a preparation for lung transplantation and in patients in whom medical treatment had failed and there were no therapeutic alternatives. The failure of AS to become established as a general treatment is likely due to the relatively high associated procedural and periprocedural mortality (5% and 16%, respectively),[5] and also to uncertainty about the optimal timing of the intervention for maximum benefit. Some studies suggest that AS would be beneficial at early stages of disease development; nonetheless, in most countries with access to high-cost medical treatments and lung transplantation, AS is conducted at late disease stages, when medical treatment has failed or as a last resort before transplantation. However, AS in terminal disease stages is associated with high mortality, and the procedure is therefore not recommended in end-stage patients.[4,5] In our series, AS was indicated in advanced disease stages when medical treatment had failed, but not as a rescue treatment in end-stage patients. The patient who died 1 week after AS had needed ultrafiltration and inotrope therapy as preparation for the procedure, and it is possible that the indication for AS was borderline in this case. No patient died as a result of the procedure. Survival in our series at 30 days was 90%, and at medium term was in line with published data related to disease progression: 75% at 6 months and 57% at 1 year.[1,4,5]

In our experience, elective AS is a therapeutic option for PAH patients in whom optimal medical treatment has failed. The procedure is associated with low periprocedural morbimortality, and delivers functional improvement in most severe PAH patients with refractory right heart failure or low cardiac output. Moreover, elective AS is effective both as a bridge to lung transplantation and as an adjunct to medical treatment.

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Growth Differentiation Factor 15, a New Prognostic Marker in Diabetic Cardiomyopathy

El factor de diferenciación de crecimiento 15, un nuevo marcador pronóstico en la miocardiopatía diabética

To the Editor,

The various clinical guidelines and consensus statements recommend a multifactorial approach to diabetes mellitus, acting on glycemia and the other associated risk factors to obtain the greatest possible reduction in macrovascular and microvascular morbidity and mortality.[1] Diabetic cardiomyopathy (DCM) is usually asymptomatic in the initial stages.[2] Growth differentiation factor 15 (GDF-15) is a cytokine secreted by macrophages and cardiac myocytes in response to oxidative stress and inflammation.[3]

Our group recently described the usefulness of GDF-15 as a screening tool in the diagnosis of DCM in asymptomatic patients with type 2 diabetes mellitus.[4] The study aimed to describe the prognostic value of GDF-15 at 1 year in a cohort of patients with DCM, evaluating the relationship between the levels of this biomarker and the combined primary endpoint of heart failure with hospital admission and/or angina with hospital admission.

The details of the study have previously been described.[4] Briefly, the study prospectively included 213 asymptomatic patients with type 2 diabetes mellitus. Diabetic cardiomyopathy was defined, according to the criteria of the European Society of Cardiology and the European Association of Diabetes, as left ventricular diastolic dysfunction (tissue Doppler with an E/É ratio $\geq$ 15) in the absence of hypertension, ischemic heart disease, or other structural heart disease.[5] For the analysis, the outcomes at 365 days of the 45 patients who had DCM were studied, as was the relationship between DCM and GDF-15 concentration.

Continuous variables are expressed as mean $\pm$ standard deviation for those with a normal distribution or median [interquartile range] for those with an abnormal distribution. Categorical variables are expressed as number (percentage). Quantitative variables were compared using the Student *t* test or Mann-Whitney *U* test. The association between qualitative variables was determined using the Pearson chi-square test or Fisher exact test. Survival analysis was performed using Cox regression, with variables with a *P*-value $<$ .2 on univariate analysis being included in the model. Risk proportionality assumption was evaluated by Schoenfeld residual analysis. The statistical analysis was performed with the SPSS program, version 20 (SPSS Inc., Chicago, Illinois, United States).

The study population characteristics are shown in the Table. The primary endpoint of the study occurred in 12 patients (26.7%). There were no statistically significant differences between the 2 groups in baseline characteristics (age, sex, left ventricular ejection fraction, hypercholesterolemia, and smoking), treatment, or laboratory data. Concentrations of GDF-15 were higher in patients with DCM who experienced a combined event than in those with no events (6458.9 pg/mL [5359.7-8681.9 pg/mL] vs 4706 pg/mL [3719-6463 pg/mL], *P* = .007) (Figure). Combined events occurred at a mean time of 162 $\pm$ 89 days. In the Cox survival

Table
Classification of Patients With Diabetic Cardiomyopathy by Occurrence of Events

	With event (n = 12)	No event (n = 33)	*P*-value
Age, y	61.3 ± 5.7	61.5 ± 6.1	.93
Male sex, n (%)	7 (58.3)	22 (66.7)	.73
LVEF, %	56.4 ± 4.9	59.3 ± 4.7	.08
Cardiovascular risk factors			
Smoking, n (%)	4 (33.3)	15 (45.5)	.47
Hypercholesterolemia, n (%)	7 (58.3)	16 (48.5)	.56
Treatment			
ACE-I/ARB, n (%)	10 (83.3)	24 (72.7)	.69
Statins, n (%)	7 (58.3)	16 (48.5)	.56
Oral antidiabetics, n (%)	9 (75)	24 (72.7)	.24
Insulin, n (%)	4 (33.3)	19 (57.6)	.15
Blood analysis			
HbA_{1c}, %	6.4 [6.3-7.2]	7 [6.4-7.2]	.29
Total cholesterol, mg/dL	173.5 [152-197.5]	165 [143-203]	.97
Triglycerides, mg/dL	145 [68-223.2]	131 [104.5-169]	.67
Apolipoprotein B, mg/dL	92 [79.5-110.2]	93 [71-106.5]	.85
BNP, pg/mL	482.8 [449-488.8]	459.7 [431.1-530.5]	.67

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; DCM, diabetic cardiomyopathy; HbA_{1c}, glycosylated hemoglobin; LVEF, left ventricular ejection fraction.

analysis, after adjustment for other covariables (treatment with insulin, mean GDF-15, and left ventricular ejection fraction), the variables shown to be independent predictors of the combined endpoint were mean GDF-15 level (hazard ratio = 4.96; 95% confidence interval, 1.24-19.77; *P* = .023) and left ventricular ejection fraction (hazard ratio = 0.83; 95% confidence interval, 0.7-0.98; *P* = .031). The discriminatory power of the model, determined using the C-statistic, was 0.826.

The originality of this study is that it demonstrates for the first time that high GDF-15 levels are associated with poor prognosis at 365 days in patients with DCM. Hyperglycemia activates signaling pathways mediated by reactive oxygen species, leading to the development of myocardial hypertrophy and fibrosis with ventricular stiffness and chamber dysfunction.[2] Experimental studies have demonstrated that cardiac DGF-15 expression significantly increases after various forms of stress, including pressure overload.[6]

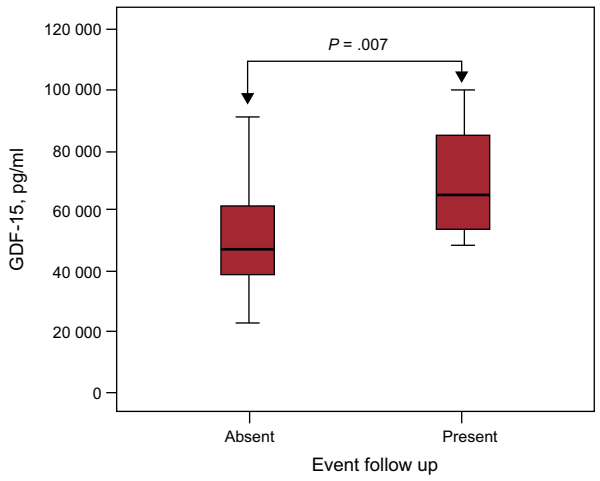

Figure. GDF-15 levels by presence or absence of combined events during follow up at 365 days. GDF, growth differentiation factor.

Given that GDF-15 is produced by several other types of cells besides cardiac myocytes (endothelial cells, adipocytes, and macrophages), it is likely that this biomarker comprises information from several disease pathways, providing the pathophysiological information necessary in patients with DCM.[4]

The main limitation of this study is its small sample size and low number of combined events and therefore it should be considered a hypothesis generator. We conclude that in patients with DCM, high GDF-15 values are associated with poor prognosis at 1 year. Randomized studies with larger sample sizes are needed to add more information on the value of this biomarker in predicting events.

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Current Management of Hyperlipidemia in Patients Discharged With a Diagnosis of Acute Coronary Syndrome

Manejo actual de la hiperlipemia en pacientes dados de alta con el diagnóstico de síndrome coronario agudo

To the Editor,

Current European[1] and American[2] guidelines on the management of hyperlipidemia concur on the advisability of intensive treatment of low-density lipoprotein cholesterol (LDL-C) in patients hospitalized with acute coronary syndrome (ACS).[3] However, they differ in their recommendations on post-discharge treatment. European guidelines have a therapeutic goal of LDL-C level < 70 mg/dL or a reduction of LDL-C > 50%. In contrast, American guidelines, based on the efficacy shown in clinical trials,[4] propose statin treatment classified according to their intensity and the theoretical percentage reduction in LDL-C they confer. As such, statins are classified into 3 categories: high-intensity (LDL-C reduction > 50%), moderate-intensity (reduction 30%-50%), and low-intensity (reduction < 30%). According to American guidelines, patients with ACS who are younger than 75 years should receive high-intensity statin therapy, while those older than 75 years should receive moderate-intensity statins. There is little focus in the guidelines on the management of atherogenic dyslipidemia (AD), which is characterized by the association of low levels of high-density lipoprotein cholesterol and high triglyceride levels, with or without increased LDL-C concentrations. Atherogenic dyslipidemia represents the main cause of residual increased cardiovascular risk once target LDL-C levels have been achieved with statins,[5] but it has been little studied in patients with ACS. Our objectives were to assess the degree of compliance with current recommendations on lipid-lowering therapy on discharge in patients with a diagnosis of ACS, and to evaluate the prevalence of AD, the variables associated with this metabolic abnormality, and its influence on clinical outcomes after discharge in these patients.

We retrospectively analyzed 856 consecutive patients discharged with a diagnosis of ACS: 506 (59.1%) had ST-segment elevation and 350 (40.9%) had no ST-segment elevation but had an objective sign of myocardial ischemia (dynamic changes in the ST-segment, raised troponin, or the presence of a coronary lesion identified as the cause of symptoms). Atherogenic dyslipidemia was defined as a high-density lipoprotein cholesterol level < 40 mg/dL in men and < 50 mg/dL in women, with triglyceride levels ≥ 150 mg/dL. We analyzed the baseline variables, the lipid profile during hospital admission and after discharge (median 3 months), and cardiovascular events–stroke or myocardial infarction–over a clinical follow-up of 12 months.

Statin therapy was prescribed in 830 patients (97%) (combined with ezetimibe in 10 patients and with fenofibrate in 18 patients). Ezetimibe alone was prescribed in 3 patients (0.4%), and fenofibrate alone in 2 (0.2%). Twenty-one patients (2.5%) received no lipid-lowering therapy. Of the 830 statin-treated patients, 570 (68.7%) received high-intensity (atorvastatin 80 mg in 77% and rotuvastatin 20 mg in 23%), 247 (29.8%) received moderate-intensity, and 13 (1.6%) received lower-intensity statins.

The percentage of patients treated with high-intensity statins was 65.2% among those older than 75 years and was 69% in those younger than 75 years. Use of high-intensity statins was associated with a greater reduction in LDL-C levels after discharge and a higher percentage of patients achieving therapeutic goals. The incidence of myocardial infarction or stroke during follow-up was higher in patients treated with lower-intensity statins than in those receiving moderate- or high-intensity statins (Table 1).

On multivariate analysis, the only variables independently related to the incidence of myocardial infarction or stroke were diabetes (odds ratio = 2.3; $P = .006$) and use of lower-intensity statins compared with high-intensity statins (odds ratio = 7.0; $P = .002$). Achieving LDL-C therapeutic goals did not affect the incidence of these events during follow-up.

A total of 228 patients met the criteria for AD (26.5%). Compared with the non-AD group, patients with AD were younger (61.1 ± 11.4 years vs 65.8 ± 12.9 years; $P < .001$), had a higher prevalence of smoking (43.9% vs 36.0%; $P = .036$) and diabetes (39.9% vs 25.4%; $P < .001$), higher body mass index (29.5 ± 4.3 kg/m^2 vs 28.4 ± 4.6 kg/m^2; $P = .004$), and a higher ischemic risk score according to the Global Registry of Acute Coronary Events (GRACE: 150.3 ± 34.3 vs 139.2 ± 35.5; $P < .001$) (Table 2). At follow up, a high percentage of patients in both groups achieved the therapeutic goals of LDL-C control. However, AD persisted in 46.9% of patients. Patients with AD had a higher incidence of stroke and myocardial infarction than patients without AD.

Table 1
Baseline Patient Characteristics, Lipid Profile on Admission, and Events and Lipid Profile After Discharge, by Intensity of Statin Therapy Prescribed on Discharge

	High-intensity (n = 570)	Moderate-intensity (n = 247)	Lower-intensity (n = 13)	*P*
Baseline LDL-C[a]	99.6 [76.2 to 123.6]	93.5 [72.7 to 117.2]	71 [63.4 to 121]	.047
HDL-C increase, %[a]	5.1 [−9.7 to 22.5]	11.1 [−7.0 to 29.3]	12.0 [−2.0 to 25.8]	.022
TG reduction, %[a]	13.6 [−15.2 to 33.3]	11.0 [−15 to 34]	−5 [−15.3 to 2.8]	.108
LDL-C reduction, %[a]	27.9 [5.9 to 44.5]	17.2 [−1.2 to 38.3]	−1 [−15.5 to 22.6]	.001
LDL-C goal achieved[b]	287 (50.4%)	94 (38.1%)	2 (15.4%)	.002
Myocardial infarction	24 (4.2%)	11 (4.5%)	2 (15.4%)	.165
Stroke	10 (1.8%)	3 (1.2%)	2 (15.4%)	.025

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
[a] Median [25th percentile to 75th percentile].
[b] LDL-C < 70 mg/dL or reduction > 50% from baseline LDL-C.