this strategy, in older patients with HT, ambulatory BP measurement and frailty evaluation should be part of routine clinical management.

As for treatment, there are little data available on the best BP goal for frail or pre-frail patients with HT, and even less data about which class of BP-lowering drug should preferably be used. Therefore, there is an urgent need to plan new studies in this group of patients, considering the possible need for patient-reported outcome measures, instead of traditional outcomes, and the use of frailty measurement tools including different aspects of this common entity.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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